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Thailand

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Contributors

MICHAEL A. APICELLA, M.D.

Professor of Medicine and Microbiology, and Director, Division of Infectious Diseases, School of Medicine, State University of New York at Buffalo School of Medicine and Biomedical Sciences, Buffalo, New York

Neisseria meningitidis: Pathogenesis and Immune Response

B. ANTHONY BELL, M.D., F.R.C.S.

Senior Lecturer in Neurosurgery, Saint George's Hospital Medical School, University of London; Consultant Neurosurgeon, Atkinson Morley's Hospital, London, England

Brain Abscess

HENRY M. BLUMBERG, M.D.

Fellow in Medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia

Spinal and Paraspinal Infections

MARK BRAUN, M.D.

Staff Physician, Mercy Hospital and Medical Center, Chicago, Illinois

Gram-Negative Bacillary Meningitis

JULIET A. BRITTON, M.R.C.P., F.R.C.R.

Senior Lecturer in Neuroradiology, St. George's Medical School, University of London; Consultant Neuroradiologist, Atkinson Morley's Hospital, London, England

Brain Abscess

CLAIRE V. BROOME, M.D.

Chief, Meningitis and Special Pathogens Branch, Division of Bacterial Diseases, Centers for Disease Control, Atlanta, Georgia

Bacterial Meningitis: Epidemiology

CHARLES E. CHERUBIN, M.D.

Clinical Professor of Medicine, University of Illinois College of Medicine; Chairman of Medicine, Mercy Hospital, Chicago, Illinois

Gram-Negative Bacillary Meningitis

STEVEN P. CONWAY, M.B. B.S., M.R.C.P., M.A.

Honorary Lecturer, Department of Paediatrics, St. James's University Hospital; Consultant Physician and Pediatrician, Department of Child Health, Seacroft Hospital, Leeds, England

Pneumococcal and Other Gram-Positive Coccal Meningitides

GORDON C. COOK, M.D., D.Sc. (Lond.), F.R.C.P., F.R.A.C.P., F.L.S.

Senior Lecturer, London School of Hygiene and Tropical Medicine; Consultant Physician, Hospital for Tropical Diseases, University College Hospital, and St. Luke's Hospital for the Clergy, London, England
Protozoan and Helminthic Infections

JOHN DE LOUVOIS, Ph.D., M.R.C.Path.

Senior Lecturer in Microbiology, Royal Postgraduate Medical School Institute of Obstetrics and Gynecology, London, England
Neonatal Meningitis

RICHARD D. DIAMOND, M.D.

Professor of Medicine and Biochemistry, Boston University School of Medicine; Head, Section of Infectious Diseases, The University Hospital, and Evans Department of Clinical Research, Boston University Medical Center, Boston, Massachusetts
Fungal Meningitis

SIMON R.M. DOBSON, M.A., M.B. B.S., M.R.C.P.

Clinical Lecturer, Department of Paediatrics, University of Oxford, Oxford, England
Haemophilus influenzae: Syndromes and Treatment

RICHARD J. DUMA, M.D., Ph.D.

Professor of Medicine, Microbiology, and Pathology, and Chairman, Division of Infectious Diseases, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia
Primary Amebic Meningoencephalitis: Infection of the Central Nervous System by Free-Living Amebae

W. EDMUND FARRAR, M.D.

Professor of Medicine and Microbiology, Medical University of South Carolina College of Medicine, Charleston, South Carolina
Meningitis Due to Listeria monocytogenes and Other Gram-Positive Bacilli

STUART M. GOLDSMITH, M.D.

Former Fellow, Department of Pediatrics, University of Alabama School of Medicine, Birmingham, Alabama
Herpes Simplex Encephalitis

MICHAEL J.G. HARRISON, D.M., F.R.C.P.

Professor in Clinical Neurology, University College and Middlesex School of Medicine, University of London, London, England
Neurologic Complications of HIV Infection

MICHAEL HUMPHRIES, M.A. (Cant.), M.B. B.S. (Lond.), M.R.C.P.

Formerly Consultant Physician, Ruttonjee Sanatorium, Wanchai, Hong Kong; Currently, Medical Director, Roche Pharmaceuticals, and Honorary Lecturer, Department of Community Medicine, University of Hong Kong, Hong Kong
Tuberculous Meningitis

MAIJA HELENA KÄYHTY, Ph.D.

Research Fellow, Academy of Finland; Staff, National Public Health Institute, Helsinki, Finland
Haemophilus influenzae Type b Meningitis: Pathogenesis and Immunology

COLIN R. KENNEDY, B.A., B.S., M.D., M.R.C.P. (U.K.)

Clinical Teacher, Southampton University, Southampton; Consultant Paediatric Neurologist for the Wessex Region, Wessex, England
Acute Viral Infections Excluding Herpes Simplex, Rabies, and HIV

JOHN SIMON KROLL, M.A., M.R.C.P.

University Lecturer in Paediatrics, Oxford University; Honorary Consultant, Paediatric Infectious Diseases, John Radcliffe Hospital, Oxford, England
Haemophilus influenzae Type b Meningitis: Pathogenesis and Immunology

HAROLD P. LAMBERT, M.D., F.R.C.P.

Emeritus Professor of Microbial Diseases, St. George's Hospital Medical School; Consulting Physician, St. George's Hospital, London, England
Meningitis: Diagnostic Problems
Meningococcal Meningitis: Treatment
Chronic and Recurrent Meningitis

ERIC L. LOGIGIAN, M.D.

Assistant Professor of Neurology, Harvard Medical School; Director, Clinical Neurophysiology Laboratory, Brigham and Women's Hospital, Boston, Massachusetts
Lyme Borreliosis

W.B. MATTHEWS, D.M., F.R.C.P.

Professor Emeritus of Clinical Neurology, University of Oxford; Honorary Consultant Neurologist, Oxford Hospitals, Oxford, England
Slow Viruses and the Central Nervous System

RUTH H. McALLISTER, B.Sc., M.R.C.P.

Research Fellow in Neurology, Institute of Neurological Studies, University College and Middlesex School of Medicine, London, England
Neurologic Complications of HIV Infection

E. RICHARD MOXON, M.A., M.B., B.Chir., F.R.C.P.

Action Research Professor of Paediatrics, University of Oxford; Chief, Department of Paediatrics, John Radcliffe Hospital, Oxford, England
Haemophilus influenzae Type b Meningitis: Pathogenesis and Immunology
Haemophilus influenzae: Syndromes and Treatment
Haemophilus influenzae: Prevention

ANNETTE C. REBOLI, M.D.

