INFECTIONS IN OBSTETRICS AND GYNECOLOGY

DAVID CHARLES, M.D.

VOLUME 12 IN THE SERIES
MAJOR PROBLEMS IN
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1980 W. B. Saunders Company Philadelphia • London • Toronto

W. B. Saunders Company: West Washington Square
Philadelphia, Pa. 19105

1 St. Anne's Road
Eastbourne, East Sussex BN21 3UN, England

1 Goldthorne Avenue
Toronto, Ontario M8Z 5T9, Canada

Library of Congress Cataloging in Publication Data

Charles, David.

Infections in obstetrics and gynecology.

(Major problems in obstetrics and gynecology; v. 12)

Includes index.

1. Generative organs, Female—Infections. 2. Communicable diseases in pregnancy. I. Title. II. Series. [DNLM: 1. Infection. 2. Genital diseases, Female. 3. Obstetrics. W1 MA492V v. 12/WP140 C475i]

RG39.M25 vol. 12 [RG218] 618s [618] 79-67789

ISBN 0-7216-2492-8

Infections in Obstetrics and Gynecology ISBN 0-7216-2492-8

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Foreword

At last an authoritative monograph on infectious diseases as they affect obstetric and gynecologic patients is available for students, residents and fellows in training, and practitioners. In this rapidly changing aspect of our discipline, it is particularly timely. It brings us up to date on considerations of diagnosis and management that are critical to patient care. Moreover, it is especially practical, comprehensible, and assimilable. This is no small accomplishment in view of the range and complexity of the subject matter it covers.

Perhaps in no other field of medicine is the disease under study so all-pervading, ever-present, and demanding. Its ubiquitous nature insists that each of us, expert and novice equally, be knowledgeable. There can be no doubt that this book will provide the foundation necessary to ensure complete understanding. By its very nature, the spectrum of relevant pathogenic organisms varies with time, as does the panoply of clinical manifestations produced. It follows that diagnostic criteria must also adjust to current ecology and that therapeutic principles will perforce accommodate as well. Both needs are here addressed and amply fulfilled for the reader.

The challenges faced daily in pursuing the practice of obstetrics and gynecology all too commonly involve infectious disease processes. Without the kind of preparation offered by the material in this volume, the physician is ill-equipped to face those challenges. It is obvious that such a deficiency constitutes a detriment to patients at risk. Advice for evaluating and treating them is presented here in a direct and practical manner so as to prove especially useful. Particularly commendable is the splendid review, in depth and in perspective, of therapeutic agents for combating specific infections. Inclusion of investigational drugs offers the added advantage of extending the practical applicability of the information for some time into the future.

The expertise that Doctor Charles brings to this subject is widely recognized. His contributions to the field are extensive. His literary skills are especially admired, and the reader is sure to derive pleasure from the rhetoric — distinct indeed from the dry scientific prose to which we are usually exposed in our literature. This style is achieved without loss of clarity. He has been able to provide us with a source of considerable wisdom in a most palatable form. It is with special pride, therefore, that we present this latest edition to the series of monographs on Major Problems in Obstetrics and Gynecology, continuing our tradition of excellence. Because this subject is so crucial to the practice of obstetrics and gynecology, we are confident that the rewards to the reader will be great.

EMANUEL A. FRIEDMAN, M.D., SC.D.

Preface

In the field of obstetrics and gynecology we are confronted with the fundamental processes of human life, and the time has passed when professional requirements can be satisfied by technical dexterity and adherence to simple rules of professional behavior.

The diagnosis, treatment, and prevention of infection are matters of singular importance in both obstetrics and gynecology. In former years the scourge of puerperal sepsis taxed all the resources available to the obstetrician and consequently was a topic dealt with in all textbooks. However, with the advent of the antibiotic and chemotherapeutic era, infection has for some time received only cursory attention by obstetricians and gynecologists.

Were it solely to reiterate what has been said in the past, this book would serve no useful purpose. However, concepts have changed, as has the bacterial flora. It is no longer possible to precisely classify microorganisms that are associated with humans as either pathogens or nonpathogens. The ascription of a causative role often depends on the circumstances in which the microbe appears rather than on its nature. Bacteria and viruses that in former years were considered to be unimportant and seldom associated with disease are now being consistently identified with clinical syndromes. Other microbial agents, such as the mycoplasmas and species of the genus *Bacteroides,* are assuming a role of increasing importance in obstetrics and gynecology.

Furthermore, the physician should take stock of the advances, or lack thereof, that have been made in diagnostic and therapeutic approaches. For example, *Trichomonas* vaginitis is a disease afflicting all strata of society, and despite the availability of a variety of topical and oral preparations everyone realizes that far too often cures are inconsistent and evanescent. Emotional factors can be associated with this entity, and the failure to adequately assess or treat such problems may account for the disappointing cure rate. Consequently, genital tract infections, such as vaginitis, tax the skill of the physician and may cause frustration because the therapeutic success is frequently no greater and sometimes less than that of earlier clinicians.

Because female genital tract infections usually result from a heterogeneous group of organisms, multidisciplinary approaches are necessary to identify and ascertain their role in the overall disease process. It is advisable to thoroughly evaluate genital tract infection using, whenever feasible, modern bacteriologic techniques. Vaginal biota vary at different stages of womanhood and, as in all areas of clinical medicine, a correct diagnosis is mandatory for successful therapy. The mere prescribing of antibiotics or chemotherapeutic agents without recognition of the etiology must be discouraged. Moreover, the physician must be aware of the risk of overtreatment and the possible occurrence of iatrogenic complications. The latter point can be well illus-

trated by the extensive vaginal moniliasis that may emerge during or following prolonged therapy with broad-spectrum antibiotics.

