Preface

Meningococcal disease, which occurs chiefly as either septicemia or meningitis, represents a major health problem worldwide. In Europe, the Americas, and Australasia these syndromes, which can occur by themselves or in combination, are principally diseases of early childhood and adolescence, whereas in Africa and Asia, especially China, large-scale epidemic or pandemic outbreaks can involve the whole community. In many industrialized countries there are few childhood diseases that parents fear more than "meningitis," the term commonly used to refer to meningococcal disease.

There are a number of good reasons for this fear. Meningococcal disease is sporadic, unpredictable, and difficult to diagnose. The disease progresses in a matter of hours from apparently trivial symptoms to a life-threatening medical emergency. Even in the presence of treatment, a positive outcome is uncertain and, frequently, victims are left with severe disabling sequelae ranging from brain damage to limb loss. Finally, the apparently most rational approach to controlling meningococcal disease, childhood vaccination, is hindered by the lack of a suitable comprehensive vaccine, a fact that can leave public health officials feeling helpless in the face of meningococcal disease outbreaks.

Many of these factors are a consequence of the natural history of *Neisseria meningitidis*, the causative agent in meningococcal disease. Perhaps the most important consideration in this regard is paradoxical for one of the most feared pathogens: the meningococcus is a normally harmless member of the commensal flora of adult humans. Asymptomatic colonization of the nasopharynx is very common, averaging at about 10% of the population in many countries, peaking at higher levels, 30–40%, in some age groups. Probably as a consequence of this ubiquity, meningococcal populations contain bewildering antigenic and genetic diversity. There are thousands of distinct meningococcal variants described to date and each of these has a sophisticated mechanism for varying its surface coat in response to immune attack. In summary, this bacterium is very well adapted indeed to living with the human immune system. This adaptation is the principal reason for the difficulties in vaccine development.

Safe, effective vaccines against meningococcal disease have been available since the late 1960s. These target the polysaccharide coat of the meningococcus, which is essential for the organism's survival in the bloodstream. From the dozen or so such coats available to the meningococcus, only five, those which define serogroups A, B, C, Y, and W-135, are associated with disease. Unfortu-

nately, vaccines that include unmodified polysaccharides are poorly immunogenic, eliciting only a temporary immune response in adults and none at all in infants. Serogroup B polysaccharide is problematic because its especially poor immunogenicity may result from immunological identity to human polysaccharides, raising concern about the safety of any vaccine based on this molecule. In addition to these polysaccharides, many research and development programs have targeted the protein components of the meningococcal coat but, as yet, despite some promising reports, none of these has resulted in a wholly satisfactory vaccine.

However, at the beginning of the 21st century, nearly 120 years after the first isolation of the meningococcus and its association with human disease in 1887, there is optimism that solutions to meningococcal disease may be on the horizon, even if comprehensive solutions remain elusive in the short or even medium term. Polysaccharide–protein conjugate vaccines, which will provide infants with life time immunity against meningococci that express the serogroup A, C, Y, and W-135 antigens, are likely to be available soon. The completion of the whole genome sequences of two meningococci and the start of the post-genomic age will provide a host of novel data and approaches to research on the development of new meningococcal vaccines. Molecular methods, combined with phylogenetic and theoretical approaches, promise accurate molecular and epidemiological descriptions of those meningococci responsible for disease, adding further knowledge to the arsenal that can be brought to bear on this difficult problem.

Meningococcal Vaccines is designed to provide a comprehensive discussion of current molecular and cellular methods relevant to meningococcal vaccine development and evaluation. The first two chapters provide the context for the book, by reviewing vaccination strategies and describing the mechanisms of immunity that are relevant to natural and vaccine-induced protection against disease. The succeeding chapters deal in detail with the many approaches available for vaccine design and the assessment of immune responses to vaccine candidates and novel vaccine formulations. The book concludes with a discussion of the implementation of a new meningococcal vaccine, based on recent experience in the United Kingdom. A companion text, *Meningococcal Disease,* is available from Humana Press; this includes overview chapters and detailed methods in the areas of diagnostic microbiology, bacterial characterization, epidemiology, host–pathogen interactions, and clinical studies.

Finally, some words of thanks to the many people who have made this book possible: the series editor, John Walker, and the staff of Humana Press for commissioning this book and seeing it through to press; the chapter authors for

their hard and always enthusiastic work in response to (frequently unreasonable) goading by the editors; our immediate colleagues who, over the years, have generously shared their knowledge, ideas, and expertise with us; and last, but by no means least, the legion of physicians and scientists who have labored in the fight against meningococcal disease since its first definitive description in 1805.

