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Infectious Diseases Associated with Complement Deficiencies

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INTRODUCTION

Functional activities attributable to the complement system were first described between 1888 and 1894 (300). First, Nuttall discovered that sheep blood had mild bacterial activity for *Bacillus anthracis* that was lost when the blood was heated to 55°C. Next, Buchner demonstrated that the bactericidal activity of fresh serum was due to a heat-labile factor that he termed alexin. In 1894, Pfeiffer found that, when blood from guinea pigs that had survived cholera was mixed with the vibrio and injected into naive guinea pigs, it prevented development of subsequent infection. In the same year, Bordet discovered that the activity of heat-inactivated immune serum could be restored by small amounts of fresh nonimmune serum that by itself had no bactericidal activity. Thus, the bactericidal activity of immune serum was dependent on both alexin and a heat-stable component.

At the turn of the century, Ehrlich proposed a model for serum immunity involving these two fractions. The heat-stable serum fraction, amboceptor or antibody, contained two binding sites; one bound to the organism and the other bound to the heat-labile factor, complement. Thus, specificity of bactericidal activity depended on antibody, not complement. Several investigators later discovered that the complement fraction consisted of more than one component.

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However, it was not until 1941 that Pillemer separated functionally distinct components of the classical pathway from various serum fractions. In the early 1950s, he and his co-workers also described and characterized an antibody-independent mechanism for complement activation which they termed the properdin pathway (211, 288, 300). However, several critics believed that Pillemer's observations were the result of small amounts of contaminating antibody and thus did not demonstrate an antibody-independent pathway. Unfortunately, protein purification techniques at that time were unable to provide components of sufficient purity to establish conclusively that such a pathway existed.

Mayer's development of a standardized method for quantitating complement-dependent hemolytic activity provided the experimental basis for a mathematical model for complement activation (300). By this model, erythrocyte hemolysis required the assembly of only one complete sequence of complement proteins per cell, a proposal that became known as the "single-hit" theory. This theory coupled with Nelson's development of reagent sera lacking individual complement component activity provided the foundation for the purification and characterization of specific complement proteins. This advance led to rediscovery of Pillemer's work and confirmation of the existence of the properdin pathway. In its entirety, the system was defined as a series of sequentially activated serum proteins (similar to the clotting cascade) the activities of which lead to hemolysis.

Recently, investigators have shown that this system consists of not only serum components deposited on the surface of microbes but also membrane-bound proteins. By protecting host cells from the detrimental effects of complement activation, these proteins provide the basis for discrimination between self and nonself (15). Thus, activation of the complement cascade participates in the development of the inflammatory response, elimination of pathogens, and removal of immune complexes without causing the destruction of host cells via the same mechanism. With the advent of the revolution in molecular biology, the primary amino acid structure of most complement proteins has been elucidated. Recombinant DNA technology is being used to delineate the structural basis underlying their function and to provide insight into the genetic basis for complement deficiency states.

Although antibody and complement are often grouped together as component of humoral immunity, several important differences distinguish their actions (298). Following initial exposure of the host to an antigen, significant delay occurs before the development of a specific antibody response. Thus, primary antibody responses affect the disease process only relatively late in its course. In contrast, complement, by virtue of its activation by a wide variety of antibody-independent stimuli, may afford the host a degree of protection early in the course of the infection. On the other hand, antibody-independent complement activation and deposition are relatively nonspecific, whereas antibody-dependent complement responses are more rapid, more efficient, and highly specific for particular antigenic epitopes. The specificity of this response directs the flow of the nonspecific arms of the immune system (phagocytes and complement) to functionally appropriate sites on the surface of invading microbes. In addition, opsonization of these infectious agents by antibodies and complement leads to more efficient ingestion and killing of the organisms by phagocytic cells than does opsonization with either system alone. Similarly, the presence of receptors on lymphocytes and other immune responsive cells for immunoglobulin and complement implies a cooperative role for the affector and effector arms of the immune response.

The purposes of this review are to explore the interaction between complement and microorganisms and to delineate the effects of various deficiency states on the host's defense against infectious agents. Initially, the biochemistry of the individual complement components will be reviewed in the context of complement activation. Subsequently, the biologic importance of the system in host defense will be discussed with respect to specific functions and underscored by examples of strategies evolved by microorganisms to evade these activities. Last, the epidemiology and the genetic basis for complement deficiency states will be reviewed in the context of the resultant pathophysiology of the associated infectious complications. We have attempted to update our previous review (303) by referencing and analyzing many of the cases published since June 1983 in the hope that this material will continue to serve clinicians and investigators and will stimulate further evaluation of the unresolved issues revealed here.

THE COMPLEMENT SYSTEM

Biochemistry of Complement Proteins

Biosynthesis. The complement system consists of 19 plasma and at least 9 membrane proteins (Tables 1 and 2; Fig. 1). Examination of complement factor polymorphisms in patients before and after orthotopic liver transplantation has shown that at least 90% of the quantity of the plasma complement proteins is synthesized by the liver (5). The vast majority of these plasma proteins reside in the blood, although mucosal secretions and tissues contain lesser amounts (perhaps 5 to 10% of the corresponding concentrations in serum) of the various complement components. However, inflammation at these sites increases complement concentration and activity presumably by increased diffusion and local synthesis of the relevant proteins. Because many of these proteins are acute-phase reactants, their concentration may fluctuate. Both in vivo and in vitro studies have confirmed that cytokine mediators of the acute-phase response, for example, the interleukins (particularly interleukin-6), tumor necrosis factor, and dexamethasone, can increase the hepatic synthesis of complement proteins two- to fivefold in cultured hepatocytes (19, 232, 237, 272). Gamma interferon and endotoxin modulate complement production by monocytes, macrophages, and fibroblasts (349, 350). In this regard, the activity of endotoxin may be a result of its potent stimulation of the synthesis and secretion of a multiplicity of monocyte-derived cytokines (350). In addition to tissue specificity, modulation of complement synthesis exhibits site specificity with respect to a given cell; for example, monocyte-derived macrophages, macrophages from lung, and breast milk monocytes differ with respect to the proportion of cells secreting C2, the average rate of production per cell, and the amount of C2-specific RNA (65). Complement synthesis by tissue monocytes and macrophages probably plays a very important role in local complement-mediated host defense. In vitro studies have demonstrated that these cells can synthesize sufficient amounts of the complement proteins to promote opsonization, ingestion, and killing of bacteria or other target cells (155).

Activation of the classical pathway. The complement cascade can be visualized as comprising the phylogenetically older alternative pathway and the classical pathway. These pathways interact at the level of C3 to from a final common

TABLE 1. Complement components in serum[a]

Component	Approx concn in serum (μg/ml)	Mol wt	Chain structure[b]	No. of genetic loci	Chromosomal assignment[c]
Classical pathway					
C1q	70	410,000	$(A--B, C)_6$	3 (A, B, C)	1p
C1r	34	170,000	Dimer of 2 identical chains	1	12p
C1s	31	85,000	2 identical chains	1	12p
C4	600	206,000	β-α-γ	2 (C4A, C4B)	6p
C2	25	117,000	1 chain	1	6p
Alternative pathway					
D	1	24,000	1 chain	1	ND[d]
C3	1,300	195,000	β-α	1	19q
B	200	95,000	1 chain	1	6p
Membrane attack complex					
C5	80	180,000	β-α	1	9q
C6	60	128,000	1 chain	1	5
C7	55	120,000	1 chain	1	5
C8	65	150,000	3 nonidentical chains α--γ,β	3 (A, B, G)	(A,B)1p (G)9q
C9	60	79,000	1 chain	1	5
Control proteins					
Positive regulation					
Properdin	25	220,000	Cyclic polymers of a single 57-kDa chain	1	Xp
Negative regulation					
C1 INH[e]	200	105,000	1 chain	1	11q
C4bp	250	550,000	7 identical α chains--1 β chain	2	1q
Factor H	500	150,000	1 chain	1	1q
Factor I	34	90,000	β-γ	1	4
Anaphylatoxin inactivator (carboxypeptidase B)	35	280,000	Dimer of 2 nonidentical chains $(H,L)_2$	ND	ND
S protein (vitronectin)	500	80,000	1 chain	1	ND

[a] Reproduced and modified from Densen (78) with permission of the publisher.
[b] For multichain components, parentheses indicate subunit structure; commas indicate noncovalent linkage of chains arising from separate genes; solid lines indicate covalent linkage of chains arising from posttranslational cleavage of a proenzyme molecule, chains being listed in order beginning at the amino terminus of the proenzyme molecule; and dashed lines indicate covalent linkage of chains arising from separate genes.
[c] p, short arm of the chromosome; q, long arm of the chromosome.
[d] ND, not determined.
[e] C1 INH, C1 inhibitor.

pathway composed of the terminal-complement components. The central role of C3 in this system is readily apparent, and its critical function is further attested to by its high concentration in serum and its many functional activities (Fig. 1).

Activation of the classical pathway occurs primarily during immunologic recognition of antigen by specific antibody that exposes a C1 binding site on the Fc portion of the antibody molecule. C1 is a trimolecular complex containing one molecule of C1q and two molecules of C1r and C1s. C1q is composed of a central core from which radiate six pods that terminate in globular heads. Antibody binds to C1q through these globular structures (70, 250). Binding of at least two distinct immunoglobulin Fc fragments is required for complement activation. Of the several immunoglobulin isotypes, only immunoglobulin M (IgM) and certain IgG subclasses (IgG3 > IgG1 > IgG2) bind C1q. However the mechanisms by which IgM and IgG bind C1q to activate complement differ. In solution or under conditions of antigen excess, IgM exists as a pentameric, planar molecule that interacts weakly with C1q. As IgM binds several antigenic epitopes, it assumes a "staple" conformation. This structural change exposes at least two additional C1q binding sites and stabilizes the interaction between C1q and IgM. Thus, a single pentameric IgM molecule is sufficient to activate the complement cascade. In contrast, monomeric IgG possesses two molecularly remote C1q binding sites. Consequently, at least two IgG molecules must bind to the target particle in order to cross-link the globular heads on C1q and initiate activation. Thousands of IgG molecules must bind to a single particle to ensure that the molecules are close enough together to form a doublet. At a functional level, therefore, IgG is less efficient than IgM in activating complement (70, 205).

During C1q binding to antibody, a conformational change occurs that promotes the autocatalytic activation of the C1r and C1s tetramer. This alteration may involve the release of C1 inhibitor from C1. C1r and C1s are genetically, structurally, and functionally related bipolar molecules, each containing a serine protease and a binding domain in the head and tail of the molecule, respectively. Two C1r subunits, linked through their catalytic heads, form the central portion of the tetramer. In turn, the C1s subunits are linked to the C1r subunits through binding sites on the tail of each of the molecules. In this manner the molecule can loop back on itself in a figure eight configuration that brings the four

TABLE 2. Plasma and membrane proteins that regulate or mediate complement activity[a]

Location and protein	Specificity	Function(s)
Plasma		
C1 INH complex	C1r, C1s	Binds to and dissociates C1r and C1s from C1
C4bp	C4b	Inhibits assembly and accelerates decay of C4b2a; cofactor for C4b cleavage by factor I
Factor H	C3b	Inhibits assembly and accelerates decay of C3bBb; cofactor for C3b cleavage by factor I
Factor I	C4b, C3b	Proteolytic inactivation of C4b and C3b
S protein	C5b-7	Binds fluid-phase C5b-7; prevents attachment of C5b-7, and C5b-9 to membranes
SP-40,40	?C5b-6	May modulate formation of MAC
Carboxypeptidase B	C4a, C3a, C5a	Inactivates these anaphylatoxins by removal of C-terminal arginine
Cell membrane		
CR1	C3b, C4b, iC3b	Inhibits assembly and accelerates decay of C3 convertases; cofactor for cleavage of C4b/C3b by factor I; binds immune complexes to erythrocytes; phagocytosis
CR2	C3d, C3dg	Phagocytosis, modulates B-cell responses, Epstein-Barr virus receptor
CR3	iC3b	Phagocytosis
CR4 (p150,95)	C3dg, C3d	Unknown
MCP	C3b, C4b	Inhibits assembly and accelerates decay of C3 convertases; cofactor for cleavage of C4b/C3b by factor I
DAF	C4b2a, C3bBb	Inhibits assembly and accelerates decay of C3 convertases; cofactor for cleavage of C4b/C3b by factor I
CD59 (MIRL)	C8 in C5b-8	Inhibits polymerization of C9
C8bp (HRF)	C8 in C5b-8	Inhibits polymerization of C9
C3a/C4a receptor	C3a, C4a	Vasodilation
C5a receptor	C5a, C5a des-arg	Chemotaxis
C1qR	C1q	Phagocytosis

[a] Reproduced and modified from Densen (78) with permission of the publisher. Abbreviations: C1 INH, C1 inhibitor; bp, binding protein; SP-40,40, serum protein 40 kDa, 40 kDa; MAC, membrane attack complex; CR, complement receptor; MCP, membrane cofactor protein; DAF, decay accelerating factor; CD, cluster of differentiation (i.e., cell surface antigen); MIRL, membrane inhibitor of reactive lysis; HRF, homologous restriction factor.

catalytic domains in close proximity to one another, thereby permitting a single catalytic subunit to activate the others (12, 205, 324).

Activated C1s cleaves a 9-kDa fragment, C4a, from the amino terminus of the α chain of C4 and thus exposes an internal thiolester bond linking the sulfhydryl group of the cysteine at position 991 with the carboxyl group from the glutamyl residue at position 994 (23). Nucleophilic attack of this bond by either hydroxyl or amino groups exposed on nearby molecules leads to the formation of ester or amide linkages, respectively, that covalently anchor the nascently activated C4 to the target surface (109, 205, 239). In addition, activated C1s cleaves C2 to produce two fragments: C2b and C2a. C2b acts locally as a proinflammatory anaphylatoxin. C2a associates noncovalently with C4b bound to the target particle to form C4b2a, the C3 convertase of the classical pathway.

These C1s-mediated events represent the initial amplification step of the classical pathway. In this manner, a single catalytic enzyme complex can lead to the activation of many substrate molecules and their subsequent deposition on the membrane in close proximity to the antibody that initially triggered the cascade. Thus, antibody serves not only to initiate the classical complement pathway efficiently but also to guide complement deposition to specific sites on the membrane.

Humans and other species produce two slightly different C4 molecules, C4A and C4B, each the product of its own gene. These molecules differ in that C4A preferentially forms amide linkages with surface molecules whereas C4B preferentially establishes ester linkages (92, 174, 207). Various experiments, including site-directed mutagenesis, have shown that this difference relates to the presence at position 1106 of aspartic acid in C4A or histidine in C4B (57). In the tertiary structure of the two types of C4, these amino acids lie near the thiolester bond and influence the type of nucleophilic attack to which it is susceptible. As a consequence of these biochemical nuances, C4A preferentially binds to proteins and can be shown to play a greater role than C4B in inhibition of immune complex formation, but C4B preferentially binds to carbohydrates or glycosylated proteins and is more hemolytically active than C4A (207, 316, 318). These structural alterations may contribute to the differences in the clinical picture observed in patients with an inherited deficiency of either C4A or C4B (240).

Activation of the alternative pathway. Although genetic, structural, and functional similarities between the components of the classical and alternative pathways and their respective C3 convertases have been demonstrated (Fig. 1), activation of the latter pathway exhibits several unique features. First, antibody is not absolutely required for activation. Second, activation proceeds both in the fluid phase and on target surfaces. Fluid-phase-activated components can be deposited in an indiscriminant manner on both microbial and host cell surfaces. Third, since C3b is both a component and a product of the alternative-pathway C3 convertase, its generation by either pathway initiates a positive-feedback loop via the alternative pathway (Fig. 1) (109, 261, 263). The time required for amplification makes complement activation by the alternative pathway three to five times less efficient than activation via the classical pathway on the same target (83). This delay in activation is characteristic for a given cell but differs among different particles (261, 263). Fourth, with no antibody to direct complement activation, C3b deposition mediated via the alternative pathway occurs randomly over the surface of the particle, and this random deposition may contribute to the relative inefficiency of activation (261, 263).

