Surgical Infections

Selective Antibiotic Therapy

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Preface

Infectious complications continue to threaten patients undergoing surgery, despite important advances in operative techniques and antimicrobial drugs. Surgical infections are divided into two major categories—exogenous, those acquired from the environment, and endogenous, those derived from the microflora of the host. By their nature, exogenous infections are constantly changing, both in terms of the microbial pathogens and the portals of entry.

Fifty years ago, hemolytic Group A *Streptococcus pyogenes* was a major scourge on surgical wards. Following the introduction of antimicrobial agents, *Staphylococcus aureus* gained ascendency as a cause of exogenous infection, and reigned supreme through the decades of the 1950s and 1960s. In the past 15 years, we have witnessed an emergence of gram-negative infections; the problem pathogens of the present era are Pseudomonas, Klebsiella, and Serratia.

New surgical techniques and mechanical equipment have provided routes of entry for these unwelcome intruders. Indwelling Foley catheters, respiratory therapy equipment, plastic venous and arterial catheters, and intra-arterial transducers have given rise to an assortment of exogenous infections in the compromised surgical patient. Even an apparently benign vehicle, such as an elasticized surgical dressing, can harbor fungi that invade the wound and produce serious infection. Such are the ironies of medical progress, and we should pause occasionally to measure the risk-to-benefit ratio of these technical advances.

The vicissitudes of surgical practice have not affected as radically the incidence of endogenous microorganisms, since the normal flora has remained stable within individual patients, and probably within the human race, for as long as we have recorded observations. The first bacteriological study of acute appendicitis, done by Veillon and Zuber in Paris in 1896, documented mixed aerobic and anaerobic organisms in 21 of 22 patients. Altemeier came to the same conclusion in a report 30 years later. Studies made during the past decade have reiterated these basic bacteriological findings. Infections within the abdominal cavity are commonly associated with a mixed flora of aerobic and anaerobic organisms that originate in the gastrointestinal tract.

Despite the diversity of clinical presentations, endogenous infections have three common characteristics. First, the pathogenic organisms, which have the capacity to destroy tissue, in fact spend the greater part of their natural existence as harmless commensals in the normal flora of the host. The second principle is that bacteria in the microflora leave their natural ecospheric niche only in the wake of a predisposing condition. Disruptions such as trauma, compromised vascular supply, tissue necrosis, and antecedent viral or bacterial infections permit the spread

of these organisms beyond the confines of the mucosal surface. The third element common to endogenous infections is the complex nature of the pathogenic flora.

Traditional teaching has indoctrinated us with the unitarian theory of infection. One organism causes one disease, which is treated by one drug—the "magic bullet." This concept of monoetiology holds for pneumococcal pneumonia, streptococcal pharyngitis, and staphylococcal wound infections. In the case of endogenous infections associated with normal flora, however, a complex infection is the general rule. Abdominal infections, for example, harbor an average of five different bacterial species, usually two aerobes and three anaerobes. Many of the organisms in this complex milieu are potential pathogens while others are only commensals.

In response to the complexity of bacterial infections, substantial progress has been made in the development of new antimicrobial agents. Perhaps the most dramatic example has been the development of the β-lactam class of antibiotics, including the penicillins and cephalosporins. The new generations of these agents have extended antimicrobial activity, improved pharmacokinetics, and better penetration into critical organ sites. As microorganisms have increased their resistance to various antibiotics, there has been a surge of new drug development. Thus, aminoglycosides have been made more potent, with extended spectrums of activity against these new resistant bacterial strains. Even the traditional antimicrobial agents have undergone change. Recently introduced congeners of tetracycline have improved pharmacologic action and drug activity. The sulfonamides have become of interest anew as a result of their combination with trimethoprim.

In this book, we have attempted to focus on the types of microorganisms involved in surgical infections, as well as their epidemiologic circumstances. In the sections dealing with antimicrobial drugs, we have endeavored to integrate the changes in surgical infections with the newer agents that have entered the marketplace. The emphasis is practical application of traditional tools in both surgical management and drug therapy. In many circumstances, the older drugs are still recommended, rather than necessarily turning to new drugs just because of their novelty. It is our hope that the blending of the classical approach with recent advances will provide a useful guide to the prevention and treatment of surgical infections.