Since it is impossible to include all infections of womanhood in a small volume, certain topics that have compelling practical applications in obstetrics and gynecology have been emphasized.

Finally, if this volume can serve as an impetus to the physician for the recognition of diagnostic dilemmas, the acquisition of new knowledge, and the negation of therapeutic empiricism, the author will consider his task complete.

Contents

Chapter One

THE CHANGING MICROBIAL ECOLOGY OF INFECTIONS

As many of the primary infections of *Homo sapiens* are controlled by improved public health measures and therapeutic advances, hospital-acquired infections assume increasing importance. They account for a significant proportion of infectious morbidity and mortality in industrialized nations. Hospital-acquired, or nosocomial, infections are a current major problem in preventive medicine. The ecology of nosocomial infections is a complex, although not a new, phenomenon. New aspects repeatedly appear, adding to the knowledge of these infections, which have in fact always been a menace to hospitalized patients. Schaffner (1976) noted that as medicine becomes more venturesome and aggressive both diagnostically and therapeutically, the hospital environment changes and new ecologic salients are discovered. Surveillance studies are essential to identify emerging problems and evaluate measures for their control and thus furnish us with qualitative and quantitative data on the changing microbial ecology of infections.

CHANGES IN THE NATURE OF ORGANISMS

There is an increasing awareness of certain changes in the nature of infection occurring in hospitals, particularly in the types of microflora. Most notably, gram-negative bacilli have attracted interest during the past decade, and other groups of organisms have also become more common. Finland (1970, 1972, 1973), in a series of peerless studies, has demonstrated the shift from gram-positive to gram-negative organisms since the advent of modern antibacterial therapy. He and his associates (1959) drew attention to the profound changes in the number and character of infections that have been encountered since the introduction and widespread use of antibiotic agents.

At that time they emphasized the numerous outbreaks of staphylococcal infections in nurseries and maternity wards as well as the high incidence of wound infections due to the *Staphylococcus*. They were concerned about the prevalence and diversity of staphylococcal resistance to antimicrobial agents. Their hope that new drugs would eliminate such infections as a cause of serious disease has always been frustrated by the emergence of new drug-resistant strains. Staphylococcal infections remained a serious problem despite the vast array of antimicrobial agents available at the time of their communication. These investigators also pointed out the increasing prevalence and seriousness of infections due to various aerobic gram-negative bacilli that were considered to be pathogenically innocent constituents of the fecal flora, such as *Escherichia coli, Klebsiella, Proteus,* and *Pseudomonas*. Concern about infections attributable to these organisms was due to their low *in vitro* sensitivity to available antibiotics. This matched the difficulty that arose in the therapy of staphylococcal sepsis.

Drug-Resistant Organisms

Finland (1970) stated that the increased frequency of serious infections and the changing etiologic patterns were not peculiar to large hospitals for the medically indigent and had been observed in most institutions. When he evaluated the major pathogens in bacteremic patients in 1935 and 1965 he found that the group B *Streptococcus* was isolated on 17 occasions in the preantibiotic year compared with only 4 times in 1965. On the other hand, gram-negative bacilli were isolated from 12 patients in 1935 compared with 50 patients in 1965. He noted that the reduced frequency and fatality rate of bacteremic infections due to group A *Streptococcus* is associated with the marked susceptibility of this organism to most antibiotics in use. The existence of many resistant strains made the reverse true of infections caused by gram-negative bacilli.

Finland demonstrated a relationship between the intensive use of antibiotics and an increased occurrence of resistant strains of several bacterial species. Consequently, he alerted physicians to the need to limit the prescription of antimicrobial agents by avoiding their unnecessary and uncontrolled use. He indicated that the use of large doses of multiple agents also eliminates the normal and susceptible organisms and thus allows replication of resistant but usually innocent species, some of which then become pathogenic. In his view, it was important that new antimicrobial agents be introduced in a way that would negate or at least minimize the development and dissemination of organisms resistant to such drugs.

Finland (1972) indicated that the changing pattern of susceptibility of pathogenic bacteria to antimicrobial agents has emanated from the inordinate use of multiple broad-spectrum antibiotics in excessive dosage. He also concluded that the widespread use of prophylactic antibiotics has promoted the emergence of resistant strains of many bacterial species. Reversal of this trend may follow if appropriate criteria are adopted for the use of antibiotics. Finland (1972) concludes with the statement, "Each new discovery of an antibiotic, or a device, or of a procedure, carries risks that must be evaluated and weighed for possible untoward effects, among which the occurrence of serious, drug resistant infections must always be borne in mind."

Increase in Gram-Negative Organisms

In a later report from a surveillance study of nosocomial infections, Finland (1973) found an increase in gram-negative bacilli between 1967 and 1970. Gram-negative bacilli other than *Escherichia coli* composed 80 per cent of the isolates from such infections in 1970 as compared with 47 per cent in 1967. He found that the most significant increases were in the number of isolates of *Klebsiella-Enterobacter* and *Pseudomonas aeruginosa*. He also found a higher incidence of *Serratia marcescens* infections.

