On the Destruction of Erythrocytes and Other Cells by Antibody and Complement*

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During the past 20 years the sequential action of the complement components and the roles of Ca++ and Mg++ have been elucidated, experimental technics for the isolation of the intermediate products have been devised, and progress has been made in separating and purifying the components of complement. These advances have brought the study of complement to a stage where it offers new opportunities for probing into the mysteries which now occupy the center of immunologic inquiry.

This brief review will not be concerned with the long history of the subject, but rather I will seek to outline its present status, to depict obstacles impeding progress, and to draw attention to problems awaiting solution. Several systematic and comprehensive accounts, including technical procedures, have been published recently (24, 31, 41).

The term "complement" was coined at the turn of the century when the complex nature of this system had not yet been recognized and when it was believed that it functions as an auxiliary to antibody. Since then, it has been learned that complement comprises at least six distinct factors or components, which act in a definite sequence to bring about cell injury. It appears to be the function of antibody to initiate the series of reactions which comprise the complement system and to give specific direction to its cytotoxic action on certain bacteria and protozoa, as well as cells of higher organisms. Complement also participates in the neutralization of some viruses, enhances phagocytosis, and plays a role in the complex events of immunologic tissue injury known collectively as allergic reactions. In general, complement, if present, and under appropriate experimental conditions, enters into combination and reacts with many kinds of antigen-antibody complexes; and, hence, its participation, whether causal or not, is a factor in various immunologic phenomena. Acting alone, antibody has the capability to neutralize toxins and some viruses, but against living cells it is usually powerless, unless the complement system or phagocytic cells, or both, also come into action.

The ease with which the hemolytic reaction can be observed and measured accurately is responsible for its widespread use in studies of the complement system. Most of the information now available has come from studies of the hemolytic reaction, and many of these basic investigations have been made with a model system comprising sheep erythrocytes, the corresponding rabbit antibody and fresh guinea pig serum as a source of complement. At present, the technical procedures developed in the study of this model system represent the most refined methods available for investigations of complement. However, the essential concepts and experimental tactics are amenable to general application and may serve as a guide to the study of the many immunologic phenomena involving complement.

HEMOLYTIC REACTION MECHANISM

Recent studies of immune hemolysis have been directed primarily toward elucidation of the successive reactions which comprise the complement system. The first step in the complex series of events to be described is the combination of at least two molecules of antibody (A) with certain antigenic sites (S) on the erythrocyte surface, the antibody molecules being located in close proximity with respect to one another, creating a receptor SA2, as postulated by Weinrach et al. (50, 51), which then reacts with the complement (C') factors C'1, C'4, C'2, C'3a, C'3b, and C'3e in a series of successive reactions according to the scheme depicted in Chart 1. Ca++ is essential as a ligand in reaction [1] and Mg++ catalyzes reaction [4], but Co++, Ni++, or Mn++ may be substituted for Mg++, though at lower efficiency. Reaction [4'] indicates that

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$SA_2C'1,4,2$ sites are unstable and revert to $SA_2C'1,4$ at a rate depending on temperature. The half-life of $SA_2C'1,4,2$ made with guinea pig complement, is about 10 hours at 0°C., about 25 minutes at 20°C., and 10 minutes at 37°C. Reaction [5] comprises three steps involving $C'3a$, $C'3b$, and $C'3c$; their sequence of action has not yet been resolved. Reaction [6] indicates that treatment of $SA_2C'1,4$ with EDTA yields $SA_2C'4, S^*$. $S^*$ denotes a lesion in the erythrocyte membrane which impairs the osmotic balance of the cell. There is no information on the chemical nature of any of these steps, except for the claims by Becker (6) and Lepow (26) that $C'1$ is an esterase.