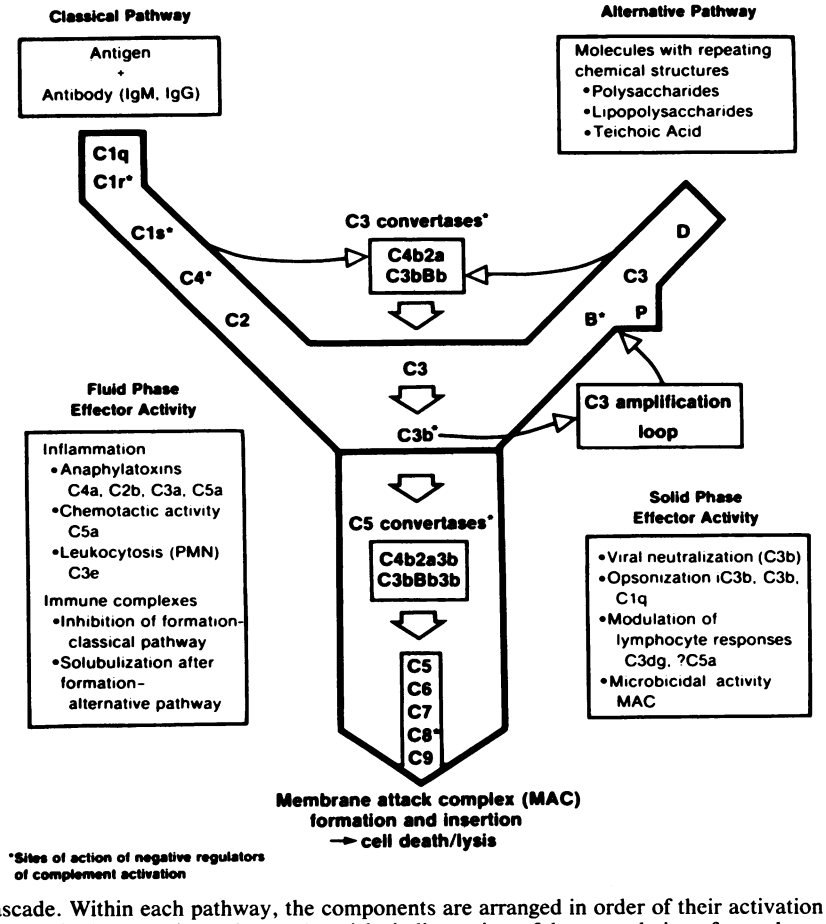

FIG. 1. Complement cascade. Within each pathway, the components are arranged in order of their activation and aligned opposite their functional and structural analogs in the opposite pathway. Asterisks indicate sites of downregulation of complement activity (Table 2). PMN, polymorphonuclear leukocytes; MAC, membrane attack complex. Reproduced from Densen (78) with the permission of the publisher.

C3 is the critical reactant in the alternative pathway. It is structurally and functionally related to C4 and contains the same internal thiolester bond. In the fluid phase, C3 undergoes spontaneous hydrolysis to form C3(H_2O). For a brief moment before inactivation by the regulatory proteins factors H and I, C3(H_2O) can form a complex with factor B. In this complex, factor B is susceptible to cleavage by factor D to form C3(H_2O)Bb, the fluid-phase C3 convertase. This complex can cleave a 9-kDa fragment from the amino terminus of the α chain of free C3, yielding C3a and C3b (261, 263), Analogous to C4 cleavage, this reaction exposes the internal thiolester bond in C3b and thereby promotes the formation of covalent ester or amide bonds with accessible hydroxyl or amino groups on the target surface (Fig. 2) (135). Surface-bound C3b binds circulating factor B, which is cleaved by factor D to produce the membrane-bound, alternative-pathway C3 convertase C3bBb. Cleavage of C3 by this enzymatic complex initiates the amplification loop and results in the rapid generation of additional C3b. Like its classical-pathway counterpart, the alternative-pathway C3 convertase is inherently unstable, with a half-life of approximately 90 s. However, the noncovalent association of properdin with the convertase serves to increase its stability 5- to 10-fold, thereby prolonging its functional activity (110, 111, 114, 261).

Although antibody is not required for alternative-pathway activity, it can facilitate activation of the pathway (243, 246, 289, 313, 314, 335, 383). The molecular basis for this effect is not clear, but carbohydrate moieties on the Fab portion of some IgG subclasses are apparently involved (55). In addition, surface-bound antibody can serve as a C3 acceptor, and C3bBb formed on IgG in this manner is relatively resistant to inactivation by control proteins (122, 183). Hence, C3b deposited on IgG may be particularly effective in promoting the many functional activities of the complement cascade.

Assembly of the membrane attack complex. Incorporation of C3b into either the classical- or alternative-pathway C3 convertase creates the respective C5 convertases C4b2aC3b and C3bBbC3b. C5 is structurally homologous to C4 and C3 except that it lacks an internal thiolester bond (217, 377). Its cleavage results in both the release of C5a, a potent anaphylatoxin and phagocyte chemoattractant, and the noncovalent deposition of C5b at exposed hydrophobic sites on cell membranes (238). In this location, C5b serves as the anchor for the formation of the membrane attack complex. The remainder of the terminal-complement components constituting the membrane attack complex (C6, C7, C8, and C9) (Fig. 1) are structurally homologous amphipathic molecules (Fig. 3) (238, 291). These molecules contain repetitive hydrophilic sequences at their carboxyl and amino termini which are separated by a relatively hydrophobic core. In contrast to the preceding complement components, these proteins lack enzymatic activity. C6 and C7 bind to C5b in sequence, creating a stable trimolecular complex, C5b67

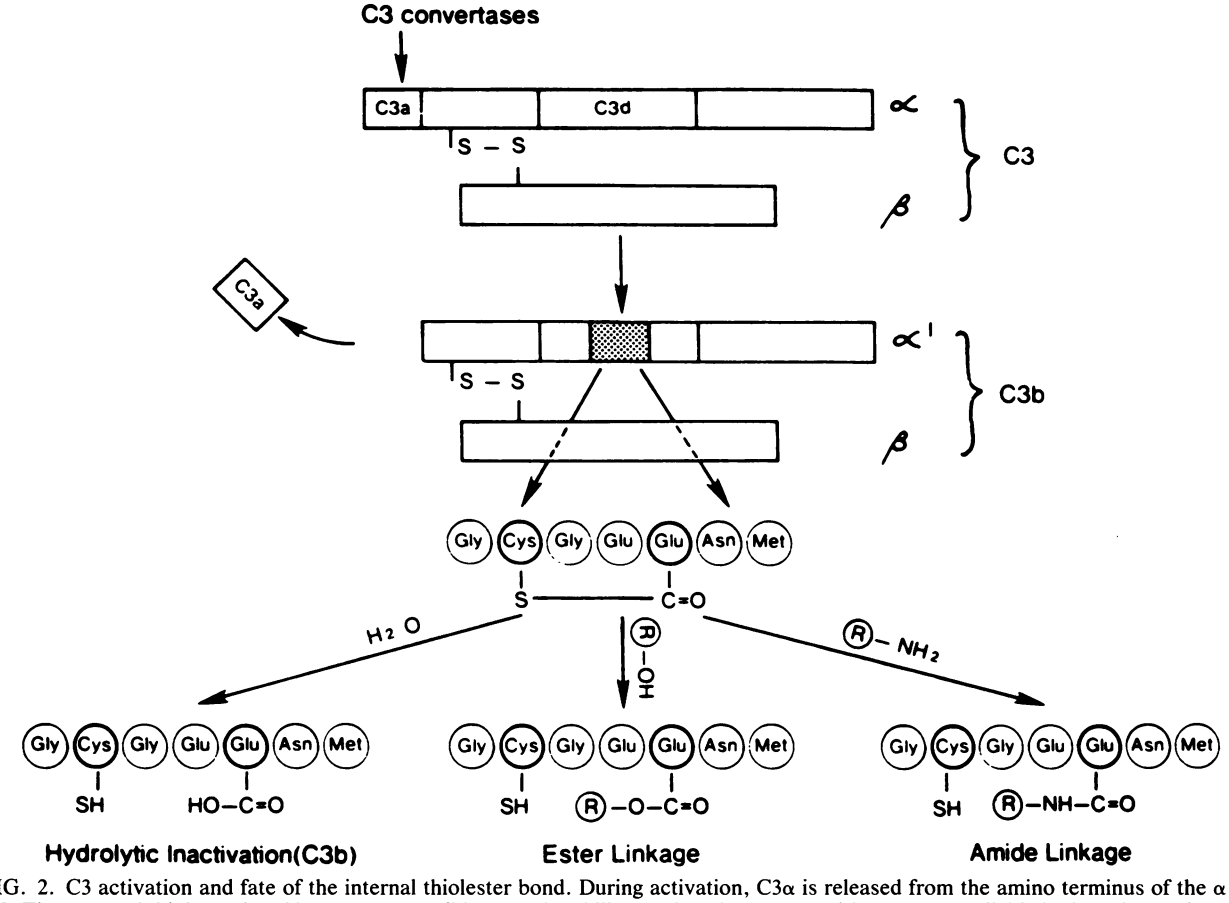

FIG. 2. C3 activation and fate of the internal thiolester bond. During activation, C3α is released from the amino terminus of the α chain of C3. The exposed thiolester bond becomes accessible to nucleophilic attack and can react with water or available hydroxyl or amine groups on cell surfaces. Analogous reactions occur with C4. Together, these reactions involving C3 and C4 are responsible for the covalent linkage of complement deposition to the cell surface. Reproduced from Gordon and Hostetter (135) with the permission of the publisher.

(238). C8, a three-chain polypeptide, binds to C5b in this complex via its β chain (235, 347). Binding of C9 to the α chain of C8 triggers polymerization of additional C9 molecules and insertion of poly-C9, with resultant membrane disruption and an influx of ions and water into the cell (238, 241). Cell death and lysis are the functional consequences of this sequence of events. The C5b-8 complex can also cause lysis of cells in in vitro systems, although such lysis proceeds more slowly and to a lesser extent than that caused by C5b-9. As a consequence, C9-deficient sera possess reduced but measurable hemolytic and bactericidal activity (151).

Complement receptors. During the last decade, an increasing number of membrane receptors for the products of complement activation have been discovered (115, 138, 301). These receptors reside predominantly on peripheral blood cells and fall into two broad categories. The first includes C1qR, CR1, CR2, CR3, and CR4, which are specific for surface-bound complement components that act as ligands between target and effector cells. Little is known about C1qR other than that it is present on phagocytic cells. Recent evidence suggests that binding between C1q and its receptor on granulocytes may help mediate particle ingestion and stimulate the respiratory burst in these cells (115, 138). CR1, CR2, CR3, and CR4, which are receptors for the cleavage products of C4 and C3, have been more extensively studied (Table 2). Although their ligands are very similar, each of these receptors is structurally distinct and has a unique pattern of tissue distribution (301, 379).

Receptors for anaphylatoxins have also been characterized. The best studied is the C5a receptor, which is present on neutrophils and monocytes (64). Its activation by C5a causes the directed migration of these cells toward the source of C5a generation. The C3a receptor has been less well characterized, but experimental evidence suggests its existence on mast cells, vascular endothelium, and guinea pig ileum (166).

Complement Regulation

Regulation of the complement cascade occurs at three levels: initiation of pathway activation, amplification, and effector function. In the classical pathway, C1 esterase inhibitor binds reversibly to C1 in the fluid phase and prevents its spontaneous activation (70). The affinity of this inhibitor for C1 is decreased during C1q binding to antibody, thereby permitting activation to proceed. Subsequently, C1 inhibitor can bind irreversibly to the active sites of C1r and C1s, thereby destroying the catalytic function of these components (70). Complete inhibition requires binding to each of the four subunits in the C1 molecule.

C3 activation plays a pivotal role in both amplifying complement function and generating effector activity. Thus,

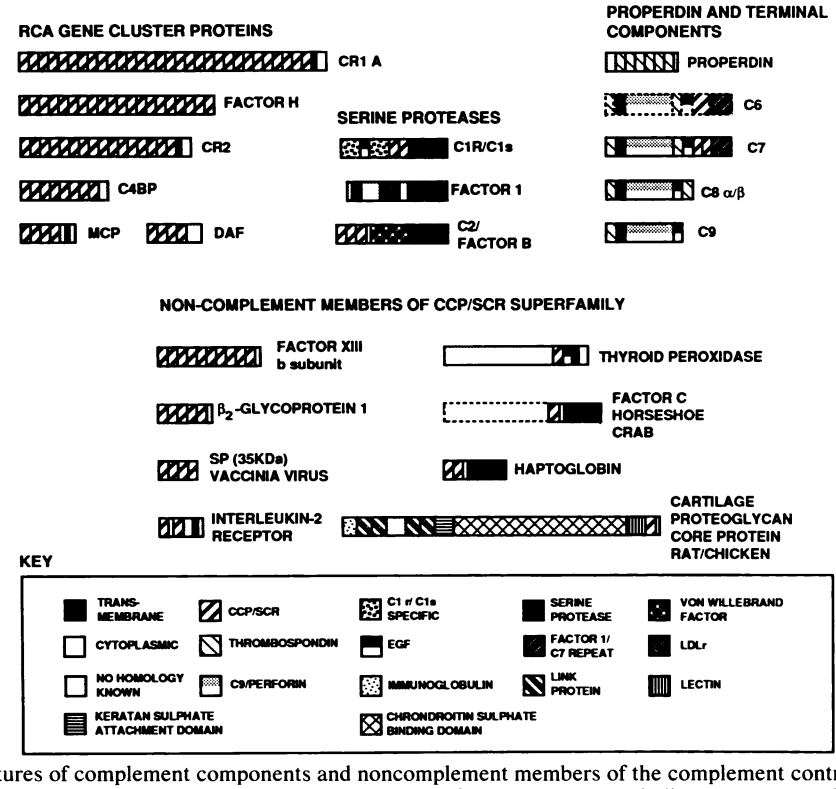

FIG. 3. Domain structures of complement components and noncomplement members of the complement control protein-short consensus repeats superfamily. All proteins are from humans unless otherwise specified. Dashed boxes indicate sequences that are either not published or not determined. C6 and C7 have two carboxy-terminal motifs that are also found in factor I. The perforin domain does not extend over as large an area as is indicated by this figure (for example, the perforinlike sequence in C9 lies between residues 294 and 522). CCP/SCR, complement control proteins-short consensus repeats. Reproduced from Reid and Day (291) with the permission of the publisher.

regulation of both C3 convertases is a critical step in the modulation of complement activity (109, 114, 261, 263). The regulation of these complexes occurs in three ways. First, they are inherently labile and decay spontaneously with the dissociation of C2a or Bb from the complex. Second, a number of proteins, including C4 binding protein (C4bp), factor H, CR1, and membrane cofactor protein (MCP) (Table 2), compete with C2a and Bb for binding sites on surface-bound C4b or C3b and accelerate the spontaneous rate of decay by binding to C4b or C3b. In addition, these proteins serve as cofactors for factor I-mediated cleavage of C4b and C3b to iC4b and iC3b, respectively (109, 114, 160, 261, 263). Third, accelerated decay inhibits amplification and prevents the formation of new convertase complexes.

The number of regulatory proteins may reflect the need for inhibitors in both the fluid and the solid phases. Factor H and C4bp are soluble molecules that are thought to exert their control predominantly on fluid-phase C3 convertases (15, 109, 160, 263). Several membrane-bound proteins exert similar effects on surface-bound convertases. These proteins include the C3b receptor (CR1), MCP, and decay-accelerating factor (DAF) (15, 160, 245). CR1 exists predominantly on the surface of peripheral blood cells, whereas both MCP and DAF are more widely distributed and play a major role in the protection of host cells against complement activity (15, 160). DAF exhibits specificity for C3b and C4b molecules on the same cell, whereas CR1 and MCP can inactivate molecules on adjacent cells as well as in solution.

Several investigators recently have shown that the membrane attack complex promotes decay of the C3 convertases. This feedback loop may help protect the host from continued activation of complement (26, 84).

During complement activation, C4b and C3b are deposited indiscriminately on both host and microbial cell surfaces. In addition to the complement-dependent, membrane-bound proteins discussed above, host cells have complement-independent mechanisms that protect them against complement actions. For example, the binding affinity of C4b or C3b for its partner in the C3 convertase is influenced by the composition of the membrane. Thus, C3b bound to a nonactivating particle binds factor H with about 100-fold-greater affinity than C3b bound to an activating particle (192). This difference seems to be mediated through a binding site for polyanions on factor H that increases its affinity for C3b (228). On host cells conditions favor slow activation and rapid decay of C3 convertases, whereas microbial cells usually provide a favorable surface for activation and amplification. Chemical constituents that have been shown to participate in this modulation include sialic acid and sulfated acid mucopolysaccharides (e.g., heparan sulfate) (108, 112). Of interest, sialic acid is a major component of the capsule of several bacteria (114). These capsules provide a form of molecular mimicry with the host, and both activate complement poorly and induce a limited immune response. Two of these organisms, K-1 *Escherichia coli* and type III, group B streptococcus, are important causes of neonatal sepsis and meningitis. Since those neonates who contract early-onset sepsis due to *E. coli* or group B streptococcus typically lack transplacental maternal antibodies against the K-1 or streptococcal capsular polysaccharides, they must rely almost

entirely on activation of the alternative pathway for complement-dependent protection. This clinical situation may provide the ideal setting for infection caused by these organisms.

Evidence suggests that other chemical constituents also play a role in controlling the competition between factors B and H for C3b. For example, both sheep and human erythrocytes have sialic acid on their surfaces and fail to activate the human alternative pathway (112, 262). Despite these similarities, only sheep cells activate the alternative pathway after sialic acid is removed by neuraminidase treatment. Moreover, the insertion of lipopolysaccharide into sheep erythrocyte membranes converts the cells from nonactivator to activator status despite the continued presence of sialic acid (262). Therefore, these cells must contain other factors, some as yet uncharacterized, to explain these phenomena.