Pollack and associates (1972) investigated the pattern of gram-negative colonization and antibiotic resistance in 300 cultures obtained from the hands and throats of 56 patients admitted to a medical unit. They found that 51 per cent of the hand cultures and 35 per cent of the throat cultures were positive for at least one gram-negative organism. *Klebsiella* species were isolated from 20 per cent of the cultures. When they compared hand colonization rates on admission with those obtained two weeks later they found that *Klebsiella* species had increased almost fourfold, while throat isolates had more than doubled. Of their 56 patients, 31 received no antibiotics during their hospitalization, and in this group there was no significant evidence of colonization. The increase in colonization with *Klebsiella* occurred almost entirely in the 25 patients who received antibiotics. In the latter group, 29 per cent of the *Klebsiella* strains demonstrated multiple-drug resistance.

Since the number of patients in this study is small, a larger series would be required to substantiate these observations. The study does demonstrate, however, the acquisition of resistant gram-negative organisms following hospital admission. It also implicates transferable episomes as mediators of antibiotic resistance in a significant proportion of these organisms. The importance of colonization with resistant strains of *Klebsiella* has also been reported by Selden and coworkers (1971), who found that 14 of 31 patients so colonized were infected by acquired resistant strains.

EPIDEMIOLOGY OF INFECTIONS

Altemeier and associates (1973) stated that despite the availability of antimicrobial agents, clinical and laboratory experience indicated that the overall incidence of infections in surgical patients has not altered significantly but that there have been significant changes in the etiologic agents. They report that between 1942 and 1956 about two thirds of surgical infections were caused by gram-positive cocci. However, since 1965 they have noted, as did Finland (1972), a greater incidence of gram-negative infections, with a relative diminution in the incidence of those due to gram-positive cocci. Between 1956 and 1970 a 14-fold increase in the number of gram-negative infections had occurred in their area; by 1973 such organisms accounted for two thirds of the infections. Although the reasons for this increase cannot be explained, they may involve the widespread use of antibiotics, the rapid extension of new and complex surgical and diagnostic procedures in elderly and high-risk patients, and changes in host resistance.

SECONDARY INFECTION

These authors indicated that the changing bacteriologic patterns could be ascribed to secondary infections developed during antibiotic therapy. Secondary bacterial infections have long been known to complicate other diseases caused by viruses and bacteria. All the references cited show that the introduction of effective chemotherapeutic agents, an advance that might have augured a decrease or even eradication of this problem, has in fact been followed by an increased frequency of secondary invasion.

Many species of the organisms involved have in the past been considered either as saprophytes or as minimal pathogens. Secondary bacterial invasion may result from an increase in number of a potential pathogen in the normal ecosystem after exposure to an antimicrobial agent. The indigenous microflora of the skin, oropharynx, upper respiratory tract, urethra, and vagina, when exposed to therapeutic doses of any antibiotic, show moderate to profound changes in the genera, species, and number of the population.

Drugs and Secondary Infections

In this regard, antibiotic combinations or broad-spectrum agents exert greater effects than do drugs with limited antimicrobial activity. Large doses of penicillin G inhibit most gram-positive organisms and allow proliferation of such microorganisms as *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, and *Serratia marcescens* as well as penicillin-resistant strains of staphylococci. In addition to inducing changes in the bacterial ecology of patients, the administration of antibiotics may lead to profound alterations in the fungal population. Antibiotics alter the number and variety of bacteria so that fungi normally present replicate, and antimicrobial agents, such as the tetracyclines, stimulate the growth of and increase the pathogenicity of *Candida* species. There is, however, evidence that hospitalized patients acquire enteric bacteria and pseudomonas on various areas of the skin; these organisms appear to emanate from the patient's own intestinal tract. Pseudomonas are also acquired by contact with intermittent positive-pressure apparatus or are disseminated from patients who carry them as members of the intestinal flora.

PSEUDOMONAS INFECTIONS

Infections caused by *Pseudomonas aeruginosa* have become more prevalent during the past decade. Bennett (1974) reported that about 7 of every 1000 hospitalized patients develop an infection with this organism. Such infections are often superinfectious and may affect any organ. The use of antibiotics, immunosuppressive agents, and radiation therapy as well as supportive procedures, such as intravenous infusion and urethral catheterization, increases the patient's susceptibility to infection.

Infection with this microbe is a major cause of morbidity and mortality in patients with altered immunologic status. Infections with *Pseudomonas aeruginosa* are also favored by circumstances that favor infections with *Escherichia coli*. Infections due to this

organism are hospital acquired and are preceded by colonization or antimicrobial therapy or both more often than most enterobacterial infections and also lead more often to septicemia and death. This organism is liable to infect neonates and, specifically, premature infants. Gastrointestinal colonization of such infants is more likely when humidification equipment is used and when incubators are poorly sterilized. Finland (1972) stated that *Pseudomonas aeruginosa* was rarely a cause of invasive infection before the era of modern chemotherapy but came into prominence in the 1960's and accounted for about 8 per cent of all cases of bacteremic infection in his hospital.

KLEBSIELLA INFECTIONS

Klebsiella species are ubiquitous and frequently responsible for hospital-acquired infections, particularly in intensive care units. However, urinary tract infections are more often primary than secondary. Septicemia may be secondary to such urinary tract infections, although on occasion it may complicate klebsiella pneumonia.

Price and Sleigh (1970) indicated antibiotic therapy played a major role in one outbreak of pneumonia and meningitis due to *Klebsiella aerogenes*. They found that the isolation of *Klebsiella* organisms from the sputum of patients in an intensive care unit correlated with the annual consumption of ampicillin and cloxacillin by patients in the unit between 1967 and 1969. Furthermore, cessation of all antibiotic therapy in a facility was associated with termination of the epidemic of pneumonia and meningitis caused by multiple drug–resistant *Klebsiella* species.

