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Interaction of Complement with *Neisseria meningitidis* and *Neisseria gonorrhoeae*

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The importance of the complement system in host defense against systemic infection caused by neisseriae is emphasized by a number of clinical observations documenting the importance of antibody-dependent, complement-mediated serum bactericidal activity in protection from systemic meningococcal disease (17) and the well-recognized association between the resistance of gonococci to complement-dependent serum bactericidal activity and the development of disseminated gonococcal infection (46, 49). Moreover, individuals with inherited complement deficiencies have a markedly increased risk (ca. 6,000-fold) of acquiring systemic neisserial infections and are subject to recurrent episodes of systemic meningococcal and gonococcal infections (37, 43). The purpose of this report is to review the complement cascade with particular reference to its importance in host defense against bacterial diseases, to compare and contrast neisserial disease in complement-deficient and complement-sufficient individuals, to examine the molecular and functional basis for the particular importance of complement in host defense against these infections, and to examine the immunologic basis for prevention of neisserial disease in complement-deficient individuals.

THE COMPLEMENT CASCADE

Activation of complement by either the classical or the alternative pathway results in the formation of C3 convertases on the bacterial surface (13). These convertases cleave C3, initiate the alternative-pathway amplification loop, and participate in the formation of the C5 convertases. The C5 convertases in turn cleave C5, thereby initiating assembly of the membrane attack complex and its insertion in the membranes of susceptible bacteria (Fig. 1).

The reactions leading to the formation of the classical pathway C3 convertase, C4b2a, are initiated upon C1q binding to immunoglobulin M (IgM) or IgG during recognition of antigen by these antibodies. In this role, antibody serves to promote complement activation in a kinetically efficient manner and to direct its deposition to specific sites on the bacterial surface (15). The classical pathway can also be activated by the direct binding of C1q to certain bacterial substrates, for example, the lipid A moiety of endotoxin.

Alternative-pathway activation exhibits several fundamental differences from that of the classical pathway. First, antibody is not required, although it facilitates the activation process (39). Second, activation occurs continuously at a low rate which is tightly controlled by factors H and I, regulatory proteins present in plasma. Effective activation occurs when this control is subverted by the introduction of an activator surface (e.g., a bacterium), on which the binding of factor B to C3b is favored over the binding of the regulatory protein, factor H (13). Third, a component of the activation process, C3b, is also a product of activation, thereby generating a positive feedback loop (13). Consequently, C3b deposition mediated by either the alternative or the classical pathway is amplified by this loop. Amplification converts alternative-pathway activation from a kinetically inefficient to an efficient process. Fourth, in contrast to the classical pathway, in which antibody directs complement deposition to specific sites on the bacterial surface, alternative-pathway activation occurs randomly on the bacterial surface.

The C3 convertases are structurally and functionally homologous complexes which are bound covalently to the bacterial surface via ester or amide bonds (25). These linkages are formed upon rupture of an internal thiol ester bond in the α chain of both C4 and C3 during the activation of either of these molecules. Thus, the array of hydroxyl or amino groups available on the bacterial surface for the formation of ester or amide bonds with C4 or C3 is an important determinant of the outcome of the interaction between the complement system and the organism.

The central position of C3 at the convergence of the two activation pathways and at the head of the terminal complement pathway, as well as its role in initiating the alternative-pathway amplification loop, emphasizes the critical importance of this molecule and make it a logical point for regulation of complement activation. Regulation is achieved in the fluid phase by factors H and I (13) and on host cells by specific surface proteins which serve to distinguish self from nonself (1). In addition, specific chemical moieties can modulate C3 convertase function. An example of this type of control is sialic acid, a constituent of many glycoproteins present on human cells. Sialic acid enhances factor H binding to C3b approximately 100-fold compared with factor B. Hence, complement activation on the surface of these cells is effectively down-regulated, and the cell is protected from complement-mediated injury (12).

At a functional level, complement activation promotes an effective inflammatory response, participates in the elimination of immune complexes, helps to neutralize viruses, is capable of directly killing some gram-negative bacteria, plays an important role in opsonizing bacteria for ingestion and killing by phagocytic cells, and may play a role in the modulation of the immune response (Fig. 1).