The final major control point for the complement cascade is at the level of the membrane attack complex. First, during fluid-phase activation, S protein in plasma binds to lipophilic sites on the C5b-7 complex and prevents its binding to membranes on bystander cells (238). Second, homologous restriction factors (CD59 and C8 binding protein [C8bp]; Table 2) present on peripheral blood and endothelial cells bind C8 and prevent C9 polymerization (163, 257, 322, 326, 388). These proteins tend to act in a species-specific manner in that they are most effective when the cells and complement source are obtained from the same species (148).

In addition, nucleated eukaryotic cells are highly resistant to complement-mediated cytolysis even in the face of a nonhomologous complement source. Resistance is correlated with a high replacement rate of cell membrane lipids and the ability to shed the membrane attack complex from the cell surface (56, 283, 319). Insertion of this complex into eukaryotic cells causes an influx of Ca^{2+} and stimulation of arachidonic acid metabolism (25, 52, 150, 170, 353). These nonlethal stimulatory events may contribute to host cell responses in certain disease states (52).

Families of Complement Proteins

Several complement components demonstrate functional and structural homology among themselves and with other functionally unrelated proteins (Fig. 3) (291). These components can be grouped into families that probably have similar origins (273, 291): (i) the serine proteases (C1r, C1s, C2, factor D, factor B, and factor I): (ii) disulfide-linked, multichained proteins, some possessing an internal thiolester bond (C3, C4, and C5); (iii) products of class III major histocompatibility complex (MHC) genes on chromosome 6 (C2, factor B, C4A, and C4B); (iv) proteins, all of which bind C3 (C4bp, factor H, DAF, MCP, CR1, and CR2) and are encoded by a superfamily of genes on chromosome 1; and (v) amphipathic proteins that bear structural homology to the low-density lipoprotein receptor, epidermal growth factor precursor, and thrombospondin (C6, C7, C8α, C8β, and C9). Of these families, considerable attention has been paid to the products of the class III MHC genes, the regulatory proteins found on chromosome 1, and the family of low-density lipoprotein receptor homologs.

The class III MHC antigens lie between the class II (Dr) antigens and the class I, human lymphocyte B antigens on the short arm of chromosome 6 (53). Sequence homology studies indicate that this region has undergone two duplication events, with the first involving the duplication of factor B to yield factor B and C2 (53, 54, 273). These molecules are 39% homologous in primary structure. The second postulated event involves duplication of the C4-21 hydroxylase pair into A and B variants. Recombination events through this area are suppressed, resulting in linkage disequilibrium and stable extended haplotypes that incorporate the gene products of the C2, factor B, C4A, and C4B loci (17). The resulting genetic patterns are referred to as complotypes and can be used to establish the inheritance of C2, C4, and factor B alleles in families (6). Thus, the association between specific C2 or C4 alleles with certain autoimmune diseases may be due in part to coinheritance of the complement genes and an immune response gene elsewhere in the MHC (277). On the other hand, evidence also suggests that the gene products or their absence may contribute directly to the development of autoimmunity (14).

Regulatory proteins encoded by genes on the first chromosome share a common organization with other proteins capable of binding C3 and C4 (e.g., C2 and factor B) and with some noncomplement proteins (202, 290). These proteins contain arrays of tandem repeats made up of approximately 60 amino acids that share a consensus sequence. Each protein has a different number of repeats (e.g., 2 in C1r, 3 in C2 and factor B, and up to 20 in factor H). The functional significance of these repeats remains to be delineated (290).

Complement proteins sharing homology with the low-density lipoprotein receptor contain cysteine-rich regions at both ends of the molecules. The N terminus holds the highest homology to low-density lipoprotein receptor, whereas the C terminus resembles the epidermal growth factor precursor (61, 91, 146). The cysteines are placed in even numbers in these regions and participate in disulfide bonding, which in turn strongly influences the tertiary structure of the molecule. It is thought that this tertiary structure facilitates the interaction between the terminal components and may be the driving force for the hydrophilic-hydrophobic transition that occurs during assembly of the membrane attack complex. Sandwiched between these homologous areas is a region of unique amino acid sequence that likely confers specificity to the sequential interaction of these components and may participate in membrane insertion (341, 366).

Complement-Mediated Functions

Complement plays an important role in several host defense and inflammatory responses, including the following: chemotaxis, clearance of immune complexes, antibody response, opsonization and phagocytosis, and cytotoxicity and lysis. The cleavage fragments C3a, C4a, C5a, and probably C2b constitute potent stimuli for the initiation of the local inflammatory response and are referred to as anaphylatoxins (166). Together they stimulate histamine release from mast cells (C3a), increase vascular permeability (C3a), and promote vasodilatation (C3a and C4a). In addition, C5a is a potent neutrophil chemotactic and activation factor, recruiting phagocytic cells locally and stimulating neutrophil responses (e.g., adhesiveness, oxidative burst, and degranulation) (64, 82, 189). Each of these anaphylatoxins contains an arginine residue at the C terminus. Removal of this residue by a carboxypeptidase in plasma results in a loss of activity (166, 269). However, the chemotactic activity of C5a lacking arginine (C5a des-arg) can be restored by association of the inactive anaphylatoxin with a cochemotaxin in serum that has been identified as a vitamin D binding protein (195, 271). Free Bb inhibits the interaction of C5a des-arg with its cochemotaxin (270). This interaction may account for the chemotactic defects reported in some patients with active

systemic lupus erythematosus (270). Not only does complement direct neutrophils to areas of inflammation, but also a small fragment, C3e, derived from the α chain of C3, promotes the development of leukocytosis. This phenomenon may contribute to the failure of some C3-deficient patients to develop leukocytosis in response to infection (109).

One of the primary clinical manifestations of patients with deficiencies of classical-pathway components is immune complex disease (14). Thus, a second important complement-mediated function relates to the clearance of immune complexes and prevention of excessive tissue injury (317). Serum from these patients is unable to solubilize immune complexes in vitro. Restoration of the deficient component corrects this defect and leads to clinical improvement in vivo (14, 344). The entire process involves the prevention of immune complex deposition, the solubilization of precipitated complexes, and the removal of C3b containing immune complexes via CR1-bearing cells. Upon interaction of antibody with its antigen, C1 binds to the immunoglobulin molecule and prevents Fc-Fc interactions while leading to complement activation and C3b generation. C3b and, to some extent, C1 and C4b are incorporated into the structure of the immune complex, thereby preventing precipitation (14, 317, 378). In addition, the solubilization of already precipitated immune complexes is facilitated by C3b. C3b within these immune complexes binds factor B and increases C3b deposition through the alternative pathway, thereby promoting solubilization (14, 317, 378). Thus, the classical pathway seems to inhibit the precipitation of immune complexes, while the alternative pathway promotes the solubilization of already precipitated complexes (14, 317, 378). Once solubilized, these immune complexes bind to the C3b receptor (CR1) on peripheral blood cells (most notably, erythrocytes, which bear 95% of the CR1 in blood) and are removed from plasma (327). CR1 acting with factor I promotes cleavage of bound C3b into additional fragments which can interact with other complement receptors in tissues. Kupffer cells appear to remove the immune complexes along with CR1 during the passage of erythrocytes through the liver (73, 327).

A third effect of complement in host defense relates to its possible participation in humoral immunity. Most evidence implicates C3 as the major complement-derived stimulus modulating immune responses. This evidence includes the observation that C3 or its fragments may enhance or inhibit both T and B cells, depending on the concentration of the relevant C3 fragment (206, 374). For example, the trapping of aggregated IgG within splenic germinal centers is dependent on the presence of C3 (265). As further evidence of the importance of C3 fragments, lymphocytes (especially B cells) express receptors (CR2) on their surfaces that bind C3dg and C3d (71). Moreover, guinea pigs and some humans deficient in one of the classical components (C2, C3, or C4) exhibit abnormally low antibody responses to primary immunization with bacteriophage ϕX174 (a T-cell-dependent antigen) (34, 255, 256). The immune response can be restored by the addition of the missing component or by repeat vaccination (255). In addition, C3-deficient animals have an impaired amnestic response and fail to undergo isotype switching after secondary antigenic presentation (34). Studies of C3-deficient dogs have also demonstrated impaired responses to T-independent antigens. In contrast to the response to T-dependent antigens, this abnormality could not be overcome by increasing the inoculum or by changing the route of administration (258).

A fourth complement-derived function involves the participation of cell-bound fragments of C3 (mainly C3b and iC3b) as bifunctional opsonic ligands linking the target particle to effector cells bearing receptors for these fragments. In the case of bacteria, opsonization with C3b or iC3b, especially in conjunction with IgG, promotes ingestion of the organism and triggers microbicidal mechanisms (82). Evidence also suggests that the terminal components (e.g., C7 and C8) may facilitate neutrophil-dependent intraphagosomal bactericidal activity (221, 357, 358). These studies suggest that *E. coli* ingested by neutrophils is not irreversibly damaged upon ingestion unless at least some of the terminal components are present on the organism.

Last, assembly and insertion of the membrane attack complex lead to cell membrane disruption and cell death. Death and lysis are independent events. In the case of bacteria, these events occur only with gram-negative organisms and may require the metabolic response of the organism before the lethal effects of the membrane attack complex are expressed (355). Complement-mediated antiviral activity has also been well described and frequently requires the deposition of only the early components of the classical pathway and/or specific antibody, which causes viral neutralization with or without lysis (72). In addition, the alternative pathway in conjunction with IgG can lyse different human cells infected with various RNA and DNA viruses (72).

Microbial Interactions with Complement

The virulence of a pathogen rests partially in its ability to avoid host defense mechanisms designed to eliminate microbial transgressors. An example of this principle and one of the first studies to suggest the importance of serum bactericidal activity in host defense was the demonstration by Roantree and Rantz that gram-negative bacteria isolated from the blood of infected patients were nearly all resistant to killing by normal serum (297). In contrast, two-thirds of the gram-negative organisms isolated from mucosal surfaces were sensitive to serum.

Resistance to the effects of complement is expressed at several levels of the cascade: (i) activation and amplification of the alternative and classical pathways, (ii) degradation of C3b, and (iii) action of the membrane attack complex. All organisms that have been investigated activate complement, although organisms that contain sialic acid (e.g., group B meningococci, K-1 *E. coli*, and type III, group B streptococci) activate complement poorly via the alternative pathway (96, 114, 176). Sialic acid increases the affinity of factor H for surface-bound C3b, which in turn inhibits amplification (108, 113, 114, 192).

In addition to sialic acid, the composition of lipopolysaccharide on gram-negative organisms plays an important role in modulating the function of complement deposited on the bacterial surface. Experiments performed with *Salmonella typhimurium* mutants, which share identical outer membrane protein patterns but possess different lipopolysaccharide moieties and manifest different degrees of virulence for mice, demonstrated that the rate of C3 activation and deposition was greatest on the least virulent organism (210). The affinity of C3b for factor H and the rate of C3b degradation were the same for all three strains. In contrast, the affinity of C3b for factor B varied among isolates and was inversely correlated to C3b deposition and virulence (144, 213, 214). Thus, minor chemical differences in the lipopolysaccharide molecules expressed on otherwise identical bac-

teria profoundly influenced the organisms' susceptibility to complement-dependent effects and hence their virulence.

Many organisms readily activate complement but provide conditions that favor C3b degradation. Most often, the mechanism entails the binding of C3b on the surface such that C3b is more susceptible to attack by regulatory proteins. For example, epimastigotes, the insect infective form of *Trypanosoma cruzi*, are efficiently killed by nonimmune human serum via alternative-pathway activation. In contrast, trypomastigotes, the human infective form, are not killed under identical conditions (180). The basis for this difference is the ability of trypomastigotes but not of epimastigotes to N-glycosylate an 87- to 93-kDa surface protein which has DAF-like activity (180, 182, 325). Although C3b is deposited on both forms, the presence of the glycosylated protein reduces the affinity of C3b for factor B and leads to more rapid C3b decay (181).

Recently, a unique protective mechanism was reported for schistosomula and adult worms of *Schistosoma mansoni* (222). These organisms are highly resistant to the effects of complement in vitro and in vivo. Resistance appears in part secondary to the presence of an innate trypsin-sensitive, membrane-bound regulatory protein that is distinct from DAF and CR1. Moreover, these organisms appear able to pirate DAF molecules from host cells for their own protection (267, 268, 282).

In addition to mechanisms that modulate the activity of bound C3, some organisms possess glycoproteins that bind C3 noncovalently and are antigenically similar to the human C3 receptor (95, 119, 120, 129). Glycoprotein C of herpes simplex virus binds C3 and subsequently confers complement resistance on this virus (224). In the case of *Candida albicans*, these surface proteins, by binding C3 in an orientation unfavorable for interaction with host cell receptors, may help the organism in resisting phagocytosis (129). One might also speculate that microbial C3 receptors aid organism adherence to host cells and prosthetic devices.

Evasion of the effects of the membrane attack complex represents the last point of escape for microbes. Nearly all gram-positive organisms and fungi are resistant to complement-mediated lysis, not because they do not activate complement, but because the thick cell wall prevents access of the membrane attack complex to their cell membrane (46).

Gram-negative organisms, on the other hand, do not have thick cell walls and are susceptible to the bactericidal and lytic effects of complement. For *Salmonella* species, the presence of long O-antigen side chains in the lipopolysaccharide molecules leads to complement activation at a distance from the outer membrane and hinders insertion of the membrane attack complex into the membrane (48, 118, 184). In this situation, the nascent attack complex is stable through the incorporation of C7 but becomes less firmly attached to the surface after the insertion of C8 and, upon incorporation of C9, is shed prior to insertion into the bacterial membrane (48, 118, 184).

Gram-negative bacteria with truncated lipopolysaccharide molecules (for example, *Haemophilus influenzae*, the meningococcus, and the gonococcus) are not innately resistant to the bactericidal effects of complement but do require specific antibody for effective sensitization and complement deposition. Thus, these organisms are effectively serum resistant under conditions in which the host lacks specific antibody. This observation may help to explain why these organisms are effective pathogens during the first 2 years of life. Moreover, gonococci isolated from patients with disseminated disease are resistant to killing by serum, while those isolated from patients with local disease are mostly serum sensitive in vitro (323). The membrane attack complex is assembled on the surface of both types of gonococci but fails to insert properly in the outer membrane of the resistant isolates (152, 186). However, insertion and killing of these strains do occur in the presence of specific IgG antilipopolysaccharide antibody found in the convalescent serum of some individuals with disseminated disease (81, 293). These findings emphasize both the importance of outer membrane composition in determining serum sensitivity and the utility of specific antibody in overcoming the resistance of these organisms to killing (118).

Another mechanism for serum resistance in gonococci is the presence in some sera of IgG antibody specific for protein 3 in the gonococcal outer membrane (294, 295). This antibody binds to its target protein in the outer membrane and inhibits the action of bactericidal antibody (i.e., it is a blocking antibody). Although blocking antibody promotes complement disposition on the organism, it apparently does so at sites that do not lead to killing (185). Blocking antibody also seems important in meningococcal infection in adults (140, 141). In contrast to the situation with gonococci, this antibody is a non-complement-fixing IgA that competes with bactericidal antibody (139, 140, 143).

COMPLEMENT DEFICIENCY STATES

Plasma Complement Proteins

Acquired deficiencies. Deficiency states may be acquired or inherited. Acquired defects are relatively common, may be acute or chronic in etiology, and are frequently reversible with treatment of the disease responsible for the defect. Infection is an uncommon complication of acutely acquired defects but is a well-recognized accompaniment of chronic deficiency states. Acquired defects are classified according to the mechanism responsible for the defect: consumptive, synthetic, or catabolic (98). Immune complex disease, thermal injury, vasculitis, and C3 nephritic factor are examples of conditions in which complement activity is low as a result of consumption. Decreased synthesis is most commonly observed in patients with severe liver disease, reflecting the major role that the liver displays in the production of individual complement proteins (98, 100, 102). Accelerated catabolism of complement proteins occurs in patients with protein-losing enteropathies or the nephrotic syndrome (98).

