Beta Hemolytic Streptococcal Diseases

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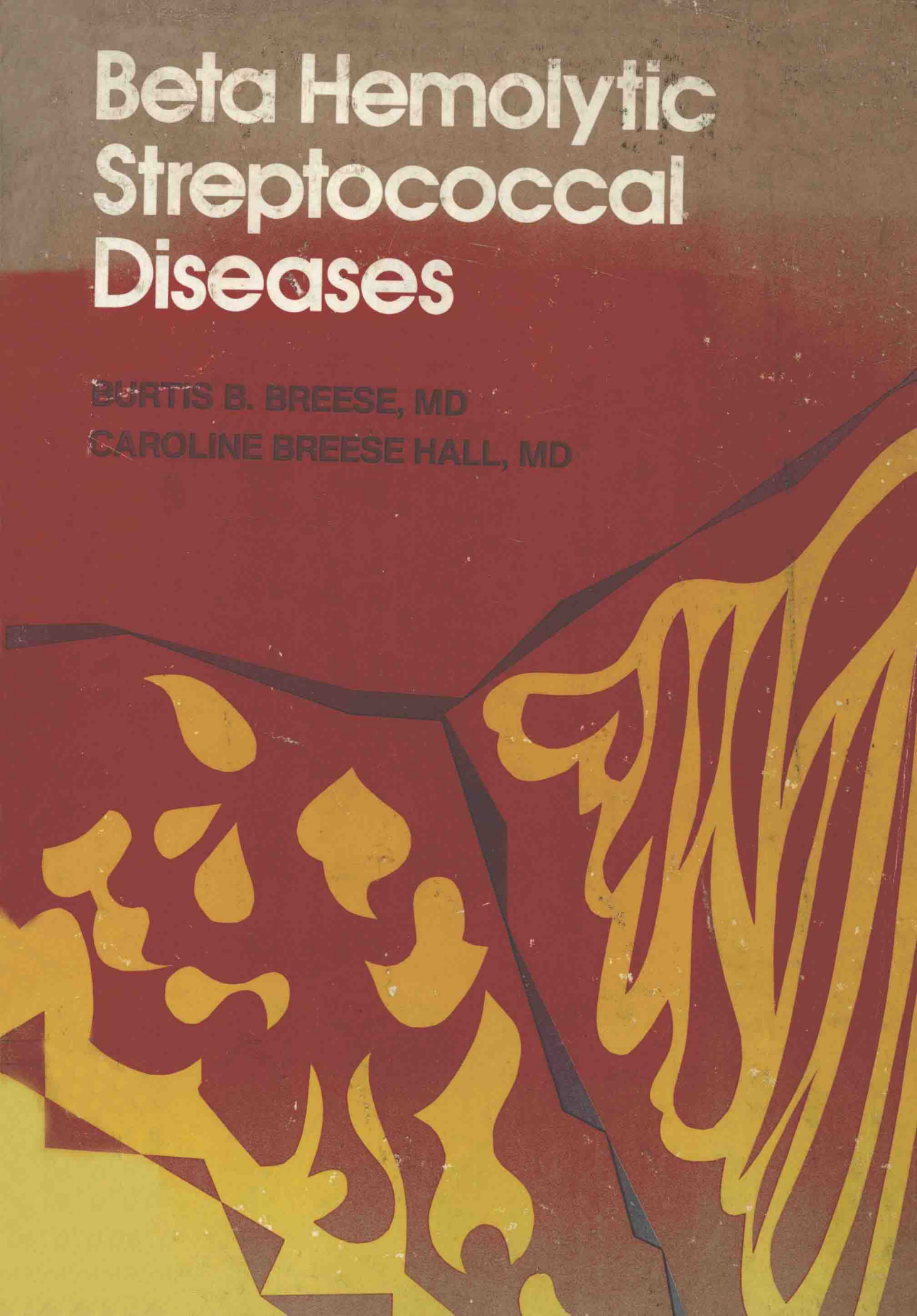

Streptococcal Diseases

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HM
MD
Houghton Mifflin Professional Publishers
Medical Division
Boston

Library of Congress Cataloging in Publication Data

Breese, Burtis B
Beta hemolytic streptococcal diseases.