Assistant Professor of Medicine, Hahnemann University School of Medicine, Philadelphia, Pennsylvania
Meningitis Due to Listeria monocytogenes and Other Gram-Positive Bacilli

W. MICHAEL SCHELD, M.D.

Professor of Internal Medicine and Neurosurgery, and Associate Chairman for Residency Programs, University of Virginia School of Medicine, Charlottesville, Virginia
Bacterial Meningitis: Pathogenic and Pathophysiologic Mechanisms

JONAS A. SHULMAN, M.D.

Professor of Medicine, Emory University School of Medicine; Chief of Medicine, Crawford Long Hospital, Atlanta, Georgia
Paraspinal and Spinal Infections

ALLEN C. STEERE, M.D.

Professor of Medicine, and Chief, Division of Rheumatology/Immunology, Tufts University School of Medicine, Boston, Massachusetts
Lyme Borreliosis

JAMES W. STONE, M.B., Ch.B., M.R.C.Path

Consultant Microbiologist, Public Health Laboratory, Royal Shrewsbury Hospital, Shrewsbury, England
Penetration of Antimicrobial Agents into the Central Nervous System

ROBERT TEOH, M.B. B.S., M.D., F.R.C.P.

Former Senior Lecturer in Neurology, Chinese University of Hong Kong; Regional Medical Director, Sandoz Pharmaceuticals, Hong Kong
Tuberculous Meningitis

EDMUND C. TRAMONT, M.D.

Professor of Medicine, Uniformed Services University of Health Sciences F. Edward Hebert School of Medicine, Bethesda, Maryland; Associate Director for HIV, Walter Reed Army Institute of Research, Washington, D.C.
Syphilis of the Central Nervous System

GARETH TUDOR-WILLIAMS, M.B. B.S., M.R.C.P.

Research Fellow, Duke University School of Medicine; Pediatric Fellow, Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina
Haemophilus influenzae: Prevention

ALLAN R. TUNKEL, M.D., Ph.D.

Fellow in Infectious Diseases, University of Virginia School of Medicine, Charlottesville, Virginia
Bacterial Meningitis: Pathogenic and Pathophysiologic Mechanisms

ROBERT A. WALL, M.B. B.S., M.Sc., M.R.C.P., M.R.C.Path

Consultant Microbiologist, Northwick Park Hospital, Middlesex, England
Meningococcal Disease: Prevention
Meningococcal Meningitis: Treatment

DAVID A. WARRELL, M.A., D.M., D.Sc., F.R.C.P.

Professor of Tropical Medicine and Infectious Diseases, University of Oxford; Honorary Consultant Physician, Oxford Area Health Authority, Oxford, England
Rabies

MARY J. WARRELL, M.B. B.S., M.R.C.P., F.R.C.Path

Formerly Research Fellow, Sir William Dunn School of Pathology, University of Oxford, and Consultant at Hospital for Tropical Diseases, Mahidol University, Bangkok, Thailand
Rabies

JAY D. WENGER, M.D.

Medical Epidemiologist, Meningitis and Special Pathogens Branch, Centers for Disease Control, Atlanta, Georgia
Bacterial Meningitis: Epidemiology

RICHARD J. WHITLEY, M.D.

Professor of Pediatrics, Microbiology, and Medicine, University of Alabama School of Medicine, Birmingham, Alabama
Herpes Simplex Encephalitis

RICHARD WISE, M.D., F.R.C.Path.

Reader and Consultant Microbiologist, Dudley Road Hospital, Birmingham, England
Penetration of Antimicrobial Agents into the Central Nervous System

Foreword

The *Handbook of Infectious Diseases* was born of the vision and the initiative of Dr. Edward H. Kass, William Ellery Channing Professor Emeritus of Medicine, Harvard University, and Director Emeritus of the Channing Laboratories, who died on January 19, 1990. Approximately 10 years ago Ed Kass envisioned the need for a multivolume series that would encompass all infectious agents and would describe the major clinical complexes caused thereby. He outlined a monumental unique work with a multinational authoritative authorship. It would sketch the historical origins of our knowledge, define the disease, and describe its epidemiology. There would be a detailed description of the causative organisms and of the pathogenesis of the diseases each produced.

In 1982, he enlisted the collaboration of the undersigned senior editors and plans were developed for a broad endeavor that would require up to 30 or more volumes divided into two series. One series would focus on individual agents, synthesizing in depth past and current knowledge. The other would deal with infectious processes affecting organ systems, for example, pneumonia and nephritis. Plans for periodic revisions in the form of updated or new editions were developed. B. C. Decker, Inc. was selected as the publisher. It was anticipated that the volumes would be the definitive work in the field of infectious diseases.

Thus, the Handbook series reflects the remarkable scientific career of Ed Kass, involving as it did basic research at the bench, direction of epidemiological studies in the field, experience as the editor of the *Journal of Infectious Diseases* and of *Reviews of Infectious Diseases*, and experience as a medical historian. His influence and investigations were global. He was involved in investigations in Jamaica and South Wales, and served as an officer of the International Congress of Infectious Diseases and the International Epidemiological Association.

The initial volumes in the Handbook series reflect Ed Kass' global contacts and his informed selection of volume editors. He was reviewing initial chapters when he died. The undersigned editors fully endorse and will pursue the objectives outlined by Ed Kass. We believe the *Handbook of Infectious Diseases* will be a fitting memorial to Dr. Kass, an individual recognized as one of the great leaders of twentieth century medicine.

David A. J. Tyrrell, M.D., F.R.S.
Thomas H. Weller, M.D.
Sheldon M. Wolff, M.D.

Preface

Infections of the central nervous system present to clinicians in such a diversity of manifestations that they are of concern to all those engaged in day-to-day medical practice, although they hold a special interest for specialists in infectious disease, pediatrics, neurology, and clinical microbiology. For this reason the contributors to this volume have taken much care to provide ample diagnostic and therapeutic detail of their topics. I hope that the book will be of real value to practicing clinicians in approaching the frequently difficult problems that these infections present.

More than that, however, infections of the nervous system are of great general interest, and their study can also be approached in the wider biological contexts of epidemiology, microbial ecology, pathogenesis, and molecular mechanisms of infection. For this reason, and in the spirit of the series of which this volume forms a part, our contributors, while doing full justice to the clinical importance of their subjects, have been encouraged to expand, wherever possible, on these wider aspects of their topics. Nor has historical background been forgotten, and this feature of the book will also provide additional interest and depth.

