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Detection of complement in relation to disease

Since the turn of the century, it has been accepted as a matter of principle that the complement system is important in mediating the host-defense process. Initial observations that complement activation was capable of lysing bacteria suggested that the system would prove vital in the control of infectious disease.¹ Early investigations demonstrated that complement proteins might be important in the erythrocyte lysis that accompanies autoimmune hemolytic anemias. In the past several decades, the importance of these earlier observations has been confirmed. Attention has turned, however, to the important function of complement in the inflammatory response and in mediating the process of opsonization, coating of bacteria and other foreign particles with specific, complement-derived peptides that interact with highly specific receptors for these peptides on the surface of cells. It is by promoting inflammation and by controlling various cellular responses via the interaction with specific complement receptors that complement appears to play its most vital role.

The complement system is comprised of a group of >25 proteins and glycoproteins that exist either

Abbreviations used

MAC:	Membrane attack complex
IC:	Immune complex
DAF:	Decay-accelerating factor
HRF:	Homologous restriction factor
CR:	Complement receptor
CH ₅₀ :	Total hemolytic complement
SLE:	Systemic lupus erythematosus
INH:	Inhibitor

free in plasma or bound to cell surfaces.¹⁻³ These proteins mediate a series of biologic phenomena critical in host defense against invading bacteria, viruses, and other foreign particles. Activation of the components of this protein system occurs in a precise sequence of reactions, leading to the generation of protein-protein complexes and protein fragments that mediate numerous biologic responses, including bacterial, viral, and cellular lysis, phagocytosis, inflammation, and immunoregulation. One important aspect of complement function is the capacity of fragments generated by the enzymatic cleavage of a number of the complement components to interact with specific surface receptors on cells of the immune system to induce various host-defense reactions. By their interaction with complement receptors, these small peptide fragments of complement components may act as potent

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inflammatory mediators. Complement fragments that remain bound to activating particles may function as opsonins that aid in phagocytosis or as regulators of other aspects of the immune response.

The identification and characterization of the complement proteins and protein fragments and the receptors for these proteins and the clarification of their function in host defense are becoming of increasing importance in clinical medicine.

THE COMPLEMENT CASCADE

The fluid-phase complement proteins exist in plasma as inactive precursors that are activated in a precise sequence of biochemical reactions. Activation of the earlier proteins or components is often associated with cleavage of the component protein into two fragments. The larger of the two fragments formed is usually responsible for continuation of the complement sequence with ultimate induction of lysis; the smaller fragment often functions to promote the inflammatory process. Complement activation may be induced by proteolytic enzymes, such as enzymes released by invading bacteria; however, more commonly, activation is induced by antigen-antibody complexes on microbial or viral surfaces.

In contrast to the fluid-phase proteins that are responsible for most of the effector functions of complement, the cell-bound complement proteins usually act as regulatory or inhibitory molecules at the cell membrane, protecting the cells of the body from the damage that might be caused by inadvertent complement activation.

Two major pathways of complement activation are recognized; they are designated as the classic and alternative pathways. The classic pathway, which was the first of the two pathways to be discovered, is comprised of nine numbered proteins or components that play a part in the lysis of most antibody-sensitized cells. Initiation of activation by the classic pathway requires the formation of an antigen-antibody complex containing one of the classes of antibody capable of binding the first component in the sequence, C1, that is, IgM, IgG1, IgG2, or IgG3. C1 exists in serum as a three-part macromolecular protein complex composed of three subunits, C1q, C1r, and C1s. After binding to antigen, the Fc fragment of immunoglobulin in the antigen-antibody complex is believed to undergo a conformational change allowing it to bind C1q. Testing for C1q binding activity in serum is one method for evaluating serum for the presence of circulating ICs. The binding of C1q with the associated C1r and C1s is followed by the activation of the C1r and C1s with the generation of proteolytic activity. Enzymatically active C1 is capable of interacting with