It has been well documented that the incidence of resistant bacterial strains of *Klebsiella* is reduced if usage of antibiotics that may select for such resistance is restricted. Bulger and associates (1970) reviewed the number of *Klebsiella* species that were resistant to streptomycin over a ten-year period in their hospital and showed a direct correlation between the amount of this aminoglycoside prescribed each year and the number of resistant strains. Between 1958 and 1968, the incidence of streptomycin-resistant strains of *Klebsiella* fell progressively from 53.3 per cent to 8.7 per cent and correlated with the fivefold reduction in streptomycin usage.

Noreiga and associates (1975) demonstrated that the incidence of gentamicin-resistant strains of *Klebsiella* declined rapidly after the restriction of the drug but increased rapidly when its prescription was resumed. Forbes and associates (1977) reported an outbreak of infection with gentamicin-resistant *Klebsiella pneumoniae* which affected 42 patients, of whom 37 were postoperative cases. In this series, 33 patients (78 per cent) had received broad-spectrum antibiotics, and of these 22 had received gentamicin. In 29 of the 42 cases a probable patient source of cross infection was identifiable. Restriction of gentamicin usage played a significant role in the reduction of the outbreak of this nosocomial infection.

These investigators indicated that gentamicin resistance was transferable from the strains of klebsiellae isolated to *Escherichia coli*, and the recipient organism was shown to acquire resistance to streptomycin, kanamycin, sisomicin, tetracyclines, and B-lactam antibiotics as well as gentamicin. In addition, they found that six of the patients from whom klebsiellae were isolated also harbored other species of Enterobacter that possessed similar transferable resistance determinants. These investigators emphasized the need for adherence to well-established but often overlooked principles for the control of infection and a more critical attitude toward the use of antibiotics.

Schaberg and associates (1976) reported that *Klebsiella* species are a frequent cause of urinary tract infections, especially in patients who require indwelling catheters. These organisms, by virtue of resistance plasmids, are well adapted to produce infections that are recalcitrant to the action of most of the available antimicrobial agents. They consider that breaks in technique by the physicians and staff who manage patients with indwelling catheters are responsible for the initiation and spread of such infections.

Thomas and associates (1977) reported an outbreak of *Klebsiella* infections in their hospital; of the 692 patients, 192 (28 per cent) harbored gentamicin-resistant strains. They demonstrated how antibiotic-resist-

ant, gram-negative bacteria have emerged as a major infectious problem in both medical and surgical patients. Because of the current dependence on gentamicin sulfate in hospital practice, when gentamicin-resistant organisms appear they frequently herald outbreaks of infections due to such gram-negative bacilli.

Virtually every survey of hospital-associated infection has revealed that urinary tract infections account for at least one third, usually following instrumentation or catheterization. Therefore, the inappropriate use of indwelling Foley catheters, the lack of adequate asepsis at the time of catheter insertion, the frequent disconnection of catheter and drainage bag for collection of urine samples as well as the placement of drainage bags above bladder level, which facilitates a backflow of potentially contaminated urine, should not be permitted.

SERRATIA INFECTIONS

During its early history, *Serratia marcescens* was considered by clinical microbiologists to be a harmless saprophyte. So firm was this belief that pigmented strains were used by investigators to examine bacterial trends and distribution in hospitals. *Serratia* has been increasingly implicated in clinical tissues and has been shown to cause respiratory, urinary tract, and wound infections as well as septicemia with a high mortality. Until the 1970's, however, only sporadic reports, generally related to isolated patients, have implicated *Serratia marcescens* as a primary or secondary cause of infection at different body sites.

Although the pathogenic potential of this organism has been known for some time, only recently has it been recognized as a problem of disquieting magnitude on the basis of its repeated isolation in hospital practice. Mostly nonchromogenic strains of *Serratia* are isolated as nosocomial pathogens. Kwitko and associates (1977) encountered 34 cases of *Serratia* infection in their hospital in a three-month period and state that 31 patients (91 per cent) had symptomatic urinary tract infection. Significant bacteremia was encountered in four of the patients with urinary tract infection, and one patient died. In this study, every patient with significant *Serratia* urinary tract infection had a history of urethral catheterization and most of them had received some form of antibiotic therapy. There were no characteristic signs specific for *Serratia* that enabled it to be distinguished clinically from other gram-negative infections. Of the 34 isolates, 7 demonstrated resistance to ampicillin, cephalosporins, nitrofurantoin, streptomycin, kanamycin, and gentamicin. These investigators demonstrated resistance transfer to sensitive *Escherichia coli* in combined culture and indicated that these organisms acted as a reservoir for antibiotic-resistant plasmids, which may pose a danger to the community. Unless clinicians and microbiologists are careful to contain this organism whenever it occurs, their problems are likely to increase. It is essential that microbiologic laboratories employ systems that accurately define all gram-negative rods isolated from patients.

Thomas and associates (1977) reported a hospital-wide outbreak of *Serratia marcescens* infections that were resistant to gentamicin and other antimicrobial agents. They also noted a striking predilection for urinary tract infection by gentamicin-resistant strains of *Serratia marcescens*. They agree with the view that patients infected by this organism are debilitated, have indwelling catheters, and have received prior antimicrobial therapy. After this outbreak of *Serratia marcescens* infections had abated, it was succeeded by an outbreak of multiply resistant infections due to *Klebsiella pneumoniae*. They sought explanations for the sequential infectious outbreaks and postulated that they were causally related because of the similarity of antibiograms, since both species were resistant to gentamicin and most of the other commercially available antibiotics. In view of similar antibiograms for gentamicin-resistant strains of both species, they concluded that related resistance plasmids were likely to be present in both.