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2

Immune Response and Host–Pathogen Interactions

Andrew J. Pollard and David Goldblatt

1. Introduction

For the most part, the relationship between the pathogen, *Neisseria meningitidis*, and humans is uneventful. Colonization of the human nasopharynx at various times during life is an almost universal experience but clinically overt disease is unusual except during epidemics. This overview considers the relationship between the meningococcus and humans, reviewing current immunological and molecular understanding of this interaction of relevance to development of immunogenic vaccines.

2. Mucosal Infection

2.1. Adhesion and Invasion

In non-epidemic situations, 10–25% of the general population are colonized in the nasopharynx by meningococci ***(1)***. Carriage may be intermittent or prolonged. During close contact with a colonized individual transmission of *N. meningitidis* to a susceptible recipient may occur. It has been suggested, at least in the case of children, that transmission is often from outside of the immediate family ***(2)***. Following transmission, probably by aerosol, to the nasopharynx of the recipient, the organism must adhere in order to avoid ingestion and destruction in the intestine. Adherence occurs through interaction between human epithelial cells and bacterial surface structures including pili ***(3)***, Opa, and Opc ***(4)***. Initial adherence is probably mediated by pili ***(5)***, and antigenic and phase variation in pilin, the subunit that forms pili, both affects the adhesiveness of the bacteria and is probably an immune-evasion mechanism ***(5)***. CD46 on the epithelial cell is one probable receptor for host-pathogen pilin interactions ***(4,6)***. Adhesion is increased by cell contact-

From: *Methods in Molecular Medicine, vol. 66: Meningococcal Vaccines: Methods and Protocols*
Edited by: A. J. Pollard and M. C. J. Maiden

dependent transcriptional upregulation of the PilC1 protein that is required for pilin assembly ***(7)***. However, tighter adherence between the organism and the epithelial cell is mediated by the bacterial Class 5 outer-membrane proteins (OMPs) including Opa, which binds to the epithelial-cell membrane surface receptor, CD66 ***(8)***. Another class 5 meningococcal OMP, Opc, is involved with adhesion of meningococci but is also critical for successful invasion of acaspulate organisms ***(9)*** via interaction with heparan sulphate proteoglycans ***(10)*** or integrins ***(11)*** on the epithelial cell surface. The polysaccharide capsule of *N. meningtidis* may interfere with these host-pathogen interactions, and it is likely that phase variation in capsule expression (by slipped-strand mispairing in the polsialyltransferase gene) facilitates adherence and invasion in vivo ***(12)***.

Methods used in the study of interactions of meningococci with epithelia and endothelial cells are considered in "Meningococcal Disease," edited by A. J. Pollard and M. C. J. Maiden, ***(12a)***. It appears that there are several bacterial-surface structures critical for adhesion to and invasion through the human nasopharyngeal mucosa. Such structures may be important constituents of future vaccines and induce mucosal immune responses.

2.2. Mucosal Immune Mechanisms and Their Avoidance

Various host factors provide some resistance to infection of the mucosa by *N. meningitidis*. Continuous washing of the nasopharyngeal mucosal surface by saliva and mucosal secretions probably plays an important role in reducing the opportunity for bacteria to adhere. Other nonspecific immune mechanisms, including the action of salivary enzymes and pH, may be of importance too. Specific immunity via immunoglobulin (Ig) A and other immunoglobulin classes can be measured in nasopharyngeal secretions and may be an important means of host defense ***(13,14)***. However, pathogenic meningococci produce IgA1 proteases, which cleave IgA1, generating (Fab) 2 IgA fragments that block binding of complement-fixing antibodies ***(15,16)***, although the significance of this and the anti-protease antibody that blocks its activity remains uncertain in vivo.

2.3. Other Nasopharyngeal Flora

Of likely importance in meningococcal colonization of the human nasopharynx is the presence of competing, commensal flora, notably *Neisseria lactamica*. *N. lactamica* colonizes the nasopharynx in over 20% of children at 18 mo ***(1)*** and over 90% of 12–18-yr-olds have bactericidal antibody to this organism in the UK ***(17)***. Conversely, colonization by pathogenic Neisseria at this age is uncommon with <0.71% of children under 4 yr of age carrying *N. meningitidis* ***(1)***.