Robert E. Condon
Sherwood L. Gorbach

Acknowledgments

The papers brought together in this book were originally presented in the *Journal of Surgical Practice* (a periodical of the McMahon Publishing Company, since transformed into *Surgical Practice News*). The series appeared from the Summer of 1977 to the Spring of 1980. Many of the papers have undergone extensive revision, primarily to bring them up to date. Although barely more than three years separate writing and rewriting, the fields being examined have been in dynamic phases, so that an authoritative discourse of 1981 is significantly more current than an authoritative discourse of three years before.

For our own part and in behalf of Williams & Wilkins, we want to express our thanks to *Surgical Practice News* (ex *Journal of Surgical Practice*) for stimulating our assembly of these papers in the first place and for extending rights for their revision and republication in the present volume.

We have already tendered thanks . . . but we are especially pleased for the opportunity now to engrave these reiterated thanks within the covers of a book . . . to our eminent colleagues for their enthusiastic participation in this symposium on surgical infections. Obviously, editors, even editors-contributors, do not produce a text all on their own. Our labors have been at once eased and made gratifying by the willingness of our colleagues to put the essences of their expert knowledge into the collaboration.

Finally, we acknowledge, with thanks, the guidance of Don deKoven, who has led us through the editorial travails with insight, a fine sense for language, and a productive mixture of pressure and patience.

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Contents

CHAPTER 1

The Normal Flora

John G. Bartlett, M.D.

The ecology of man and microorganisms pathogenic for man has changed somewhat over the past few decades. Formerly, the major expressions of infectious disease were those caused by communicable organisms exogenous to the hosts—*e.g.*, tuberculosis, salmonellosis, puerperal sepsis caused by group A β-hemolytic streptococci. Such conditions are less frequent in the present era. Now a major portion of infections are acquired from the bacteria that normally colonize the host's own mucocutaneous surfaces. Examples of these endogenous infections include most dental infections, aspiration pneumonia, intra-abdominal sepsis, and nonvenereally transmitted infections of the female genital tract.

Thus, it has become apparent that a knowledge of the normal flora is required for a basic understanding of the pathophysiology of many infections commonly encountered in current clinical practice. Contemporary concepts of surgical infection, in particular, derive directly from the importance of resident normal flora in the pathophysiology of infection. An ecologic arrangement exists which is harmless to the host; some other agency intercedes and transforms the arrangement so that it is no longer harmless to the host. Instrumentation, manipulation, or the implantation of a foreign body (even though sterile) may function as this intrusive agency and precipitate the transformation. Either a focal environment is altered so that a fastidious bacteria *in situ* that has been innocuous becomes infectious; or bacteria are transported from a site where they are innocuous to a site where they flourish and cause infection. Even an antibacterial agent may disturb an innocuous ecologic arrangement and, by clearing some resident microflora, open the way for another resident, opportunistic microflora to thrive and produce infection.

Several unifying concepts applicable to floral analysis warrant being noted here:

1. Studies of the microflora are extremely arduous and should be undertaken only by the most ambitious investigators. A relatively complete study requires countless media, extraordinary skills for recovering fastidious bacteria, rigid controls, and extensive identification procedures. The term "relatively complete" is used because experience has shown that even seemingly exhaustive work does not permit recovery of all strains; moreover, many of the organisms that are isolated cannot be classified by current taxonomic criteria.

2. The prevalence and predominance of anaerobic bacteria in the normal flora is to be emphasized. Studies of the microflora in former years were often restricted to aerobic cultures, possibly because aerobic bacteria

were most easily recovered and identified. An important lesson from more recent studies is that anaerobes are the predominant organisms colonizing most mucous membrane sites. These data provide an important correlate to the observation that most endogenous infections also involve oxygen-sensitive forms.

3. It has been hypothesized that endogenous infections reflect the flora at adjacent mucosal surfaces. This is true only to a limited extent since clinical specimens contain but a fraction of the bacterial species found in the normal flora. For example, intra-abdominal infections following colonic perforation contain an average of five different microbes, whereas the stool flora, the source of the initial inoculum, contain some 200–400 bacterial species. The factors that account for the survival of bacteria at infected sites are poorly understood but, presumably, they relate to pathogenic potential of the microorganisms and the environmental conditions at their new location (Table 1.1 and Fig. 1.1).