the next component in the complement sequence, C4, cleaving this molecule to form two fragments, C4a and C4b. The small peptide, C4a, is released and the larger fragment, C4b, binds covalently to the antigenic surface to continue the cascade. In the presence of magnesium ions, C4b acts as a site for the binding of the next component in the reaction sequence, C2, which, after binding, is cleaved by the C1 enzyme into two fragments, C2a and C2b. Once again the larger fragment, C2a, remains target bound. The peptide complex formed of C4b and C2a acts as a new enzyme, a C3 convertase, that cleaves C3. C3b, the major cleavage fragment of C3 formed by the convertase, is covalently bound at the activation site, and the small C3a fragment is released. C3b molecules bound in proximity to the complexed fragments of C2 and C4 form a larger complex capable of binding and cleaving the next component in the pathway, C5, into two fragments, C5a and C5b. Again, the larger fragment, C5b, associates with the activation site, and the C5a fragment is released. The general pattern of activation is continued for C6, C7, C8, and C9. Activation of the later components, however, does not appear to involve cleavage. Rather, there is simply binding and a conformational change. The series of reactions, starting with C5 cleavage, leads to the formation of the hydrophobic MAC, which has a hydrophobic surface and a hydrophilic core. The MAC is capable of insertion into the lipid bilayer of the cell membrane. Insertion of the MAC into the bilayer leads to disruption of the bilayer via the formation of a donut-like lesion with a hydrophilic center through which ions pass freely. Thus, a cell membrane may be destabilized in such a way that the cell lyses.

The existence of a second, or alternative, pathway of complement activation, important in control of microbial infection, was first suggested by Pillemer^{2,3} in 1954. We now know that the alternative pathway does not use C1, C4, or C2 but joins the classic pathway at the level C3. Since the alternative pathway does not require antibody and does not use C1, C4, or C2, the complement proteins specifically engaged by immunoglobulin, it is of particular importance in controlling infection before the production of specific antibodies. The reaction steps of the pathway are similar to reactions of the early steps of the classic pathway but do not appear to be as efficient as are the classic pathway interactions. Critical to the understanding of alternative pathway function was the recognition that the C3 molecule is held in a strained configuration by the presence of an internal thiolester. On removal of the C3a peptide during C3 cleavage, the internal thiolester present in the large fragment C3b is exposed, and the thiolester reacts either with reactive

groups on an antigenic surface nearby to form an amide or ester bond or with water and is hydrolyzed. Cleavage of the thiolester is followed by a major conformational change in the C3b. In intact C3, the internal thiolester is not completely stable and may undergo slow hydrolysis to form inactivated C3, iC3, which also has undergone the conformational change. In the presence of magnesium, C3b, with its opened thiolester, or iC3 with its hydrolyzed thiolester, can interact with a C2-like protein of the alternative pathway, factor B. In turn, in the presence of factor D, an alternative pathway C1s-like protease, factor B, is cleaved, forming a complex of the altered C3 with the cleavage fragments of bound factor B (C3bBb or iC3Bb). This newly formed complex of the alternative pathway, like the complex composed of C4b and C2a of the classic pathway, can bind and cleave additional intact C3 into C3a and C3b, and the newly formed C3b can, in turn, continue alternative pathway activation. Thus, the pathway has an intrinsic feedback amplification capability, which allows it to cleave serum C3 in multiple cycles of activation, thereby initiating the subsequent formation of C5b-C9 complex. Properdin is a blood protein that stabilizes the alternative pathway convertase, allowing for continued C3 cleavage.

Many of the steps of both the classic and alternative pathways are under active regulation by control proteins in serum or by cell membrane-associated inhibitory proteins. These control proteins serve to prevent spontaneous activation that could lead to unregulated complement-mediated damage. Each of the early components of the classic pathway, C1, C2, C4, and C3 is under some form of regulation once it is activated. Regulation of the C5b67 complex and the terminal components, C8 and C9, also occurs.

Activated C1 is inactivated by a serum protein, the C1 inhibitor, which disassociates the C1 subunits C1r and C1s, leaving only C1q bound to the antigen-antibody complex, thus blocking the continuation of the complement cascade. Once C1q is freed of C1r and C1s, it can interact with cell-surface C1q receptors to mediate certain host-defense effects.