The intermediate products, at a cellular level, are designated by the symbols, $EA$, $EAC'1$, $EAC'4$, $EAC'1,4$, $EAC'1,4,2$, and $E^*$. The symbol $EA$ designates cells with one or more $SA_2$ receptors, the number of these, of course, depending on the antibody multiplicity—i.e., the number of antibody molecules per cell. Each sheep erythrocyte can combine with as many as 5,000 molecules of $A$, but usually experiments are performed with an antibody multiplicity of about 1,000, and it has been estimated that this will yield approximately 125 $SA_2$ receptors per cell. The intermediate product $EAC'1$ refers to cells with at least one $SA_2C'1$ site. Similarly, $EAC'1,4$ designates cells with one or more $SA_2C'1,4$, the upper limit with respect to the number of such sites per cell being the number of $SA_2$ per cell. The same considerations apply to the intermediates $EAC'1,4,2$ and $EAC'4$. The symbol $E^*$ refers to damaged cells which lyse spontaneously. One $S^*$ is sufficient to transform a cell to the state $E^*$, as explained in a later section on the one-hit theory of immune hemolysis.

During the past 7 years experimental methods have been developed by which sheep erythrocytes can be transformed into each of these intermediates by appropriate treatments with rabbit antibody and guinea pig complement or complement fractions. Furthermore, fractionation methods for the separation of the complement factors from guinea pig and human serum have been devised, and with these technical advances it is now possible to study the complement reaction steps individually, with certain exceptions to be noted.

Action of $C'2$.—Through the work of Borsos et al. (8–10), who has developed a simple and reliable procedure for separation of guinea pig $C'2$ in a state of functional purity, i.e., free of other $C'$ factors, as well as devoid of inhibitors, more definitive information exists on the action of this component than of any of the other $C'$ factors. In rigorous quantitative experiments, Borsos has shown that the generation of $SA_2C'1,4,2$ by action of purified $C'2$, followed by decay to $SA_2C'1,4$, may be performed repeatedly in a series of "cycles," without loss of $SA_2C'1,4$ receptors. $C'2$ is used up stoichiometrically in the generation of $SA_2C'1,4,2$. It follows from these observations that decay of $SA_2C'1,4,2$ probably involves release of $C'2$ in inactive form. The nature of this process is currently under study with the aid of specific antibody to $C'2$.

A theory for reactions [4] and [4'] has been developed and evaluated, yielding the following relationship:

$$-\log c (1 - y_{1,4,2}) = \frac{k_1A_0B_0}{k_1A_0 - k_2} [e^{-k_1t} - e^{-k_2A_0t}]$$

where,

$A =$ average number of $SA_2C'1,4$ per cell at time $t$

$A_0 =$ initial value of $A$

$B =$ number of $C'2$ molecules (expressed on "per cell basis") at time $t$

$B_0 =$ initial value of $B$

$C =$ average number of $SA_2C'1,4,2$ per cell at time $t$

$k_1 =$ specific rate constant of formation of $SA_2C'1,4,2$

$k_2 =$ specific rate constant of decay of $SA_2C'1,4,2$

$y_{1,4,2} =$ fraction of cell population in the state $EAC'1,4,2$

For the special case when $k_1A_0 = k_2$, the appropriate relation is:

$$-\log c (1 - y_{1,4,2}) = k_2B_0e^{-k_2t}.$$
With the aid of these equations it is possible to perform measurements of C'2 on an absolute molecular basis. As explained in a later section, there is the possibility and even likelihood of unfruitful reactions, and consequently Borsos' method of titration, though absolute, furnishes only minimal estimates. This limitation is recognized by expressing the results of C'2 titration in terms of "effective" molecules of C'2.

The ability to measure C'2 with a degree of precision approaching that of many chemical analytical methods has facilitated studies on its characterization. C'2 is a protein which is stable up to 45°C; but can be reversibly denatured by heat at 56°C; the reversibility exhibits sharp temperature dependence. C'2 is stable between pH 4.6 and 11.5. Ultracentrifugal measurements with the separation cell indicate a sedimentation coefficient of about 7.8.

Action of C'3.—The classical definition of C'3, based on its removal by zymosan, has lost its specific meaning in view of the demonstration by Nelson that this process is a complement fixation reaction (40). Furthermore, from kinetic and theoretical analyses, Rapp deduced that C'3 comprises at least two factors, and subsequently he separated these by fractionation of guinea pig serum (44). Amiraian, Plescia, and Heidelberger (4) arrived at the same conclusion by a different approach. Recent unpublished experiments by Rapp have indicated that there are three distinct C'3 factors. Taylor and Leon (48) have separated two C'3 factors from human serum and obtained a new intermediate. Müller-Eberhard et al. (36, 37) have isolated a β1 glycoprotein from fresh human serum which may represent one of the C'3 components. The sequence of action of these factors has not yet been established definitively.