Hereditary deficiencies. (i) Frequency. In contrast to acquired complement deficiency states, inherited defects affecting individual complement proteins are uncommon (about 0.03% prevalence) in the general population (153). Data on the prevalence of individual complement deficiency states in the population at large are generally lacking. When such data are available, they often reflect the ethnic bias of Western Europe and North America and thus are applicable largely to Caucasian populations. With this caveat in mind, homozygous C2 deficiency appears to be one of the most common inherited defects in the complement cascade, occurring in 0.009 to 0.01% of normal individuals as determined by haplotype analysis or by functional studies of normal blood donors (4, 204). Because two structural genes encode distinct but functionally active forms of C4 (see above), heterozygous C4 deficiency is extraordinarily common, occurring in approximately 25% of the normal Caucasian population (20, 154). Conversely, complete homozygous C4 deficiency is very rare. C9 deficiency appears to be uncommon in Caucasian populations, but its reported prev-

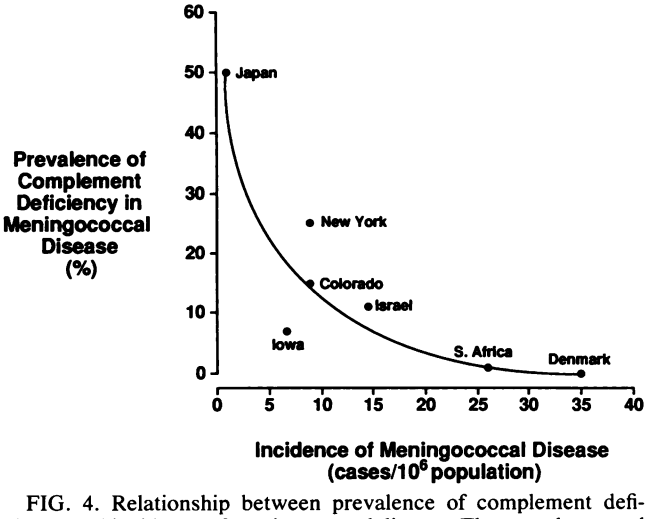

FIG. 4. Relationship between prevalence of complement deficiency and incidence of meningococcal disease. The prevalence and incidence data for complement deficiency and meningococcal disease, respectively, for various locations were obtained as indicated from the literature or by personal communication with Frank Riedo at the Centers for Disease Control in Atlanta, Ga.: Denmark (286) (276); South Africa (21) (F. Riedo); Israel (321) (321); Colorado (101) (320, 376); Iowa (85) (85); New York (209) (320, 376); Japan (241) (241).

alence among normal Japanese blood donors is between 0.045 and 0.104% (241). This frequency contrasts with the prevalence (0.005%) of C7 deficiency in the same population. Data on the prevalence of other complement deficiency states are not yet available. However, according to data obtained from diseased populations, C7 and C8β deficiencies appear to occur predominantly in Caucasians, C6 and C8α-γ deficiencies appear to be more common in blacks, and C5 deficiency occurs about equally in the two races (Table 3) (303). These data underscore the importance of the ethnic background in determining the prevalence of deficiency states in various populations. In addition, since these inherited conditions are uncommon, screening tests will have their greatest usefulness in populations that display the clinical correlates of abnormal complement inheritance, that is, in individuals with rheumatologic diseases or recurrent bacterial infections or both.

In one such study (131), a single individual with homozygous C2 deficiency and 19 individuals with definite, probable, or possible heterozygous C2 deficiency were detected among 545 patients with rheumatologic disorders, whereas only 6 possibly heterozygous C2-deficient individuals were detected among 509 unaffected persons. The frequencies of homozygous (0.2%) and heterozygous (3.5%) C2 deficiency in this study are approximately 10- and 3-fold greater, respectively, than those in the general population. Thus, this study provides clear support for the association of complement deficiency states with certain rheumatologic disorders, especially systemic lupus erythematosus.

The recognition of an association between systemic meningococcal and gonococcal infections and an inherited deficiency of one of the terminal-complement components (99, 274, 303) has led to a number of studies on the frequency of these defects among patients with these infections (21, 99, 101, 103, 209, 241, 251, 286, 321). In these studies, the reported frequency of this association ranged between 0 and 50% among individuals presenting with a first episode of documented meningococcal disease. A number of factors probably contribute to this variation, including a disproportionate genetic influence in relatively insular populations, the incidence of neisserial disease in the general population, the number and age of the patients studied, the type of study (prospective or retrospective), and the degree of ascertainment.

One recent prospective study examined the prevalence of complement deficiency states in 544 individuals with meningitis or bacteremia caused by encapsulated bacteria (85). Seven unrelated complement-deficient individuals were detected: two had C2 deficiency, one had properdin deficiency, three had C7 deficiency, and one had C8β deficiency. Of these seven individuals, six had meningococcal disease and one experienced pneumococcal bacteremia. The prevalence of complement deficiency states among individuals with meningococcal disease (6 of 85 people [7%]) was significantly greater than that among individuals with pneumococcal or *H. influenzae* infection. The absence of individuals with C5, C6, and C8α-γ deficiency in this study of a predominantly Caucasian population is consistent with the hypothesis that ethnic background is a major variable in the reported frequency of the association of these deficiency states with neisserial disease. Nevertheless, the results support the contention that the frequency of inherited complement deficiency states among patients with endemic neisserial disease is about 5 to 10%, although the likelihood of complement deficiency increases dramatically (31%) among individuals who have had more than one episode of meningococcal infection (229).

An examination of studies (21, 85, 101, 209, 241, 286, 321) reporting widely disparate frequencies (0 to 50%) of complement deficiency among individuals with meningococcal disease reveals an interesting relationship between these factors in the general population (Fig. 4). The lowest frequency (0 of 47 [≤2.1%]) was noted in Denmark (286), where meningococcal disease is epidemic (~35 cases per 10^6 people per year). An intermediate frequency (6 of 85 [7%]) was found in the Midwestern United States (85), where meningococcal disease is endemic (~7.3 cases per 10^6 people per year). The highest frequency (8 of 16 [50%]) was reported in Japan (241), where meningococcal disease occurs sporadically (~1 case per 10^6 people per year). This inverse relationship suggests that the spread of an epidemic strain in a population in which most individuals are susceptible will affect more normal than complement-deficient individuals because there are significantly more of the former than the latter. Development of immunity in the general population is associated with a disproportionately greater decrease in susceptibility to infection in normal individuals. As this occurs, complement deficiency becomes a greater determinant of the risk of infection. Consequently, the prevalence of these deficiencies among individuals with meningococcal disease increases. Thus, the incidence of meningococcal disease in the general population is an important determinant of the frequency with which these defects are observed among individuals with this infection.

(ii) Functional consequences of specific deficiencies. The complement system is a principal mediator of inflammation and a major effector mechanism for the expression of antibody-dependent activity. As discussed above, it plays an important role in processing immune complexes, initiating the inflammatory response, promoting the directed migration of phagocytic cells to inflammatory sites, enhancing the uptake of microorganisms by phagocytic cells, modulating the immune response, and mediating direct bactericidal

TABLE 3. Update of reported complement-deficient homozygotes[a]

Deficiency and patient	Kindred	Deficiency	Age (yr)[b]	Sex[c]	Ethnic origin[d]	Infection[e]	Other diagnoses[f]	Reference(s)
C1								
23	15	C1q	7	F	W	Sepsis on immunosuppression	GN, SLE-like syndrome	147
24	15	C1q	4	F	W		GN, SLE-like syndrome	147
25	15	C1q	42	M	W	Chronic bronchitis	MGN, SLE-like syndrome	147
26	16	C1q	10	M	W		SLE	342, 363
27	16	C1q	7	M	W		SLE	342, 363
28	17	C1q		F	W			342
29	18	C1q	19	F	O		SLE	259
30	19	C1r	35	F	B	DGI		99
31	20	C1r	1	M	H	Multiple respiratory infections, *Staphylococcus aureus* liver abscess, *Streptococcus pneumoniae* bacteremia, *S. aureus* adenitis		147
C4								
13	10	C4	66	F	W		Scleroderma, hemolytic anemia, IgA deficiency	187
14	11	C4	2	F	Oth	Recurrent respiratory infections	SLE-like syndrome	223, 231
15	11	C4	1.5	F	Oth	Recurrent respiratory infections, pneumonia with pleurisy	SLE-like syndrome	223, 231
16	12	C4	16	F	W	Whipple's disease	SLE	97
17	13	C4	32	F	W		SLE	200
18	14	C4	6	F		Meningitis	SLE	231
19	15	C4	26	M	Oth		SLE	128
20	16	C4		M	W		SLE-like syndrome	173
21	17	C4	9	F			SLE	375
C2								
78	57	C2	27	F			SLE	231
79	58	C2	4	M		Otitis media	Icthyosis	231
80	59	C2	36	M	W		Hemophilia	175
81	60	C2	36	F	W		SLE	123, 344
82	61	C2 & P[g]	1	M	W	Recurrent otitis media, *S. pneumoniae* bacteremia 3 times		124
83	62	C2	44	M	W			79
84	62	C2	16	F	W			79
85	62	C2	7	M	W	*N. meningitidis* meningitis		79
86	63	C2	1	M	W	*S. pneumoniae* bacteremia 2 times, *H. influenzae* bacteremia with orbital cellulitis		79
87	63	C2	2	M	W	Recurrent respiratory infections, orbital cellulitis		79
88	64	C2	4	M	W	*S. pneumoniae* bacteremia		79
89	65	C2	2	M	W	*S. pneumoniae* disease 3 times		199
90	66	C2	35	M	W	*H. influenzae* meningitis		63
91	67	C2	28	F	W		Cutaneous lupus	50
92	67	C2	31	F	W		Cutaneous lupus	50
93	67	C2	28	M	W		Cutaneous lupus	50
94	67	C2						50
95	68	C2	55	M	W	*S. aureus* bacteremia	Vasculitis, cirrhosis	24
96	69	C2				*N. meningitidis* meningitis		251
97	70	C2				*N. meningitidis* meningitis		251
98	71	C2 & C4				*N. meningitidis* meningitis		251
99	72	C2	37	F	W	Recurrent respiratory infections	SLE	385
100	73	C2	16	M	W	*N. meningitidis* meningitis, recurrent otitis media		208
101	74	C2	42	F	W		SLE	343
102	74	C2	Child	F	W	Recurrent respiratory infections		343
103	75	C2	Child	M	W	Recurrent respiratory infections, *H. influenzae* meningitis, *S. pneumoniae* bacteremia		332
104	76	C2	Adult	M	W	Recurrent bronchitis, pyelonephritis	DLE	37
105	76	C2		F	W			37
106	77	C2	3	M	W	N. meningitidis meningitis		321
107	78	C2	0.6	F	W	*S. pneumoniae* meningitis		39
108	79	C2	28	F	W	Recurrent bronchitis, pneumonia	Vasculitis	172
109	79	C2		M	W			172

Continued on following page

TABLE 3—*Continued*

Deficiency and patient	Kindred	Deficiency	Age (yr)[b]	Sex[c]	Ethnic origin[d]	Infection[e]	Other diagnoses[f]	Reference(s)
C3								
15	10	C3	0.83	M		*S. pneumoniae* meningitis with many relapses		106
16	11	C3	0.25	M	W	*N. meningitidis* meningitis 3 times, bronchopneumonia 4 times, otitis media 4 times, osteomyelitis 2 times, UTI, giardiasis	Aseptic arthritis	145
17	12	C3	16	M	W	*N. meningitidis* disease		116
18	13	C3	Infant	M		Otitis media, streptococcal pharyngitis	Erythema multiforme	36
19	14	C3	Child	M	O	*S. pneumoniae* meningitis 2 times, lobar pneumonia 3 times	GN	31
Factor H								
3	3	H		F		*N. meningitidis* bacteremia	MPGN	216
4	3	H		F		*N. meningitidis* bacteremia	MPGN	216
5	3	H		F			MPGN	216
6	4	H	10	F	W	*N. meningitidis* meningitis 2 times		248
7	5	H		F	W		SLE	40
8	5	H		M	W	Meningitis		40
9	5	H		M	W	Several viral infections		40
10	6	H	49	F	W	*N. meningitidis* disease	SLE	116
11	7	H				*N. meningitidis* meningitis		251
12	8	H		M	O	Frequent respiratory infections	GN	212
13	8	H		M	O	Frequent respiratory infections, *E. coli* bacteremia	GN	212
Factor I								
7	6	I	0.06			*S. pneumoniae* bacteremia 2 times, osteomyelitis	Coomb's positive anemia	18
8	7	I	19	F	W	*N. meningitidis* meningitis, septicemia (unknown cause)		287, 359
9	8	I	13	M	W	*N. meningitidis* meningitis 4 times, multiple respiratory infections		287
10	9	I		F	W		PAN	287
11	10	I	0.3	F	W	*S. pneumoniae* meningitis, *N. meningitidis* meningitis 2 times, meningitis (unknown cause) 4 times		219
12	11	I	9			Multiple respiratory infections, *N. meningitidis* arthritis		278
13	12	I	9				Arthritis	278
14	12	I	11			*N. meningitidis* arthritis		278
C5								
14	8	C5	15	F	W	*N. meningitidis* meningitis, malaria	Seizures	127
15	8	C5	19	M	W	*N. meningitidis* meningitis		127
16	9	C5	12	M		*N. meningitidis* meningitis, chronic meningococcemia	Mild head injury	299
17	10	C5	23	M	W	*N. meningitidis* meningitis		60
18	10	C5	18	M	W	Meningitis (unknown cause)		60
19	11	C5	23	M	W	*N. meningitidis* disease 2 times		116
20	12	C5	16	F	W	*N. meningitidis* disease		116
21	13	C5	36	F	W	*N. meningitidis* disease 3 times		116
22	14	C5	5	M	W	*N. meningitidis* meningitis 4 times		219
23	14	prob[h] C5	2	M	W	Meningitis (unknown cause) *N. meningitidis* meningitis		219
24	15	C5	19	M	W	*N. meningitidis* meningitis 2 times		249
25	15	C5	19	M	W	*N. meningitidis* meningitis		249
26	16	C5	20	F	W	*N. meningitidis* meningitis 2 times		30
27	17	C5	20	F	W	DGI		30
C6								
34	25	C6	15		B	*N. meningitidis* meningitis 2 times		260, 279
35	25	C6			B			260, 279
36	26	C6	12		B	*N. meningitidis* meningitis 2 times		260, 279
37	26	C6			B			260, 279
38	27	C6	8		B	*N. meningitidis* meningitis 2 times		260, 279
39	27	C6	12		B	*N. meningitidis* meningitis		260, 279
40	27	C6	7		B	*N. meningitidis* meningitis 3 times		260, 279
41	28	C6	2		B	*N. meningitidis* meningitis 2 times		260, 279

Continued on following page

TABLE 3—*Continued*

Deficiency and patient	Kindred	Deficiency	Age (yr)[b]	Sex[c]	Ethnic origin[d]	Infection[e]	Other diagnoses[f]	Reference(s)
42	28	C6			B			260, 279
43	29	C6	16		B	*N. meningitidis* meningitis 2 times		260, 279
44	29	C6			B			260, 279
45	30	C6	13		B	*N. meningitidis* meningitis 2 times		260, 279
46	30	C6			B			260, 279
47	30	C6			B			260, 279
48	31	C6	21		B	*N. meningitidis* meningitis 5 times		260, 279
49	31	C6	21		B	*N. meningitidis* meningitis		260, 279
50	31	C6			B			260, 279
51	32	C6	13		B	*N. meningitidis* meningitis 2 times		260, 279
52	32	C6	14		B	*N. meningitidis* meningitis		260, 279
53	32	C6			B			260, 279
54	33	C6	21		B	*N. meningitidis* meningitis 3 times		260, 279
55	34	C6	16		B	*N. meningitidis* meningitis 2 times		260, 279
56	35	C6	18		B	*N. meningitidis* meningitis 3 times		260, 279
57	36	C6	5		B	*N. meningitidis* meningitis 3 times		260, 279
58	37	C6	21		B	*N. meningitidis* meningitis 4 times		260, 279
59	38	C6	0.75		B	*N. meningitidis* meningitis 3 times		260, 279
60	38	C6	14		B	*N. meningitidis* meningitis 2 times		260, 279
61	39	C6 & C7[i]	21	F	W	Toxoplasmosis, persistent vaginal candidiasis		236
62	40	C6	36	F		Psoas abscess with *S. albus*, bronchopneumonia	Anemia, adenopathy, arthritis, aortic aneurysm	384
63	41	C6	18	M	B	*N. meningitidis* meningitis		49
64	42	C6	50	F			SLE-like syndrome	292
65	42	C6		F			Anemia since childhood	292
66	42	C6		F				292
67	42	C6		F				292
68	42	C6		F			Thalassemia minor	292
69	43	C6	0.4	M	B	*N. meningitidis* meningitis 2 times		167
70	43	C6	0.4	M	B	*N. meningitidis* meningitis		167
71	44	C6		M	W			386
72	45	C6	25	M	W	*N. meningitidis* disease		116
73	46	C6	43	M	B	*N. meningitidis* meningitis, meningitis (unknown cause) 3 times		69
74	47	C6		M	B	Gonorrhea	SLE, hyperthyroid, Sjögren's syndrome	365
75	47	C6		F	B			365
76	48	C6	20	F	B	Meningococcemia		345
77	49	C6		M	B	*N. meningitidis* meningitis	MGN, uveitis	59
C7								
23	17	C7	14	M	O	*N. meningitidis* meningitis		241
24	17	C7	17	M	O	*N. meningitidis* meningitis		241
25	18	C7	15	M	O	*N. meningitidis* meningitis		241
26	19	C7	16	M	O	*N. meningitidis* meningitis		241
27	20	C7 & C6[i]	21	F	W	Toxoplasmosis, persistent vaginal candidiasis		236
28	21	C7	3	F	W	*N. meningitidis* meningitis 3 times		253
29	22	C7	22	M	W	*N. meningitidis* meningitis		348
30	22	C7	19	M	W	*N. meningitidis* meningitis		348
31	23	C7	16		W	*N. meningitidis* meningitis 2 times		281
32	24	C7	28	M		*N. meningitidis* meningitis, myopericarditis		62
33	24	C7		M				62
34	25	C7	21	M	H	*N. meningitidis* meningitis 3 times	IgA deficiency	177
35	26	C7	8	F	O	*N. meningitidis* meningitis		233
36	27	C7	19	F		*H. parainfluenzae* meningitis		285
37	27	C7		M				285
38	28	C7	40	M	W	Chronic meningococcemia		1
39	29	C7	26	M	SJ	Meningitis (unknown cause)		390
40	29	C7	21	F	SJ	*N. meningitidis* meningitis		390
41	29	C7		M	SJ			390
42	30	C7	5	F	SJ	*N. meningitidis* meningitis		390
43	30	C7		F	SJ			390
44	31	C7		F	SJ			390
45	31	C7	7	M	SJ	*N. meningitidis* meningitis		390