The hemolytic activity of the large cleavage fragment of C4 is destroyed by the proteolytic enzyme, factor I (the C3b/C4b inactivator), which may act in conjunction with a serum cofactor, the C4b binding protein (C4bp). C4bp enhances factor I cleavage of bound C4b and is required for factor I cleavage of fluid-phase C4b. The activity of C3 and its fragments is also closely regulated. The rigid regulation of C3b activity is physiologically relevant, since functionally active C3b interacts with late components of the classic pathway to cause membrane damage and recruits

alternative pathway factors as well. As with C4b, factor I enzymatically degrades C3b. Another serum protein, factor H, acts as a cofactor to enhance C3b cleavage. Factor I cleavage of C3b produces an inactive form of the molecule, iC3b, which is incapable of engaging C5 or factor B, but is capable of binding to CRs on phagocytes to promote several biologic effects, including phagocytosis (see below).

CRs, present on many cell surfaces, play a critical role in the regulation of the complement cascade, particularly with components bound at the cell surface. For instance, the CR for C3b/C4b, termed CR1, also acts as a cofactor to facilitate factor I-mediated cleavage of bound C4b to a decay product C4d and C3b to iC3b. In addition to the roles of CRs as cofactors for factor I cleavage of C3b, factor H and CR1 regulate further activation of the complement sequence by accelerating the functional decay of the C3 convertase of the classic and alternative pathways, thus reducing amplification of the C3 step. Furthermore, in the presence of CR1, factor I can proceed to degrade iC3b to form a small membrane-bound degradation fragment, C3dg, and a larger fragment, C3c, which is released from the membrane surface. Notably, under physiologic conditions, CR1 is very efficient in promoting factor I cleavage of iC3b, whereas factor H is not. CR1, which is present on human erythrocytes and many types of leukocytes, is therefore of major importance in control of C3b activation. The major blood pool for CR1 is on erythrocytes. CR1 on red cells binds ICs with bound complement and transports them to the reticuloendothelial system.

A receptor, termed CR3 on phagocytic cells, recognizes iC3b and aides in the phagocytosis of iC3b-coated particles. Two additional CRs recognize further C3 degradation fragments. The C3dg fragment may be degraded further to C3d by serum enzymes, such as elastase, trypsin, or plasmin. The C3dg and C3d fragments contain the antigen-binding site of C3b, which allows them to remain attached to the activating surface. C3dg and C3d interact with specific cell receptors that recognize these fragments, namely, CRs type 4 and type 2 (CR4 and CR2) (see below). Interestingly, CR2 is reported to have a similar role to that of CR1 in factor I cleavage of iC3b.

There is evidence that other cell-surface glycoproteins, in addition to CR1 and CR2, function to regulate C4b and/or C3b and thus block further complement activation. These cell-surface proteins do not act as CRs per se. One such glycoprotein on leukocytes, referred to as membrane cofactor protein, acts as a cofactor in factor I-mediated cleavage of C3b. Another well-studied membrane protein, DAF, is a 70 kb intrinsic membrane protein that binds to C4b and

to C3b and destabilizes and increases the rate of decay of both the classic and alternative pathway C3 convertases. Notably, it has no cofactor activity for factor I-mediated cleavage of C4b or C3b. DAF is found in some body fluids and on a wide variety of cells, including erythrocytes, leukocytes, and platelets. This protein is usually linked to the cell membrane by a phospholipid linkage, which allows for considerable lateral mobility in the membrane, presumably enhancing its effect as a complement-activation inhibitor. Its net effect is to protect host cells from complement-mediated damage by limiting the deposition of C3b. Both of the last acting components in the complement sequence, C8 and C9, are under regulation by several membrane proteins. One, referred to as HRF, prevents their insertion into the cell membrane, thereby limiting cell damage. Like DAF, it appears that HRF is linked to the cell via a phospholipid bond. Both DAF and HRF are absent from erythrocytes of patients with the disease, paroxysmal nocturnal hemoglobinuria. Yet another 20 kd membrane protein, CD59, has been demonstrated to have a regulatory effect on late component activity.