These investigations have laid the foundation for a new definition of C'3, namely, a group of factors which convert $SA_2C'_{1,4,2}$ to $S^*$. Fortunately, from a technical standpoint, whole guinea pig serum treated with EDTA can be used as a potent source of the C'3 factors, since the chelating agent, in proper concentration, blocks the preceding C' reaction effectively, but does not affect conversion of $SA_2C'_{1,4,2}$ to $S^*$. A reagent for measurement, but, as pointed out in a later section, this reagent does not satisfy rigorously the requirements for precise quantitation. Attempts to measure C'1 quantitatively in terms of formation of EAC'1 from EA, or conversion of EAC'4 to EAC'1,4, are still in an early stage, and until the problem of quantitation can be solved it will be difficult to exclude the possibility that the esterase may be a contaminant. The confusion surrounding the esterase question has not been alleviated by the divergent claims as to the capacity, or lack of capacity, of "converted" C'1 to act as C'1 in various cytotoxic reaction systems. The esterase question has been discussed in more detail elsewhere (19, 24).

Action of C'4.—In terms of the currently accepted reaction scheme, this component is defined as a factor that converts EAC'1 to EAC'1,4, which is recognized by its capacity to react with C'2. This definition is more specific and therefore preferable to the classical one based on inactivation by ammonia or primary amines (cf. 49). Becker (7) has found that elution of C'1 from EAC'1,4 by EDTA leaves the cells in the state EAC'4. This intermediate does not react with C'2, unless C'1 is restored, and hence it can be used for detection and measurement of C'1, as pointed out before.

Kinetic measurements, as well as end-point titrations by Hoffmann (19), have shown that formation of EAC'1,4 from EAC'1 is a one-hit reaction (cf. later section on the one-hit concept), in the sense that a cell with a single $SA_4C'_{1,4}$ site is susceptible to lysis if treated with C'2 and the C'3 factors in high concentration. Thus, there exists direct proportionality between the quantity of C'4 used for treatment of EAC'1 and $-\log(y_{1,4})$, where $y_{1,4}$ represents the fraction of cells in the state EAC'1.4.

THE ONE-HIT THEORY OF IMMUNE HEMOLYSIS

From studies of the action of C'2 (8–10) definitive evidence has been obtained that the immune hemolytic reaction is a "single-hit" and not a "multiple-hit" process. Alternatively, and perhaps preferably, we might say that the hemolytic action of complement is "non-cumulative" rather than "cumulative." This distinction is of fundamental importance, because it holds the key to the development of a quantitative relationship between the molecular reactions of cell constituents with antibody and the complement components, and the
final event at a cellular level, namely, hemolysis, on which experimental observation and measurement are based.

The concept of a one-hit reaction is a familiar one in the infection of cells by viruses, but in the case of hemolysis by antibody and complement its definition presents a more complex situation because of the multicomponent nature of complement. It is postulated that the six complement factors react at discrete loci upon the cell surface, each locus being created by the union of two antibody molecules, as postulated by Weinrach et al. (50, 51), with an antigenic site, $S$, on the surface of the cell. These sensitized sites, $SA_2$, react with the complement factors in the proper sequence, and this leads to damage of an unknown nature to the structure of the cell membrane at or near this locus. Such a damaged site is designated by the symbol $S^*$. The one-hit theory postulates that the production of one $S^*$ upon a cell is sufficient for lysis. In applying this definition it is recognized that the production of one $S^*$ requires action of antibody and six complement components, and the possibility that more than one molecule of any one of these factors may act at a single site is not necessarily excluded.

The old hypothesis that immune hemolysis is a multiple-hit or cumulative process had its origin in the work of Leschly in 1913 (28), who showed that the dose-response curve describing the lysis of sensitized erythrocytes by complement is sigmoidal. This was explained in terms of a cumulative damage model by Brooks (11) and more explicitly by Alberty and Baldwin (2), who deduced from published dose-response curves that lysis of an erythrocyte occurs when approximately ten sites upon its surface have reacted with antibody and complement.