The finding that the molecular weights of plasmid DNA from selected resistant strains of *Serratia* and *Klebsiella*, as determined by gel electrophoresis, were essentially identical further supported a causal relationship. They concluded that an unchecked hospital-wide *Serratia* epidemic should be considered not only as serious in

its own right but as a possible forerunner of a resistant *Klebsiella* epidemic.

Finland (1977) emphasized that serious infections with nonpigmented *Serratia marcescens* were rare before the extensive use of modern antimicrobial agents, particularly aminoglycosides, but are now commonplace. He reported no bacteremic infections due to this organism at Boston City Hospital in 1961, but in 1972 there were 20 such cases. In discussing hospital outbreaks of infection, he is of the opinion that the species of organism is related to the virulence and invasiveness of the strain as well as to the conditions favoring its spread to susceptible patients.

Verbist and associates (1978) studied the susceptibility of 146 clinical isolates of *Serratia marcescens* to aminoglycosides and found that all strains were susceptible to amikacin and netilimicin. They postulated that the activity of these newer aminoglycosides may be abolished very quickly if other R factors are introduced into the hospital environment.

Nevertheless, the present trend of hospital-acquired infections can be reversed only by a drastic change in attitude to excessive chemotherapy, by strict enforcement of hygienic measures to prevent cross contamination, and by attention to detail with respect to asepsis and antisepsis. Today, more than a century after Semmelweis emphasized the need for basic aseptic techniques in infection control and Lister the use of antisepsis in surgery, the principles must still be observed. The new challenge resulting from the evolution of the antibiotic-resistant strains of gram-negative organisms may be far removed from the puerperal sepsis Semmelweis had to contend with, but it is now recognized that hospital-acquired infection is an ever-present menace.

PENICILLIN AND ANTIBIOTIC RESISTANCE

Soon after penicillin was introduced as an antimicrobial agent, it became evident that staphylococci were becoming resistant to it. This resistance was due to the ability of this organism to produce the enzyme penicillinase, which destroyed the antibiotic. The widespread overuse of penicillin within a decade accounted for the appearance of penicillin-resistant staphylococci in hospitals and to a lesser degree, in the community.

The resistance of bacteria to penicillin was foreseen by Abraham and Chain (1940), who reported that they had isolated an enzyme from *Escherichia coli* that had the potential to inactivate penicillin. Subsequently, many strains of *Escherichia coli* and other bacteria were shown to have this capacity. The enzyme elaborated is now known as beta-lactamase, as it catalyses the hydrolysis of the amide bond of the beta-lactam ring of the 6-amino-penicillanic acid or 7-amino-cephalosporanic acid component of the various derivatives of these two substances, which constitute the nucleus of penicillins and cephalosporins.

This pattern of antimicrobial resistance has characterized virtually all these agents after their clinical use. The widespread usage of antibiotics in both veterinary and human medicine has resulted not only in the selection of resistant mutants within the bacterial species for which the agent was prescribed but also in the changed epidemiology of infectious diseases. Bacteria that rarely caused disease prior to the era of modern antimicrobial agents have become common and often demonstrate wholesale resistance to a large variety of antibiotics, necessitating the use of more toxic or, on occasion, less effective drugs. The elucidation of the mechanisms of such resistance has been one of the most important contributions of basic science to the treatment of bacterial infections.

It is now known that antibiotic resistance in numerous species of bacteria is frequently controlled by extrachromosomal genetic elements known as plasmids. Since these plasmids may be transferred among members of the same bacterial species or to bacteria of a different species or genus, they add to the difficulties of providing effective antimicrobial therapy for infectious diseases. In the majority of beta lactamase–producing strains of *Staphylococcus aureus* the genetic information required for the synthesis of this enzyme is located on a plasmid. Likewise, the intracellular genetic elements that transfer drug resistance markers to other bacteria, known as R factors, have become increasingly common in gram-negative enteric organisms.

Such extrachromosomal markers can be transferred to other bacteria by conjugation, which results from cell-to-cell contact, or by transduction, which depends on the ability of DNA (the genetic material containing the information for antibiotic resistance in one bacterium) to transfer this information by means of a temperate phage to another organism. Although the origin of R factors has not been fully elucidated, the R factors possessing multiple resistance are currently of great clinical and biologic importance among almost all genera of the Enterobacter. The possession of plasmids may be disadvantageous to bacteria by producing a slower growth rate. However, if they are encoded for multiple antibiotic resistance the host bacteria will possess a marked selective advantage. This poses a serious problem in hospitals where there is widespread use of antibiotics, and it can be controlled only by more rational use of these drugs.

The appearance of penicillin-resistant beta lactamase–producing strains of *Neisseria gonorrhoeae* has caused great concern since they were first reported in patients in the United States by Ashford and associates (1976) and in England by Phillips (1976). It is now essential that all physicians recognize that if penicillin is unsuccessful in the treatment of gonorrhea the strains of *Neisseria gonorrhoeae* must be isolated, identified, and tested for penicillinase production.