Includes index.
1. Streptococcal infections. 2. Streptococcus.
I. Hall, Caroline Breese, joint author. II. Title.
[DNLM: 1. Streptococcal infections. WC210 B832b]
RC116.S84B73 616.9'2 78-26749
ISBN 0-89289-400-8

ISBN 0-89289-400-8

LCCCN 78-62749

Sources and Acknowledgments

The material on which this monograph is based comes from several sources — personal observations, and those of my associates during more than thirty years in private pediatric practice in Rochester, New York; my experiences as an epidemiology officer in the Navy during World War II; and very importantly, as with most technical or scientific works, the literature.

The information used from our pediatric practice dates back to 1946 at which time it was first recorded in retrievable form in our patients' clinical records and office laboratory books. Additional bacteriologic data, especially related to grouping and typing were frequently gathered for us in laboratories better equipped with know-how, supplies, and personnel than were we — although we attempted many of these procedures ourselves. These laboratories included those of the U.S. Center for Disease Control in Atlanta, Georgia, under Max Moody, and recently Richard Facklam; those of Charles Rammelkamp in Cleveland, Harry Feldman in Syracuse, Dr. Bergner-Rabinowitz in Jerusalem, and Hugh Dillon in Birmingham, Alabama. Others who processed a limited number of strains so long ago that I have only vague recollections also gave their help. To all we are thankful.

For about the last twenty-five years we have used a special "strep card" record for all patients with positive cultures who participated in special studies and for many other strep-positive patients as well. These specially designed IBM cards contained spaces not only for the streptococcal data but also for other clinical information. The completeness of these records varied depending on how busy we (physicians, office and laboratory personnel) were, and whether the subject was "a study case" — that is, usually one in a therapeutic trial. In general, both initial and follow-up data collection was fairly

good in routine cases and excellent in study cases. Over 15,000 such cards have been analyzed; they form the basis for much of this book.

Most of the photographs in this volume are of private patients seen and photographed by me. Those illustrating cat-scratch disease were kindly supplied by Dr. Andrew Margileth. The source of the others is acknowledged in the text. I thank all of these individuals for permission to include them in this book. Though many of the photographs taken by me are of poor quality because of their age, my photographic ineptitude, or modest equipment, they are irreplaceable because the entities they represent are now so uncommon.

Additionally, over the years our pediatric group has become involved in a number of therapeutic trials in search of the "perfect" drug for streptococcal infection. At first these studies were limited in scope and paid for by us. Later, we received aid from various pharmaceutical firms — Abbott Laboratories, Beecham Laboratories, Bristol Laboratories, Dista Products Co., Hoffman-LaRoche, Inc., Lederle Laboratories, Eli Lilly and Co., Merck Sharp and Dohme, Pfizer Laboratories, Roerig, ER Squibb and Sons, The Upjohn Company, and Wyeth Laboratories. Their contributions to our investigative efforts have varied from monetary grants to drugs, data, or computer service. We also obtained funds from the U.S. Public Health Service in the sixties, those halcyon days of liberal funding.

From the beginning, my associate Dr. Frank Disney helped plan these studies and gather data. In the past 15 years, Dr. William Talpey, our younger associate, and more recently, Dr. John Green have also cooperated in keeping our data current and carrying on the sometimes taxing therapeutic studies we have made as a group. In all of this, our office staff, particularly Noreen Ireland, who has been with us for over twenty years and who loves nothing better than "a good study," has been invaluable. Modest as our contributions are, none would have been possible without their understanding and cooperation.

During these years I have received personal help from a great many people. A list of them includes the names of most of those investigators who have contributed in one way or another to our understanding of streptococcal disease. Many of them are now dead, but more remain active and are still streptococcal "addicts." Of those now deceased, Drs. Armine Wilson, Alvin Coburn, T. Duckett Jones, Frances Schwentker, and Lowell Rantz were particularly stimulating to me and left important streptococcal legacies.

Of those still living, Drs. Rebecca Lancefield, Charles Rammelkamp, Jr., Benedict Massell, Elaine Updyke, Max Moody, Gene Stollerman, Milton Markowitz, Hugh Dillon, and Carol Baker have all made valuable contributions to my streptococcal recollections or to data presented in this volume. I thank them all.