Infections of the central nervous system have shared fully in the explosive advances in infectious diseases during the last decade. The most dramatic of the advances, for example, the impact of HIV infection on the nervous system and the discoveries in Lyme disease, are well represented here, but there has also been much important progress in the more common and better-known infections. We have been careful to maintain a sound perspective by paying full attention to the common forms of meningitis in all their aspects and by including discussion of preventive measures as well as the treatment of established illness. For these reasons a number of chapters are devoted to meningococcal and *Haemophilus* meningitis, reflecting the importance of this infection in most communities.

I hope this volume will be of real interest and value to all who are concerned with these fascinating and important infections.

Harold P. Lambert, M.D., F.R.C.P.

Contents

CHAPTER 1

Bacterial Meningitis: Pathogenic and Pathophysiologic Mechanisms*

Allan R. Tunkel, M.D., Ph.D.
W. Michael Scheld, M.D.

Bacterial meningitis is a common and devastating illness worldwide. Since its historic description in 1805 as "epidemic cerebrospinal fever,"[143] physicians observed its almost uniformly fatal course until the introduction of antiserum in the early twentieth century.[40] Although the intrathecal administration of antiserum reduced the mortality of meningococcal meningitis from about 70 to 30 percent, the greatest decrease in mortality rates followed the introduction of antibiotics.[19] However, bacterial meningitis continues to be an important cause of morbidity and mortality despite the availability of effective bactericidal antibiotics. Case fatality rates for the three most common etiologic agents of bacterial meningitis, *Haemophilus influenzae, Neisseria meningitidis*, and *Streptococcus pneumoniae*, were 6.0, 10.3, and 26.3 percent, respectively, in the United States from 1978 to 1981.[113] These mortality rates have changed little over the last 30 years. In addition, there is a high incidence of long-term neurologic sequelae in children and adults with bacterial meningitis.[11,29] This stable, but unsatisfactory, situation spanning four decades indicates the need to focus on the pathogenesis and pathophysiology of neurologic impairments that can result from CNS infections[123] in an attempt to improve the response to conventional antimicrobial therapy.

Many advances in the understanding of the pathogenesis and pathophysiology of bacterial meningitis have been noted in recent years. Most studies have employed experimental models of this disease to investigate pathogenesis and pathophysiology, and each model has inherent strengths and weaknesses. The experimental models of meningitis that have been used differ in the route of inoculation employed, the pathogen administered, and the animal host selected. The infant rat model of experimental meningitis, first described in 1974, demonstrated that infant rats develop meningitis after intranasal challenge with *H. influenzae* type b.[83] This model most closely simulates the presumed pathogenesis of *H. influenzae* meningitis in humans, with an initial nasopharyngeal focus leading to hematogenous dissemination and an age-dependent susceptibility to bacterial meningitis during bacteremia. The infant rat model has been particularly useful in delineating the early pathogenic sequences in hematogenously induced *H. influenzae* meningitis, including the determinants of nasopharyngeal colonization and translocation into the blood stream, intravascular survival and bacteremia, and the factors responsible for meningeal invasion. At 48 hours after intranasal inoculation of the organism, the meningitis that was induced was age dependent, with a higher incidence in 5-day-old as compared with 20-day-old rats.[80] The occurrence of meningitis, irrespective of age, was directly related to the intensity of the bacteremia. A disadvantage of this model is the animal's small size (only 7 to 25 μl of CSF is obtainable in a 5- to 10-day-old rat), precluding frequent sampling of CSF.

The experimental models of meningitis in adult animals, utilizing rabbits or rats predominantly in recent years, rely on the direct intracisternal inoculation of bacteria for the initiation of infection.[24,94] These models reliably produce lethal infections with a predictable time course but bypass the natural dissemination of bacteria from the blood to the CSF, so the pathogenesis is artificial. However, these models are extremely useful for the study of the pathophysiologic sequences in bacterial meningitis after the organisms have reached the subarachnoid space (SAS) (e.g., postinductive phenomena).

This review focuses on several aspects of the pathogenesis and pathophysiology of bacterial meningitis as depicted

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in Figure 1–1. Each area is discussed with respect to the various host factors (e.g., antibody, complement, leukocytes) and microbial virulence factors (e.g., capsule, lipopolysaccharide) that are important to the development of bacterial meningitis. In addition, the roles of inflammatory mediators (e.g., interleukin-1, tumor necrosis factor) are explored and their potential relevance to clinical disease is discussed. These new areas of investigation may lead to improvements in the refractory mortality and unacceptable morbidity in patients with bacterial meningitis.

Mucosal Colonization and Systemic Invasion

A critical first step initiating infection in meningitis requires acquisition by the host of a new organism through nasopharyngeal colonization. The colonization rate is variable and depends upon numerous immunologic and socioeconomic factors. For example, about 25 percent of the population becomes colonized with a new strain of *S. pneu-*