THE UPPER AIRWAYS

The mucosal surfaces of the nasal passages, oral cavity, and pharynx normally harbor a luxuriant microbial population including both aerobic and anaerobic bacteria. The tracheobronchial tree and nasal sinuses are sterile, or have only a sparse flora, despite physical continuity with the bacteria-rich adjacent structures. An important mechanism of defense in the sinuses and lower airways is a mucous layer which moves unidirectionally by the wafting motion of underlying cilia. Upon exposure, bacteria and particulate matter become embedded in the mucous layer and are subsequently transported into the nose or pharynx. Additional defense mechanisms include local antibody and, in the lower airway, the alveolar macrophage.

The flora of the upper airways comprises multiple bacterial species representing some 21 genera. The findings of Dr Sidney Socransky at the Forsyth Dental School exemplify the complexity of the normal oral microbiota. Socransky isolated over 60 different microbes from one square millimeter of a healthy tooth surface. According to current estimates, the healthy mouth harbors at least 200 microbial species. Many of these have relatively little pathogenic potential.

Certain virulent aerobes are so frequently present that they must also be considered normal flora. For example, studies have shown the following colonization rates among healthy individuals: *Streptococcus pneumoniae*, 35–70%; *Haemophilus influenzae*, 25–85%; group A β-hemolytic streptococci, 5–10%; *Neisseria meningitidis*, 5–15%; and *Staphylococcus aureus*, 5–20%. The wide variations noted for these organisms arise from differences in bacteriological tech-

Table 1.1
The normal flora of mucosal surfaces in humans

	Total bacterial concentrations	Ratio anaerobes: aerobes
Upper respiratory tract		
Nasal washings	10^3–10^4	3–5:1
Saliva	10^8–10^9	3–5:1
Tooth surface	10^{10}–10^{11}	1:1
Gingival crevice	10^{11}–10^{12}	100–1000:1
Gastrointestinal tract		
Stomach	10^2–10^5	1:1
Proximal small bowel	10^2–10^4	1:1
Ileum	10^4–10^7	1:1
Colon	10^{11}–10^{12}	100–1000:1
Female genital tract		
Endocervix	10^8–10^9	5–10:1
Vagina	10^8–10^9	5–10:1

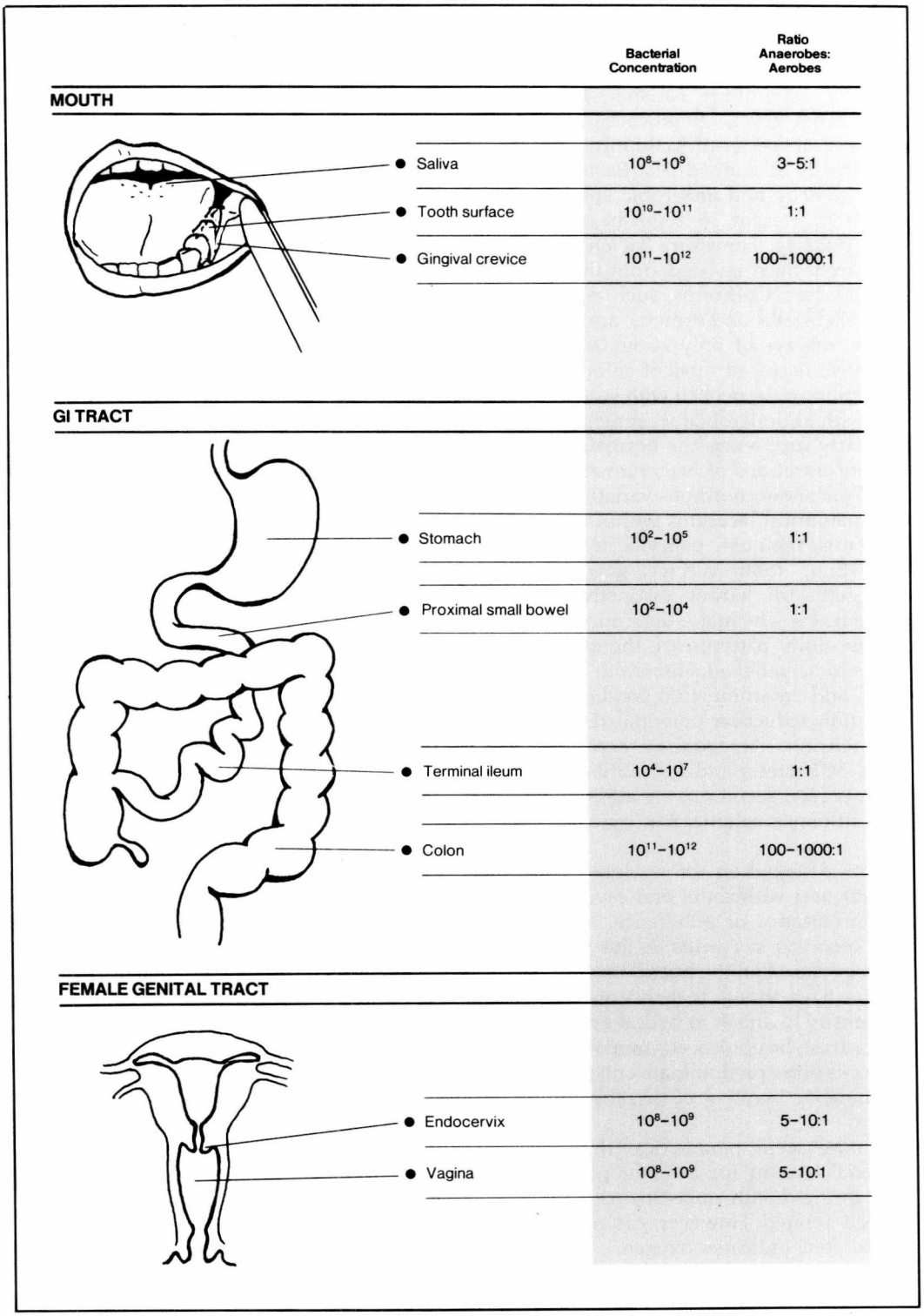
Bacterial Concentration
Ratio Anaerobes: Aerobes
MOUTH
Saliva
10^8–10^9
3–5:1
Tooth surface
10^{10}–10^{11}
1:1
Gingival crevice
10^{11}–10^{12}
100–1000:1
GI TRACT
Stomach
10^2–10^5
1:1
Proximal small bowel
10^2–10^4
1:1
Terminal ileum
10^4–10^7
1:1
Colon
10^{11}–10^{12}
100–1000:1
FEMALE GENITAL TRACT
Endocervix
10^8–10^9
5–10:1
Vagina
10^8–10^9
5–10:1

