**Textbook of Oral and Maxillofacial Surgery**

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**Chapter 9**

# Surgical bacteriology

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## Infection

An ever present problem in the field of oral surgery is infection. Under normal circumstances the oral cavity is never sterile, and, if it were not for certain intrinsic and extrinsic factors, the care of a dental patient would be immeasurably more difficult.

The intrinsic factors include the normal regional immunity of the host to the bacterial flora of the mouth, the natural slough or desquamative function of the adjacent epithelium, the abundant blood supply present in the oral cavity, and the immediate response of the leukocytes when bacteria invade the host. In addition, saliva has been found to have an inhibitory effect on some bacteria, particularly those foreign to the normal flora. The normal flora also acts as a barrier to invading microorganisms.

The extrinsic factors that may aid in the control of oral infections are many; the most notable are the observance of good surgical and aseptic techniques (discussed in detail in Chapter 2) and the use of antibiotics and chemotherapeutic agents. The philosophy behind the use of antibiotics and chemotherapeutic agents is similar, and although the terms are not technically interchangeable because of their derivation, the former term shall be used henceforth for the sake of brevity and simplicity. Other factors aid in the control of infection, but a review of the source and physiological response, both local and systemic, should be evaluated before specific therapy is discussed.

In any discussion of surgical bacteriology applicable to the oral cavity and its adjacent structures, one must be aware of the existence of innumerable microorganisms that are normal inhabitants of this region. The most common bacteria found in the mouth include the alpha and beta streptococci, nonhemolytic streptococci, *Staphylococcus aureus, Staphylococcus albus,* Vincent's spirochetes, and fusiform bacillus. Increasing numbers of antibiotic-resistant organisms have been noted in saliva, particularly those resistant to penicillin. The virulence and quantity of these bacteria are generally controlled in the oral cavity by the mild bactericidal effect of saliva and the deglutition of oral fluids into the stomach, where the pH level is sufficient to destroy the majority of the bacteria and digest the balance. These two factors are not always sufficient to abort an infectious process; therefore, those factors that contribute to an inflammatory reaction will be considered first.

## Local factors

A mouth that is already chronically infected or contains large deposits of calculus and debris is a poor environment for a surgical procedure. Chronic irritation damages tissues to the point at which the normal resistance is markedly impaired, and the area is therefore more prone to infection. Invading bacteria will frequently destroy the protective reparative properties of the blood clot, preventing normal consolidation by the adjacent tissues. Operating in a mouth in which evidence of necrotic gingivitis is present is extremely hazardous. The gingival structures are necrotic, and a surgical procedure performed in this field places the general health of the patient in jeopardy, not only because of localized infection and pain in the field of operation but also because the fascial spaces of the head and neck may be readily invaded, and a general septicemia may result if the bacteria are of sufficient virulence.

## Systemic condition of the patient

Numerous factors of a systemic nature play a role in the predisposition to infection. Diabetes mellitus is a classic illustration of a disease that, if uncontrolled, provides a poor environment in which to perform surgery. This is a disease of carbohydrate metabolism, characterized by hyperglycemia and glycosuria, and is directly related to insufficient insulin. A characteristic feature of diabetes is increased susceptibility to infection, and, once established in diabetics, infection can proceed rapidly. Under these conditions, insulin demand is increased enormously, leading to additional complications. The oral manifestations of the diabetic, such as dryness of the mouth, lingual edema, and periodontal disease, are well known but may not be demonstrable on clinical examination if the disease is partially controlled. Surgical intervention, however, may precipitate an infectious process because of the lowered local and systemic resistance. Impaired healing may also occur, making the patient more susceptible to infection.

Patients who give any indication of diabetes, either by history or by clinical examination, should be evaluated carefully. If the patient is under a physician's care and his condition is under control, surgery can be performed in the usual manner. If, on the other hand, some doubt exists about the diabetic status, treatment should be deferred until a physician has been consulted and a urinalysis and fasting blood sugar study completed.