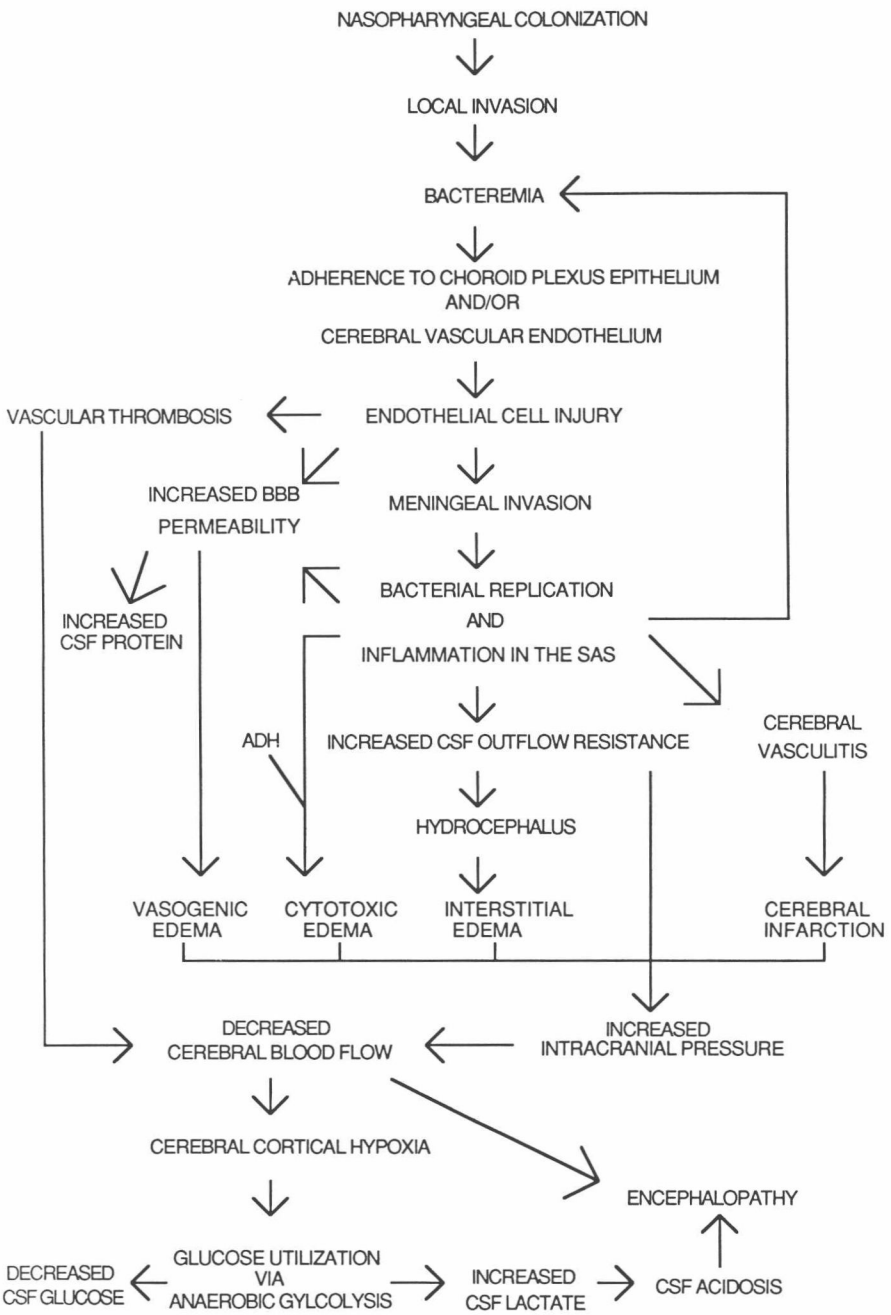

Figure 1–1 Hypothetical scheme depicting the pathogenic and pathophysiologic mechanisms in bacterial meningitis. BBB = blood-brain barrier; SAS = subarachnoid space; CSF = cerebrospinal fluid; ADH = antidiuretic hormone.

moniae yearly, with 20 to 60 percent colonized at any given time.[55,73] However, the risk of disseminated infection is greatest in persons recently colonized. For the three major meningeal pathogens, *H. influenzae, N. meningitidis*, and *S. pneumoniae*, the factors that mediate dissemination from the nasopharynx are largely unknown, although lack of specific bactericidal antibody appears critical to this event. Only persons lacking specific antibody directed against the colonizing serotype are susceptible to invasive systemic disease. However, dissemination after colonization appears to be a rare event and is highly dependent on other immunologic factors. For example, blocking IgA antibody may paradoxically favor the development of invasive disease with *N. meningitidis*.[53,65]

In addition to important host factors, certain microbial virulence factors, specifically specialized surface components, are important for mucosal adhesion. Among the 84 known serotypes of pneumococci, certain capsular types are associated with a propensity for invasion and the development of systemic disease. Eighteen serotypes are responsible for 82 percent of cases of bacteremic pneumococcal pneumonia,[4,36] and there is a close correlation between bacteremic serotypes and those implicated in meningitis.[13,42,50] The various factors responsible for enhanced invasiveness and lethality among pneumococcal serotypes remain undefined and require further study.

Other major meningeal pathogens also possess surface characteristics that enhance mucosal attachment and dissemination. The most extensively studied surface components are the fimbriae, or pili, of *N. meningitidis*. Fimbriae are specialized protein surface appendages and were found in 80 percent of primary meningococcal isolates from nasopharyngeal carriers as well as from the CSF of meningitis patients, although fimbriae are lost on serial subculture of the organism.[26] Nasopharyngeal epithelial cells possess cell surface receptors for meningococcal fimbriae that govern the nasopharyngeal colonization by this organism.[122] After initial attachment to the mucosal surface, meningococci are transported across specialized nasopharyngeal cells within a phagocytic vacuole,[75,121] with the resultant propensity for hematogenous dissemination. This latter step in the early pathogenic sequence is greatly enhanced in complement-deficient hosts.[105]

Strains of *H. influenzae* can be classified into encapsulated (types a through f) and nonencapsulated groups based on agglutination with specific antisera, and there is evidence that both groups adhere to upper respiratory tract epithelial cells. Virtually all children by 3 months of age harbor *H. influenzae* in the nasopharynx, but the great majority of these events involve unencapsulated strains and only 5 percent are type b.[117] Elegant experiments employing laboratory transformants have shown that while all encapsulated strains (types a through f) have the potential for systemic infection after intraperitoneal inoculation into rats, type b strains are the most virulent and unencapsulated strains are not invasive after this route of inoculation.[81,103] In addition, only *H. influenzae* type b strains are invasive after intranasal inoculation, indicating that this capsular polysaccharide confers unique virulence characteristics that correlate with a propensity for invasive disease in humans.

The presence of serum antibodies to the capsular polysaccharide of type b isolates, polyribosyl-ribitol phosphate (PRP), may be protective against invasive disease.[2] Antibodies to PRP are almost uniformly detectable in humans by age 3 to 4 years, despite no known exposure to *H. influenzae* type b in many instances, and it has been suggested that colonization in the gastrointestinal tract with commensal bacteria possessing antigens that cross-react with PRP (e.g., *Escherichia coli* K100) stimulates anti-PRP antibody production.[79,115] Lack of sufficient concentrations of this antibody correlates with an increased risk of invasive disease. Recent studies have examined other surface properties (e.g., lipopolysaccharide [LPS] and various outer membrane proteins) of *H. influenzae*, and antibodies against these components confer protection upon repeated challenge with the organism.[3,54,56,67] However, the precise roles of capsular polysaccharide, LPS, or outer membrane proteins in mucosal translocation and blood stream invasion of *H. influenzae* (and other major meningeal pathogens) remain incompletely defined.