Of all my confreres, I have particularly admired Dr. Horace Hodes, a contemporary of Navy days. Now professor emeritus of pediatrics and departmental chairman at Mt. Sinai Hospital in New York City, he is a scientist for all seasons. In bacteriology, virology, and pediatrics he has been outstanding. Although compared with his other activities those in the streptococcal field have been tangential, he has been interested in this organism for as long as

I have. I therefore greatly appreciate his willingness to write the introduction to this book.

I am also particularly indebted to Dr. Chinh Le, formerly a pediatric fellow in Infectious Diseases at the University of Rochester School of Medicine. With his extraordinarily keen, critical mind and utmost tact, he carefully dissected my original manuscript on treatment and reassembled it into an up-to-date résumé of the subject. He has helped greatly to produce a chapter that is, I think, a credit to us both.

Last, I acknowledge with great pleasure and utmost pride my coauthor Dr. Caroline Hall. Her contribution of Chapter 6 ("Nonstreptococcal Pharyngitis and Differential Diagnosis") and Chapter 12 ("Streptococcal Infections in the Neonate") is most welcome. Dr. Hall is assistant professor of pediatrics at the University of Rochester School of Medicine and Dentistry in the Division of Infectious Diseases. She has contributed a number of clinical and epidemiologic papers and continues active research. In addition, she is responsible for producing the Rochester-based *Infectious Disease Newsletter,* a bimonthly report, which is gaining a reading public far beyond that city. She is also assistant editor of the *American Journal of Diseases of Children.* She has three charming children, Amity, Burry, and Kelly Ann. This last is no doubt irrelevant to her contributions to the text, but then, I am very proud of my three grandchildren.

Burtis B. Breese

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February 1978

Introduction

This book by Dr. Burtis Breese and his daughter, Dr. Caroline Breese Hall, is a remarkable volume in many ways. To a large degree it represents the senior author's ideas about streptococci — ideas which have been developed and tested through a lifetime of experience studying the biopathology of these organisms in a number of different settings.

Perhaps most valuable and most rare is Dr. Breese's careful study of the patients in his own busy private practice. One such study, for example, documents why pediatricians who treat children of middle- and high-income families so rarely see acute nephritis or rheumatic fever in their patients. Dr. Breese and his associates showed that only 4% of the children in their practice had throat cultures that were positive for beta hemolytic streptococci when they were not ill. Furthermore, fewer than half of the cultures yielded a large number of streptococci. This result is in marked contrast to those obtained from children of low-income families, in whom the carrier rate for beta hemolytic streptococci has been found to be as high as 60%.

The author's explanation of this difference is very persuasive, underscoring a failing in our medical-care system that should be corrected. This explanation is set forth in the chapter on carriers. Dr. Breese states that, since most patients with streptococcal disease recover spontaneously, many children return to school untreated. This is especially true of poor children, whose families are seldom aware that "just a sore throat" may cause serious consequences. Knowledge of the potential dangers of streptococcal infections is more widespread among the more affluent, however, and medical advice is thus more likely to be sought by this group. Most pediatricians secure throat cultures in these circumstances, making a specific bacteriologic diagnosis

possible. When this is done, adequate antibiotic therapy is instituted in nearly every case at the present time. For these reasons, a lower carrier rate is found among the more affluent, and the incidence of streptococcal disease and its sequelae is less among them. It is difficult to escape the conclusion that more effort toward popular education and improved case finding on a national and local level would improve our control of streptococcal disease, nephritis, and rheumatic fever.

This volume also contains an excellent section on the microbiology of the streptococcus. Included is much that is of practical importance to the practitioner. The best methods for obtaining cultures and for transporting them are described. Methods of identification of group A streptococci are discussed. A succinct and very useful biologic profile of the streptococcus is included. Means of identifying and differentiating group A organisms are delineated. There is a good discussion of the significance of the number of streptococci found on a culture plate. The methods for grouping and typing streptococci are described in sufficient detail for the reader to comprehend the advantages and limitations of the various techniques. The importance of the various antigens of group A streptococci in disease production and in immunity are discussed with brevity and clarity.