The small cleavage fragments of C3, C4, and C5 also bind to specific receptors on a variety of cells to induce numerous biologic effects. These effects include contraction of smooth muscle in various tissues, including airways, triggering of mast cells, and, in the case of the potent chemotactic peptide, C5a, the directed migration of phagocytic cells. The later components in the complement cascade appear to have no receptor-specific interactions and exert their effects directly on the target cells to which they are bound.

General considerations

The differential diagnosis of hypocomplementemia can best be approached by considering the pathophysiology of complement activation and the factors that influence the level of any circulating protein. As discussed earlier, the early acting components of the complement cascade circulate in inactive form. Activation of the complement sequence leads to use, or as the early workers termed it, "fixation" of the components with a fall in their level in the blood. The blood level is the sum of the rates of synthesis, degradation, and use of the components. Thus, the blood level is a static measurement that is used as a guide to indicate whether the complement system has been activated by an immunologic and/or pathologic mechanism. Because this level is a static measurement of a dynamic process, the blood levels may be perfectly normal in a number of situations in which complement is consumed. For example, in the disease, primary biliary cirrhosis, the serum C3 level is usually ele-

vated. As is true of most of the complement proteins, C3 acts as an acute phase reactant, and the presence of an inflammatory disease process within the liver leads to elevated serum levels of C3. If turnover studies are performed, however, it is found that the C3 turnover rate is actually markedly increased. Thus, these data obtained from static measurements of blood levels lead to an incorrect conclusion about complement activation in this particular disease.

Complement proteins may be very efficient in mediating certain biologic functions. Therefore, complement activation can be involved in a disease process in the presence of normal serum levels of the individual components. Complement acting on a cell membrane may be quite efficient in molecular terms. Thus, relatively few molecules on a cell surface may mediate either opsonization or cytotoxic destruction of the cells. Although complement levels may be low, the number of molecules per milliliter is high. The plasma level of C4 is 50 $\mu\text{g/ml}$. This represents 1.5×10^{14} mol/ml. When serum complement levels are considered in terms of the number of available component molecules, it becomes clear that an efficient molecular process leading to cell destruction may not lower the titer of a component below the normal range. Thus, certain cytotoxic or opsonic mechanisms may be associated with no lowering of the complement titer, even though complement is mediating the damage. Examples of this situation include IgM antibody-mediated hemolytic anemia and paroxysmal nocturnal hemoglobinuria. In normotensive patients with bacterial sepsis, the presence of cleavage products of activated complement proteins may be the only indication of the complement activation.

The various body compartments may be isolated from one another with respect to transport of complement components. Thus, complement may be activated in the joint space in patients with rheumatoid arthritis, but this may not be reflected in an abnormality in serum complement. The blood-brain barrier prevents access of the complement proteins to the brain, except in inflammatory states, and, again, the compartmentalization of these rather large protein components may be important in determining whether or not the titer is lowered.

Interpretation of hypocomplementemia

Let us begin our consideration of the differential diagnosis of hypocomplementemia by considering complement in a static fashion. The components of the complement sequence are usually considered in groups: (1) the classic complement pathway, with its early components, C1, C4, and C2, (2) the components of the alternative pathway, properdin factors D

TABLE I. Assays of complement components

Method	Sensitivity	Use
CH ₅₀	Fair	Good screen for complement deficiency or gross activation of complement
Radial immunodiffusion	Fair	Standard for C3, C4, and factor B determinations
Hemolytic assay of components	Excellent	Exquisite sensitivity for individual complement components but <i>use</i> limited to research laboratory; range of normal is wide and activation of small amounts may be missed
Immunofluorescence	Good	Demonstration of complement components in tissue

and B, and properdin, and (3) the later components of the complement sequence, C3 to C9. If the classic complement pathway is activated, use of the components C1, C4, C2, and C3 to C9, and a lowering of the titers of these components as they are "fixed" by antigen-antibody aggregates, would be expected. If the alternative pathway is activated, a marked lowering of factor B, properdin, and other components of the alternative pathway, as well as a fall in the levels of C3 to C9, the late-acting complement components, would be expected.