Elwell and associates (1977) demonstrated that beta-lactamase production by such strains is plasmid mediated and presented evidence that the beta-lactamase genes were the same as those in *Hemophilus influenzae*. The same workers had previously demonstrated (1975) that *Hemophilus influenzae* had acquired a similar penicillinase plasmid that can be conjugally transferred. Chloramphenicol resistance by *Hemophilus influenzae* was first reported by Manten and associates (1976). It was shown by Kattan (1976) to be due to acetylation of the drug, the identical mechanism by which chloramphenicol resistance is exhibited by *Escherichia coli*. Van Klingeren and associates (1977) demonstrated that chloramphenicol and tetracycline resistance can be transferred not only to other strains of *Hemophilus influenzae* but also to *Escherichia coli*.

The reports cited demonstrate that plasmid-mediated antibiotic resistance can no longer be regarded as a phenomenon mainly associated with the enterobacters. Consequently, the appearance of resistant variants of the classic bacterial species requires constant surveillance and evaluation. To reduce the hazard of infection with antibiotic-resistant organisms, restricted use of antimicrobial agents is mandatory in order to avoid undue ecologic pressures caused by their presence. The modern antimicrobial era has not eliminated infectious problems from the practice of obstetrics and gynecology but has demonstrated that antibiotics are not the panacea of bacterial infections. When overused they are associated with perpetuation of often multiple resistant organisms in the obstetric, gynecologic, and nursery areas of the hospital.

Owing to the availability of easily utilized anaerobic microbiologic techniques a greater understanding of the role of anaerobic organisms in obstetric and gynecologic patients has developed during the past decade. However, anaerobic infections do not represent a change in the bacterial ecology of infections but instead reflect our present awareness of them and a rediscovery of facts already appreciated at the turn of the century. Microbial agents that were formerly considered to be seldom, if ever, associated with disease are being consistently identified with clinical syndromes.

Because life is being prolonged, a vulnerability to microbial disease that did not previously exist is being seen, particularly in patients with metabolic problems, in debilitated individuals, and in those on steroid therapy or chemotherapeutic agents that depress the normal immune mechanisms. These individuals are probably prone to microbial disease because they offer the infectious agent an opportunity for excessive propagation. In some cases, one suspects that the organisms have always had the potential to produce disease, but only lately have they assumed importance, as exemplified by *Listeria monocytogenes* and *Chlamydia trachomatis* in perinatal infections.

The impulse to ameliorate the human condition has traditionally been directed to control of the environment. Now human beings have turned their attention to the internal ecology. The use of antibiotics on human microflora is an exploration into the

unknown and has often been indiscriminate and ill judged. It may be compared to the misuse of agricultural science in exploiting tracts of land that subsequently degenerated into the great dust bowls. It may be that the use of antibiotics, by distorting the natural environmental flora, may in certain circumstances be equally disastrous. The physician must ensure that the biologic environment is not destroyed, since the microecology of the body is no less part of the human environment than are the sky, the earth, and the sea.

References

Abraham, E. P., and Chain, E.: An enzyme from bacteria capable of destroying penicillin. Nature *146*:837, 1940.

Altemeier, W. A., Hummel, R. P., Hill, E. O., et al.: Changing patterns in surgical infections. Ann. Surg. *178*:436–445, 1973.

Ashford, W. A., Golash, R. G., and Hemming, V. G.: Penicillinase-producing *Neisseria gonorrhoeae*. Lancet 2:657–658, 1976.

Bennett, J. V.: Nosocomial infections due to *Pseudomonas*. J. Infect. Dis. *130*:54–57, 1974.

Bulger, R. J., Larson, R. N., and Sherris, J. C.: Decreased incidence of resistance to antimicrobial agents among *Escherichia coli* and *Klebsiella Enterobacter*. Ann. Intern. Med. *72*:65–71, 1970.

Elwell, L. P., de Graff, J., Seibert, D., et al.: Plasmid-like ampicillin resistance in *Haemophilus influenzae* type B. Infect. Immun. *12*:404–410, 1975.

Elwell, L. P., Roberts, M., Mayer, L. W., et al.: Plasmid mediated beta-lactamase production in *Neisseria gonorrhoeae*. Antimicrob. Agents Chemother. *11*:528–533, 1977.

Finland, M.: Changing ecology of bacterial infections as related to antibacterial therapy. J. Infect. Dis. *122*:419–431, 1970.

Finland, M.: Changing patterns of susceptibility of common bacterial pathogens to antimicrobial agents. Ann. Intern. Med. *76*:1009–1036, 1972.

Finland, M.: Excursions into epidemiology: selected studies during the past four decades at Boston City Hospital. J. Infect. Dis. *128*:76–124, 1973.

Finland, M.: Nosocomial epidemics seriatim. Multidrug-resistant bacteria and R factors. Arch. Intern. Med. *137*:585–587, 1977.

Finland, M., Jones, W. F., Jr., and Barnes, M. W.: Occurrence of serious bacterial infections since the introduction of antibacterial agents. JAMA *170*:2188–2197, 1959.

Forbes, I., Gray, A., Hurse, A., et al.: The emergence of gentamicin-resistant klebsiellae in a large general hospital. Med. J. Aust. *1*:14–16, 1977.

Kattan, S.: Chloramphenicol resistant *Haemophilus influenzae*. Lancet *1*:814, 1976.

Kwitko, A. O., Hamra, L. K., and Atkinson, J. M.: Serratia: opportunistic pathogen of increasing clinical importance. Med. J. Aust. 2:119–121, 1977.