Continued on following page

TABLE 3—*Continued*

Deficiency and patient	Kindred	Deficiency	Age (yr)[b]	Sex[c]	Ethnic origin[d]	Infection[e]	Other diagnoses[f]	Reference(s)
46	32	C7	17	F	SJ	*N. meningitidis* meningitis		390
47	32	C7		F	SJ			390
48	32	C7	10	M	SJ	*N. meningitidis* meningitis 2 times		390
49	33	C7	15	F	W	*N. meningitidis* disease, toxoplasmosis, mononucleosis	CVA	116
50	34	C7	21	M	W	*N. meningitidis* disease 2 times		116
51	35	C7	4	M	W	*N. meningitidis* disease 4 times		116
52	36	C7	16	M	W	*N. meningitidis* meningitis 4 times		79
53	36	C7	21	M	W	*N. meningitidis* meningitis		79
54	36	C7	20	M	W	*N. meningitidis* meningitis		79
55	37	C7	19	M	W	*N. meningitidis* disease 2 times		79
56	38	C7	41	M	W	*N. meningitidis* disease		79
57	39	C7	17	F	W	*N. meningitidis* meningitis 3 times		219
58	40	C7	20	F	SJ	*N. meningitidis* bacteremia	Head trauma	234
59	40	C7	25	M	SJ	*N. meningitidis* meningitis		234
60	40	C7		M	SJ			234
61	41	C7				*N. meningitidis* meningitis		251
62	42	C7	8	M	O		Hematuria	311
63	42	C7		M	O			311
64	43	C7		M		Recurrent *N. meningitidis* meningitis		74
65	43	C7		M		Recurrent *N. meningitidis* meningitis		74
66	44	C7		M				74
67	44	C7		M				74
68	45	C7	6	F	SJ	*N. meningitidis* meningitis		321
69	46	C7	13	M	SJ	*N. meningitidis* meningitis		321
70	47	C7	21	M	SJ	*N. meningitidis* meningitis		321
71	48	C7	18	F	SJ	*N. meningitidis* meningitis		321
72	49	C7	38	M	SJ	*N. meningitidis* meningitis		321
73	50	C7	15	M	W	*N. meningitidis* meningitis 3 times		28, 296
C8								
32	23	C8β	12	M	W		SLE	367
33	24	C8β	16	F	W	Recurrent bronchitis, sinusitis	Atopic dermatitis	367
34	25	C8	26	M	SJ			389, 390
35	25	C8β	16	M	SJ	*N. meningitidis* meningitis 4 times		389, 390
36	25	C8β	24	M	SJ			389, 390
37	26	C8β	8	M	SJ	*N. meningitidis* meningitis 2 times		390
38	26	C8β		M	SJ			390
39	27	C8β	9	F	SJ	Meningitis (unknown cause)		390
40	27	C8β	17	F	SJ	Meningitis (unknown cause)		390
41	27	C8β	15	M	SJ	*N. meningitidis* meningitis		390
42	28	C8α-γ	26	M	SJ	*N. meningitidis* meningitis		390
43	29	C8β	21	F	SJ	*N. meningitidis* meningitis 3 times		390
44	30	C8β	18	M	SJ	*N. meningitidis* meningitis		390
45	31	C8	11	M	W	*N. meningitidis* disease 2 times		116
46	32	C8	30	F	W	*N. meningitidis* disease		116
47	33	C8	13	M		*N. meningitidis* meningitis 2 times, aseptic meningitis 4 times		94
48	33	C8	36	F		*N. meningitidis* meningitis		94
49	33	C8	6	M		Meningitis (unknown cause)		94
						N. meningitidis meningitis		
51	35	C8β	17	F	W	*N. meningitidis* meningitis 2 times		79
52	36	C8β	15	F	W	*N. meningitidis* bacteremia 2 times		63
53	37	C8β	16	F	W	*N. meningitidis* meningitis 2 times		93, 121
54	37	C8β	16	F	W			121
55	37	C8β	11	F	W			121
56	37	prob C8β		F	W	*N. meningitidis* disease		121
57	38	C8β	Adult	M	W	*N. meningitidis* disease		125
58	38	C8β	Adult	F	W	*N. meningitidis* disease		125
59	39	C8α-γ	30	M	B	*N. meningitidis* disease, DGI		266
60	40	C8β	13	F	W	*N. meningitidis* meningitis 2 times		284
61	41	C8β				*N. meningitidis* meningitis		251
62	42	C8	1.83	M		*N. meningitidis* meningitis with relapse 2 times		215
63	43	C8	10	F	W	*N. meningitidis* disease with relapse 2 times		193
64	44	C8β	27	M	W	Tuberculosis		41

Continued on following page

TABLE 3—*Continued*

Deficiency and patient	Kindred	Deficiency	Age (yr)[b]	Sex[c]	Ethnic origin[d]	Infection[e]	Other diagnoses[f]	Reference(s)
65	45	C8				*N. meningitidis* meningitis		68
66	46	C8β	18	M	W	*N. meningitidis* meningitis		67, 179
67	47	C8β		M	A	*N. meningitidis* disease		126
68	48	C8α-γ	0.4	F	B	VP shunt infection, *S. pneumoniae* bacteremia		382
69	49	C8α-γ	20	F	B	DGI, gonococcal meningitis		76
70	50	C8β	12	M	SJ	*N. meningitidis* meningitis		321
71	50	C8β		M	SJ			321
72	51	C8β	7	F	SJ	*N. meningitidis* meningitis		321
73	52	C8β	8	M	SJ	*N. meningitidis* meningitis		321
C9								
6	6	C9	7	M	O	*N. meningitidis* meningitis		241
7	7	C9	12	F	O	*N. meningitidis* meningitis		241
8	8	C9	16	M	O	*N. meningitidis* meningitis		241
9	9	C9	32	F	O	*N. meningitidis* meningitis		241
10	10	C9	27	F	O		SLE	191
11	11	C9		F	O		Gastric Ca	203
12	11	C9		F	O			203
13	11	C9		F	O			203
14	12	C9	17	F	H	*N. meningitidis* meningitis		117
15	13	C9	23	M	W	Meningitis (unknown cause) *N. meningitidis* meningitis		339, 391
16	14	C9	47	F	O		PNH	387
17	15	C9	48	F	O		SLE, sicca syndrome	352
18	15	C9		M	O		SLE, sicca syndrome	352
Properdin								
5	2	prob P	6	M	W	*N. meningitidis* meningitis, sepsis		38, 330, 331
6	2	prob P	31	M	W	Meningitis–presumed meningococcal; sepsis		38, 330, 331
7	2	prob P	6	M	W	Sepsis, headache		38, 330, 331
8	3	P	11	M	W	*N. meningitidis* bacteremia		250, 330
9	3	prob P	20	M	W	*N. meningitidis* bacteremia		250, 330
10	3	P	0.9	M	W	*N. meningitidis* bacteremia		250, 330
11	3	P		M	W			250, 330
12	4	P	18	M	W	*N. meningitidis* meningitis, recurrent respiratory infections		330, 337
13	4	P	6	M	W	Presumed Lyme disease, *S. pneumoniae* pneumonia		330, 337
14	4	P		M	W			330, 337
15	5	P	30	M	W	*N. meningitidis* meningitis		88, 330
16	5	prob P	18	M	W	*N. meningitidis* meningitis		88, 330
17	5	prob P	4	M	W	Meningitis (unknown cause), "black measles," *N. meningitidis* meningitis		88, 330
18	5	P		M	W			88, 330
19	5	P		M	W			88, 330
20	6	P & C2[g]	1	M	W	Recurrent otitis media, *S. pneumoniae* bacteremia 3 times		124, 330
21	7	P	11	M	W	*N. meningitidis* disease		116, 330
22	8	P	17	M	W	*N. meningitidis* disease		116, 330
23	9	P	22	M	W	*N. meningitidis* disease, sepsis		116, 330
24	10	P	13	M	W	*N. meningitidis* disease		116, 330
25	11	P	13	M	W	*N. meningitidis* disease		116, 330
26	12	P	17	M	W	*N. meningitidis* disease		116, 330
27	13	P	14	M	W	*N. meningitidis* disease		116, 330
28	14	P	13	M	W	*N. meningitidis* meningitis		330, 338
29	14	P	15	M	W	*N. meningitidis* meningitis		330, 338
30–35	14	P		M				330, 338
36	15	P	58	M	W			330, 334
37	15	P	29	M	W			330, 334
38	16	P	4	M	W	*N. meningitidis* bacteremia		79, 330
39	17	P		M	W		DLE	164, 330

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TABLE 3—*Continued*

Deficiency and patient	Kindred	Deficiency	Age (yr)[b]	Sex[c]	Ethnic origin[d]	Infection[e]	Other diagnoses[f]	Reference(s)
40	17	P		M	W		DLE	164, 330
41	17	P		M	W		DLE	164, 330
42	17	P		M	W		DLE	164, 330
43–45	18–19	P		M	W	*N. meningitidis* meningitis in 2 patients		251, 330
46	20	P	61	M	W	*N. meningitidis* meningitis, *E. coli* bacteremia		330, 333
47	20	P	2	M	W	*N. meningitidis* bacteremia, bronchopneumonia		330, 333
48	20	P	12	M	W	*N. meningitidis* bacteremia		330, 333
49	20	P	12	M	W	*N. meningitidis* meningitis		330, 333
50	20	P	4	M	W	Meningitis (unknown cause)		330, 333
51	20	P	53	M	W	Recurrent otitis media, epididymitis	Scleroderma	330, 333
52	20	P		F	W			330, 333
53	20	P		M	W			330, 333
54	20	P		M	W			330, 333
55	20	P		M	W			330, 333
56	20	P		M	W			330, 333
57–65	20	prob P		8M&1F	W	Meningitis–presumed meningococcal		330, 333
66	21	P	14	M	SJ	*N. meningitidis* meningitis		321, 330
67	22	P	16	M	SJ	*N. meningitidis* meningitis		321, 330
68	22	P		M	SJ			321, 330
69	23	P	10	M	W	Recurrent *N. meningitidis* meningitis, chronic meningococcemia		252, 275, 330
70	23	prob P	20	M	W	Meningitis (unknown cause)		252, 275
Factor D								
1	1	D	14	M	W	*N. meningitidis* meningitis, *N. gonorrhoeae* bacteremia 2 times		157
2	2	D	7	F	W	Recurrent respiratory infections with *H. influenzae*, *Proteus* sp., and *Pseudomonas* sp.		201
3	2	D	8	F	W	Recurrent respiratory infections with *H. influenzae*, *Proteus* sp., and *Pseudomonas* sp.		201
C4bp								
1	1	C4bp	28	F	W		Bechet's-like syndrome and angioedema	364
2	1	C4bp		M	W			364
3	1	C4bp		F	W			364

[a] The numbering system continues from that of Ross and Densen (303).
[b] When information was available, the age at which the first infection or rheumatologic disease occurred was recorded.
[c] F, female; M, male.
[d] W, Caucasian; B, black; H, Hispanic; O, Oriental; SJ, Sephardic Jew; A, Asian; Oth, other.
[e] DGI, disseminated gonococcal infection; UTI, urinary tract infection; VP shunt, ventriculoperitoneal shunt.
[f] SLE, systemic lupus erythematosus; DLE, discoid lupus erythematosus; GN, glomerulonephritis; MGN, membranoglomerulonephritis; MPGN, membranoproliferative glomerulonephritis; CVA, cerebrovascular accident; Ca, cancer; DIC, disseminated intravascular coagulopathy; PAN, periarteritis nodosa.
[g] This patient is reported in both C2 and P lists.
[h] prob, probable. This modifier is used when the clinical history strongly supports the diagnosis but diagnostic testing was not performed.
[i] This patient is reported in both C6 and C7 lists.

activity against certain gram-negative bacteria. Because individual proteins often subserve unique functional activities and are activated in a stepwise manner, complement deficiency states are associated with predictable defects in complement-dependent functions. Activities mediated by components proximal to a specific defect are preserved, while functions mediated by components distal to the defect tend to be absent (Table 3). These conclusions are supported by an analysis of the individual complement deficiencies as well as by an analysis of cases grouped by the portion of the complement cascade affected by the defect (Table 4).

Thus, individuals with a deficiency of C1, C4, or C2 who possess a functionally intact alternative pathway demonstrate delayed complement activation, impaired immune complex handling, and a suboptimal immune response. Conversely, persons lacking either factor D or properdin have an intact classical pathway but, in the absence of specific antibody, exhibit impaired complement activation. In contrast, the critical position and function of C3 in the complement cascade predict that C3-deficient persons will exhibit multiple functional defects that will result in associated serious illness. In addition to defective immune complex clearance and immune responses, these individuals demonstrate markedly abnormal complement-dependent op-

sonophagocytic killing and lack complement-mediated bactericidal activity. Chemotaxis and the ability to mount a granulocytic response may also be defective. With the exception of impaired complement-dependent chemotactic responses in individuals with C5 deficiency, the sole defect in persons with a deficiency of C5, C6, C7, C8, or C9 is the inability to generate serum bactericidal activity.

(iii) Diseases associated with complement deficiencies. (a) Deficiencies of classical-pathway proteins. The association of immune disorders, in particular, systemic lupus erythematosus, with complement deficiency states is most evident in individuals lacking one of the early components of the classical pathway (Tables 3 and 4). Studies in populations with rheumatologic disorders have contributed to the notion that infection is an uncommon accompaniment of these deficiencies (131). However, the frequency of C2 deficiency in individuals with meningitis or bacteremia in the study described above (85) is comparable to that in individuals with rheumatologic disorders and is approximately 10-fold greater than that in the general population. These data and an accumulation of case reports (32, 168, 244, 312, 362) indicate that systemic infection with encapsulated bacteria, as well as systemic lupus erythematosus, should be recognized as a manifestation of these deficiencies. These results also underscore the inherent bias of prevalence studies in selected patient populations.

The clinical presentation of systemic lupus erythematosus in these individuals differs from that in the general population (2). In particular, the typical female predominance of this disorder is less striking, evidence of severe renal disease is less common, antinuclear antibody titers are often low or absent, and there appears to be an increased prevalence of Ro antibodies (231, 280). Additional clinical features suggesting a diagnosis of C1, C4, or C2 deficiency are the younger age of the patients at the time of initial infection and the occurrence of infection caused by a variety of different encapsulated bacteria, including the pneumococcus, the meningococcus, and *H. influenzae* (Table 5). Infection in these individuals most commonly involves the sinopulmonary tree, blood, or meninges. These features mimic those of persons with congenital hypogammaglobulinemia but distinguish individuals with classical-pathway defects and infection from those with alternative-pathway or late-complement-component deficiencies in whom the initial infection typically occurs at a later age and is almost always caused by a neisserial species, in particular, the meningococcus (Table 5).

The basis for the development of collagen vascular diseases in individuals with C1, C4, C2, and C3 deficiencies has not been precisely delineated. Both impaired immune complex handling and the tight genetic linkage of the C2 and C4 loci with class I and II MHC loci as well as other genes in this region that encode a number of cytokines may contribute to this association (75). As discussed above, the C2 and C4 null genes occur predominantly as part of distinct extended haplotypes. For C2 deficiency, this haplotype is DR2, C2Q0, BfS, C4A-4, C4B-2, B18, A25 (16); for C4A deficiency, it is DR3, C2C, BfS, C4AQ0, C4B-1, B8 (194). Multivariate analysis of DR and C4 allotypes has confirmed an independent contribution of the DR2 antigen and C4AQ0 but not C4BQ0 to the development of systemic lupus erythematosus (165). However, that the association with lupus is apparent in each of these deficiency states but only C2 and C4 are MHC linked suggests that impaired immune complex clearance is an important pathogenic factor in the development of collagen vascular disorders in these patients. The preference of the internal thiolester in C4A to form amide bonds during complement activation and to react with immune complexes may provide a chemical basis linking these two pathogenic factors to the development of systemic lupus erythematosus (174, 207, 318).

Similarly, the failure of an intact, functionally active, alternative pathway in individuals with C1, C4, or C2 deficiency to provide protection against infection raises questions about the completeness of our understanding of the basis for these infections. On the one hand, the frequent occurrence of these infections early in life may merely reflect the requirement for both antibody and complement for the efficient handling of encapsulated organisms by the host. On the other hand, abnormal regulation of the humoral immune system and suboptimal production of antibody have been demonstrated in C2- and C4-deficient guinea pigs (35). These defects can be corrected by replacement of the missing complement component. Consequently, complement deficiency and its associated immune dysregulation may collectively increase the susceptibility of these individuals to infection.