I found the authors' discussion of the carrier state most valuable. In it, they give statistics showing the difference between clinically ill patients and symptomless carriers as a source of infection to members of their families. They call attention to the importance of anal carriers of beta hemolytic streptococci, citing instances in which outbreaks of streptococcal disease occurred on obstetrical and surgical services as a result of hospital personnel who were anal carriers.

Additionally, the publication contains a clear and detailed chapter on the treatment of streptococcal pharyngitis and scarlet fever. The various antibiotics effective against streptococci are discussed in detail. There is an excellent section on antibiotics that describes the pharmacology of penicillin and adverse reactions to it. This chapter includes a very useful table summarizing the clinical aspects of penicillin allergy and showing the relationship of the various types of reaction to immunoglobulin mediators.

Also included in this chapter is a very interesting section on therapeutic failures and on recurrences of streptococcal infection after what ordinarily constitutes adequate penicillin therapy. As the authors state, recurrences are very distressing both to the parents and to the physician. We are conditioned to believe that streptococcal infections are readily cured by penicillin, and a recurrence thus tends to come as an unpleasant surprise. The author's very complete discussion of this complicated subject is the best that this writer has ever seen.

One of the outstanding chapters in the book deals with the epidemiology of streptococcal infections. The authors write that, today, streptococcal disease is endemic, and no large epidemics have occurred since World War II. Nevertheless, it is clear that the incidence of streptococcal respiratory disease remains very high. This conclusion derives very largely from data obtained by physicians practicing outside of institutions. Dr. Breese and his colleagues

are among the foremost contributors to this body of knowledge. They have shown that, in their practice, streptococcocal respiratory illness is responsible for more than 11% of all patient visits to their office. Nearly 25% of the acute infections in these patients were caused by beta hemolytic streptococci. These figures are similar to those for infections of viral etiology.

The latter chapter contains interesting information on the relation between communicability and the point after onset of disease at which treatment of the index case was begun. Breese and colleagues found that, among nearly 500 children treated within 48 hours of onset, the secondary-attack rate among siblings was 16%. In contrast, the secondary-attack rate was 35% among siblings exposed to 156 children who were treated more than 48 hours after the illness had begun. Although this result is to be expected with antibiotic treatment, which rapidly eliminates streptococci from the patient's throat, its documentation reinforces the view that prompt treatment is the best means of preventing secondary cases.

In the epidemiology chapter, the authors include a very interesting discussion of the effect of antibiotic use on immunity. The authors quote their own work, as well as data from others, on the suppressing effect of penicillin on the production of antistreptococcal antibodies. Breese and his colleagues showed that the antistreptolysin titer did not rise as much in patients treated early with penicillin as it did in those who were treated late in their illness. Furthermore, they found 187 penicillin-treated patients whose second attacks yielded a streptococcus of the same M type.

Because of such data, some have recommended that penicillin treatment be postponed until the seventh day of illness to allow the full development of antibodies. However, young adults do not contract streptococcal infection as frequently as do schoolchildren, and the age distribution of streptococcal disease has not shifted from young schoolchildren to older age groups. Dr. Breese concludes that there is no evidence that early antibiotic treatment has really interfered with herd immunity to streptococci. There appears to be no reason to delay early antibiotic treatment.

In the section on epidemiology, Dr. Breese states that he is "reasonably well convinced" that the removal of tonsils and (usually) adenoids reduces the incidence of streptococcal sore throats. Most authors do not share this opinion, and the weight of evidence seems to be tilting against it. In fact, recent studies by Paradise strongly suggest that tonsillectomy does not reduce the incidence of streptococcal infection.

Included in this volume is a clear, first-rate chapter on nonstreptococcal pharyngitis and differential diagnosis of streptococcal pharyngitis. This section, written by Dr. Caroline Hall, deals with the differentiation of viral and mycoplasmal infections from streptococcal pharyngitis. It is one of the clearest and most concise statements of this difficult subject that I have ever read. Dr. Hall shows that viruses cause nearly all cases of pharyngitis in children under two years of age. School-age children have pharyngitis more often than does any other group, with beta hemolytic streptococci being the most frequent etiologic agent. In fact, this situation holds through 14 years of age. Streptococci cause most of the pharyngitis in children 9 to 14 years

old, and viruses are isolated and identified in only 10% of cases. The occurrence of streptococcal pharyngitis declines during the teens, at which point viral infections become more prominent. Among college students, pharyngitis is again more often caused by viruses than by streptococci.