Manten, A., van Klingeren, B., and Dessens-Kroon, M.: Chloramphenicol resistance in *Haemophilus influenzae*. Lancet *1*:702, 1976.

Norreiga, E. R., Leibowitz, R. E., Richmond, A. S., et al.: Nosocomial infection caused by gentamicin-resistant, streptomycin-sensitive klebsiellae. J. Infect. Dis. *131*:S45–S50, 1975.

Phillips, I.: Beta-lactamase producing, penicillin-resistant gonococcus. Lancet 2:656–657, 1976.

Pollack, M., Nieman, R. E., Reinhardt, J. A., et al.: Factors influencing colonization and antibiotic-resistance patterns of gram-negative bacteria in hospital patients. Lancet 2:668–671, 1972.

Price, D. J. E., and Sleigh, J. D.: Control of infection due to *Klebsiella aerogenes* in a neurosurgical unit by withdrawal of all antibiotics. Lancet 2:1213–1215, 1970.

Schaberg, D. A., Weinstein, R. A., and Stamm, W. E.: Epidemics of nosocomial urinary tract infection caused by multiple-resistant gram-negative bacilli. Epidemiology and control. J. Infect. Dis. *133*:363–366, 1976.

Schaffner, W. A.: The on-going problem of hospital infections. Adv. Intern. Med. *16*:173–187, 1976.

Selden, R., Lee, S., Wang, W. L. L., et al.: Nosocomial *Klebsiella* infections, intestinal colonization as a reservoir. Ann. Intern. Med. *74*:657–664, 1971.

Thomas, F. E., Jackson, R. T., Melly, A., et al.: Sequential hospital-wide outbreaks of resistant *Serratia* and *Klebsiella* infection. Arch. Intern. Med. *137*:581–584, 1977.

van Klingeren, B., van Embden, D. A., and Dessens-Kroon, M.: Plasmid mediated chloramphenicol resistance in *Haemophilus influenzae*. Antimicrob. Agents Chemother. *11*:383–387, 1977.

Verbist, L., Vandepitte, J., and Vandeven, J.: Activity of eight aminoglycosides against isolates of *Serratia marcescens* from four hospitals. J. Antimicrob. Chemother. *4*:47–55, 1978.

Chapter Two

SEXUALLY TRANSMITTED DISEASES

The five classic venereal diseases — syphilis, gonorrhea, chancroid, granuloma inguinale, and lymphogranuloma venereum — remain with us and still present both diagnostic and therapeutic problems to the clinician. Today, the spectrum of sexually transmitted diseases has been expanded to include roles for bacteria, *Chlamydia*, viruses, protozoa, fungi, and parasites (Table 2–1). Although advancements in mi-

Table 2–1. Sexually Transmitted Diseases

Class of Organism	Specific Organism	Disease
Bacteria	*Neisseria gonorrhoeae*	Gonorrhea
	Treponema pallidum	Syphilis
	Hemophilus ducreyi	Chancroid
	Calymmatobacterium granulomatis	Granuloma inguinale
	Corynebacterium vaginale	Vaginitis
	Group B beta-hemolytic streptococcus	Perinatal infection
	Mycoplasm hominis	?Vaginitis
		?Salpingitis
	Ureaplasm urealyticum	?Vaginitis
		?Salpingitis
Chlamydia	*Chlamydia trachomatis*	Perinatal infection
		Pelvic inflammatory disease
	Chlamydia trachomatis, immunotypes L1, L2, L3	Lymphogranuloma venereum
Viruses	Herpes virus hominis, types 1 and 2	Herpes genitalis
		Perinatal infection
	Cytomegalovirus	Vaginitis
		Mononucleosis type disease
		Perinatal disease
	Epstein-Barr virus	Infectious mononucleosis
	Hepatitis type B	Hepatitis
	Human papillomavirus type 4	Condylomata acuminata
	Molluscum contagiosum virus	Molluscum contagiosum
Protozoa	*Trichomonas vaginalis*	Vaginitis
Fungi	*Candida albicans*	Vaginitis
		Perinatal infection
	Torulopsis glabrata	Vaginitis
	Epidermophyton inguinale	Tinea cruris
Parasites	*Acarus scabiei*	Scabies
	Phthirus pubis	Pediculosis pubis

crobiologic and immunologic methods have improved both knowledge and treatment of these conditions, much concern exists because in most countries these infections occur predominantly in people under the age of 25 years. This disturbingly high incidence among the young is partly explained by increasing urbanization and the decline of the nuclear family.

Social pressures, materialism, and increased leisure drive the adolescent to seek escape from the trammels of immaturity by sexual gratification. The media suggest that the attributes of a good life include sex and imply to the adolescent that sexual relationships are essential to happiness. The greater sexual freedom of the young has been aided by the availability of steroidal antifertility agents. Full sexual equality with men has given women equal rights to experiences that may lead to the expansion of sexually transmitted diseases. Twenty-five years ago, gonorrhea was considered a disaster and a stigma. Today, owing to the availability of antibiotics, it is looked upon as no more inconvenient than the common cold. The present climate of opinion concerning sex can hardly be conducive to the suppression of sexually transmitted diseases.