NEISSERIAL DISEASE IN COMPLEMENT-DEFICIENT INDIVIDUALS

The frequency of inherited complement deficiency states in the general population is about 0.03% (16). Several studies have reported that the frequency of complement deficiencies among individuals with systemic neisserial disease ranges from 0 of 47 (<2%) to 3 of 20 (15%) (11, 38). This wide range is probably related to the ages of the patients in the studies, the relatively small number of patients studied, and a disproportionate genetic influence in relatively insular populations. The best estimate of the frequency of inherited complement deficiency states among patients with endemic neisserial disease is probably about 5 to 10%, although the

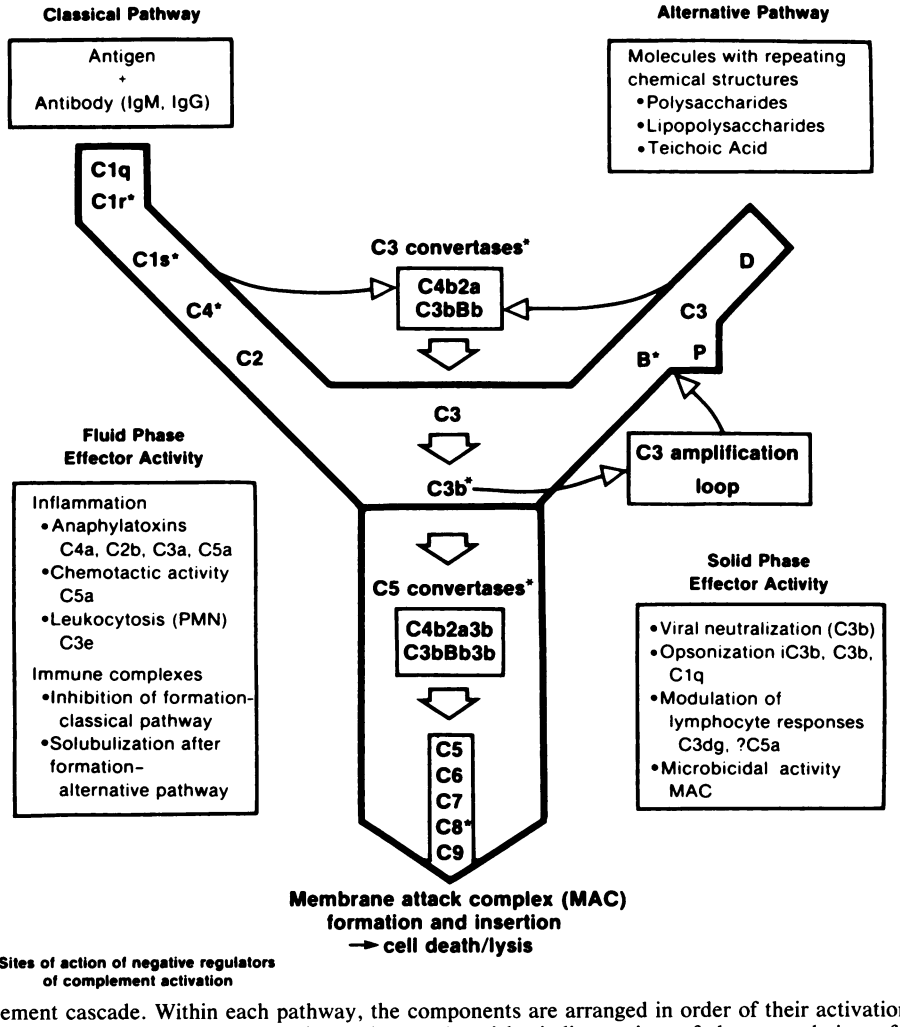

FIG. 1. The complement cascade. Within each pathway, the components are arranged in order of their activation and aligned opposite their functional and structural analog in the opposite pathway. Asterisks indicate sites of down-regulation of complement activity. Reproduced from P. Densen, *in* G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett, ed., *Principles and Practice of Infectious Diseases*, 3rd ed., Churchill Livingstone, Ltd., Edinburgh, in press, with permission of the publisher.

likelihood of a complement deficiency increases dramatically (31%) among individuals who have had more than one episode of meningococcal infection (35). Thus, complement deficiency states occur approximately 150 to 300 times more frequently among individuals with systemic neisserial disease than in the noninfected general population.