In addition to the difference in age incidence, Dr. Hall cites a number of clinical features that help differentiate streptococcal pharyngitis from viral and mycoplasmal infections. For streptococcal infection, these factors include an abrupt onset and a high frequency of systemic symptoms, such as headache, nausea, and vomiting. In contrast, nonbacterial infection usually begins more gradually; and, while general malaise may be present, symptoms are more localized to the throat, with nasal congestion and discharge, sneezing, laryngitis, and coughing being prominent. Enlarged and tender cervical lymph nodes are frequently present in streptococcal infection, in contrast with viral disease. An excellent table that summarizes other important differential features is delineated in the chapter. Dr. Hall also sets out excellent capsule summaries of the epidemiology and clinical profile of the viruses involved in the differential diagnosis of streptococcal disease. These include *Mycoplasma pneumoniae,* influenza, parainfluenza, respiratory syncytial virus, herpesviruses, and adenoviruses. This section will certainly be of very great value to the clinician who is faced with treating patients with respiratory infections many times each day.

This writer found most interesting Dr. Hall's discussion of the change in the immunity to herpesvirus that has occurred in our population during the past 30 years. There is good evidence that before World War II, the great majority of our children became infected with herpes simplex (herpes hominis) virus and had antiherpes antibody by the time they were 10 years old. The situation today is quite different; some authors have found that in some studies only 30% of students have antibodies against herpesvirus when they enter college. Furthermore, it is probable that the primary herpesvirus infection is more likely to be pharyngitis rather than gingivostomatitis. Dr. Hall cites a study of college students, made between 1965 and 1971 in North Carolina, showing that herpesvirus hominis was the most common etiologic agent causing pharyngitis. About 25% of the cases were caused by this virus, and only 18% by group A streptococci. The study also pointed out that on clinical grounds, herpes pharyngitis usually could not be readily differentiated from streptococcal pharyngitis: an exudate is frequently present in both kinds of pharyngitis, and classical herpes lesions were present on the buccal mucosa in only 11% of the herpes patients.

Also included is a very thorough discussion on group B beta hemolytic streptococcal infection in the neonate. The authors trace the rise of the importance of this type of disease and cite references to show that it has replaced *E. coli* as the most dangerous organism in the neonatal period. The characteristics of group B streptococcal disease occurring in the first few days of life are described and contrasted with the clinical picture of infection occurring after the infant is several weeks old. The microbiology, epidemiology, and pathogenesis are discussed, and various forms of antibiotic treatment and their limitations are described.

The possibility has been raised in the past few years that penicillin given to every newborn infant in the delivery room might reduce the incidence of the early form of group B streptococcal disease. The authors do not discuss this point, probably because evidence for this hypothesis has been entirely retrospective in nature. A prospective study giving positive results has been reported in abstract from Dalhousie University during the very recent past, but even this report does not deal with an alternate-case, double-blind study. Such studies are being conducted at at least two medical centers at the present time.

Since group B streptococcal infections of the newborn are so important, this writer believes that the information on possible prevention of these infections should be summarized briefly herein, with the understanding that when the studies previously referred to are completed, they may show that immediate injection of the newborn with penicillin is not useful.

In the 1940s, several authors who were not satisfied with silver nitrate prophylaxis for gonorrheal ophthalmia decided instead to administer 50,000 units of penicillin to every newborn infant by intramuscular injection. This method was instituted by the writer in 1952, when the Mount Sinai Hospital of New York opened its obstetrical service and its nursery for newborns. Since that time, every infant born at the Mount Sinai Hospital has been given 50,000 units of aqueous crystalline penicillin G by intramuscular injection before leaving the delivery room. Between 1952 and 1978, more than 100,000 infants have been born at Mount Sinai, and all have been given penicillin prophylaxis in the delivery room. Not one case of gonorrheal ophthalmia has occurred among these infants. Published studies made on a large sample of these infants at one year and again at four years of age showed that tests for sensitivity to penicillin gave the same results as that for a group of age-matched controls.