2.4. Host Genetic Susceptibility

Genetic variation in the host, particularly in the genes encoding receptors involved in bacterial adhesion and invasion, may play an important role in determining the success of this human-bacterial interaction. Few data are available concerning these host susceptibility factors. Meningococcal disease is more common in nonsecretors of the ABO blood-group antigens ***(18)*** and these individuals also produce lower levels of IgM in their nasopharyngeal secretions ***(18)***.

2.5. Integrity of the Mucosal Barrier and Disease

The observation of an association between recent influenza infection and invasive meningococcal disease and the increased risk of meningococcal disease and carriage associated with exposure to tobacco smoke ***(19)*** both suggest that the integrity of the mucosal surface is important in resisting colonization and invasion by meningococci. Recent data suggest that the charge and hydrophobicity of the mucosa are affected by exposure to tobacco smoke and that this in turn increases bacterial adhesion ***(20)***.

Following invasion into the epithelial cell, capsulate organisms appear to be enclosed in large vacuoles and acaspulate bacteria are found within membrane-bound vesicles ***(21)***. The bacteria translocate through the mucosa and some traverse the endothelium into the blood.

3. Bacteraemia

Both during invasion through the mucosa and when meningococci gain access to the blood, there are a number of host-immune mechanisms to be overcome. In the immunologically-naïve individual, innate immune mechanisms provide defense for the host. Various bacterial virulence factors resist these host immunologic mechanisms. Methods for measuring opsonophagocytosis (*see* **Chapter 23**) are considered and methods for measuring specific antibody (*see* **Chapters 18** and **19**) or measuring functional antibody levels (*see* **Chapters 20** and **21**) are described in this volume.

3.1. Phagocytosis

The relative contribution of phagocytes to natural immunity to meningococci in healthy individuals is unknown.The polysaccharide capsule of the meningococcus is antiphagocytic and resists this immune mechanism. Non-opsonic phagocytosis of bacteria probably occurs in the tissues or circulation through the interaction of bacteria with phagocyte pattern-recognition receptors such as macrophage mannose receptor, macrophage scavenger receptor, CD14 (which recognizes lipopolysaccharide; LPS), and complement receptor-3 (CR3). Non-opsonic phagocyte interactions may be directed at Opa and Opc

on the bacterial surface, through receptors such as CD66, which is known to the host receptor for bacterial Opa ***(8)***. However, such interactions may be inhibited by sialylation of surface polysaccharide ***(22,23)***. Nonspecific serum opsonins, including complement- and mannan-binding lectin, are important in enhancing phagocytosis. Opsonophagocytosis by specific antibody is also likely to be an important immunologic mechanism for host defense, particularly for serogroup B meningococci ***(24)***. For serogroup A and Y meningococci, anticapsular polysaccharide antibodies enhance phagocytosis in vitro ***(25)*** and opsonic antibody, which seems to be directed at conserved regions, is also generated against other surface structures after infection ***(26)***.

Opsonized bacteria are probably removed from the circulation by splenic phagocytes, because asplenia and splenectomy are risk factors for disease ***(27,28)***.

3.2. Complement-Mediated Bacteriolysis

The role of complement in protection against infection with *N. meningitidis* is reviewed in some detail in "Meningococcal Disease," edited by A. J. Pollard and M.C.J. Maiden ***(12a)***. Presence of complement-fixing antibody in the blood correlates with immunity to serogroup A and C meningococci and induction of such antibodies is the goal of vaccination. In immunization studies, serum bactericidal antibody is measured as an in vitro correlate of immunity. Complement may be directly deposited on the bacterial surface or deposited following activation by Mannan Binding Lectin (MBL)-associated serine proteases, leading to the formation of the membrane-attack complex and lysis of the organism. However, antipolysaccharide-capsule specific complement-binding antibody is believed to be the primary acquired immune mechanism that protects against the non-B serogroups of meningococci. The presence of in vitro serum bactericidal activity against serogroups A, B, and C is inversely correlated with the age-related incidence of disease ***(29)***. Moreover, presence of anti group A or C serum bactericidal antibody in blood protects against disease during an outbreak ***(30–33)***, providing compelling evidence that anticapsular antibodies are important in host defense. Indeed, *complement* is essential for the protection afforded by specific antibody as witnessed by the increased risk of disease in individuals with complement deficiency ***(34)***, who nevertheless may have adequate levels of specific antibody. Antibody is required, as shown by the increased risk of disease in individuals with hypogammaglobulinaemia ***(35,36)***. It seems necessary that this antibody should bind the bacteria with high avidity to facilitate complement-mediated lysis of all serogroups of meningococci ***(37,38)***.