Willcox (1977), in discussing the prevention of venereal disease, writes

> The present state of venereal disease prophylaxis can be summed up in one, if long, sentence. Venereal disease can be prevented if before sexual intercourse the man applies a condom, the woman an antiseptic cream, and if afterwards the man immediately passes water and anoints his genitalia with a prophylactic ointment while the woman has a prophylactic douche: both should then have a bath before spraying each other with an antiseptic lotion, and they should visit a physician to receive 2.4 megaunits of procaine penicillin by injection plus 1.0 g of probenecid by mouth — which should prevent gonorrhoeae and syphilis — plus a ten-day course of oral tetracycline to prevent non-gonococcal urethritis and a one- or two-day course of metronidazole or nimosazole against trichomoniasis — even with such commendable caution the risk is not entirely removed of infection from the viruses of condylomata acuminata, molluscum contagiosum or even that of hepatitis B: neither would it be beneficial for venerophobia!

This quotation aptly portrays the sentiments of those who have to deal with sexually transmitted diseases. Despite the ever-expanding number of diseases that are known to be sexually transmitted, only the following — gonorrhea, syphilis, chlamydial infections, lymphogranuloma venereum, granuloma inguinale, chancroid, trichomoniasis, corynebacterium vaginale vaginitis, and condylomata acuminata — will be presented in this chapter.

Reference

Willcox, R. R.: How suitable are available pharmaceuticals for the treatment of sexually transmitted diseases? 2. Conditions presenting as sores or tumours. Br. J. Vener. Dis. 53:340–347, 1977.

GONORRHEA

Gonorrhea is the most common communicable disease in the world, yet despite its venerable history and its importance as a public health problem, little is known about its pathogenic mechanisms. The causative organism is a member of the genus *Neisseria* and as such is a gram-negative nonmotile diplococcus. Although information regarding the biology of *Neisseria gonorrhoeae* has increased rapidly during the past 15 years, relatively little is known about the role of host defense in controlling the disease process.

Organism

The virulence of the organism was shown by Kellogg and coworkers (1963) to be associated with specific colony types. These investigators identified four morphologically distinct types of the diplococcus.

Colony types 1 and 2 were present on initial isolation from infected patients, while types 3 and 4 emerged on nonselective subculture media in the laboratory. Only types 1 and 2 were capable of causing infection in volunteers.

The virulent strains belonging to colony types 1 and 2 were shown by Jephcott and associates (1971) and Swanson and associates (1971) to possess pili on their surface, which are lacking in the avirulent organisms of types 3 and 4. Swanson (1973), by *in vitro* studies, showed that the pili enhance attachment of the gonococcus to human amnion cells. Ward and coworkers (1974) demonstrated by perfusion culture of the human fallopian tube and scanning electron microscopy that pili anchor the gonococci to the epithelial surface. Tebbutt and associates (1976) showed that adhesion of gonococci to cervical epithelium and the mucosa of the fallopian tube was by pilation.

Pearce and Buchanan (1978) examined the attachment of isolated pili of gonococci to various human cells, including samples of fallopian tube mucosa and cervical and vaginal epithelial cells. They noted a cell specificity of attachment of the pili to the cells from sites involved in gonococcal disease. Their data suggest that more binding sites exist on the surface of cervical epithelial cells than on red blood cells or polymorphonuclear neutrophils. These investigators also found that attachment was inhibited by antibody to the pili. They believed, however, that protection against gonococcal infection as a result of inhibition of pili-mediated attachment may be of only limited value because of the marked antigenic heterogeneity among pili. This postulation is supported by their observation that blockage of pili attachment is maximal only with antibody specific to pili of the infecting strain.

Further evidence to support the importance of pili in the pathogenesis of gonorrhea is the evasion of the host's phagocytic defense. This was demonstrated by Ofek and associates (1974), who noted that gonococci attach by pili to polymorphonuclear neutrophils and resist phagocytosis. Although it has been classically taught that the gonococci seen in association with polymorphonuclear neutrophils in Gram-stained smears are intracellular, these investigators showed that many of the organisms are actually attached to the cell surface.

Densen and Mandell (1978) confirmed these observations and indicated that in this extracellular but attached location the organisms remain viable, apparently immune to the microbicidal effects of the polymorphonuclear leukocytes. To determine the factors responsible for the survival of the attached diplococci, they investigated the morphologic and metabolic consequences of polymorphonuclear neutrophil–leukocyte interaction with virulent, piliated type 1 gonococci, which adhere to cells but resist phagocytosis, and with avirulent nonpiliated type 3 gonococci, which are readily phagocytosed.

Their studies suggest that the mode of attachment of piliated and nonpiliated gonococci to polymorphonuclear neutrophils may differ and that these differences may determine the outcome of their interaction with polymorphonuclear neutrophils. They found that despite the failure of polymorphonuclear neutrophils to ingest piliated gonococci adherent to the cell surface there is a significant burst of polymorphonuclear neutrophil metabolism similar to that observed during ingestion of nonpiliated organisms. In addition, the polymorphonuclear neutrophil metabolic responses to piliated gonococci were similar whether serum was present or not. The inability of normal polymorphonuclear neutrophils to kill virulent attached type 1 gonococci appears from these studies to be the result of both inadequate release of enzymes from the granules of the leukocyte and failure to incorporate type 1 gonococci into a phagocytic vacuole.

Punsalang and Sawyer (1973) demonstrated that pili are antigenic and that antibodies raised to them inhibit both agglutination of erythrocytes and attachment to squamous buccal cells by piliated gonococci. Buchanan and associates (1973) published the first report on antibodies to gonococcal pili in human sera. They compared by radioimmunoassay the levels of antibodies to gonococcal pili in patients with gonococcal infection with those of control groups. Their results appeared promising, especially as a method of detection of asymptomatic female carriers, who continue to be an important problem in the epidemiology of gonococcal disease. In most coun-