Meningococcal disease is the most common infection experienced by complement-deficient individuals (43), although the frequency of infection differs among individuals with defects affecting different segments of the complement cascade. The low frequency of infection (20%) in individuals with a deficiency of C1, C4, or C2 compared with other component deficiencies (Table 1) is attributed to the presence of an intact alternative pathway in these patients (43). In contrast, although individuals with alternative-pathway defects can activate the classical pathway normally in the presence of specific antibody, the absence of antibody, coupled with a defective alternative pathway, leads to a profound abnormality in complement activation and serum bactericidal activity. Consequently, infection in such individuals might be expected to have dire consequences, a prediction borne out by statistics for properdin-deficient individuals (Table 1) (8, 47).

With the exception of C9 deficiency, individuals lacking one of the terminal complement components exhibit a striking susceptibility to systemic neisserial infection (37, 43). The basis for this association is the inability to express complement-dependent serum bactericidal activity. Support for this conclusion stems from the observation that the serum from C9-deficient individuals can kill meningococci, albeit at a lower rate than normal, a finding consistent with the fact that C9 is not absolutely required for complement-mediated lysis of erythrocytes and presumably accounts for the relative absence of meningococcal infections in these individuals (22).

The clinical pattern of meningococcal infection differs in complement-deficient and normal individuals (Table 1). In particular, in properdin deficiency, which is an X-linked trait, meningococcal disease occurs in males, and the first episode of infection usually occurs during the teenage years. The clinical course is frequently fulminant, and there is an associated high mortality rate; presumably, this is a consequence of low levels of specific antibodies, leading to an impaired capacity to utilize the classical pathway to opsonize bacteria and develop serum bactericidal activity (8, 47). The severity of the disease in these individuals contrasts with that in individuals with late complement component deficiencies, presumably because the former are unable to

TABLE 1. Comparison of meningococcal disease in normal, late complement component-deficient, and properdin-deficient individuals[a]

Type of host	Characteristics of individuals and infections[b]								Infecting serogroup		
	No. of homozygotes	No. with meningococcal disease	Frequency of infection (%)	Male/female ratio	Median age (yr) at 1st episode	Recurrence rate (%)	Relapse rate (%)	Mortality per episode (%)	No. of isolates	% B	% Y
Normal			0.0072	1.3:1	3	0.34	0.6	19	3,184	50.2	4.4
Late complement component deficient	195	124	64	2.8:1	17	46.2	4.7–5.8	1.6–2.7[c]	48	20.8	41.7
Properdin deficient	41	14–26	34–63	14:0–25:1	14–11.5	0 (<2.4)	0 (<2.4)	43–65	11	27.3	27.3

[a] Reproduced from P. Densen, *in* G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett ed., *Principles and Practice of Infectious Diseases*, 3rd ed., Churchill Livingstone, Ltd., Edinburgh, in press, with permission of the publisher.

[b] Where a range is given, the first number refers to documented cases of meningococcal infection and the second number refers to documented plus probable and possible cases of meningococcal disease.

[c] The larger estimate includes two deaths in individuals with unconfirmed late complement component deficiency. The corresponding mortality rate per patient is 2.4 to 4.0%.

effectively recruit any C3-dependent host defense mechanisms, whereas the latter can express these activities to some degree. A striking finding in individuals with late complement component deficiencies compared with normal persons is the low mortality rate associated with meningococcal disease (43). This observation suggests that exuberant complement activation may contribute to the mortality rate in normal individuals and that this contribution is dependent in part upon the assembly of an intact membrane attack complex.