Figure 1.1

niques, anatomical sites sampled, and populations surveyed.

Anaerobic bacteria are regularly present even in edentulous patients. Fusobacteria, Peptostreptococci, Peptococci, Veillonella, and several species of Actinomyces are found in virtually all individuals; *Bacteroides melaninogenicus* and anaerobic spirochetes are regularly present in tooth-bearing mouths after puberty. However, *Bacteroides fragilis* has rarely been isolated from the upper airway sources. Coliforms, such as *Escherichia coli*, Klebsiella, and Proteus, are found in the upper airways of only about 3% of healthy persons. Increased rates of colonization with coliforms are associated with serious illnesses and with antimicrobial treatment which concurrently suppresses the normal oral flora.

Concentrations of bacteria within the normal flora show enormous variations at different anatomical locations within the oral cavity. Thus, the nose, pharynx, tongue, buccal epithelium, tooth surface, gingival crevice, and gums all harbor distinctive microbial populations. The major determinants in these unique floral patterns are thought to be vagaries in bacterial attachment to different cell types and environmental conditions such as oxidation-reduction potential (Eh) and oxygen tension. Antagonism between certain types of bacteria and IgA antibodies in respiratory tract secretions are additional factors that influence colonization by certain bacteria.

The distribution of various species of streptococci within the oral cavity illustrates the importance of adherence. For example, *Streptococcus salivarius* is the predominant microbe found on the buccal mucosa. *In vitro* studies have shown that this organism has a propensity to attach to buccal epithelial cells. By contrast, *Streptococcus mutans* and *Streptococcus mitis* predominate on tooth surfaces, presumably because of an affinity for this tissue.

It may seem paradoxical that anaerobic bacteria account for a major portion of the flora in the mouth since this zone appears to be well-aerated. However, gas analysis of the buccal fold indicates oxygen concentrations there of less than 1%. Apparently, there is minimal gas exchange where the cheek approximates gingival and tooth surfaces. The Eh may be even more important in supporting anaerobic growth than oxygen tension. The Eh values of the periodontal pockets, plaque, and gingival crevice are −50mv, −200mv, and −300mv, respectively. An Eh of −300mv simulates the oxidation-reduction potential of the colon, and is sufficient to promote growth of the most extremely oxygen-sensitive bacteria. This would appear to account for the observation that anaerobes outnumber aerobes in the gingival crevice by a factor of 1000:1.