For serogroup B meningococci, the polysaccharide covering of the organism does not seem to be an important target for antibody-mediated bacteriolysis because the capsule of this organism is both poorly immunogenic (so there are low antibody titers) ***(39)*** and resists complement deposition ***(40,41)***. Although often assumed, it is not clear if bactericidal antibody directed against other outer-membrane structures contributes significantly to natural immunity to serogroup B meningococci, although in vitro most bactericidal activity seems to be directed at noncapsular antigens ***(42)***. However, the presence of hypermutable regions in the genes encoding the surface exposed sequences of these antigens (*see* **Subheading 5.2.2.**) suggests that meningococci have evolved means of evading this host-immune mechanism, and further suggesting that these antibodies exert evolutionary pressure on the bacteria. Indeed, there are likely to be a number of genes expressed following entry into the blood that enable metabolic adaptation and may be targets for antibody.

In addition to complement deficiency and deficiency of MBL ***(43)***, which enhances susceptibility to meningococcal infection, there are probably several more subtle polymorphisms in the genes encoding the effector mechanisms of the immune response to meningococci that increase susceptibility. For example, CD32 (FcγRIIa) polymorphisms are found more commonly in children with meningococcal disease ***(44)*** and a combination of FcγRIIa and FcγRIIIb polymorphisms are associated with an increased risk of meningococcal disease in individuals with a late complement component deficiency ***(45)***.

3.3. The Endothelium and the Inflammatory Response

During growth in the blood, meningococci, in common with other Gram-negative bacteria, shed LPS-containing blebs of outer membrane. These blebs contain a full complement of meningococcal surface exposed structures and might act as a decoy for the host-immunologic defenses. Proliferation of meningococci in the blood lead to endothelial activation ***(46,47)*** and LPS activates the inflammatory cascade following binding to CD14 on macrophages. In turn, inflammatory mediators are released by the macrophage (including those resident in the spleen and liver), inducing a range of downstream effects that culminate in shock. However, because bacteraemia is possible in the absense of shock (indeed, this is the more usual situation), it seems likely that there is a dose-dependent relationship between the amount of LPS in the circulation and the inflammatory response. Support for this comes from the observation that the number of bacteria in the blood ***(48,49)*** and the concentration of LPS in the blood ***(50,51)*** correlates with the severity of disease. Thus, in individuals with mild disease, bacteria may be present at <1–240 cfu/mL ***(52)*** and in severe disease levels from 5×10^2–10^5 cfu/mL have been recorded ***(51–53)***.

Methods for studying interactions of meningococci with endothelia are described in Chapter 38 in "Meningococcal Disease," edited by A. J. Pollard and M. C. J. Maiden ***(12a)***.

4. Central Nervous System Infection

Invasion from the blood to the central nervous system (CNS), or to other sites following bacteraemia, is thought to follow pilus-mediated adhesion to the endothelium ***(54,55)***. Expression of PilC may be an important factor in this interaction ***(55,56)*** and invasion of endothelial cells may be enhanced by Opc expression ***(9,11)***. It is not certain how or where the meningococci cross the blood-brain barrier (BBB) and enter the CNS. This subject is discussed in more detail in "Meningococcal Disease," edited by A. J. Pollard and M. C. J. Maiden, drawing on data from in vivo and in vitro models ***(12a)***. After invasion through the endothelium, meningococci gain access to the sub-arachnoid space, probably via the choroid plexus. In the CSF meningococci proliferate, shed LPS ***(57)*** and induce the release of pro- and anti-inflammatory cytokines ***(58–60)***.

5. The Host-Immune Response

Previously we have considered the innate and acquired immune-effector mechanisms that must engage the meningococci during infection. It remains unclear how the different effector mechanisms relate to one another in importance for the host, although it seems certain that high-avidity, complement-binding antibody directed at the polysaccharide capsule is the most effective mechanism for non-serogroup B organisms. It is likely that opsonophagocytosis and innate immune mechansims also play a role.