It should be stressed that although surgery is sometimes more hazardous in the diabetic patient, the elimination of oral infections is most important. Surgery should be done as soon as practical, since the removal of an infectious process may aid in the control of the disease symptoms.

### *Blood dyscrasias*

Several blood dyscrasias are predisposing factors of oral infection, the most notable of which are the leukemias. In acute leukemia and acute exacerbations of chronic leukemia, infections of the oral cavity are frequently seen and are difficult to treat. Surgical intervention in patients so afflicted is hazardous not only because of the excessive hemorrhages that frequently occur in these patients but also because of these patients' susceptibility to infection

and poor healing qualities. The use of antibiotics is imperative if surgery must be done, and these drugs are often used to reduce the oral symptoms of the disease.

Agranulocytosis and the anemias cause a general lowering of the host's ability to resist infection, and serious consequences may result if the dyscrasia is marked. In agranulocytosis, spontaneous hemorrhages of the oral cavity are not unusual, and this condition may be accompanied by various ulcerations of the mucosa. The clinical picture of anemia in the oral cavity is exactly what one would expect to find in a situation in which either a decrease in the number of red cells or a decrease in the hemoglobin content of the cells is present. The lips and mucosa are pale in color and delicate in texture. The tongue is often smooth, glossy, and painful. This may be the first clue to the systemic problem and should never be ignored. The decreased number of leukocytes and the subnormal oxygen-bearing elements are the systemic manifestations and make the patient easily susceptible to infection.

### *Malnutrition*

Malnutrition may result from the failure to ingest, assimilate, or utilize any or all substances essential for normal body metabolism. In some parts of the world, starvation may be the predominate cause of malnutrition, but in a modern society the most obvious causes are probably a poorly balanced diet, alcoholism, and old age.

Longevity, one of the accomplishments of modern science, has presented dentistry with many new problems, including denture construction on atrophied ridges, poor tissue tolerance to stress, and impaired healing. In the elderly patient and the alcoholic, the digestive tract may not have the ability to properly assimilate amino acids or other substances necessary to tissue repair. When this happens, the patient is more susceptible to infection and may require parenteral therapy with antibiotics and vitamins.

A thorough past history is important relative to tissue healing and other untoward sequelae resulting from prior surgery. Suspected impaired antibiotic function, from whatever cause, cannot be ignored and should be treated accordingly.

### *Miscellaneous systemic problems*

Numerous other systemic diseases have some direct or indirect relationship to infections of the oral cavity and adjacent tissues, either preoperatively or postoperatively. Any debilitating disease or affliction of the host can cause impairment of healing and decreased body resistance to infection.

**Liver diseases.** In the field of oral surgery one normally is concerned with cirrhosis of the liver, hepatitis, and other liver diseases because of the impaired clotting mechanism. A sufficient degree of liver damage can cause considerable impairment of the healing process associated with the resultant anemia and poor metabolism. Any patient having the obvious clinical manifestations of jaundice should be carefully evaluated before surgery is attempted.

**Renal diseases.** The kidneys are responsible, in part, for the elimination of the nitrogenous waste of the body, in maintaining the normal fluid and electrolyte balance, and in maintaining the proper level of plasma protein. Any disease or abnormality of these organs

may well complicate the progress of a patient undergoing a surgical procedure and may in fact cause the death of the patient if sufficient caution is not exercised. It is generally agreed that an abnormal immune response to the hemolytic streptococcus usually precedes glomerulonephritis. Although this disease entity usually gives a history of prior respiratory tract infection, the possible occurrence of hemolytic streptococcus in the oral cavity cannot be ignored by the dentist. A history of oral infections predisposing to nephritis, pyelitis, and other kidney diseases is not uncommon, and one must be careful about subjecting a patient with a history of kidney disease to reinfection. Patients with active renal disorders should definitely be protected with prophylactic antibiotics for two reasons. First, the renal function has been impaired by disease and any bloodborne infection, however transient, may produce serious consequences. Second, local resistance and healing properties of the tissues operated on have been reduced because of the increased uremia and other waste materials in the blood. Infection after surgery is not uncommon in patients so afflicted, and every supportive measure available must be instituted.