The development of the one-hit or noncumulative theory has been reviewed recently (32). Briefly, this concept had its origin in the observation by Charles C. Croft that the absolute speed of hemolysis in the reaction between optimally sensitized erythrocytes and complement is sigmoidal. This was explained in terms of a cumulative damage model by Brooks (11) and more explicitly by Alberty and Baldwin (2), who deduced from published dose-response curves that lysis of an erythrocyte occurs when approximately ten sites upon its surface have reacted with antibody and complement.

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stitute independent events. This formulation would recognize the possibility that some sites that have reacted with each of the complement components are not \( S^* \).

**THE LIMITING COMPONENT CONCEPT**

This idea, advanced by Hegedus and Greiner (18), represents an attempt to explain the meaning of the hemolytic titer of complement. In light of the information which emerged from the work of Borsos *et al.* on \( C^2 \), the validity of this principle can be evaluated, and the meaning of the "titer" can be explained.

In the limited complement system, the condition prevailing in the titration of complement, the intermediate \( S_A C^1,4,2 \) piles up because its reaction with the \( C^3 \) factors is slow relative to the preceding reaction steps. Furthermore, \( S_A C^1,4,2 \) decays to \( S_A C^1,4 \), and the former can be regenerated by \( C^2 \). The decay of \( S_A C^1,4,2 \) and its regeneration by \( C^2 \) can be regarded as a cyclic process which will proceed as long as \( C^2 \) is available. If the ratio of \( C^2 \) to \( S_A C^1,4 \) is large, a steady state ensues, maintaining \( S_A C^1,4,2 \) at a constant level for awhile; but eventually no more \( S_A C^1,4,2 \) can be generated, because \( C^2 \) is exhausted. In addition, there is slow destruction of \( S_A C^1,4 \) by factor present in guinea pig serum. It is obvious that the longer the cells are maintained in the state \( EAC^1,4,2 \), the greater their chance to react with the \( C^3 \) factors and, hence, the higher the degree of lysis. In essence, therefore, the overall hemolytic titer of complement depends on the supply of \( C^2 \); but there are important qualifications which complicate this simple interpretation. First, the supply of \( C^1 \) and \( C^4 \) exerts a slight influence on the over-all titer because of its effect on the efficiency of utilization of \( C^2 \). In addition, the concentration of the \( C^3 \) factors influences the rate of conversion of \( EAC^1,4,2 \) to \( E^* \), and the higher this rate the smaller the loss of reactive sites by decay. This state of affairs can be summarized by saying that the over-all titer reflects the supply of \( C^2 \) but is influenced strongly by the concentrations of the \( C^3 \) factors; the quantities of \( C^1 \) and \( C^4 \) also affect the titer, though to a small extent. Thus, the simple limiting component principle enunciated by Hegedus and Greiner does not describe the mechanism adequately.

**SUMMARY OF CURRENT CAPABILITIES AND LIMITATIONS**

Although all the intermediates, except some within the \( C^3 \) stage, can be made, current methods are not satisfactory from the standpoint of controlling the number of intermediate sites per cell. In the case of \( EAC^1,4,2 \), this problem has been solved partially by use of a known number of \( C^2 \) molecules for treatment of \( EAC^1,4 \). However, the number of \( S_A C^1,4 \) sites on these cells cannot be controlled precisely, partly because of the present uncertainty surrounding the nature and action of \( C^1 \), and also for lack of adequately purified preparations of \( C^4 \). The importance of proper site control cannot be over-emphasized, because it represents the foundation of quantitative evaluation, which, in turn, is the cornerstone of sound interpretation. Many of the uncertainties and apparent contradictions, as in the esterase problem, are probably due to lack of proper quantitation.

The new analytical technics are based on the simple principle that each factor of the \( C^3 \) system should be measured in terms of the rate or extent of conversion of the appropriate precursor to its successor. Although this approach necessitates preparation of the requisite intermediate product, as well as purification of the \( C^3 \) factors, its theoretical and practical advantages over the classical technics, in which the complement factors are assayed with the reagents \( R1, R2, R3, \) and \( R4 \), are so great that I expect general adoption of the new technics within the next few years. The most compelling reason for this assertion is the virtual impossibility of obtaining preparations of \( R1, R2, R3, \) and \( R4 \) which meet the essential requirements necessary for their use, namely, that they supply an adequate excess of all the \( C^3 \) factors except the one to be titrated and, conversely, that they be completely free of the latter. Moreover, they should be free of interfering factors ("not anti-complementary"). Existing methods for the preparation of these reagents fall far short of this goal, and there appears to be no likelihood that they can be improved sufficiently to come anywhere near the necessary specifications (24). This criticism is not intended to imply that these reagents are without value. In the unfolding of our knowledge of the complement system during the past 80 years they have played an indispensable role toward achieving a first-stage resolution, but as the study of the cytotoxic action of complement enters more refined stages of exploration, the necessary strategies cannot be satisfied by these reagents. Therefore, much of our effort during the past 10 years has been devoted to the development of more satisfactory analytical methods.