5.1. Acquisition of Immunity

Antimeningococcal-specific immunity develops during childhood and there is thus likely to be variation in the importance of different effector mechanisms dependent on the age of the child. Immunity is almost certainly acquired through exposure to related Neisseria ***(61,62)*** and other bacteria in the gut and nasopharynx whose antigenic constituents cross-react with those of *N. meningitidis* ***(26,63–65)***, inducing and boosting immune responses ***(66)***. In the newborn, disease is rare as a result of placental transfer of maternal antibody, providing passive protection through opsonization or bacteriolysis ***(29)***. The peak incidence in most industrialized countries of disease occurs between the ages of 6 mo to 2 yr. For children in this age group, susceptibility to disease is the consequence of a number of factors, including the loss of maternal antibody, the inability of young children to respond to pure polysaccharide antigens, and insufficient opportunity for immunity to develop through exposure

to antigenic stimuli from related species. During this time, innate immune mechanisms may be central to protection including non-opsonic phagocytosis, opsonic phagocytosis with nonspecific opsonins (such as complement and MBL), and direct bacteriolysis following deposition of complement on the bacterial surface.

As a result of exposure to related bacteria during childhood, adult levels of antibody are reached in the second decade and are able to mediate opsonophagocytosis and antibody-directed, complement-mediated bacteriolysis. A comprehensive array of acquired and innate immune mechanisms is thus active from early adulthood, and the incidence of disease is lowered considerably.

5.2. Specificity of Antibody

5.2.1. Polysaccharide

As mentioned earlier, the specificity of antibody in vivo that it responsible for acquired immunity is unknown, although it is likely that the most effective protection for non-group B organisms following vaccination resides in anticapsular polysaccharide, complement-binding IgG. Antibody responses to the majority of pure polysaccharides (with *N. meningitidis* an important exception) are known to be age dependent and are designated T-independent, as T-lymphocytes are not required or ordinarily involved in induction of immune responses directed against them ***(67)***. T-independent responses are age dependent (not usually seen in those under 18 mo) and do not result in the generation of memory. Conjugation of capsular polysaccharides can overcome the nonresponsiveness of young infants to polysaccharide antigens and can induce memory ***(67)***.

The immune response to capsular polysaccharide when encountered on the surface of organisms in vivo is not as well-characterized as the response to pure polysaccharides when used as vaccine antigens. Recent data from studies on the naturally acquired immune response to the capsular polysaccharide of *Haemophilus influenzae* type b and pneumococcus would suggest that such antibodies are induced by a T-dependent mechanism ***(68,69)***. Thus the observed rise in antibody titers in older children and adults following vaccination with plain meningococcal polysaccharide ***(70)***, probably represent secondary immune responses following the induction of memory brought about by natural exposure to capsular polysaccharides cross-linked to other meningococcal surface structures.

The delay in the acquisition of naturally induced meningococcal anticapsular polysaccharide antibodies in those under 2 yr of age may thus be a general manifestation of the immaturity of the developing immune system.

Repeated dosing with meningococcal serogroup C vaccines induces hyporesponsiveness as measured by antibody titers *(70,71)*. Plain polysaccharide may induce terminal differentiation of polysaccharide-specific B cells, without generation of new memory B cells. Repeated dosing could deplete the polysaccharide-specific B-cell pool leading to a diminishing antibody response until a further conjugate stimulus generates new memory cells and boosts the immune response *(72)*. Conversely, A/C conjugate vaccines generate immunologic memory and boosting of antibody levels with subsequent doses *(70)* and can also overcome the hyporesponsiveness induced by prior administration of plain A/C polysaccharide *(73)*.

The quality of antibody induced following natural exposure or vaccination may vary depending on a number of factors, including the age of the individual being studied and the type of vaccine administered. The measurement of such qualitative aspects of antibody function is increasingly being recognized as an important component of such studies. The discrepancy between the level of antibody induced by plain meningococcal C polysaccharides vaccine (as measured by enzyme-linked immunosorbent assay ELISA) and antibody function as measured by a bactericidal activity has led to modifications of the ELISA as described in Chapter 21. The improvement in correlation between ELISA and bactericidal activity is most likely owing to restricting the ELISA to the measurement of higher avidity, and by implication more functional, antibody. Antibody responses to conjugate vaccines are, by virtue of the T-cell help induced, of higher avidity and thus modifications to the standard ELISA in the context of sera from conjugate vaccine recipients are probably not required. In addition to the correlation between avidity and function, antibody avidity has recently been used as a surrogate marker for the successful generation of memory following conjugate vaccination *(74)*. Owing to the T-cell help recruited by the glycoconjugate vaccines, antibody avidity increases in the naïve recipient in the weeks and months following vaccination and this can be measured by a modified ELISA. After a single dose of Men C Conjugate vaccine, avidity has been noted to increase, suggesting that a single dose is sufficient to induce immunological memory *(75)*.