GASTROINTESTINAL TRACT

The gastrointestinal tract harbors an abundant flora which varies considerably in longitudinal distribution. In the upper tract—including the stomach, duodenum, jejunum, and proximal ileum—bacteria are relatively sparse; concentrations seldom exceed 10^5/ml. The principal components of this flora are the bacteria washed down from the oropharynx, such as streptococci, lactobacilli, and anaerobes other than *B. fragilis*. Coliforms and enterococci are usually absent, or present in very low concentrations.

The major mechanism of controlling bacterial population control in the stomach is gastric acidity; gastric pH values and bacterial concentrations are directly correlated in the upper gastrointestinal tract. In the proximal small bowel, a major determinant of bacterial colonization is intestinal motility. Any interruption of small bowel propulsive activity results in a shift toward a colonic type flora with high concentrations of anaerobes. Examples of conditions associated with this type of change are blind loops, giant diverticula, strictures, and small bowel obstruction. Bile in the small bowel may also play a role in colonization since bile acids are toxic to a number of oropharyngeal bacteria.

The ileum is the transition zone between the upper tract and the colon. Coliforms are usually found in this zone but total bacterial concentrations are in the range of 10^4–10^7/ml.

The colon contains an extraordinarily complex ecosystem of aerobic and anaerobic bacteria. Total microbial concentrations in stool are $10^{11.4}$–$10^{11.8}$/gm dry weight. This approximates the limit of bacterial space-occupa-

tion. The major components of this flora are anaerobes, which outnumber aerobes by factors of 100–1000:1. Current microbiological techniques do not permit recovery of all organisms, but extrapolation from the available data suggests that there are 200–400 distinctive bacterial species in a single stool specimen. The numerically dominant organisms, which are found almost universally, are *B. fragilis*, Eubacteria, Bifidobacteria, Clostridia, and anaerobic cocci. Among the aerobes, the major types are coliforms (especially *E. coli*), streptococci including enterococci, and *Bacillus* sp. The colonic flora is relatively stable so that only minimal changes are detectable by periodic sampling of healthy individuals, even after major alterations in diet.

There are several factors responsible for maintaining this floral pattern in the colon. First, the large bowel is relatively static and not subject to the rapid transit times associated with the small bowel. The colon, also, has an extremely reduced atmosphere that permits the growth of the most fastidious anaerobes. Presumably, this condition is attributable to the indigenous flora itself, since the colonic Eh of −50mv in germfree animals decreases to −230mv when the animals are reassociated with a normal flora. In addition, Bacteroides located in the colon produce short chain organic acids which, in an anaerobic environment, inhibit the growth of other organisms and limit intrusions by certain intestinal pathogens such as Salmonella.

FEMALE GENITAL TRACT

The female genital tract harbors an endogenous flora in the vagina and proximal endocervical canal. The uterine cavity and Fallopian tubes are normally sterile.

One of the first studies of the vaginal flora was done by Döderlein, who reported aerobic lactobacilli to be particularly prominent. The finding that "Döderlein's bacillus" produced lactic acid from glycogen metabolism led to the impression that lactic acid accounted for the low vaginal pH which, in turn, served as a mechanism of bacterial population control. This hypothesis has not held up, however, since there is no correlation between vaginal pH measurements and recovery rates of lactobacilli. It is now thought that lactobacilli commonly colonize the vagina in a woman of reproductive age simply because these bacteria can tolerate the low pH which is actually hormonally controlled.

Following Döderlein's work, there have been a number of extensive studies showing that the vaginal flora is more complex than originally thought. Nevertheless, compared to that of the gastrointestinal tract or the oral cavity, this flora is relatively simple. According to several studies employing optimal microbiological techniques, the average number of bacterial species in cervical or vaginal specimens is five to eight. These include aerobic bacteria in virtually all individuals, and anaerobic bacteria in 80–90%. The predominant aerobic bacteria are lactobacilli, streptococci, corynebacteria, and *Staphylococcus epidermidis*. Each of these organisms is generally recovered from 40–80% of women of reproductive age. Coliforms, especially *E. coli*, are found in 20–30% of healthy women. The predominant anaerobic bacteria are peptococci, peptostreptococci, anaerobic lactobacilli, eubacteria, and *Bacteroides* sp.