Two reports, which examined a relatively small number of patients, suggest that C4B deficiency may occur with increased frequency among children with bacterial meningitis (27, 309). These reports are intriguing, given the preference of C4B to form covalent ester bonds during complement activation and the abundance of available hydroxyl groups on the surface of the usual bacterial pathogens responsible for meningitis (174, 207, 318). A third study involving a much larger number of patients of all ages with different types of meningitis (58) and a narrowly focused study examining the frequency of C4BQ0 in patients with meningococcal disease and a deficiency of one of the terminal-complement components (107) did not support a relationship between C4B deficiency and meningitis. The statistical power of the latter two studies suggests that, by itself, C4B deficiency does not constitute a major risk factor for the development of systemic infection caused by encapsulated bacteria, although in conjunction with other defects, it may contribute to this risk.

An inadequately explained aspect of deficiency states involving one of the early components of the classical pathway is the observation that, despite similar functional defects, many of these individuals exhibit predominantly rheumatologic manifestations without evidence of infection, whereas others present with recurrent infection without rheumatologic disease even when observed for extended periods. This observation suggests that important genetic or environmental factors contributing to the development of these diseases in these patients remain to be elucidated.

The molecular basis for the various complement deficiency states is beginning to yield to the burgeoning revolution in molecular biology and, not surprisingly, reflects the gamut of known mechanisms accounting for other types of inherited disorders. Thus, gene deletion appears to be a common mechanism underlying C4A deficiency (194). The molecular basis for C2 deficiency has not been fully established. The recognition that approximately 93% of C2-deficient individuals possess similar haplotype markers and only 7% exhibit completely different markers suggests the existence of at least two different types of C2 deficiency (4, 16). This conclusion has been borne out by recent studies demonstrating that the gene in both types of deficiencies is grossly intact (66) and can be transcribed (178). In the more common type, so-called typical C2 deficiency, translation of the C2 message appears to result in low levels of an intra- and extracellular C2 that is slightly smaller than normal and

TABLE 4. Complement deficiency state[a]

Source and component	No. of reported patients	Mode of inheritance	Functional defect	Disease associations
Classical pathway				
C1qrs	31	ACD	Impaired IC handling, delayed C activation	CVD, 48%; infection (encaps bact), 22%; both, 18%; healthy, 12%
C4	21	ACD		
C2	109	ACD		
Alternative pathway				
D	3	ACD	Impaired C activation in absence of specific antibody	Infection (meningococcal), 74%; healthy, 26%
P	70	XL		
Junction of classical and alternative pathways				
C3	19	ACD	Impaired IC handling, opson/phag; granulocytosis, CTX, and absent SBA	CVD, 79%; recurrent infection (encaps bact), 71%
Terminal components				
C5	27	ACD	Impaired CTX; absent SBA	Infection (*Neisseria* spp., primarily meningococcal) 59%; CVD, 4%; both, 1%; healthy, 25%
C6	77	ACD	Absent SBA	
C7	73	ACD		
C8	73	ACD		
C9	18	ACD	Impaired SBA	Healthy, 92%; infection, 8%
Plasma proteins regulating complement activation				
C1 INH	Many	AD, Acq	Uncontrolled generation of an inflammatory mediator upon C act	Hereditary angioedema
Factor H	13	ACD	Uncontrolled AP act → low C3	CVD, 40%; CVD + infection (encaps bact), 40%; healthy, 20%
Factor I	14	ACD	Uncontrolled AP act → low C3	Infection (encaps bact), 100%
Membrane proteins regulating complement activation				
DAF, CD59, HRF	Many	Acq	Impaired regulation of C3b and C8 deposited on host RBC, PMN, platelets → cell lysis	Paroxysmal nocturnal hemoglobinuria
CR3	>20	ACD	Impaired PMN adhesive functions, i.e., margination, CTX, iC3b-mediated opson/phag	Infection (*S. aureus*, *Pseudomonas* sp.), 100%
Autoantibodies				
C3 nephritic factor	>59	Acq	Stabilizes AP, C3 convertase → low C3	MPGN, 41%; PLD, 25%; infection (encaps bact), 16%; MPGN + PLD, 10%; PLD + infection, 5%; MPGN + PLD + infection, 3%; MPGN + infection, 2%
C4 nephritic factor	4	Acq	Stabilizes CP, C3 convertase → low C3; CVD, 50%	Glomerulonephritis, 50%

[a] Reproduced and modified from Densen (78) with the permission of the publisher. Abbreviations: ACD, autosomal codominant; Acq, acquired; act, activation; AD, autosomal dominant; AP, alternative pathway; C, complement; CTX, chemotaxis; CVD, collagen vascular disease; encaps bact, encapsulated bacteria; HRF, homologous restriction factor; IC, immune complex; INH, inhibitor; MPGN, membranoproliferative glomerulonephritis; opson/phag, opsonophagocytosis; PLD, partial lipodystrophy; PMN, polymorphonuclear neutrophil; RBC, erythrocytes; SBA, serum bactericidal activity; XL, X linked.

lacks functional activity. An abnormal C2 message is suspected in this type of deficiency. In contrast, atypical C2 deficiency appears to be associated with greater than normal amounts of C2 message and the accumulation of intracellular C2 that does not appear to be secreted (178). Further work is needed to elucidate fully the basis for these two deficiency states.

(b) Deficiencies of alternative-pathway proteins. Inherited deficiencies of the components of the alternative pathway have been described only recently and appear to be less common than those of other complement proteins. The clinical picture differs depending on whether or not the deficiency secondarily leads to C3 consumption (factor H and factor I deficiency [see below]). To date, no individuals with homozygous factor B deficiency have been described. Meningococcal disease, often fulminant and fatal, characterized the initial descriptions of properdin deficiency (38, 88, 331). As more properdin-deficient individuals have been identified, it has become increasingly clear that, while meningococcal infection is the predominant clinical manifestation, it does not always carry the poor prognosis reported initially (329, 330).

Properdin deficiency is unique among the inherited defects involving the complement cascade because it is an X-linked trait. Both the deficiency and the structural gene map close to DXS-255 on the short arm of the X chromosome near the centromere, indicating that the deficiency results from an abnormality in the structural gene (134, 136, 372). Although their molecular bases are unknown, three properdin-deficient variants have been described. Type 1 deficiency is characterized by extremely low levels of detectable properdin (<0.1 μg/ml) and undetectable properdin function (88, 331). The serum from individuals with type 2 deficiency contains low levels (~2 μg/ml) of antigenically detectable properdin. Properdin from these individuals has a normal monomolecular weight, but polymer formation and function

TABLE 5. Comparison of the frequency of occurrence of *Neisseria* sp., *S. pneumoniae*, and *H. influenzae* infections in patients with complement deficiencies

Deficiency (no. of homozygotes)	No. of patients (%) with:			Total (%)[a]
	Neisseria sp.	*S. pneumoniae*	*H. influenzae*	
C1, C4, C2 (161)	9 (5.6)	20 (12.4)	8 (5.0)	32 (20)
C3, I, H (46)	17 (37)	12 (26)	2 (4.4)	25 (54)
P, D (57)	25 (44)	2 (3.5)	2 (3.5)	29 (51)
C5–9 (267)	151 (57)	2 (0.8)	0 (0)	150 (56)
Total (531)	202 (38)	36 (6.8)	12 (2.3)	236 (44)

[a] Total patients with infection caused by any of the three specified encapsulated organisms. Each patient is counted only once.

are impaired. The abnormal properdin polymers do not appear to support alternative-pathway activation in the fluid phase but do so on target particles, albeit slowly (334). Type 3 properdin deficiency is characterized by normal amounts of antigenically detectable properdin (~25 μg/ml) but absent function (333).

(c) C3 deficiency. Relatively few individuals with C3 deficiency have been identified. These individuals exhibit profound defects in complement-mediated functions as a consequence of the crucial position of C3 in the complement cascade and the resultant inability to use either the classical or the alternative pathway. Impaired immune complex solubilization, altered immune responses, defective complement-dependent opsonophagocytosis and chemotaxis, and absent complement-dependent bactericidal activity contribute to the clinical manifestations of this condition (Table 4). Consequently, it is not surprising that 70 to 80% of these individuals develop a collagen vascular disease or infection or both. Typically, these infections are recurrent and severe; involve the sinopulmonary tree, meninges, and bloodstream; and are caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *H. influenzae* (Table 5). A similar clinical presentation is observed in individuals with an inherited deficiency of either factor H or factor I (3, 303) and in individuals who develop C3 nephritic factor, an autoantibody that stabilizes the alternative-pathway C3 convertase and prolongs its half-life. These abnormalities result in uncontrolled activation of the alternative pathway and lead to C3 levels that are <10% of normal. However, the presence of even small quantities of C3 tends to ameliorate the clinical picture such that the frequency and severity of infection and the occurrence of collagen vascular disorders are less striking. Individuals with C3 nephritic factor also exhibit an increased prevalence of membranoproliferative glomerulonephritis and partial lipodystrophy, although the basis for these associations is unknown (171, 328).

Recently, Botto et al. used the polymerase chain reaction to characterize the molecular basis for the defect in an individual with inherited C3 deficiency. These investigators demonstrated the presence of a G→A mutation in the consensus donor splice sequence within intron 18 in C3 genomic DNA. Failure to use the normal splice site resulted in the use of a cryptic site within the adjacent downstream exon, leading to an internal deletion and frameshift in the mRNA. Use of the altered reading frame generated a premature stop codon downstream from the cryptic splice site and resulted in the production of a truncated nonfunctional C3 protein (36).

(d) Deficiencies of late-complement components. The association of meningococcal disease with deficiencies of the late-complement components is striking in terms of both the frequency of infection (approximately 50 to 60%; Table 5) and the frequency with which these deficiencies occur in individuals with meningococcal disease (5 to 10%; see above). The basis for this association is the inability of these sera to express complement-dependent bactericidal activity. This conclusion is supported by both laboratory and clinical observations. First, serum from C9-deficient individuals can kill meningococci, albeit more slowly than normal, a finding consistent with the fact that C9 is not absolutely required for complement-mediated lysis of sensitized erythrocytes (151). Second, a carefully performed study reported that the risk of meningococcal disease among C7- and C9-deficient Japanese was approximately 10,000- and 1,400-fold greater, respectively, than that in the complement-sufficient Japanese population (241). These data convincingly demonstrate the increased susceptibility of C9-deficient individuals to meningococcal infection and support a dose-response relationship between the rate of meningococcal killing and the risk of infection. Thus, the ability of C9-deficient sera to support limited meningococcal killing is associated with a 10-fold reduction in the risk of meningococcal disease compared with the risk for individuals missing one of the other terminal-complement components, whose sera completely lack the ability to kill meningococci (241).

In addition to defective complement-mediated bactericidal activity, serum from C5-deficient persons also fails to support complement-dependent chemotactic responses. Despite this additional abnormality, individuals with C5 deficiency do not differ from other persons with terminal-component defects with respect to the bacterial etiology of systemic infection (>95% *Neisseria* sp.), the frequency and severity of infection (77% meningitis), or the frequency of recurrent disease (42%) (Table 3) (303).

The basis for deficiencies of the late-complement components in humans has not yet been adequately detailed at the molecular level. In part, this has been due to the lack of a readily available cell source capable of producing sufficient quantities of these proteins to permit adequate studies at the DNA, RNA, and protein levels. The recent demonstration of the expression of these proteins in both peripheral monocytes and fibroblasts may provide a way to circumvent these difficulties (373). Nevertheless, it is clear that different mechanisms account for these deficiencies. For example, the highly homologous genes for C6 or C7 are tightly linked on chromosome 9 (158). Individuals with C6, C7, and combined C6-C7 deficiencies have been described (236). C6-deficient individuals are predominantly black, whereas C7 individuals are predominantly Caucasian, and individuals with combined C6-C7 deficiency are white (Table 3). These observations suggest the existence of at least two separate mechanisms accounting for C6 and C7 deficiencies.

Similarly, C8β and C8α are tightly linked on the short arm of chromosome 1 (190). Whereas individuals with reported C8β deficiency have been predominantly Caucasian, persons with C8α-γ deficiency are predominantly black or Hispanic (Table 3). In contrast to the situation with C6 and C7, a combined deficiency of C8α and C8β has not yet been recognized. In general, sera from individuals with C8β deficiency contain little if any dysfunctional C8β protein. Consistent with this observation is the recent finding that, although C8β message can be detected in monocytes from deficient individuals, it is present in reduced amounts (373). The sera from these individuals contain C8α-γ in amounts

approximating those present in normal individuals. Interestingly, specific C8α-γ polymorphic variants are present in these sera, implying a tight linkage between the C8β null gene and the C8α gene encoding these variants (254). This observation suggests the existence of a limited number of molecular bases for C8β deficiency, analogous to the situation in typical and atypical C2 deficiencies described above (178).

In contrast to C8β deficiency, sera from individuals with C8α-γ deficiency contain markedly reduced (~0.5% of normal) amounts of antigenically detectable but apparently dysfunctional C8α-γ (356). Because the hemolytic activity of the C8α-γ subunit resides in the α chain, it seems likely that a defect in the C8α gene is the basis for C8α-γ deficiency. However, a preliminary report suggests that C8α mRNA is present in normal amounts in fibroblasts from deficient individuals (87). This finding underscores the fact that the role of C8γ in the function of C8α-γ remains undefined and that a defect in C8γ may need to be considered as a possible basis for this deficiency. Deficiency of C8α-γ is associated with less C8β in serum than occurs in normal individuals (356). At present, it is unclear whether the reduction in C8β reflects the tight 5′-3′ linkage between the C8α and C8β loci (190) or stems from a posttranslational requirement of C8α-γ for either C8β secretion or protection from intracellular proteolysis.

Deficiencies of Membrane Complement Proteins

Leukocyte adhesion deficiency (CD11–CD18 deficiency or CR3 deficiency). Classically, patients with leukocyte adhesion deficiency present with prolonged or recurrent staphylococcal and pseudomonas infections beginning in infancy, often in the perinatal period. Severely affected individuals frequently have a history of delayed separation of the umbilical cord and may develop omphalitis. Infections involving the soft tissues, mucosal surfaces, and intestinal tract are common and may cause progressive necrosis of extensive areas. Acute gingivitis is a universal manifestation of individuals reaching childhood. Although survival to adulthood has been described, almost half the affected individuals die before the age of 2 years. In addition to these unique clinical manifestations, the disorder is further characterized by a persistent leukocytosis. Cell counts typically range from 2 to 20 times normal and remain elevated even in the absence of infection, probably because of impaired cellular margination and egress from the vascular tree (7, 8).

The physiologic basis for this deficiency lies in the absence of CR3, p150-95, and lymphocyte-function-associated antigen (LFA-1) from the surface of neutrophils and monocytes and of LFA-1 on the surface of lymphocytes. These transmembrane glycoproteins are members of the integrin or leukocyte cell adhesion molecule family of related molecules (169) that play a critical role in the adhesion of phagocytic cells and lymphocytes to endothelial cells and migration through the soft tissues. Consequently, neutrophil adhesion, chemotaxis, iC3b-dependent opsonophagocytosis, and the resultant respiratory burst are impaired in these patients. Clinically, the disorder is inherited in an autosomal recessive fashion and both severe and moderate phenotypes are recognized. The phenotypic expression of this disorder correlates with the extent of CR3 expression on the surface of phagocytic cells. Severely affected individuals express <0.3% and moderately affected individuals express 2 to 6% of the quantity of CR3 present in healthy people. Surface expression of these proteins is also inversely correlated with survival (7, 8, 169, 340).

Integrins are heterodimers sharing identical β chains but possessing distinct α chains (169, 340). The β chain (CD18) and the α chain (CD11) are encoded by separate genes. Phagocytic cells from individuals with this disorder lack or have markedly reduced quantities of both β and α chains on their surface (340). However, the α chain but not the β chain is present in normal amounts within the cell, indicating that the defect lies in the synthesis of the β chain and that assembly of the α,β heterodimer is required for transport of the α chain to the cell surface. This conclusion has been confirmed by transfection of affected Epstein-Barr virus-transformed B lymphocytes with β-subunit cDNA, resulting in the normal expression of LFA-1 on the surface of these cells and correction of the functional defect (156).

The molecular basis for this disorder is heterogeneous (197). A spectrum of mutations affecting the β gene has been identified. These range from the failure to produce mRNA in some individuals with severe disease to the production of specific mRNA that is reduced in quantity, altered in size, or apparently normal. Aberrant splicing has been described in individuals with abnormally sized β-chain mRNA (198), whereas point mutations have been defined in affected individuals with mRNA of an appropriate size (13). These defects affect widely separated but highly conserved portions of the primary structure of the mature β chain. In each case, association of the β subunit with the α subunit fails to occur. Thus, these mutations serve to define structural domains in the β chain that are important for its association with the α chain (13, 198).

PNH. Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder affecting adults in the third to fifth decade of life. Hemolytic anemia, occurring either as a chronic process or in episodic fashion, is the cardinal manifestation of this disease. Major thrombotic events and a mildly increased susceptibility to infection further characterize this disorder. Although infection is not a prominent feature of PNH, consideration of this entity is important because it provides a powerful testimony to the importance of specific membrane-bound proteins in regulating complement activation and deposition on host cells (305, 308).