Bacteremia

Once the mucosal barrier is crossed, the bacteria may gain access to the blood stream and must overcome additional host defense mechanisms to sustain intravascular survival and facilitate meningeal invasion. In this regard, the most important bacterial virulence factor is surface encapsulation, which, by effectively inhibiting neutrophil phagocytosis and resisting classic complement-mediated bactericidal activity, may enhance blood stream survival and facilitate intravascular replication to high bacterial densities. The most common meningeal pathogens (e.g., *S. pneumoniae, N. meningitidis, H. influenzae, E. coli, Streptococcus agalactiae*) are all encapsulated. Approximately 84 percent of cases of neonatal meningitis due to *E. coli* are caused by strains bearing the K1 antigen, which is antigenically identical to the capsular material of serogroup B meningococci and type III group B streptococci and serves as a marker for "neurovirulence."[102] In the absence of K1-specific host antibody, these organisms are profoundly resistant to phagocytosis.[22] Human monoclonal antibodies with specific reactivity for epitopes on the K1 capsule of *E. coli* and/or the group B polysaccharide of *N. meningitidis* may be useful for preventing and/or treating blood stream infections with these organisms.[97]

Fortunately, host defense mechanisms may counter the antiphagocytic capacity of the bacterial capsule. For example, the alternative complement pathway is directly activated by capsular polysaccharides of *S. pneumoniae*, thereby cleaving C3 and allowing attachment of C3b to the bacterial surface, which facilitates opsonization, phagocytosis, and intravascular clearance of the organism.[35] Isolated preparations of pneumococcal cell walls also activate this pathway with the generation of C5a, which increases leukocyte margination and leads to granulocytopenia and pulmonary sequestration through interactions with granulocyte surface receptors.[148] When alternative pathway activation is impaired, as in patients with sickle cell disease,[92] opsonization and phagocytosis are deficient, which may predispose these patients to invasive pneumococcal disease (e.g., meningitis). *H. influenzae* type b also activates the complement cascade,[96] and experimental studies utilizing C3-depleted infant rats found that intravenous and intraperitoneal challenge with *H. influenzae* of varying serotypes (a, b, c, or d) led to a greater magnitude and incidence of bacteremia than in control animals without affecting the incidence and severity of meningitis.[21,23,155] In contrast to systemic inoculation, intranasal challenge with the different serotypes resulted in blood stream invasion and meningitis only after challenge with type b organisms. The terminal complement components (C5, C6,

C7, C8, and perhaps C9) are especially important in host defense against meningococcal infections, and congenital or acquired deficiencies in any of these components may predispose patients to recurrent or chronic infections with *N. meningitidis*.[104,105]

The bacteremia associated with meningitis is usually assumed to be primary; that is, it follows nasopharyngeal colonization and leads to CNS invasion. Studies in infant rats and primates have supported this concept, since the production of meningitis depends strongly on the age of the animal and the size of the inoculum, preceding bacteremia is necessary for meningitis to occur, and the magnitude of the bacteremia is important. Greater than 10^3 cfu of *H. influenzae* per milliliter of blood is necessary, but not always sufficient, for the production of meningitis.[80,112] However, it is important to emphasize that meningitis is a dynamic disease and that a "secondary" bacteremia may result from the local suppurative process itself in the CNS, causing a nearly constant reseeding of the CSF.

Bacteremia does occur after the intracisternal inoculation of dogs with pneumococci.[93] The transport of bacteria from the CSF to the blood in this dog model occurs only after active microbial multiplication within the CSF and before the height of the febrile response or CSF pleocytosis.[111] This early transport is presumed to be transendothelial through arachnoid villi containing "pores" large enough to accommodate bacteria. Constant reinfection of the CNS and the inability to contain the infection contribute to the relentless course of the untreated disease and may place particular patients at risk of a slow response to therapy, sequelae, and death despite appropriate antimicrobial therapy.

Blood-Brain Barrier Penetration

The mechanism of bacterial transport across a presumably intact blood-brain barrier (BBB) is largely unknown. The entry of *H. influenzae* into the CSF may depend, in part, on the concentration of organisms in the blood,[83] but this is not the only factor, since encapsulated organisms (e.g., *H. influenzae, N. meningitidis, S. pneumoniae*) frequently invade the CNS, whereas unencapsulated organisms (e.g., *Streptococcus viridans*) rarely invade despite the presence of bacteremia. Early experimental studies that utilized fluorescein-conjugated rabbit antiserum against *H. influenzae* type b (to detect the organism in situ) suggested that the route of invasion into the CSF from the blood stream was the dural venous sinus system.[83] Subsequent experiments provided strong evidence of a hematogenous route of dissemination into the SAS and suggested that nonspecific, sterile, focal inflammation above the cribriform plate (potentially due to underlying bacterial replication in the nasopharynx) facilitated CNS invasion at this site during the ensuing *H. influenzae* type b bacteremia.[88]

Additional studies on the pathogenesis of *H. influenzae* meningitis in infant rats and primates have suggested that the first site of CNS inflammation is the choroid plexus, which has an exceptionally high blood flow, and that bacterial densities early in disease are higher in the lateral ventricles (by way of the choroid plexus) rather than the supracortical, cisternal, or spinal SAS.[118] Cells in the choroid plexus and/or cerebral capillaries may possess specific receptors for adherence of certain bacteria, allowing transport into the CSF. Fimbriae can mediate adhesion of bacteria to epithelial or endothelial cell surfaces,[5] and a recent study has shown that the S fimbriae of *E. coli* specifically bind to the luminal surface of vascular endothelium and to the epithelium lining the choroid plexus and brain ventricles in infant rats as demonstrated in cryostat sections of cortical slices in vitro.[90] This binding is almost totally inhibited by the trisaccharide receptor analogue of S fimbriae and by neuraminidase treatment of the tissue, removing sialic acid–containing residues. Fimbrial phase variation in vivo, to the nonfimbriated phase, may be necessary for the bacteria to pass through the vascular endothelium.[106]

Other microbial virulence factors appear important for CNS invasion of bacteria. As previously discussed, the polysaccharide type b capsule of *H. influenzae* plays a major role in the ability of this organism to cause invasive infections.[81] LPS may also contribute to the pathogenicity of *H. influenzae* as well as of *N. meningitidis* in this early invasive state.[1] The role of outer membrane protein differences among subtypes is less clear, although a recent report has suggested that *H. influenzae* strains with outer membrane protein subtype 1c cause more episodes of meningitis and less epiglottitis than strains of subtype 1,[128] possibly as a result of the ability of each subtype to release LPS in vivo under appropriate conditions. Further studies are needed to clarify these issues, as the mechanism(s) for bacterial transport into the CNS during bacteremia or by spread from contiguous foci of infection remains obscure. Additional studies in this important area may suggest new and novel preventive strategies.