The new analytical approach, based on use of appropriate intermediates as substrates, has been used most extensively in studies of purified \( C^2 \). In its present form the method is not applicable to titration of \( C^2 \) in whole serum, because \( C^1 \) and \( C^4 \) from the serum modify the substrate \( EAC^1,4 \) with respect to the number of \( S_A C^1,4 \), causing apparent increase of \( C^2 \) titer. Furthermore, \( C^3 \) factors contributed by the serum influence the result by affecting the efficiency of conversion of

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SA2C1,4,2 to S*. Still another complication in analyses for C'2 in blood serum is the presence of a factor which destroys SA2C1,4 sites.

**CYTOTOXIC ACTION OF COMPLEMENT ON CELLS OTHER THAN ERYTHROCYTES**

The cytotoxic action of antibody and complement on certain bacterial genera, such as Vibrio, Salmonella, Shigella, or Escherichia, has been studied extensively with respect to its significance in immunity. It is known that C'1, C'2, C'3, and C'4, as well as Mg++, are necessary, but there is no detailed information on intermediate products and the properties of the individual reaction steps (30).

Most bactericidal studies have been made by the plate count technic, but a photometric assay method devised by Muschel and Treffers (38, 39), appears to be less laborious and more accurate. A quantitative bacteriolytic technic, developed by Amano et al. (3), has been used by Inoue et al. (25) to study the action of lysozyme, which converts E. coli to spheroplasts following treatment with antibody and complement.

The immobilization of *Treponema pallidum* by syphilitic antibody and guinea pig complement has found widespread diagnostic application. An interesting feature of this reaction is the unusually long period of time required for immobilization. Unpublished studies by Seldeen indicate that there is a delay of several hours in the sensitization of the treponemes by antibody. It is believed that T. pallidum, when freshly isolated from a syphilitic lesion, may have a surface layer of nonantigenic material, which is presumably lost slowly on incubation. Antibody can combine with the treponemes only after this protective layer is gone, and in turn, the complement system can begin its destructive work only when sensitization has taken place. As shown by Metzger, Hardy, and Nell (34), treponemes become reactive with immobilizing antibody more rapidly if treated with lysozyme.

There has been a notable increase in studies of the action of complement on various mammalian cells other than erythrocytes. Of special interest are the investigations by Goldberg and Green (15), as well as Green et al. (16, 17), with Krebs ascites tumor cells, as well as erythrocytes, which have shed new light on the morphological and chemical events, and especially the nature of the E* intermediate. On exposure to antibody and complement, Krebs ascites tumor cells exhibit cytoplasmic swelling, rapid loss of intracellular K+, amino acids, and ribonucleotides, and a less rapid loss of cell protein and ribonucleic acid. At the same time, the cells become permeable to the Na+ of the medium. These changes can be explained by assuming production of "holes" in the cell membrane large enough to permit rapid exchange of inorganic cations and small molecules, but not of macromolecules. The resulting disturbance of osmotic regulation leads to swelling, and consequently macromolecules become able to pass the cell membrane. In addition, if protein is added to the medium in concentrations sufficient to balance the colloid osmotic pressure of the cells, swelling is prevented. Under these conditions the cells lose K+ and take up Na+, but macromolecules are not lost from the cells. Similar experiments with erythrocytes suggest that E* is a cell which has suffered impairment of osmotic regulation and that the transformation of E* to ghosts is a process of osmotic lysis. These findings by Green et al. are compatible with the one-hit theory.