Uncommon meningococcal serogroups, in particular group Y strains, cause disease relatively more commonly among complement-deficient than normal individuals (43). This altered serogroup distribution appears to stem in part from the fact that group Y organisms are more serum sensitive but exhibit a more stringent requirement for elimination by phagocytic cells than group B strains (45). However, the neisseriae infecting complement-deficient patients are not more serum sensitive than the comparable organisms isolated from normal individuals. In particular, disseminated gonococcal infection in these individuals is caused by typical serum-resistant gonococci (42). This suggests that factors other than serum sensitivity and resistance (e.g., tissue invasiveness) contribute to the pathogenesis of neisserial infection.

MOLECULAR AND FUNCTIONAL BASIS FOR THE IMPORTANCE OF COMPLEMENT IN HOST DEFENSE AGAINST NEISSERIAE

A complete understanding of the interaction of complement with neisseriae requires the definition of the relevant antibody isotype (IgM versus IgG), its epitopic specificity, and the utilization of neisserial isolates with a defined surface composition (capsule, outer membrane protein, and lipooligosaccharide [LOS]). Ideally, such studies will examine the binding of multiple complement components as well as the functional activity of those bound components. At present, our knowledge of these variables is incomplete, so that the emerging picture of these interactions reveals a measure of complexity rather than detailed understanding. This section is an attempt to provide an understanding of these variables as they relate to complement activation by neisseriae at present.

A number of clinical studies have reported extensive complement consumption in individuals with fulminant meningococcal disease and have demonstrated a direct correlation between the presence of capsular polysaccharide in serum and the degree of complement consumption (2, 18, 24, 52). Complement consumption appears to occur via both the classical and alternative pathways, but the relatively normal C4 levels in association with the dramatic reduction in factor B concentration observed in these patients suggests that activation occurs primarily via the alternative pathway (24).

In vitro studies examining the pathway of complement activation by meningococci have confirmed that both group A and group B meningococci activate the classical pathway in normal serum (10). In contrast, only group A strains activate the alternative pathway (10, 28), a finding attributed to the fact that the group B capsular polysaccharide is a homopolymer of sialic acid (9, 29), which is known to inhibit alternative-pathway activation (12). This finding suggests 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.

From the investigational standpoint, the capsular polysaccharides of group Y and W135 meningococci contain substituted sialic acid residues. Comparison of the effects of these defined variants upon alternative-pathway activity might shed further light on the mechanism by which sialic acid inhibits this activity (9, 29). Another aspect of this phenomenon is the observation of Zollinger and Mandrell that bactericidal titers of human antibody to group B meningococci are low when a human source of complement is used in the assay but are high when rabbit serum is used as the complement source (51). The explanation for this finding has not been rigorously examined, but it is probably due to the reported species specific capacity of sialic acid to inhibit alternative-pathway activity in humans but not rabbits.

Studies examining complement activation by gonococci incubated in chelated serum indicated that both pathways were utilized but that gonococcal serum bactericidal activity was associated primarily with activation of the classical pathway (26). Subsequently, we used complement-deficient serum samples from individuals not previously infected with neisseriae to reexamine this issue and to assess the contribution of both pathways to C3 fixation on serum-sensitive and serum-resistant strains (6). We found that the kinetics of gonococcal killing were identical in normal and in properdin-deficient serum containing an intact classical pathway. In contrast, achieving an equivalent degree of gonococcal killing in C2-deficient serum, which contained only an intact alternative pathway, took approximately three to four times

as long (6). Although different serum sources were used in these experiments, isotype-specific titers for gonococcal outer membrane proteins and LOSs did not differ among the serum sources used at the concentration employed in the assay. These data convincingly confirm the findings of Ingwer et al. (26) that activation of complement by and killing of gonococci in normal serum is mediated primarily through the classical pathway.