Bacterial Survival Within the Subarachnoid Space

After the successful CSF penetration of the invading pathogen, the dominant host defense mechanisms are inadequate within the CSF to control the infection. Therefore, bacterial meningitis should be considered an infection in an area of impaired host defense (analogous to endocarditis or bacteremia during granulocytopenia) requiring bactericidal antibiotics for optimal treatment. The following host defense mechanisms are potentially operable in the SAS during bacterial meningitis.

Cerebrospinal Fluid Complement–Mediated Opsonic and Bactericidal Activity

Assays for complement components in normal CSF are usually negative or reveal only minimal concentrations.[16,98,116,133] Meningeal inflammation leads to increased (although low) concentrations of complement components within the CSF. The highest concentrations of C3 and C4 were recorded in tuberculous and meningococcal meningitis,[74,147] although similar elevations have been noted in viral and aseptic meningitis, cerebral hemorrhage, ischemia, and seizures. However, the actual concentrations of complement components in the CSF are of only minor value in the differential diagnosis of febrile CNS syndromes.

The importance of this relative complement deficiency in normal and infected CSF may be critical, since specific antibody and/or complement is essential for opsonization of the encapsulated meningeal pathogens, efficient phagocytosis, and removal from the circulation by the spleen.[14,15] These control mechanisms appear to be ineffective in the CSF. An analysis of CSF samples obtained from 18 patients with a variety of forms of meningitis revealed absent or barely detectable opsonic and bactericidal activity.[116] Experiments

utilizing the rabbit model of meningitis have shown that opsonization of a serum-sensitive *E. coli* strain was apparent in vitro when incubated with the CSF from animals with experimental *Staphylococcus aureus* meningitis, but was absent when the CSF was obtained from rabbits challenged with *E. coli* K1.[6] The presence of some measurable opsonic activity may correlate with a favorable outcome, as has been shown in concentrated CSF from 15 of 27 patients with bacterial meningitis.[156] However, all these studies document low or absent functional opsonic and bactericidal activity in the CSF during bacterial meningitis and suggest the need for bactericidal antibiotics for the optimal therapy of this disease.[25,68]

A number of factors may be responsible for the low concentrations of functional complement in purulent CSF, including insufficient transport across the BBB, variable SAS inflammation, enhanced clearance or removal from the SAS, low production rates in the CNS, or degradation at the site of infection. The last possibility is plausible because leukocyte proteases degrade functional complement components (e.g., C3b) with the formation of nonopsonic breakdown products (e.g., C3d). These C3 breakdown products were detected in 100 percent (6/6) of CSF samples from patients with meningococcal meningitis.[147] In the rabbit model of experimental pneumococcal meningitis, the intracisternal inoculation of phenyl-methyl-sulfonyl-fluoride, a nonspecific protease inhibitor, led to a decline in CSF pneumococcal concentrations, perhaps by influencing leukocyte protease–mediated complement destruction.[108] Therefore, leukocyte proteases released into the CSF during bacterial meningitis may degrade complement components crossing through the BBB into the SAS, resulting in inefficient opsonic and/or bactericidal activity at the site of infection.

Cerebrospinal Fluid Antibody

The immunoglobulin concentrations in normal CSF are exceedingly low; the blood-to-CSF ratio of gamma G immunoglobulin (IgG) is 800:1. Although immunoglobulin concentrations increase in the presence of meningitis, they are still extremely low in comparison to simultaneous serum concentrations.[119,147] This relative lack of CSF antibody, in concert with the local complement deficiency, contributes to the regional host deficiency in the CSF during bacterial meningitis. However, local antibody synthesis within the CSF does occur in some forms of infectious meningitis and encephalitis and in patients infected with the human immunodeficiency virus.[52,66,100] The presence of type-specific antibodies in the CSF may be critical for defense against bacterial meningitis. Repetitive intracisternal inoculations into animals of serotype-specific immune serum against pneumococci decrease CSF bacterial concentrations of pneumococci although at rates slower than those obtainable with appropriate bactericidal antibiotics.[108] This effect can be abolished by preadsorption of the immune serum with homologous type III pneumococci for 18 hours at 4 °C. Similarly, pneumococci grow more slowly and reach lower final CSF concentrations after the intracisternal inoculation of immunized rabbits with this organism.[31] Indeed, cures of bacterial meningitis were achieved in the preantibiotic era by the direct CSF instillation of immune serum supplemented with complement.[37,41] The role of type-specific antibodies has recently been clarified by administration of a bactericidal monoclonal antibody directed against the PRP capsule of *H. influenzae* type b.[46] After intravenous administration, the monoclonal antibody crossed the BBB poorly (5.5 percent or less of concurrent serum concentration) despite high serum concentrations of the antibody and the presence of meningeal inflammation.[47] It remains to be determined if there is sufficient complement in the CSF for the optimal function of intrathecally administered antibody in vivo at the site of infection. Therefore, the potential use of monoclonal antibodies and/or complement as adjunctive therapy for bacterial meningitis requires additional study, but systemic administration of these components alone is unlikely to favorably influence the course of the disease.

Cerebrospinal Fluid Leukocytes

One of the major hallmarks of SAS inflammation during meningitis is a CSF pleocytosis, usually predominantly neutrophilic. The mechanism of leukocyte transport across the BBB is unknown, but purulent CSF is chemotactic for leukocytes.[51,152] Experimental models of pneumococcal meningitis have identified at least one chemotactic substance as C5a,[32,86] with chemotactic activity appearing in the CSF 2 to 4 hours before the influx of neutrophils, coincident with the time period when CSF protein concentrations began to rise after intracisternal inoculation. Other non–complement-derived factors may also play a contributing role in the CSF-induced chemotactic process.[32]