In 1975, Dr. Alex Steigman, a member of the Mount Sinai Hospital staff, noted that the incidence of the early type of group B streptococcal disease at Mount Sinai Hospital appeared to be zero. It is certainly possible that the hospital's bacteriologic techniques are faulty. Against this, however, is the fact that we have found that the colonization rate of our newborns for group B streptococci is similar to that reported in the literature. Furthermore, the incidence of the "late" form of these infections is also similar to that experienced by other hospitals. Dr. Steigman has raised the possibility that the single injection of penicillin, given immediately after birth, limits the multiplication and disease-producing capacity of group B streptococci, although it does not prevent colonization.

The report from Dalhousie referred to above was presented at the 1978 annual meeting of the Society for Pediatric Research. An abstract of this paper (by David J. Lloyd and colleagues) was published in *Pediatric Research,* Volume 12, 1978, page 495. These workers found that, from 1969 to 1974, the mortality rate from group B streptococcal disease among their newborn infants was 0.58 per thousand for all live births. For premature infants it was 8.3 per thousand. In June 1974, these authors began to give penicillin to all premature infants in their hospital. The death rate from

group B streptococcal disease among these infants from June 1974 to November 1977, when the penicillin regimen was in force, was zero.

This volume also contains a most complete bibliography that includes very recent references as well as important papers published at the beginning of the modern era of streptococcal biology. The book contains numerous helpful tables and graphs that illustrate the text. There are numerous excellent clinical photographs taken over the many years of Dr. Breese's practice which vividly illustrate many of the clinical points made in the text.

Beta Hemolytic Streptococcal Diseases is an essential book for every physician who is interested in the biopathology of one of the most important of the pathogenic bacteria that afflict mankind. It will also be most useful to the practitioner for the many practical details of diagnosis and treatment that it contains.

Horace L. Hodes

Contents

chapter 1

Historical Perspectives

Of the infections afflicting man, those caused by the streptococcus have been and still are among the most common and frequently among the most devastating. Even a casual perusal of the history of this organism's assaults on the health and life of man, and man's two-century effort to contain them leaves one with grudging appreciation of the potential and adaptability of these tiny organisms. On the other hand, one must admire the host of workers whose discoveries, dedication, and ingenuity have made possible a substantial but precarious control.

In no case is this history better illustrated than in that of puerperal sepsis, that fearsome scourge of lying-in hospitals which was responsible for the death of thousands of young women in the prime of life. In an admirable summary of the history of the disease Watson (JAMA, 206:344, 1968) notes that Dr. Charles White in Manchester, England and Dr. Alexander Gordon in Aberdeen, Scotland in 1773 and 1775, respectively, recognized the contagion of puerperal sepsis. The former devised rules for its prevention which included "good ventilation, clean room, clean linen, isolation of affected patients in separate rooms, and immediate removal of those affected from other patients." Dr. Gordon, from observation of 77 patients, concluded that the disease was a "specific contagion—for the disease seized only such women as were visited or delivered by a practitioner or taken care of by a nurse who had previously attended patients affected by the disease." He admitted that "I myself was the means of carrying the infection to a great number of women."

It was almost a century later that Holmes in America (1843) and Semmelweis in Austria (1861) published their classics on the infectious

nature and iatrogenic origin of these fatal illnesses. As might be anticipated, this thesis was not popular with entrenched medical opinion and it was only when Pasteur in 1889 demonstrated the presence of and later cultured the streptococcus in chains from the lochia, uterus and blood of patients that this thesis was accepted as fact.

Of similar interest to the history of puerperal sepsis is the history of scarlet fever, a fearsome disease whose known relation to the streptococcus has only relatively recently (1924) been proven. In 1971, the *American Journal of Diseases of Children* published as a medical classic a translation of "Streptococcal Erythemas and the Relationship to Scarlet Fever." In the 1907 original, Gabritschewsky had described his and others' experiments in Moscow. He stated, "The evidence in human beings that punctiform erythema and all the other symptoms of scarlet fever appear after the administration of scarlet fever vaccine made from streptococci represents a decisive factor favoring recognition of the streptococcus as the specific agent of scarlet fever." Even earlier (1893) Beige, based on his own clinical observations, had linked scarlet fever to the streptococcus.