The clinical basis for this disorder is the heightened susceptibility of affected individuals' erythrocytes to complement-mediated lysis. The peripheral blood of these individuals contains various proportions of three populations of erythrocytes. PNH type 1 cells are normal, whereas type 2 and 3 cells exhibit a 3- to 6- and a 15- to 25-fold increase, respectively, in sensitivity to complement-mediated lysis. The severity of the clinical picture correlates best with the number of type 3 cells present (306).

The physiologic basis for the increased susceptibility of affected erythrocytes to complement-dependent lysis is the absence or reduction of a number of surface glycoproteins, including DAF, CD59, and C8bp, that modulate complement deposition on host cells (149, 161, 247, 264). The variability in sensitivity to complement-mediated lysis reflects both the number of missing proteins and the extent of their reduction (162). For example, normal erythrocytes behave like PNH type 2 cells if they are treated with antibody to DAF. Conversely, if DAF is inserted in the membranes of type 2 cells, they behave like normal cells. In contrast, insertion of DAF into the membranes of PNH type 3 cells has no effect on the increased susceptibility of these cells to complement-mediated lysis (226). Thus, although PNH type 2 and 3 cells both lack DAF, the greatly increased sensitivity to comple-

ment-mediated lysis of the latter cells is due to the absence of CD59 and C8bp, which modulate the activity of the membrane attack complex (149, 161, 162, 226, 306).

That the absence of DAF is not the sole physiologic explanation for this disorder is demonstrated further by studies of the susceptibility to lysis of erythrocytes bearing the rare Inab phenotype. These cells lack the Cromer related blood group antigens that are borne on the DAF molecule but possess normal amounts of CD59 and C8bp. Individuals with this phenotype do not experience hemolytic anemia, and their erythrocytes are not inordinately sensitive to complement-mediated lysis in the laboratory (230, 360, 361).

The molecular basis for PNH is unknown. However, that these complement regulatory proteins are present in normal quantities on endothelial cells indicates that PNH is a clonal disorder arising from a somatic mutation in the pluripotential stem cells that give rise to erythrocytes, platelets, and neutrophils. The complement regulatory proteins missing from the bone marrow-derived cells have in common the fact that they are linked to the cell membrane through their carboxy terminus via a phosphatidylinositol linkage (227, 307). This linkage may be an important aspect of their function, because it confers a high degree of lateral mobility on these proteins. This feature may be important for the expression of their regulatory effects on nascent complement complexes freshly deposited on the cell membrane (307). Nevertheless, the basic defect in this disorder may not lie in the assembly of the phosphatidylinositol linkage, because these proteins appear to be present on precursor bone marrow cells and are lost during maturation (315, 368). In addition, proteins other than those bearing the phosphatidylinositol linkage are also absent from PNH cells (242). Last, the pattern of glycosphingolipids present in erythrocyte cell membranes is altered in PNH cells, the biggest difference being the loss of a sialosylparagloboside. Thus, both glycoproteins and glycolipids are affected in this disorder, which suggests that the basic defect involves altered metabolism of membrane glycoconjugates (242).

INFECTION IN COMPLEMENT DEFICIENCY STATES

Epidemiology

Overall, about half (267 of 553) of all reported complement-deficient individuals experience systemic infection. The bulk of these infections (219 of 267 [82%]) are caused by *Neisseria* species. However, interesting differences exist in the frequency of systemic infection, the median age at time of first infection, the most common infecting organism, and the frequency of recurrent infection with the same organism, depending on the segment of the complement cascade affected by the deficiency (Tables 5 and 6). These differences presumably reflect the functional abnormalities that result from the deficiencies, as discussed above. Thus, approximately 20% of individuals with a deficiency of one of the early components of the classical pathway experience systemic infection. Infections typically occur at a median age of 2 years, and over half of these are caused by *S. pneumoniae*. Although recurrent bouts of otitis and sinusitis occur in 40 to 50% of individuals with these deficiencies, systemic infection caused by the same organism is unusual (6.3%). By comparison, 70% of individuals with primary or secondary C3 deficiency acquire systemic disease. Like patients with C1, C4, or C2 deficiency, these individuals experience infection early in life (median age of first infection, 2 years), and their infections are caused predominantly by *Neisseria* species (55%) and *S. pneumoniae* (39%). Unlike persons with defects in one of the early-complement components, virtually all C3-deficient individuals with systemic infection experience recurrent disease with the same organism. In contrast, 50 to 60% of individuals with properdin, factor D, or terminal-component deficiencies sustain bacterial infections. Infection typically occurs in the mid-teenage years and is caused almost solely by *N. meningitidis*. Recurrent disease is uncommon (3.5%) in properdin deficiency but common (50%) in terminal-component defects.

TABLE 6. Comparison of meningococcal disease in normal, late-complement component (LCCD), and properdin-deficient individuals[a]

Parameter	Normal	LCCD	Properdin deficient[b]
No. of homozygotes		267	54–70
No. with meningococcal disease		151	25–37
Frequency of infection (%)	0.0072	57	46–53
Male/female ratio	1.3:1	2.2:1	21:0–37:1
Median age (yr), first episode	3	17	14–11.5
Recurrence rate (%)	0.34	41	2–1.4
Relapse rate (%)	0.6	7.6	0
Mortality/100 episodes (%)	19	1.5	12–51.4
Infecting serogroup			
No. of isolates	3,184	67	16
% B	50	19.4	18.7
% Y	4.4	32.8	37.5

[a] Reproduced and modified from Densen (78) with the permission of the publisher.

[b] When a range is given, the first number refers to documented cases and the second number refers to documented plus probable and possible cases.

Meningococcal Disease in Complement Deficiency

Pathogenesis of meningococcal disease. Substantial evidence supports a unique role for the complement system in the prevention of meningococcal disease (77, 140, 303). First, complement-dependent serum bactericidal activity is inversely correlated with the age-related incidence of disease. Second, bactericidal activity is present in 6% of susceptible individuals and 82% of controls. Third, of exposed susceptible individuals, as defined by the absence of serum bactericidal activity, 46% developed disease, but none of the nonexposed susceptible and nonsusceptible individuals developed disease. Fourth, meningococcal disease is the single most common infection sustained by complement-deficient individuals. Fifth, recurrent meningococcal infection is a hallmark of individuals with terminal-complement-component deficiencies whose sera lack complement-dependent bactericidal activity. Sixth, the efficacy of meningococcal vaccines correlates with the induction and persistence of complement-dependent bactericidal antibody. Seventh, the presence of IgA blocking antibody that prevents IgM- and IgG-mediated, complement-dependent bactericidal activity correlates with susceptibility to meningococcal disease in adults (140).

Evidence also supports a role for complement in both the pathogenesis of clinical manifestations and the outcome of meningococcal infection. Clinical studies have demonstrated a direct correlation between the presence of capsular polysaccharide in serum and the degree of complement consumption (21, 137, 159, 392). Recent detailed clinical investigations have also indicated a strong correlation be-

tween complement activation, as measured by the presence of both fluid-phase C3 activation products and terminal-complement-component complexes, and the concentration of meningococcal lipopolysaccharide in the plasma of infected individuals (44). Moreover, continued complement activation was observed in a number of patients with fatal meningococcemia. However, it is unclear from these studies whether meningococcal lipopolysaccharide is driving complement consumption or whether complement activation and insertion of the membrane attack complex in the outer membrane of invading meningococci are driving lipopolysaccharide release (84, 354, 380, 381). Regardless of which event occurs first, the concentration of circulating endotoxin is directly correlated with activation of the fibrinolytic system, development of disseminated intravascular coagulopathy, multiple organ system failure, septic shock, and death (42, 43, 45, 104). Moreover, the concentration of circulating meningococcal lipopolysaccharide is correlated further with the concentration of circulating cytokines that are presumably released from monocytes and macrophages following stimulation by the circulating endotoxin (130, 369–371). The concentrations of tumor necrosis factor alpha and interleukins have been directly associated with a fatal outcome in meningococcal disease. Tumor necrosis factor alpha seems particularly important in this regard (130, 370), and the sequential appearance of tumor necrosis factor alpha, interleukin-1 and interleukin-6 in the plasma of infected individuals provides support for a primary role for tumor necrosis factor in determining both the clinical outcome and the secretion of other cytokines (369). These data are also consistent with important interactive effects among lipopolysaccharide, cytokines, the inflammatory response, and outcome.

In vitro studies have demonstrated that both group A and group B meningococci activate the classical pathway in normal serum (90). In contrast, only group A strains activate the alternative pathway, a finding attributed to the fact that the group B capsular polysaccharide is a homopolymer of sialic acid, which is known to inhibit alternative-pathway activation. This finding is consistent with the hypothesis that the absence of specific antibody to initiate classical-pathway activation coupled with capsular sialic acid-mediated inhibition of alternative-pathway activity may contribute to the prevalence of group B meningococcal disease in young children. Serogroup Y and W135 meningococci possess capsular polysaccharides containing substituted sialic acid residues, suggesting that an examination of the effects of these defined variants on alternative-pathway activity might shed further light on the mechanism by which sialic acid inhibits this activity.

Meningococcal disease in late-complement-component deficiency states. That 75 to 85% of the identified systemic bacterial infections occurring in individuals with complement deficiency are caused by meningococci not only confirms the importance of the complement cascade in protection from meningococcal disease but also suggests that important insights regarding the pathogenesis of infection may be revealed by the study of meningococcal disease in complement-deficient individuals. Consistent with this hypothesis are a number of features that appear to distinguish meningococcal disease in normal persons from that in persons lacking the late-complement components (Table 6). These features, identified originally by Ross and Densen (303), have been confirmed in subsequent studies. The frequency of meningococcal disease in unselected complement-deficient individuals is not known. However, these features are unlikely to be a result solely of ascertainment bias, because each of them has been borne out by an analysis of complement-deficient families following exclusion of the proband.

These features include, first, that the risk of infection in the deficient individuals is 7,000- to 10,000-fold greater than in normal individuals, and approximately 50 to 60% of the deficient persons will experience at least one episode of meningococcal disease.

Second, 40 to 50% of infected deficient individuals will experience an additional episode of infection: a recurrence rate that is approximately 100 to 150 times greater than that observed in the normal population. Recurrent disease occurs both in the form of new infection (more than 1 month following the initial episode) and as relapse of an initial infection (infection with the same serogroup occurring less than 1 month after the initial infection). This relapse rate is approximately 10-fold greater than that in the normal population and suggests that, in the absence of effective complement-dependent bactericidal activity, meningococci may be sequestered intracellularly where they may be relatively protected from phagocytic killing mechanisms and antibiotics. This hypothesis implies that the terminal components contribute to intracellular killing, and it is supported by recent reports (221, 357).

Third, the initial episode of meningococcal disease occurs at a median age of 17 years in persons lacking one of the late-complement components but at 3 years of age in the general population. Thus, most deficient individuals pass through the time of life when the deficiency might be expected to increase maximally their susceptibility to meningococcal disease without evincing evidence of that susceptibility. This paradox is only partially explained by the fact that deficient individuals are at risk of infection for a lifetime, whereas normal individuals are generally at risk only early in life (303). This observation suggests that unidentified factors may enhance the susceptibility of deficient individuals to infection later in life.

Fourth, despite the marked increase in susceptibility to meningococcal infection, there is a striking reduction in the mortality of this disease in deficient individuals, in terms of both the mortality rate per initial infection and the mortality rate per hundred episodes of infection. This observation suggests that the correlation between mortality in meningococcal disease and exuberant complement activation is dependent in part on assembly of the membrane attack complex. Assembly of this complex might be linked to outcome in meningococcal disease either via meningococcal outer membrane disruption, endotoxin release, and resultant endotoxic shock, as discussed above (84), or via an injurious effect of the complex on bystander host cells. Both of these postulated mechanisms would be blocked in complement-deficient individuals.

Because of their lower mortality, it has been suggested that individuals lacking late-complement components have milder disease. This suggestion is difficult to support with the data reported, which frequently are not sufficient for assessing the severity of disease. However, disseminated intravascular coagulopathy and hypotension are well documented in individual cases. Nevertheless, in a preliminary report, Beloborodov and Platonov (22) used a grading system based on clinical variables to compare the severity of meningococcal disease in 12 normal patients with that in 17 deficient patients with 28 episodes of infection. Their data support the existence of milder disease in the deficient patients and also demonstrate less extensive complement consumption via the

classical and alternative pathways in these individuals. Meningococcemia alone was uncommon in deficient patients, occurring in only 10% of the episodes. This finding compares favorably with that (15% occurrence) culled from the literature (303) and this review (Table 3). This result contrasts with the reported frequency of meningococcemia in the general population (21 to 31%) and tends to refute the notion that chronic meningococcemia is more common in deficient patients. Rather, meningitis, which has a lower case fatality rate than meningococcemia (10), may be more common in deficient than in normal individuals.

Fifth, disease caused by uncommon meningococcal serogroups appears more common in complement-deficient than in normal individuals (303). This conclusion is further supported by the observation that the prevalence of late-complement-component deficiencies is increased among individuals with meningococcal disease caused by these uncommon serogroups (116). The basis for the altered distribution of meningococcal serogroups in complement-deficient individuals may relate in part to the propensity of these organisms to cause disease in older individuals (9). In addition, although group Y organisms are more susceptible to complement-dependent killing, they exhibit a greater opsonophagocytic requirement for elimination by phagocytic cells than do group B isolates (304). However, it should be noted that the absence of complement-dependent bactericidal activity in individuals with late-complement-component deficiencies does not automatically provide access to the bloodstream by particularly serum-sensitive organisms, since meningococci isolated from complement-deficient individuals do not differ significantly in their sensitivity to killing by normal human serum from those isolated from complement-sufficient individuals (302). This conclusion is supported further by the finding that most, although not all (76), of the gonococci isolated from complement-deficient individuals exhibit the same auxotroph requirements and resistance to serum-mediated killing reported for gonococci causing disseminated gonococcal infection in normal individuals (302). These observations suggest that serum-sensitive organisms normally present on mucosal surfaces lack determinants in addition to serum resistance (e.g., tissue invasion factors) that contribute to the pathogenesis of infection.

Meningococcal disease in properdin deficiency. Similar to the situation with late-complement-component deficiencies (Table 6), meningococcal disease occurs in slightly more than half of properdin-deficient individuals, tends to occur at an older age than in the general population, and is frequently caused by meningococcal serogroups that are relatively uncommon in the general population. In contrast to its occurrence in individuals with terminal-complement-component deficiencies, recurrent meningococcal disease is uncommon in properdin-deficient individuals, perhaps in part because of the higher fatality rate of these infections as well as the ability of these individuals to activate the classical pathway normally once they have developed specific antibody (88, 335, 336). However, as pointed out by Sjöholm (329, 330), neither of these factors is likely to provide the entire explanation for this phenomenon, because the sole individual with factor D deficiency and meningococcal infection experienced recurrent disease and survived. Since properdin is required only for maximal efficiency of alternative-pathway activation (110, 310), this observation raises the possibility that specific antibody, which acts synergistically with properdin (335), may help to ameliorate the deficiency by facilitating the activity of the unstabilized alternative-pathway C3 convertase. If so, it is unclear why antibody-dependent defense mediated through the alternative pathway should be of decisive importance in the presence of a fully functional classical pathway (329, 330). Moreover, such an effect, if present, would not account for the apparent discrepancy between the case fatality rates of meningococcal disease in people with properdin and factor D deficiencies, although too few cases with the latter deficiency have been reported to establish that a difference truly exists. An additional paradox is the apparent requirement for alternative-pathway activity in the host defense against meningococci, which, except for serogroup A, possess sialic acid or substituted sialic acid polysaccharide capsules that activate the alternative pathway poorly or not at all (90). Further studies are needed to provide a physiologic basis for these apparent discrepancies. Such investigations may uncover previously unsuspected interactions between individual complement proteins as well as between the two activation pathways.

IMMUNE RESPONSE TO MENINGOCOCCAL DISEASE

Normal Individuals

The classic studies by Goldschneider and colleagues (132, 133) on human immunity to meningococci demonstrated an inverse association between serum bactericidal activity and the age-specific incidence of meningococcal disease. Bactericidal activity was dependent on the presence of specific IgG that appeared naturally with age as well as following meningococcal disease. The development of natural immunity followed acquisition of carrier strains of nontypeable "meningococci," many of which were shown to ferment lactose in addition to glucose and maltose and hence to fit current criteria for *N. lactamica*. Subsequent studies demonstrated that vaccination with purified capsular polysaccharide and the resultant antibody formation afforded protection from disease caused by meningococcal serogroups represented in the vaccine. These antibodies enhanced complement-dependent, serogroup-specific, opsonophagocytic and serum bactericidal activities. However, despite the presence of serum bactericidal activity, adult sera contained only low concentrations of anticapsular antibodies. This observation coupled with the fact that recurrent disease in normal individuals was exceedingly uncommon despite the existence of multiple meningococcal serogroups led to the recognition that natural immunity is a consequence of the development of bactericidal IgG specific for cross-reactive subcapsular antigens (132, 133, 140, 142, 196, 303).