The role of the neutrophil in inflammatory responses has recently been examined utilizing cultures of human endothelial cells. The adhesiveness of neutrophils to vascular endothelial cells in vitro is enhanced by factors that are chemotactic for neutrophils,[59,120] such as C5a,[134] which, as described above, has been shown to be chemotactic when present in CSF in the experimental model of pneumococcal meningitis.[32,86] Neutrophil adherence to vascular endothelial cells is enhanced by pretreatment of the endothelial cells with LPS[114,132] as well as with inflammatory cytokines such as interleukin-1 (IL-1) or tumor necrosis factor (TNF).[10,114,142] This "priming" is particularly interesting because a recent report demonstrated that administration of pentoxifylline, a methylxanthine derivative that decreases cytokine-induced neutrophil adherence, to dogs treated with *Salmonella enteritidis* endotoxin reduces endotoxin-induced lung neutrophil sequestration.[146] This endothelial adhesiveness for blood neutrophils can be blocked by transforming growth factor-beta (TGF-β) even in the presence of TNF,[43] suggesting an anti-inflammatory role for TGF-β. A cell surface glycoprotein molecule, endothelial leukocyte adhesion molecule-1 (ELAM-1), and others appear to mediate the adhesion of blood neutrophils to cytokine-activated endothelium.[9] It remains to be determined whether similar mechanisms of adhesion are present between neutrophils and the cerebrovascular endothelium, although a recent study utilizing a monoclonal antibody directed against epitopes of the adhesion receptors (CD18 family) of leukocytes suggested that these receptors are necessary for movement of leukocytes across the BBB in response to microbial products within the CSF in vivo.[137]

Despite the entry of leukocytes into the CSF, host defenses remain suboptimal. The lack of functional opsonic and bactericidal activity in CSF early in the disease course leads to inefficient phagocytosis and often huge bacterial densities in patients with meningitis.[33,34] Gram's stain of purulent CSF before therapy usually reveals that the majority of the organisms remain extracellular.

The relative contribution of the neutrophil to host defenses within purulent CSF remains unsettled, since inflammation within the SAS may exert both beneficial and detrimental ef-

fects. Low CSF leukocyte concentrations are associated with a high mortality from bacterial meningitis in both experimental animal models[45,110] and humans.[34,57,145] However, other studies do not support these observations. The mean survival in leukopenic dogs after intracisternal inoculation of pneumococci was actually longer than in controls with a normal peripheral blood leukocyte concentration (62 versus 47 hours), although the small number of animals studied precluded statistical analysis.[93] A subsequent study[30] of experimental pneumococcal meningitis in rabbits rendered leukopenic by the prior intravenous injection of nitrogen mustard extended these observations. Despite the lack of neutrophils in the CSF of leukopenic animals, the bacterial growth rate, final bacterial concentrations in CSF, and CSF protein, glucose, and lactate concentrations after intracisternal inoculation of pneumococci did not differ from those values observed in normal rabbits. The magnitude of the resultant bacteremia, however, was higher (approximately 100-fold) in the leukopenic animals, suggesting that neutrophils either retard transport of pneumococci from CSF to blood or enhance elimination from the blood stream at extraneural sites. Therefore, bacterial eradication from the CSF during the early stages of meningitis is leukocyte independent, supporting the concept of a regional host deficiency in this disease.

Induction of Subarachnoid Space Inflammation

The process of meningeal inflammation induced by bacteria is poorly understood. Despite the fact that the bacterial strains that most commonly produce meningitis are encapsulated, the capsular polysaccharides are remarkably noninflammatory. Several lines of investigation are being pursued to determine the bacterial cell component(s) responsible for the inflammatory response in the SAS.

Recent studies that examined several bacterial cell surface components of *S. pneumoniae* offer further insight into this problem. CSF inflammatory changes (including pleocytosis) were elicited in rabbits by the intracisternal inoculation of both encapsulated and unencapsulated *S. pneumoniae*, heat-killed unencapsulated pneumococci, and pneumococcal cell walls, but not by the intracisternal injection of heat-killed encapsulated strains or isolated pneumococcal capsular polysaccharides.[138] The pneumococcal cell wall appeared to be the most potent surface component that induced CSF inflammation. Intracisternal inoculation of the major components of the pneumococcal cell wall, a peptidoglycan and a ribitol-phosphate teichoic acid, also induces CSF inflammation,[139] indicating that the generation of free wall components in the CSF during treatment with antibiotics that are bacteriolytic as well as bactericidal may contribute to increased inflammation in the SAS. Indeed, ampicillin-induced killing of pneumococci in vivo, which entails such lysis, is associated with a transient enhancement of the CSF inflammatory response.[140] The CSF inflammatory response was reduced by inhibiting the cyclooxygenase pathway of arachidonic acid metabolism; methylprednisolone and oxindanac were particularly potent inhibitors, whereas indomethacin and diclofenac sodium were less effective.[140] An inhibitor of the lipoxygenase pathway (nordihydroguaiaretic acid) was ineffective in preventing cell wall–induced inflammation. Direct measurements of arachidonic acid pathway metabolites, specifically prostaglandin E_2 (PGE_2), correlated positively with the number of leukocytes in the CSF in response to live pneumococci or pneumococcal cell walls. In addition, CSF PGE_2 concentrations decreased after treatment with cyclooxygenase pathway inhibitors.

Meningeal inflammation was also induced by purified LPS of *H. influenzae* type b in a time- and dose-dependent manner following intracisternal inoculation of adult rabbits.[126] It appeared that the lipid A region of the LPS was responsible for this inflammatory response, since polymyxin B, a cationic antibiotic that neutralizes the bioactivities of LPS by binding to the lipid A region of the molecule,[62] significantly inhibited the inflammatory effect of the LPS. In addition, partial deacylation of *H. influenzae* LPS by neutrophil acyloxyacyl hydrolase reduced the potency of LPS by reducing its tissue toxicity (decreased CSF pleocytosis) without destroying its immunostimulatory potency. A monoclonal antibody to the oligosaccharide portion of the LPS did not reduce the inflammatory potential of this molecule. Similar results were observed with the intracisternal inoculation of *H. influenzae* outer membrane vesicles,[124] which may represent a relevant nonreplicating vehicle in which *H. influenzae* LPS is released into CSF during *H. influenzae* meningitis and thus contributes to tissue injury.

The mechanism through which pneumococcal cell walls or *H. influenzae* LPS elicits inflammation in the SAS has not yet been defined, although evidence is accumulating that these bacterial cell components stimulate the release of inflammatory mediators such as IL-1 or TNF within the CSF in vivo.[8,27,78,135] Several studies, presented in abstract form, have shown that pneumococcal cell wall components induce IL-1 production by human monocytes in vitro[101] and that the intracisternal inoculation of *H. influenzae* LPS into rats leads to elevated CSF concentrations of both IL-1 and TNF within 30 to 120 minutes.[151] Elevated CSF concentrations of TNF have also been observed after the intracisternal inoculation of *H. influenzae* LPS into rabbits, and CSF TNF activity was reduced by pretreatment of animals with dexamethasone.[84] In addition, the presence of TNF in CSF may be specific for bacterial meningitis. This was suggested in a recent study in which TNF concentrations, measured in mice and human subjects with either bacterial or viral meningitis, were found to be elevated in the CSF only during bacterial meningitis.[70]

The source of these inflammatory cytokines within the CNS is as yet undetermined. Many cell types are known to produce IL-1, including brain astrocytes,[27] and recent reports have shown that vascular endothelial cells can produce IL-1 in response to stimulation with LPS or TNF.[72,77,85] Further studies are needed to clarify these issues as they pertain to bacterial meningitis and other CNS inflammatory disorders.