The polysaccharide capsule of meningococci is highly conserved between strains, with only A, B, C, Y, and W135 polysaccharides being commonly associated with disease and providing the possibility of inclusion of a limited number of antigens in a broadly protective vaccine. Such a vaccine based on the plain polysaccharides of serogroup A, C, Y, and W135 is widely used for protection of travelers and in outbreak control *(76,77)*. Serogroup C conjugate vaccines have been recently introduced in the UK, and appear effective against this serogroup *(78)*. A combination conjugate A, C, Y, and W135 vaccine

is likely to be available within the next few years. Unfortunately, serogroup B polysaccharide is poorly immunogenic, and no vaccines have yet been produced that have successfully provided protection against disease in humans using this bacterial product. Chemical modification of the serogroup B polysaccharide is being studied as a means of overcoming the immunogenicity problems described earlier ***(79)*** although the structural homology between B capsular polysaccharide and human neural-cell adhesion molecule (NCAM) ***(80)*** raises concerns about this approach. Development of a vaccine against serogroup B meningococci is mainly directed at noncapsular antigens and it is likely that these are also the targets of the natural immune response to this organism. Antibody directed against noncapsular antigens of other serogroups are also present in sera of adults or after infection, but their role in defense against disease caused by these organisms in contrast to that of polysaccharide is unknown.

5.2.2. Noncapsular Antigens

Noncapsular antigens are also targets of the antibody response following colonization, infection, or vaccination. It seems unlikely that natural acquired immunity to meningococci resides in opsonic or complement-binding antibody directed against a single antigen or epitope. Specific immunity in older children and adults probably results from the combined effect of antibody directed against a variety of antigens on the meningococcal surface. Indeed, antibody directed at PorA ***(81)***, PorB ***(82)***, Class 5 proteins ***(83)***, lipopolysaccharide ***(84)***, IgA1 protease ***(85)***, neisserial surface protein A ***(86)***, transferrin-binding proteins ***(87)***, H.8 ***(88)***, ferric-binding proteins ***(89)***, and lactoferrin-binding protein A ***(90)*** have all been documented following infection. Methods for analysis of B-cell epitopes on these proteins are considered in Chapter 26. Unfortunately, the relative importance of each of these outer-membrane components in directing immune responses via opsonization or complement-mediated bacteriolysis is unclear. The availability of the meningococcal genome will introduce many more candidates to be considered as targets for natural immunity and vaccine development in the future.

5.3. T-Cell Immune Responses

T cells are important in providing help for antibody production in the generation of specific immunity against meningococci. In vitro T-cell proliferative responses (*see* Chapter 24) to PorA, Opa, Opc, and outer-membrane vesicles (OMVs) have been documented in normal adults ***(91)*** and after vaccination ***(92,93)*** or infection ***(94)***. T-cell epitopes for PorA and Por B proteins appear to be in highly conserved regions of these porin proteins ***(95–97)***. T-cell

epitope mapping is described in Chapter 25. The pattern of cytokines produced by T cells following meningococcal infection or colonization ***(94)*** may be important in directing maturation of the antibody response and age-dependent differences in T-cell responses or their interactions with B cells could be responsible for the low-avidity antibody observed in young children ***(37)***.

6. Conclusion

The nature of the human immune response to *N. meningitidis* has been evaluated in vitro and through epidemiologic observation, but the relative contribution of various immunologic factors to natural immunity to this organism remains incompletely understood. The chapters in this book provide the tools for the further investigation of these fundamental issues relevant to a better understanding of meningococcal pathophysiology. A better understanding of these will allow more rational development of not only better therapeutic strategies but also better vaccine design. Antibodies to the non-B serogroup meningococci have been proven be critical for protection and polysaccharide vaccines are able to induce this in the short term. With protein-polysaccharide conjugate vaccines for serogroup C meningococci available, and others on the horizon, the potential to provide life-long protection is tantalizingly in our grasp. For serogroup B meningococci, further evaluation of the nature of natural immunity and the immunogencity of noncapsular surface antibodies may hold the key to developing a protective vaccine directed against all disease-associated serogroups of meningococci. It is here that postgenomic science is likely to make a major contribution.

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