Therefore, it is useful to study a serum sample for its levels of the following components: C4, a component of the classic pathway; factor B, a component of the alternative pathway; and C3, a component of both pathways. If C4 and C3 are low and factor B is normal, as is often found in patients with lupus erythematosus, the classic complement pathway may be suspected to have been activated. If, in contrast, low levels of properdin factor B and C3, are found, alternative pathway may be suspected to play the prime role in complement activation. Such is often the case in membranoproliferative glomerulonephritis.

As previously mentioned, the complement level is the result of a number of dynamic interactions. A low C3 level can be the result of decreased synthesis or increased catabolism. In some, but not all, patients with MPGN, the low C3 levels are due to a decrease in synthesis of C3 rather than an increase in use, as had been postulated. In fact, in a number of disease states associated with low levels of complement components, decreases in synthesis have been observed rather than the expected increases in catabolism. The reasons for this effect are still not clear. It is quite possible that complement-degradation products feed back to regulate the rate of synthesis of component proteins. Thus far, it has not been proven, and only now are we beginning to learn about the factors that govern the levels of complement protein in serum and their rates of synthesis.

The complement proteins themselves turn over very rapidly, even in the resting state. The turnover of most

of the components that have been examined is about 2% per hour or about 50% per day.

It is clear that regulatory factors in the blood contribute to regulating this turnover of proteins. Patients who are missing the regulatory protein, factor I, have very low levels of C3 in their circulation. As discussed earlier, small amounts of C3 are continuously hydrolyzed under normal circumstances, and small amounts of iC3 are generated. In the presence of factors H and I, the iC3 is cleaved and inactivated. In the absence of factor I, however, the iC3 is not destroyed and is capable of interacting with components of the alternative pathway to mediate greatly increased C3 cleavage. Thus, the absence of a regulatory protein, factor I, leads to marked C3 cleavage via activation of the alternative pathway with resulting low serum C3 levels.

Assays

There are now a large number of different types of assays in testing for complement activation. Many of the newer assays may prove to be more informative than assays in general use. Unfortunately, the newer assays have become available only recently and are, in general, not available in most hospitals. The type of test chosen will markedly influence the type of information obtained (Table I). Let us begin with those assays that are available in most hospitals. Most hospital laboratories have tests available for C3 (β -1C) and C4. These tests, available in commercial kits, evaluate the level of a component by means of radial immunodiffusion. A glass plate coated with agar gel is impregnated with antibody to the specific component under study. The patient's serum or plasma is placed in a hole in the gel layer of the plate and is incubated for 24 to 48 hours. After incubation, a ring of precipitation is formed that reflects the formation of antigen-antibody complexes in the gel. The diameter of the ring is directly proportional to the concentration of the serum protein.

This antigenic analysis is most useful in following patients with diseases in which complement activation

is massive, leading to a marked decrease in the antigenic level of circulating component. For example, following the levels of C3 or C4 by this assay is of value in evaluating disease activity in patients with SLE. In general, decreases in component levels often indicate a worsening of the pathophysiologic process. Antigenic analysis of this type elicits no information as to the functional activity of the protein under study. If a patient were to be found with a nonfunctioning C3 or C4, such a test would miss this abnormality. Nonfunctioning complement proteins have not been discovered thus far; however, a nonfunctioning inhibitor of one of the complement components, C1, is present in about 15% of patients with hereditary angioedema. Such a nonfunctioning protein would be missed if only the level of C1 INH in serum by antigenic analysis was evaluated.