With respect to C3 deposition, our data indicated that substantially greater amounts of C3 were bound to serum-sensitive than resistant gonococci, although the pattern of deposition with respect to the pathway of activation was the same for both isolates (6). However, more interesting was the finding that more C3 was deposited on organisms incubated in normal serum than on those incubated in properdin-deficient serum, despite identical bactericidal kinetics in the two sera. Moreover, incubation of gonococci in C2-deficient serum for a period sufficiently long to allow a degree of killing equivalent to that in normal and properdin-deficient serum resulted in even greater C3 deposition. These data indicate that maximal C3 fixation to gonococci varies among sera, even though killing does not, and suggest that C3 binding to gonococci may occur at biochemically different sites on the organism surface and that some of these sites may be pathway specific (6).

Other investigators have observed that despite the presence of a hexosamine-containing LOS epitope for bactericidal IgM, gonococci exhibit a spectrum of sensitivity to lysis by normal human serum. Moreover, absorption of normal serum with these gonococci depleted alternative-pathway activity in proportion to the degree of their serum sensitivity and to their ability to bind purified properdin. These investigators suggested that classical pathway-initiated lysis of gonococci is variously augmented by the alternative pathway as a function of the ability of a given strain to bind properdin and that the titer at which a strain is lysed reflects this alternative-pathway augmentation (21, 27). Expressed differently, the greater the serum sensitivity of a specific organism, the greater the alternative-pathway augmentation. Thus, these results appear to contradict our findings that killing of an exquisitely serum-sensitive strain could be mediated solely by the classical pathway (6). Although the basis for this discrepancy is unresolved, one possibility is that the function of properdin in the complement cascade is believed to relate to its ability to bind to C3b (34) and to stabilize the alternative-pathway convertase (14), not to any intrinsic ability of this cationic protein to bind to a negatively charged target surface per se. This belief may require further scrutiny.

Serum-sensitive and resistant gonococci have been compared with respect to the outcome of a number of complement-mediated functions including opsonophagocytosis (C3b/iC3b), chemotaxis (C5a), and killing (C5b-9—the membrane attack complex) (5, 23, 31, 44). In each situation, complement activation was functionally effective when deposition occurred on sensitive but not on resistant gonococci. For example, sensitive strains were more rapidly ingested and killed by neutrophilis in C8-deficient serum than resistant strains were (8.8% ± 3.4% versus 64.4% ± 7.7% survival at 30 min [$P < 0.005$]). Serum-sensitive isolates consumed and fixed C3 more rapidly and in greater amounts than did resistant strains (44). However, the difference in C3 consumption and fixation did not account for the difference in phagocytosis, because killing of sensitive strains was still greater than that of resistant strains under conditions of equal C3 fixation. More importantly, C3 bound to serum-resistant gonococci during incubation in normal human serum had no effect on promoting phagocytic ingestion and killing, since the slope of the plot of gonococcal survival versus C3 fixation was zero. In contrast, C3 fixation to sensitive strains made an important contribution to phagocytosis, since ingestion and killing were significantly decreased when the serum was heated to inactivate complement (44).

Other investigators have demonstrated that complement activation by gonococci leads to the assembly of the membrane attack complex and its association with the gonococcal outer membrane (23, 31). C9 consumption and the number of C5b-9 complexes deposited on sensitive and resistant strains were equivalent, despite the different functional outcome resulting from this association. However, twice as many of these complexes could be removed from the resistant strain than from the sensitive strains by trypsin treatment, indicating that the complexes were inserted differently in the outer membranes of the two types of gonococci (31). In addition, the complexes were stably associated with distinctive proteins in the outer membrane of sensitive but not resistant strains (32). Moreover, treatment of resistant isolates with immune antiserum promoted both association of the membrane attack complex with these proteins and killing of the isolates (32). These data also demonstrate that resistant strains are not innately immune to complement-mediated attack.

Together, these data demonstrate the critical contribution of effective complement activation by serum-sensitive gonococci to multiple levels of host defense. Conversely, the ineffectiveness of this process in promoting neutrophil chemotaxis, phagocytosis, and serum bactericidal activity for serum-resistant gonococci is probably a significant factor in the pathogenesis of disseminated gonococcal infection and probably contributes to the relatively sparse discharge and lack of genital symptoms observed in this disease. The fact that resistant strains stimulate inadequate complement-mediated activities at multiple levels of the cascade (C3, C5a, and C5b-9) indicates that the basis for the impaired interaction between complement and these isolates must occur at a step preceding or involving C3 deposition. Moreover, these data suggest that immune antibody alters this process by directing complement deposition to specific sites on the organism surface (15).