Immune cytotoxic studies with mammalian cells other than erythrocytes have not yet reached a refined stage with respect to the intermediate steps of the complement system, but a beginning has been made in a recent study by Ross and Lepow with normal human amnion cells (27, 47). These investigators have shown that C'1, C'2, C'3, and C'4, as well as Ca++ and Mg++, are required in this reaction, and that sensitized amnion cells first react with "C'1-esterase" and then with C'2, C'3, and C'4; but the sequence of action of the latter factors was not investigated, their source being the reagent R1.

**EXPERIMENTAL ENHANCEMENT OR DEPRESSION OF COMPLEMENT LEVEL IN VIVO**

Studies on the role of complement in immunity against infectious agents, in auto-immune diseases, in the homograft reaction, and in various allergic phenomena would be aided materially if it were possible to increase or decrease the complement level of animals by experimental manipulation. For example, in a recent study by Winn (52) on the destruction of lymphoma cells by antibody and complement, it was shown that protection of mice against this tumor can be enhanced by administration of fresh guinea pig serum as a source of complement. Thus, the complement system is a limiting factor determining the development of this tumor in the mouse. Recent progress in the purification of C' factors by application of chromatographic technics (7, 45, 48) lends substance to the hope that studies of the effect of passive enhancement of C' activity in vivo will become a useful tool in future investigations.

Conversely, depression of complement activity in vivo has also been used as an experimental device, notably in studies on the possible role of complement in allergic reactions. For example, rats
can be "decomplemented" by injection with appropriate antigen-antibody systems, and it was shown in this manner that complement may play a role in anaphylaxis (42). This experimental approach is limited, because it is difficult to achieve substantial depression of complement activity without killing the experimental animal. Furthermore, the reasoning underlying this line of experimentation is circular, since the treatment used for decomplementation is the same as that which evokes the anaphylactic reaction. In view of the evidence which has been presented that the effect of zymosan on complement operates by way of complement fixation (40), in vivo depression of complement activity following treatment of experimental animals with zymosan is open to the same objection.

Studies of the mechanism of the immune hemolytic reaction have led to the discovery of certain inhibitors, such as di-isopropyl fluorophosphate (5, 29), salicylaldoxime (55), and phlorizin (46). Continued investigation of inhibitors appears promising.

Another approach for inhibition of C' in vivo involves the use of specific antibodies against the complement components (23). Rabbit antisera to guinea pig complement have been shown to react with C'4 (43), but antibodies to the other C' factors may also be present. Progress in this field will depend on further purification of the C' factors and improvement of analytical technic.

This brief account would be incomplete without recalling Hyde's work with C'3-deficient guinea pigs which have been lost unfortunately (20).

CONCLUSIONS

Several areas of immunology, notably hypersensitivity, the homograft reaction, and auto-immune disease, are currently attracting much attention, and these frontiers of immunology are not without opportunity for students of complement, though I believe that the time is not yet propitious for a broad assault. As I have briefly outlined in this presentation, new analytical approaches are currently under development, and there has been progress in the purification of the C' factors, but more time is needed for fuller development of these capabilities.

In view of the possibility that autochthonous tumors may not evoke formation of cytotoxic antibody, I want to recall in these concluding remarks that cytotoxic action of the complement system need not necessarily depend on specific antibody. The sensitizing action of tannic and silicic acids has long been known, and more recently it has been recognized that certain synthetic polymers like polyethylene glycol and polyvinylpyrrolidone, as well as polysaccharides like dextran, can sensitize erythrocytes for attack by complement (12). Furthermore, it is pertinent to mention the phenomena of passive hemolysis (14) and bacteriolysis (1), in which certain antigens, notably polysaccharides, coat these cells, rendering them reactive with the corresponding antibodies, and thus sensitizing them for complement attack.

I also want to point out that the cytotoxic reaction systems offer a tool of exquisite sensitivity and specificity in the search for distinct antigens of malignant cells. If one S; receptor makes a tumor cell susceptible to destruction by complement, as in the case of the sheep erythrocyte, one or two dozen molecules of antibody are likely to suffice for sensitization of one cell. By use of appropriately designed test systems, it is therefore possible to detect and measure minute quantities of cytotoxic antibody.

This conference will fulfill its purpose if it serves to outline the challenge and opportunities; but I hope, above all, that we will realize the need for more effort at the laboratory bench to fashion the basic tools. Although I believe that the dark ages of complementology are behind us, we are still a long way from understanding what complement is and how it acts.

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