These early studies were largely ignored for the next twenty years until the husband-and-wife team of George and Gladys Dick in Chicago showed, by inoculation of volunteers (including themselves), that a strain of streptococcus isolated from a case of scarlet fever could produce the disease in those individuals who showed a local erythema to an injection of streptococcal toxin (Dick positive). No disease developed in those who showed no such reaction (Dick negative). After an extensive series of tests confirming their original observations they wrote in 1924: "Since the streptococci used in these experiments have fulfilled all the requirements of Koch's laws, it may be concluded that they cause scarlet fever."

However, although these basic facts have now long been known, much of the more effective control of streptococci has occurred within the last fifty years. During this time it has been my privilege to be an observer and a participant in the unfolding drama of the continuing struggle between man and this infamous bug. These have been eventful years.

Much of the ground work on which these efforts were based had been laid in the years between World War I and II. An important part of the basic bacteriology was done in the Rockefeller Institute. It was there just after World War I that Brown classified the streptococci on the basis of their activity against mammalian red cells. Later, also at the Rockefeller Institute, Rebecca Lancefield's meticulous work further subdivided streptococci into groups and types. This institute—housed in the unpretentious yellow brick building—was a mecca for some of the world's foremost bacteriologists of the time, Dochez, Avery, Swift, and Rivers, and became a mecca for young scientists. The streptococcal laboratories there attracted many of the best young minds and a large proportion of the investigators in the field served or still serve time there.

Meanwhile in the streptococcal laboratories at Colingdale, England, with similar objectives and quality of investigators, the brilliant Griffith (later killed during a bombing of London) had perfected the alternative "T

method" of typing streptococci. This is now utilized widely throughout the world particularly in studies on pyoderma.

But the investigations at this time were not limited to bacteriology. In the late twenties and early thirties, a great deal of well-deserved clinical attention was directed toward the nonsuppurative complications of streptococcal illness—namely acute glomerulonephritis and rheumatic fever. It was then (1931) that I—as a newly licensed physician—began to do battle with rales, rhonchi, and cardiac murmurs. There were plenty of such cardiac murmurs in most of the hospital wards as the result of acute rheumatic carditis.

At the Johns Hopkins Hospital where I served my first internship, each of us was required to spend a month in the hospital bacteriology laboratory. Here the beta hemolytic streptococcus became a familiar and readily recognizable visitor. On the contagion wards its effects were also apparent often as fulminant scarlet fever or its complications.

In the following year at the Boston Children's Medical Center, its tragic potential was sadly underscored by the isolation in our laboratory of these organisms from the blood stream of an admired professor's wife confirming a fatal sepsis. Subsequently, on the wards of the New York and Strong Memorial Hospitals, encounters with streptococcal illness—ranging from simple pharyngitis to meningitis (and much of it nosocomial)—left little question that this was an important primary disease. And, the constant influx of patients with rheumatic fever, chorea and nephritis emphasized its significance as the source of nonsuppurative, but highly important secondary illness.

In Boston, T. Duckett Jones, the fiery and charming Virginian, and his confreres had brought together many of the unfortunate young victims of the disease in the wards of the Good Samaritan Hospital. For over forty years this exemplary institution and its able staff served as a center for clinical diagnoses, treatment, teaching, and research on rheumatic fever and the role of the streptococcus in that disease. This role had been firmly established by Alvin Coburn, who, as a young resident at Presbyterian Hospital in New York City, had shown beyond reasonable doubt by his observations on nurses that the streptococcus was the villain in these often tragic dramas. His classic monograph, "The Factor of Infection in the Rheumatic State," published in 1931, convinced most of the medical profession that in addition to scarlet fever, pharyngitis, and their common suppurative infections, the streptococcus was also the cause of rheumatic fever. Thus, this disease—along with acute glomerulonephritis, which had, since its original description by Bright in 1836, been linked with scarlet fever—was finally recognized as a complication of streptococcal infection. What the pathologic mechanism was, how the disease could be prevented and cured were unclear except that answers to these obscurities would probably be dependent on the control of streptococcal infection. With the means available to us in the thirties this goal was largely a hope.

Then came the advent of chemotherapy with the sulfonamides. Introduced in Europe after sitting on the shelf as an unused dye for many years