Alterations in the Blood-Brain Barrier

The BBB can be divided into the blood-brain and blood-CSF barriers.[12] The barrier separates the CSF and the brain from the intravascular compartment and acts as a regulatory interface with functions including active transport, facilitated diffusion of various substrates (e.g., hexoses, amino acids), aqueous secretion forming CSF, and, most importantly, maintenance of homeostasis within the CNS.[48,89] The major sites of the BBB are the arachnoid membrane, choroid plexus epithelium, and endothelial cells of the cerebral microvasculature.

Bacterial meningitis, like many other disease states, increases the permeability of the BBB to various substances, including proteins, hexoses, and ions. Previous morpholog-

ic studies have demonstrated an intact arachnoid membrane in animals with experimental meningitis[144]; therefore, the increased BBB permeability characteristic of this disease must occur at the choroid plexus epithelium, the cerebral microvascular endothelium, or both. We have selected the latter barrier site for intensive study.

Cerebral capillaries differ from most other systemic capillaries throughout the body because the adjacent endothelial cells are fused together by pentalaminar tight junctions (zonulae occludens) that prevent intercellular transport. In addition, pinocytotic vesicles are rare or absent and mitochondria are abundant in cerebral capillaries, the pattern opposite to that observed in fenestrated systemic capillary endothelium. Increased permeability of the BBB at the level of the cerebral capillary endothelial cell may result from opening of the tight junctions, from increased pinocytosis, from both alterations, or from processes as yet unknown. Since the CSF is in direct continuity with the extracellular fluid space of the brain parenchyma, bacteria (or their products and/or inflammatory components) could damage the endothelial cells of the cerebral microvasculature, thus resulting in increased permeability of the BBB.

Our laboratory has utilized an adult rat model to investigate the propensity for bacterial meningitis to induce functional and morphologic alterations in the BBB.[94] A reproducible, highly characterized, uniformly lethal (if untreated) experimental model of meningitis in adult rats was developed by the intracisternal inoculation of *E. coli, S. pneumoniae*, or *H. influenzae*. Morphologic alterations in the BBB were assessed by methods to harvest cerebral microvessels from the rats utilizing homogenization, dextran centrifugation, and collection on 53-μm nylon filters,[7,49] followed by transmission electron microscopy examination. Functional alterations of BBB integrity were assessed by measuring the blood-to-CSF transfer of circulating ^{125}I-albumin (normally excluded by an intact BBB) in the identical rats subjected to morphologic analysis. The results clearly document the following: (1) There was a uniform host response to experimental meningitis with all three encapsulated pathogens at the level of the cerebral capillary endothelium; (2) this uniform response was characterized by an early and sustained increase in pinocytotic vesicle formation as well as a progressive increase in separation of intercellular tight junctions observed during the natural history of infection (from 4 to 18 hours after inoculation); (3) both morphologic changes appear to contribute to the functional penetration of albumin across the BBB, with the highest values for albumin entry found at 18 hours when both morphologic changes were evident; (4) inoculation with an unencapsulated *H. influenzae* (Rd strain) led to an increase in pinocytotic vesicle formation, but as the organisms were removed from the CSF by host defense mechanisms (as opposed to sustained CSF and blood concentrations after challenge with *H. influenzae* type b, Eagan strain), separation of tight junctions did not occur (Table 1–1).

Subsequent experiments were performed to define the role of the host leukocyte response on altered BBB permeability late in the infection and to clarify further the importance of encapsulation of *H. influenzae* on these changes.[71] The experimental model described above was modified to include rats rendered leukopenic by the intraperitoneal injection of cyclophosphamide 4 days before bacterial challenge (nadir). New strains of *H. influenzae* were also chosen for analysis: Rd$-$/b$+$/0$_2$ was obtained by transformation of strain Rd using donor DNA from strain Eagan (type b) and Rd$-$/b$-$/0$_2$, which is a spontaneous, one-step, capsule-deficient mutant derived from Rd$-$/b$+$/0$_2$. These strains have identical LPS profiles, but strain Rd$-$/b$-$/0$_2$ does not make any detectable PRP capsule as assessed by currently available techniques.[58,81] The results demonstrated that both normal and leukopenic rats had increased BBB permeability (assessed by ^{125}I-albumin penetration from blood to CSF) 18 hours after inoculation of either encapsulated or unencapsulated strains of *H. influenzae*, although permeability was greater after challenge with the encapsulated strain (Fig. 1–2). In addition, significant increases in BBB permeability occurred in the absence of CSF leukocytes, but the presence of CSF leukocytes augmented changes in permeability. Type b capsule inhibited host clearance mechanisms in the CSF but was not essential for altered BBB permeability, and BBB permeability correlated with bacterial concentrations within the CSF late in the disease course.

Given the above data, the next logical step was to examine BBB injury after challenge with purified *H. influenzae* LPS.[149] Intracisternal inoculation of the LPS resulted in the following: (1) dose-dependent increases of BBB permeability from 2 pg to 20 ng, with significant attenuation in the peak response after challenge with 500 ng and 1 μg; (2) time-dependent increases in BBB permeability with a delayed onset

Table 1–1 Correlation of Morphologic and Functional Alterations of the Blood-Brain Barrier in *Haemophilus influenzae* Meningitis

	Inoculum	Mean Log_{10} cfu/ml CSF	Mean CSF Penetration of ^{125}I-Albumin	Change in Blood-Brain Barrier Morphology
4-hour	Saline	0	0.26%	—
	H. influenzae Rd	5.25	4.12%*	↑PV
	H. influenzae type b	6.26	3.80%*	↑PV
18-hour	Saline	0	1.25%	—
	H. influenzae Rd	3.32	4.64%*	↑PV
	H. influenzae type b	8.06†	8.10%†	↑PV+↑SJ

*$p < 0.05$ compared with control.
†$p < 0.05$ compared with *H. influenzae* type b at 4 hours and *H. influenzae* Rd at 18 hours.
From Quagliarello, Long, and Scheld, 1986.[94]