Further support for this conclusion stems from our studies of the epitopic specificity of antibodies in normal and immune sera (4) and from experiments with monoclonal antibodies (33). In these studies we demonstrated a direct correlation between the titer of IgM anti-LOS for individual serum-sensitive strains and the complement-dependent chemotactic activity generated by the strain (4). Such a relationship was not demonstrated for serum-resistant gonococci, even though in some cases the individual IgM anti-LOS titer was higher than that for serum-sensitive strains. Nor was a correlation observed between complement-mediated activities and IgG anti-LOS titers or titers of either isotype against outer membrane proteins from any of the isolates. In convalescent-phase sera, IgM titers to outer membrane antigens of the homologous serum-resistant strain did not differ substantially from those in normal serum and recognized identical epitopes on Western immunoblots of purified LOS from the resistant strain. In contrast, in the convalescent-phase serum, IgG titers to outer membrane antigens were markedly elevated, were associated with effective complement-mediated activity, and recognized a unique LOS epitope not detected by normal IgG (4).

Joiner et al. (33) used a panel of monoclonal antibodies with overlapping isotype and subclass characteristics and sharing antigenic specificity for gonococcal outer membrane protein I to demonstrate that equal binding of these antibodies resulted in a range of gonococcal killing from 10 to 90%. This wide range in killing occurred despite the deposition of nearly equivalent numbers of C3 and C9 molecules on the organisms in the presence of these antibodies (33). In summary, both of these studies lend additional support to the importance of epitopic specificity in mediating effective complement disposition. This result is distinct from the effect of blocking antibodies (IgG specific for protein III on serum-resistant gonococci [40, 41] and IgA specific for capsular polysaccharide on meningococci [19, 20]), which compete with bactericidal antibody for binding sites on the organism. In the case of gonococci, blocking antibody also enhances complement deposition at sites which do not result in complement-dependent killing (30).

As a consequence of these findings, we examined the rate of cleavage of C3 covalently bound to serum-sensitive and resistant gonococci during incubation in normal human serum (C. McRill and P. Densen, unpublished data). As in our previous studies, more C3 was bound to sensitive than to resistant strains. Initial deposition of C3b on the sensitive strains was followed by its cleavage to iC3b, C3dg, and C3d, beginning within 5 min of incubation in serum. As C3b was cleaved to iC3b, factor B present as Bb bound to C3b was progressively lost from the cell surface, consistent with the decay of the alternative-pathway C3 convertase. In contrast, C3b deposition on resistant strains was not observed until after 10 min of incubation, and factor B, although bound by resistant strains, was neither cleaved to Bb nor shed from the cell surface. These studies demonstrate a difference in the rate of C3 cleavage on the two types of isolates as well as a difference in the interaction of factor B with C3b bound to them and suggest that the very rapid cleavage of C3b to iC3b on resistant strains may contribute to their resistance by preventing initiation of the assembly of the membrane attack complex (McRill and Densen, unpublished). The molecular basis underlying the difference in these reactivities requires further elucidation.