Functional assays allow the determination of whether the protein is present and whether it has normal functional activity. These assays are considerably more difficult to perform, and they are less available than antigenic analyses. Tests for specific components are considerably more sensitive than antigenic analyses and often are able to detect components at high dilutions of serum or other body fluids. The most commonly used functional analysis of complement activity is the CH_{50} . This test examines the ability of fresh serum to lyse antibody-sensitized sheep erythrocytes. Thus, it reflects activity of all the numbered components, C1 to C9. Unlike most functional tests, this test, however, is relatively insensitive. Normal values obtained vary considerably according to the actual technique followed and may range in various laboratories from 20 to a range of 300. In general, functional titers obtained for individual components are much higher. Nevertheless, if a genetically controlled total deficiency of any one of the numbered components is present, a CH_{50} titer approaching 0 is found. If a titer of zero is found, the serum titer should be repeated, and the serum should be examined in further detail.

There are now a series of new techniques that may ultimately replace the above-mentioned methods, but they are still in the process of being evaluated. The first series tests for the presence of the split products of complement activation. In some cases these may be biologically active peptides. For example, assays are available for the biologically active anaphylatoxins released by cleavage of C4, C3 and C5, C4a, C3a, and C5a. In theory, these assays should provide needed information when complement is active in causing inflammation. However, these highly active peptides may not remain in the circulation. C5a, when it is generated, binds rapidly to cells like polymor-

phonuclear neutrophils with high-affinity C5a receptors. The peptide may disappear rapidly from the circulation. However, the larger fragment of C5 that remains in the plasma, when complement is activated, C5b, may be identified. Assays are available for C3b, C3d, Bb, etc.; these fragments may remain in the circulation providing a better index of activation.

When complement is activated, new complexes are formed. For example, activation of C1 is followed by its inactivation by C1 INH; a complex consisting of C1 INH, C1r and C1s, is formed. Detection of this complex suggests ongoing activation of the classic pathway. Activation of the alternative pathway is similarly attended by formation of C3-properdin complexes. Detection of C1 INH-C1s complexes or properdin-C3 complexes is reported to be far more sensitive than detection of depressed complement protein levels. Similarly, activation of late-acting components by the formation of complexes between various late-acting components can be detected.

When complement is activated and complexes are formed, new antigens are generated that are not present in any individual component. These "neoantigens" can be detected providing yet another type of complement assay. Each of these fragments, complexes, and neoantigens can be detected in a variety of assays, including immunoprecipitation, radioassays, and ELISA assays.

Although it is not the focus of this article, there is great interest at present in identification, quantification, and characterization of various complement receptors and regulatory proteins present on cell surfaces. In general, these are detected by the binding to the cells of tagged monoclonal antibodies to these cell-surface proteins or by binding of their specific ligand. Often, the fluorescence-activated cell sorter or analyzer is used.

Interpretation of hypocomplementemia

The presence of depressed levels of several components of the classic and/or alternative pathway suggests that complement is being activated in serum. Many factors can activate the complement cascade. Such nonspecific activators as proteolytic enzymes released from dying cells, from phagocytic cells during phagocytosis, and from metabolizing bacteria have all been demonstrated to activate the complement sequence in the absence of true, immunologic recognition. Nevertheless, when depressed levels of complement components are found, an ongoing, immunologic process, leading to use of components and depression of complement levels, is considered. In many cases, depressed component levels are associated with the presence of circulating ICs.

TABLE II. Pathway primary activated in hypocomplementemias

Disease	Alternative	Classic
Infectious		
Bacterial		
Gram-negative sepsis	+++	+
Pneumococcal sepsis	++	++
Viral		
Dengue fever		+++
Hepatitis B		++
Fungal		
Disseminated cryptococcosis	++	
Parasitic		
Malaria paroxysm	+	++
Trypanosomiasis	++	++
Rheumatology		
SLE (active)	+	+++
Rheumatoid arthritis (joint fluid)		++
Serum sickness		++
Vasculitis		+
Hematology		
Transfusion reaction		++
Neutropenia of dialysis	++	
Nephrology		
MPGN (with C3Nef)	+++	
Poststreptococcal	++	
Miscellaneous		
Hereditary angioedema		++++
C3-inactivator deficiency	++++	
Urticaria		+

+, Described; ++, occasional; +++, frequent; +++, usually.