Subcapsular antigens include outer membrane proteins (classes I to V, as well as other nonclass proteins, e.g., iron-regulated proteins), lipopolysaccharides, and the H.8 determinant. Many of these outer membrane antigens demonstrate both inter- and intrastrain variability. This variability accounts for the serotype-specific responses observed following natural disease. Recognition of these antigens led to the development of both outer membrane protein- and lipopolysaccharide-based serotyping systems. Several commonly expressed and antigenically conserved neisserial antigens have also been described, including a 37-kDa iron-regulated outer membrane protein, a 70-kDa outer membrane protein, the H.8 antigen, the class IV (OmpA-related) outer membrane protein, IgA protease, and a high-molecular-weight outer membrane protein complex (11, 29, 218). Antibodies to many of these antigens are present in normal adult sera, and appropriate increases in concentrations have followed natural infection (11, 29, 105, 188, 218, 220, 351).

However, the few studies that have examined the immune responses of many patients with meningococcal disease to the entire repertoire of outer membrane antigens have yielded somewhat different results (11, 218, 351). Even fewer studies have attempted to correlate immune responses to outer membrane antigens with functional activity in in vitro assays thought to reflect natural immunity (29, 142). Limited trials of a vaccine employing well-defined outer membrane protein antigens have not been successful in preventing meningococcal disease (33). In contrast, the administration of a vaccine composed of a meningococcal outer membrane preparation is reported to have controlled a meningococcal epidemic in Cuba (51).

In summary, natural immunity appears to reflect the development of antibody to subcapsular, cross-reactive meningococcal antigens. The nature of these antigens has proved elusive, and it is unclear whether protection reflects the response to a single antigen or the conglomerate response to multiple antigens. Antibody response to at least some subcapsular antigens is associated with the development of bactericidal activity, although the role of this antibody in opsonophagocytosis is less clearly defined.

Complement-Deficient Individuals

The immune responses to meningococcal disease of persons lacking one of the late-complement components have been assumed to be similar to those of normal persons. Features of meningococcal disease in these individuals (Table 6) that challenge this assumption include, first, that meningococcal disease in deficient persons is not most common when maternal antibodies are low. Only 11 (7.5%) of 151 deficient individuals with meningococcal disease reported in the literature were <5 years of age, whereas 53% of the persons with this disease in the general population are in this age group (10). This finding is unlikely to be due solely to ascertainment bias, because the relationship is also apparent in individual families where ascertainment is complete. In addition, in our prospective study (85) of the frequency of these disorders in patients with meningococcal disease, no cases were detected in individuals <15 years of age. Second, both natural antibody and that occurring after meningococcal infection might be expected to afford a degree of protection from infection or recurrent disease in late-component-deficient persons, as it does in the normal population. As pointed out by Beloborodov and Platonov (22), this expectation can be addressed in part by examining the proportion of complement-deficient individuals with 0, 1, 2, . . . n episodes of meningococcal disease (Fig. 5). In this formulation, the null hypothesis states that the risk of meningococcal disease is independent of prior infection; that is, prior infection conveys no immunity to subsequent disease. If this hypothesis is correct, then the risk of developing one infection is the same as developing a second infection; that is, the risk of each infection is constant. Since the risk (chance of infection) applies to populations of individuals, the number of individuals experiencing infections can be determined by multiplying the number of people at risk by the risk. Moreover, if the risk of acquiring one infection is x, then the risk of experiencing two infections is x times x or x^2 and that of experiencing three infections is x^3; that is, the relationship is exponential. Thus, if the null hypothesis is correct, then a plot of the logarithm of the number of individuals with various episodes of infections versus the number of episodes should yield a straight line, and the antilog of the slope of this line represents the risk of a single infection.

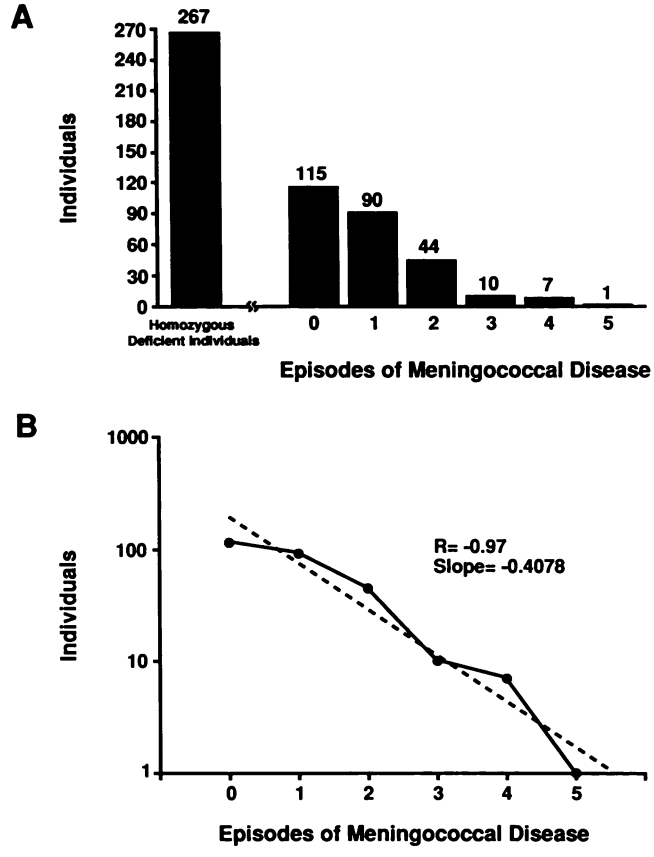

FIG. 5. Effect of meningococcal disease on susceptibility to subsequent infection in individuals lacking one of the late-complement components. (A) Depiction of data culled from the literature (Table 3 and reference 303). The number above a given histogram represents the number of individuals experiencing only the number of episodes of meningococcal disease shown below the histogram. (B) Logarithmic transformation (solid line) of the observed data in panel A and its comparison to the best-fit straight line (dotted line) obtained by least-squares analysis of the observed data. The coefficient of correlation (R) is high, indicating a good fit of the data. This result is consistent with the interpretation that the risk of each episode of meningococcal disease is independent of prior episodes of infection and that this risk is 39.1% (see text).

Application of this approach to data obtained from the literature (Fig. 5A) generates a nearly straight line ($r = -0.97$) with a slope of -0.4078 (Fig. 5B). This result is consistent with the hypothesis that prior meningococcal disease does not convey any protection from subsequent infection in individuals lacking one of the late-complement components and that the risk of each infection is 39.1%. Although these data are limited by the absence of information regarding the length of follow-up and whether or not affected patients were vaccinated or given antibiotic prophylaxis, it is apparent that prior disease does not dramatically reduce the risk of subsequent meningococcal infection in these individuals.

This observation is consistent with several possible interpretations, including (i) the absence of an immune response to meningococci, (ii) complement-dependent bactericidal activity being absolutely required for protection from meningococcal disease and the intact complement-dependent opsonophagocytic mechanisms in these individuals not con-

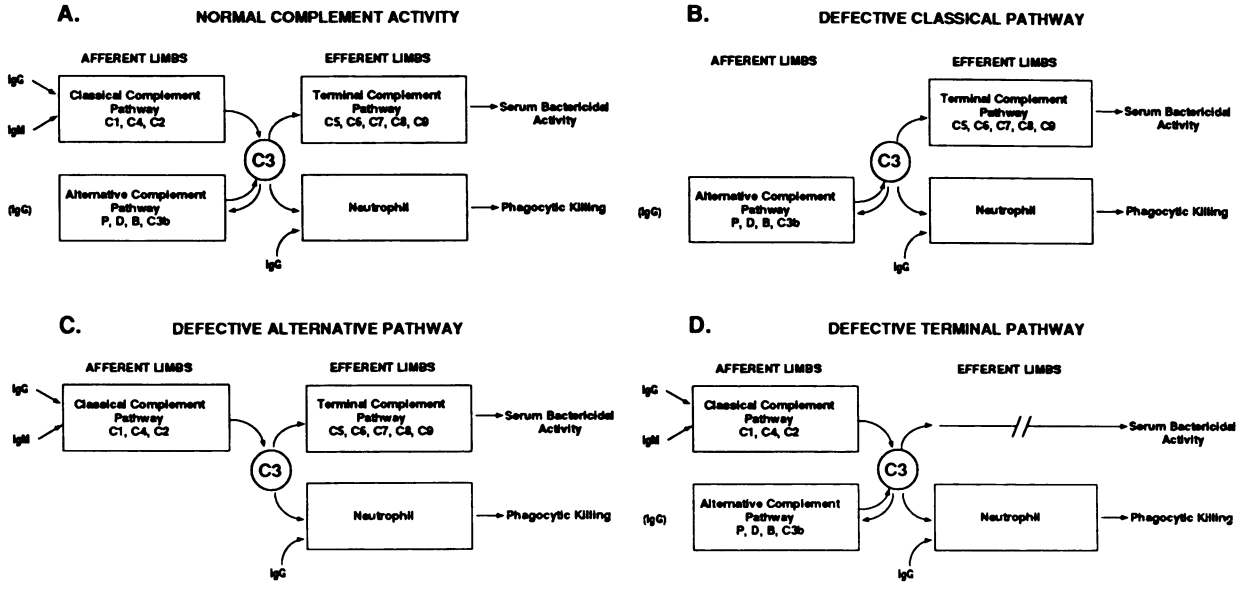

FIG. 6. Rationale for vaccination of complement-deficient persons. Recruitment of enhanced complement-mediated host defense by specific IgG and IgM in normal individuals (A) is contrasted with that in individuals with a defect in the classical (B)-, alternative (C)-, or terminal (D)-complement pathway. Individuals with C3 deficiency are unable to recruit any complement-dependent functions, but vaccination may enhance complement-independent, antibody-mediated phagocytic killing. Modified and reproduced from Ross et al. (304) with the permission of the publisher.

tributing to host defense against meningococci, and (iii) the immune response to meningococci in some way facilitating recurrent infection.

As a consequence of these considerations, we have examined the immune responses to meningococcal disease of persons lacking one of the late-complement components (86, 89). Our studies and those reported recently by Potter et al. (279) indicate that an impaired antibody response to meningococcal antigens is not the basis for enhanced susceptibility to meningococcal infection. In fact, deficient individuals respond to a single meningococcal infection with the production of as much as 10-fold-greater amounts of antibody than that of complement-sufficient individuals of comparable age infected with the same serogroup of meningococcus. This response is directed at a broad array of subcapsular antigens, including both outer membrane proteins and lipopolysaccharide. These antibodies are associated with enhanced bactericidal activity when added to an intact complement source. A substantial proportion of the bactericidal antibody appears directed at lipopolysaccharide antigens. Preliminary data also suggest that the IgG subclass responses to meningococcal antigens may differ in complement-deficient individuals (89). Factors that may contribute to this enhanced response in deficient individuals include (i) a greater organism load during infection, (ii) the relative lack of outer membrane disruption as a consequence of the inability to form the membrane attack complex (77, 354, 380, 381), (iii) prolonged survival of meningococci within phagocytic cells (221, 357), (iv) altered antigen presentation, and (v) altered display of C3 cleavage fragments on the organism surface (225), which might modulate the immune response to these antigens via the respective complement receptors on appropriate cells. In contrast to the enhanced responsiveness of these individuals to subcapsular meningococcal antigens, the immune response to capsular polysaccharides following infection does not appear to differ from that observed in normal individuals (86, 89). These observations suggest that, although the immune response to meningococcal antigens responsible for natural immunity is enhanced in deficient individuals, recurrent disease may occur because expression of the protective potential of these antibodies requires complement-dependent bactericidal activity. This requirement coupled with the relative absence of antibody to meningococcal capsular polysaccharide that may express its protective potential through both complement-dependent opsonophagocytic and bactericidal mechanisms could account for the susceptibility of deficient individuals to recurrent infection and the apparent lack of protection provided by prior disease. Precedent for this scenario exists in pneumococci, for which capsular and cell wall antibodies both promote C3 deposition at their respective locations but only the former promotes opsonophagocytic clearance of the organism (47).

Prevention of Infection in Complement-Deficient Individuals

Vaccination. The availability of the tetravalent meningococcal capsular polysaccharide vaccine coupled with the hypothesis presented above provides a rationale (Fig. 6) for prevention of meningococcal disease, not only in individuals with late-complement-component deficiencies but also in persons with defects affecting the classical and alternative pathways. Vaccination of normal individuals promotes complement activation via both pathways, with resultant C3 deposition at both the capsular and subcapsular locations. Antibody bound to the capsule alone or in conjunction with C3 should promote elimination of the organism by phagocytic cells within the tissues or reticuloendothelial system. C3 deposited at subcapsular locations should promote assembly and insertion of the membrane attack complex, with resultant disruption of meningococcal membranes and cell death (304).

Providing anticapsular antibody to individuals with a

defect in the classical pathway should facilitate use of the alternative pathway and the ultimate expression of both opsonophagocytic and direct bactericidal activities. In preliminary experiments we have found that approximately four- to eightfold-greater amounts of anticapsular antibody are required in C2-deficient serum than in normal serum to produce a degree of meningococcal killing comparable to that in normal serum. In addition, high levels of antibody appear to facilitate use of the classical pathway in an alternative-pathway-dependent manner (346).

The utility of vaccination in bypassing these genetic defects and preventing the consequences of meningococcal infection is best documented by in vitro studies with sera from properdin-deficient individuals. The responses of these individuals to the meningococcal vaccine are associated with efficient utilization of the classical pathway and the development of both opsonophagocytic and bactericidal activities (88, 335, 336). The association of killing in these in vitro assays with protective immunity in vivo and the high mortality from meningococcal infection in these patients makes vaccination of these individuals mandatory.

Although vaccination of individuals with primary C3 deficiency would not be expected to improve complement-dependent host defense mechanisms, anticapsular antibody may facilitate opsonophagocytic clearance of these organisms in a non-complement-dependent manner (304). The frequency of infection caused by other encapsulated bacteria in these and other patients with C1, C4, or C2 deficiency indicates that they should also be vaccinated with the pneumococcal and *H. influenzae* vaccines.

As discussed above, the presence of anticapsular antibody in individuals deficient in one of the late-complement components should facilitate complement utilization and C3 deposition on the capsular surface and in subcapsular locations via both complement pathways. In conjunction with antibody, C3 deposited on the capsular surface should facilitate opsonophagocytic clearance of the organism even in the absence of its ability to promote membrane attack complex formation. Even though these individuals do not produce enhanced quantities of anticapsular antibody in response to meningococcal disease, they respond to the meningococcal capsular polysaccharide vaccine as well as normal individuals (86, 89).

Antibiotic prophylaxis. A limitation of the attempts to prevent meningococcal infection in complement-deficient individuals by immunoprophylaxis is the absence of group B capsular polysaccharide in the meningococcal vaccine and the failure of humans to generate a significant humoral response to this sialic acid homopolymer. Despite the relatively greater frequency of meningococcal infection caused by unusual serogroups in complement-deficient compared with normal individuals (116, 203), group B meningococcal disease still accounts for a significant proportion of meningococcal infections in deficient persons (Table 6) (303). Consequently, Potter et al. (279) used monthly injections of benzathine penicillin G as prophylaxis for recurrent meningococcal disease. Complement-deficient patients receiving prophylaxis during a 2- to 4-year period of observation experienced significantly fewer episodes of neisserial infection than deficient individuals not receiving prophylaxis. Antibiotic prophylaxis thus represents a successful therapeutic strategy. However, it is unclear whether prophylaxis should be lifelong or whether the development of antibiotic resistance by meningococci will limit the efficacy of this approach.

Recommendations. Given the high prevalence of meningococcal infection in complement-deficient individuals and its propensity to cause an untoward outcome in at least some of these individuals, a prudent recommendation based on the currently available data is to administer the tetravalent meningococcal vaccine to all such individuals. We disagree with the concern raised by Potter et al. (279) that vaccination may give rise to antibodies detrimental to antineisserial host defense mechanisms, because the vaccine is clearly efficacious in preventing disease in large populations of normal individuals. Antibiotic prophylaxis might reasonably be used in addition to vaccination when group B meningococcal disease is epidemic or when recurrent episodes of disease occur during a short period of time (80). The pneumococcal and conjugated *H. influenzae* vaccines should be administered to individuals with inherited defects involving the components of the early classical pathway or C3. These vaccines should be administered as early in life as possible. However, impaired responsiveness of children under 2 years of age to polysaccharide antigens may necessitate reimmunization against pneumococci and meningococci between ages 5 and 10. The established safety of the pneumococcal and conjugated *H. influenzae* vaccines, their low cost, and their demonstrated utility suggest that they may be warranted for properdin-deficient and late-complement-deficient individuals despite the relative infrequency of such infections in these persons.

When deficient individuals with presumed or documented infection are admitted to the hospital, appropriate antibiotics should be initiated promptly and continued for a complete course of therapy. The administration of fresh frozen plasma as a source of missing complement components has been used in an uncontrolled manner as adjunct therapy in a few deficient individuals with severe infection or uncontrolled collagen vascular disease and appears to have been beneficial (18, 284, 344). Development of antibody to the missing complement component following infusion is likely to limit the usefulness of this approach as a routine measure.

To conclude, the study of complement-deficient individuals has provided a wealth of pathophysiologic insight into collagen vascular disorders, host defense mechanisms, meningococcal disease, and the molecular bases for these genetic disorders. These important insights should encourage all physicians and investigators to continue making clinical observations, pursuing them in the laboratory, and reporting them in the literature.

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