During the course of these studies, we sought to control the bacteriolytic effect of complement on these two types of isolates by using either C8-deficient serum or normal human serum immunochemically depleted of C8. We expected that these reagents would allow unencumbered C3 deposition on serum-sensitive strains but prevent C5b-9-mediated gonococcal lysis, thereby allowing sensitive strains to remain intact and morphologically analogous to serum-resistant strains. We were surprised to discover that although the total amount of C3 bound to serum-sensitive strains did not differ between complement-sufficient and deficient sera, factor B, present as Bb, was bound stably to C3 on sensitive gonococci incubated in complement-deficient but not in complement-sufficient serum (7). Reconstitution of the complement cascade by the addition of purified C8 to C8-deficient serum led to the loss of factor B and properdin previously bound to these organisms. Consistent with these observations was the finding of a delay in C3 cleavage on organisms incubated in deficient but not in sufficient serum. Additional studies demonstrated that this effect required C8 but not C9 in the nascent membrane attack complex, although the presence of C9 further enhanced factor B loss from the organisms (McRill and Densen, unpublished). When membrane disruption was prevented by depleting normal serum of lysozyme instead of C8, gonococcal killing and factor B loss occurred normally. These studies establish the existence of a novel feedback mechanism in which the assembly of the membrane attack complex promotes decay of the alternative-pathway C3 convertase, C3bBb/P, resulting in the release of factor B and properdin but not C3 from the organism surface (7). This effect does not require the gross morphologic disruption of the outer membrane. However, the extensive loss of outer membrane components containing endotoxin that occurs during incubation of neisseriae in complement-sufficient serum (7, 50), but not in deficient serum, may contribute to the higher mortality rate associated with meningococcal disease in normal individuals compared with that in patients with late complement component deficiencies (Table 1). In addition, the altered display of C3 cleavage products on organisms incubated in complement-deficient sera may lead to a difference in complement-dependent enhancement of immune responses.

IMMUNOLOGIC BASIS FOR PREVENTION OF NEISSERIAL DISEASE IN COMPLEMENT-DEFICIENT INDIVIDUALS

There is a sound theoretical and experimental basis for the use of capsular vaccines to prevent infection in individuals with inherited defects affecting either the classical or alternative pathway. In the former situation, specific antibody acts synergistically with properdin to enhance alternative-pathway activation and function (48), and postvaccination serum from these individuals demonstrates improved meningococcal killing (P. Densen, unpublished data). Similarly, we and others have shown that administration of the meningococcal vaccine to properdin-deficient individuals enhances the use of the classical pathway and the killing of meningococci (8, 48). Given the high mortality rate associated with meningococcal disease in these individuals, vaccination represents an important therapeutic strategy.

The theoretical basis for immunization of individuals with an inherited deficiency of one of the late complement components is less well established, since anti-capsular antibody cannot enhance serum bactericidal activity in individuals with a defective killing system. However, complement-dependent opsonization is unimpaired in patients with an inherited deficiency in one of the late complement components (36). We have shown that vaccination enhances the phagocytic elimination of meningococci from their serum (45). Nevertheless, phagocytic cells in the tissues and reticuloendothelial system do not seem to prevent recurrent neisserial infection in these patients. The reason for this apparent failure seems to be that the serum from unvaccinated and previously uninfected deficient patients, as well as serum from normal individuals, contains low levels of specific IgG anticapsular antibodies. Bactericidal antibody in these individuals is directed primarily at subcapsular antigens. Consequently, C3 is probably deposited at these sites rather than on the meningococcal capsule, resulting in impaired opsonization analogous to that described previously for pneumococci (3). Thus, the complement deficiency accounts for the susceptibility of these patients to meningococcal disease, but the associated lack of anticapsular antibody contributes to this susceptibility by impairing effective elimination of meningococci by phagocytes. Consequently, vaccination, by generating anticapsular antibody, should help protect these individuals by recruiting the phagocytic arm of host defense.

During recent studies of the immune response of late complement component-deficient individuals to meningo-

coccal infection, we observed that the levels of bactericidal antibody for group B meningococci did not differ among normal and complement-deficient individuals who had not experienced meningococcal infection (P. Densen, C. McRill, and M. Sanford, unpublished data). However, the serum samples from complement-deficient individuals with previous meningococcal infection contained significantly higher titers of bactericidal antibodies than did the serum samples of normal individuals with the same infection. This difference was independent of the number of infections, the time since the infection, the age of the patient, and the infecting meningococcal serogroup. Preliminary studies suggest that a likely target of this antibody is meningococcal LOS (Densen, et al., unpublished). These data suggest that there may be a subtle difference in antigen presentation in late complement component-deficient individuals. They also suggest the possible utility of LOS antigens as candidate vaccines in complement-sufficient individuals, particularly in the prevention of group B meningococcal disease.

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