This list is not meant to be all inclusive, since complement levels have been measured in many disease states. There also may be a wide range of complement levels in an individual pathologic entity. For instance, complement levels are more apt to be lowered in shock than in normotensive patients with gram-negative sepsis.

There are other factors that may activate complement and lower complement levels by nonimmunologic mechanisms. Certain polyanions, such as heparin or heparin-protamine complexes, can activate complement. Even C-reactive protein, binding to its substrate on the C-polysaccharide of pneumococci, can activate the complement cascade. Various exogenous factors, such as the dialysis membrane in an artificial kidney, may activate complement directly via the alternative pathway. For these reasons, it is impossible to be certain of immunologic activation when depressed levels of complement components are observed.

The alternative pathway can be activated in the absence of specific antibody acting as a recognition factor. Antigen-antibody complexes of many classes, however, including IgA and IgE, can activate the alternative pathway, although, in general, large quantities of complexes are required. Many infectious organisms can interact directly with the proteins of the

alternative pathway and mediate depressed levels of complement components (Table II).

Component interactions

If depression is found in the level of a component, either by antigenic analysis or by CH_{50} , the first reasonable question to ask is, "Does this finding represent the absence or depression of an individual component or of all of the components of the pathway?" The presence of complexes, split products, or neoantigens suggests complement activation. Factors that regulate the interaction of components are still only partially understood. Thus, patients with hereditary angioedema, missing C1 esterase inhibitor, have unopposed activation of C1, which cleaves C4 and C2. Nevertheless, their C3 level is normal, as is the level of all of the later components. In this case, the presence of a regulatory protein is believed to prevent C3 activation. Other disease processes stop with the activation of C3 and/or C5. Therefore, it is not surprising

TABLE III. Hereditary deficiencies of complement

Component	Clinical findings
C1q	Combined immunodeficiency, glomerulonephritis, SLE
C1r	SLE, glomerulonephritis
C1s	SLE
C4 (two Loci C4A, C4B)	SLE
C2	Most common hereditary deficiency; spectrum ranges from normal to SLE, DLE, vasculitis, glomerulonephritis, anaphylactoid purpura, JRA
C3	Recurrent infections, glomerulonephritis
C5	SLE, recurrent <i>Neisseria</i> infection
C6	Repeated <i>Neisseria</i> infections
C7	Raynaud's syndrome, <i>Neisseria</i> infections
C8	SLE, <i>Neisseria</i> infections
C9	None identified
C1 INH	Hereditary angioedema
Factor D	Recurrent infections
CR1	Association with SLE
CR3	Leukocytosis, recurrent infections
Factor I	Repeated infections
Factor H	Glomerulonephritis
Properdin	Recurrent infections, fulminant meningococemia

DLE, Discoid lupus erythematosus; JRA, juvenile rheumatoid arthritis; INH, inhibitor.

to observe lowered titers of several, but not all, components of a pathway. As an example, it has been reported that patients with MPGN tend to have low levels of factor B, but relatively normal levels of properdin. In contrast, many patients with poststreptococcal glomerulonephritis have very low levels of properdin, but relatively normal levels of factor B. The reasons for this difference in the amount of activation of components of a pathway are totally unknown. During the next several years, we will observe the publication of articles comparing results obtain with a variety of complement assays in specific disease situations. As this material becomes available, we will begin to understand the functions of these proteins in disease states.

Summary

If a single component is lowered, it is reasonable to question whether the patient has a genetically-controlled defect (Table III). Studies of family members may be required. If split products, complexes, or neoantigens are present, it is likely that there is ongoing complement activation. If most of the components of a pathway are lowered, a reasonable supposition is that complement is being activated. We then turn to a consideration of the factors that may

activate complement. When hypocomplementemia is associated with a decrease in titer of several components, it is often possible to determine whether the classic or alternative pathway is the major pathway being activated; this, in turn, may suggest certain diagnoses and rule out other diagnoses (Table II). The nature of the circulating complexes or split products may provide the same information. Thus, a consideration of the pathophysiology of the complement system and of the factors that activate complement provides an approach to an understanding of the function of complement and the role of complement causing a damage in a clinical setting.

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