B. fragilis is seldom found in the vaginal flora, although it is frequently involved in infections of the upper female genital tract. This observation illustrates the discrepancy sometimes noted in comparing the microorganisms causing endogenous infections with the flora that is, presumably, the source of the inoculum. In this particular instance, the source of *B. fragilis* in the infected female genital tract may be, in fact, the bowel. A significant proportion of such infections are sequelae of hysterectomy or parturition, and rates of colonization with *B. fragilis* are known to increase in these settings.

The vast majority of vaginal floral studies have been qualitative, with little or no attempt at enumeration. Recent work in our laboratory using quantitative techniques shows mean counts of aerobes of $10^{8.1}$/ml; and of anaerobes, $10^{8.9}$/ml. These data indicate that anaerobes outnumber aerobes by a factor of 5–10:1, which approximates their relative concentrations in saliva.

The cervix is more alkaline than the vagina and endocervical cells are columnar, while those of the vaginal vault are stratified epithelial cells. These observations suggest that different bacteria may associate with these

distinctive "ecologic niches" in the lower genital tract. Indeed, duplicate samples from the same patients have shown a distinctive flora in the cervix and vaginal vault. Nevertheless, cultures from a large number of women will show the concentrations of bacteria, the ratio of anaerobes to aerobes, and the bacteria species to be approximately the same for the cervix and the vagina.

An additional consideration is the stability of the flora in an anatomical site that is subject to frequent hormonally controlled changes. One study has shown, through bacteriologic analysis of sequential samples obtained from menstruating women, that the total counts of aerobes and anaerobes remain relatively stable throughout the cycle until the last premenstrual week, when the counts of aerobes decrease approximately 100-fold. Qualitative assessment of these results showed no distinctive pattern of bacterial species associated with specific times of the cycle. The bacteria recovered at periodic intervals varied considerably, and these variations, which were manifest in all women participating in this study, appeared to be haphazard. Thus, although each vaginal sample yielded an average of seven microbial species, there were 25–35 different bacteria when multiple specimens from each individual were considered. These data support the previous statement that the vaginal or cervical flora is relatively simple when assessed in a single specimen. However, compared to that of the oral cavity or the gastrointestinal tract, the flora of the female genital tract shows considerable instability.

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CHAPTER 2

The Penicillins

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The discovery of benzylpenicillin in the 1940s made a great impact on the physician's ability to cure disease. Developments in sanitation had already reduced the incidence of many bacterial illnesses remarkably, but mortality from organisms which today the hospital-based physician considers minor, such as the pneumococci and streptococci, was significant. Resistance to penicillin G was quick to develop and by the 1950s the major infectious problem was penicillin-resistant staphylococci. Developments in the technology of isolation of the penicillin nucleus made possible the production of antistaphylococcal penicillins, methicillin, and later the isoxazolyl penicillins, such as oxacillin and cloxacillin (Fig. 2.1). Simultaneously with that development came the ability to produce a penicillin with increased gram-negative coverage, namely, ampicillin which was effective against most isolates of *Escherichia coli*, Salmonella, and Shigella. Progress in hospital support systems to care for patients with hematologic malignancies, respiratory insufficiency, and burns made *Pseudomonas aeruginosa* an important organism. To attack these bacteria, new penicillins had to be developed—and they were, starting with carbenicillin. Recently, newer semisynthetic penicillins have been synthesized which have appreciable activity against *Klebsiella pneumoniae* and anaerobic species such as *Bacteroides fragilis*. One of these latter agents, piperacillin, has recently become available in the United States.

Penicillins, as is apparent from this introduction, can be divided into five classes on the basis of antibacterial activity (Table 2.1). Great overlaps do exist, but differences within a group are usually of a pharmacologic nature, although one compound in a group may be more active than another. The oral absorption, distribution in the body, and renal excretion in healthy and diseased states may be remarkably different for compounds of virtually identical antibacterial activity. Thus, it is important to understand the antimicrobial spectrum and pharmacology of the different penicillins to use these compounds most effectively.

MECHANISMS OF ACTION

Penicillins are bactericidal antibiotics which destroy bacteria by causing lysis of the cells. Penicillins bind to a number of receptor proteins that are involved in bacterial cell wall biosynthesis. When penicillin has bound to these enzymes, an unstable cell wall is created, with the result that the bacteria is lysed because of increased intracellular pressure. It is important to realize that penicillins act only on growing bacteria and bacteria that are in an environment in which lysis will occur. Differences in the "activity"—that is the amount of a particular penicillin needed