**Cardiovascular diseases.** All patients who have a history of cardiovascular disease should receive special attention at all times, but the treatment varies considerably, depending on the type of cardiac disease. In angina pectoris, coronary occlusion, hypertension, and congestive failure, the primary concern of the dentist is the control of pain and apprehension that may precipitate a relapse. A history of rheumatic fever, chorea, congenital heart disease, or cardiovascular surgery requires specific attention for an entirely different reason - infection. These cardiovascular problems are often aggravated by a transient bacteremia, however brief, and the literature is replete with cases showing the relationship of extractions and bacterial endocarditis. Alpha hemolytic streptococcus is the organism usually responsible for this cardiac complication. These organisms can be found almost routinely in a blood culture after an extraction or extensive periodontal therapy. Consequently, it is good medical and dental practice to protect patients with rheumatic or congenital heart disease by prophylactic measures.

The procedures that would fall within the scope of dental interest include root canal therapy, periodontal treatment regardless of its extensiveness, and, of course, all surgical procedures within the oral cavity. If uncertainty exists about the degree of gingival manipulation that may produce a transient bacteremia, then antibiotics should be administered. Although the exact dosage and duration of therapy are somewhat empirical, it is generally agreed that high concentrations are desirable before any dental procedure is undertaken.

The American Heart Association constantly reviews and evaluates the need for and modality of antibiotic therapy in patients with structural heart disease. The following discussion reflects some of their philosophies and recommendations in the administration of antibiotics.

Bacterial endocarditis remains one of the most serious complications of cardiac disease. Surgical procedures or instrumentation involving the upper respiratory tract, genitourinary tract, or lower gastrointestinal tract may be associated with transitory bacteremia. Bacteria in the bloodstream may lodge on damaged or abnormal valves such as are found in rheumatic or congenital heart disease or on endocardium near congenital anatomic defects, causing bacterial endocarditis or endarteritis.

Prophylaxis is recommended in those situations most likely to be associated with bacteremia since bacterial endocarditis cannot occur without a preceding bacteremia. Antibiotic prophylaxis is recommended with *all* dental procedures (including routine professional cleaning) *that are likely to cause gingival bleeding.* Chemoprophylaxis for dental procedures in children should be managed in a manner similar to that used in adults.

In general, parenteral administration of antibiotics provides more predictable blood levels and is preferred when practical, especially for patients thought to be at high risk to develop bacterial endocarditis.

Since it is not possible to predict those patients with structural heart disease in whom this infection will occur nor the specific casual event, optimal prophylaxis requires proper consultation between the treating dentist and the patient's physician to determine whether the patient is a high risk and should be given parenteral prophylactic antibiotics or a relatively low risk and can be covered with oral prophylactic antibiotics. The determination as to the relative risk (high or low) should be made by the patient's physician, not the dentist. In cases where the patient's physician is not available for consultation the parenteral route is preferred.

Table 9-1 contains suggested regimens for chemoprophylaxis for dental procedures or surgical procedures and instrumentation of the upper respiratory tract. The order of listing does not imply superiority of one regimen over another, although parenteral administration is favored when practical. The authorities favor the combined use of penicillin and streptomycin (Regimen B), or the use of vancomycin in the penicillin-allergic patient, in those patients felt to be at high risk (such as those with prosthetic heart valves).

**Table 9-1.** Prophylaxis for dental procedures and surgical procedures of the upper respiratory tract*

| | **Most congenital heart disease3; valvular heart disease; idiopathic hypertrophic subaortic stenosis; mitral valve4 prolapse syndrome with mitral insufficiency** | **Prosthetic heart valves5** |
|---|---|---|
| All dental procedures that are likely to result in gingival bleeding1,2 | Regimen A or B | Regimen B |
| Surgery or instrumentation of the respiratory tract | Regimen A or B | Regimen B |

1 Does not include shedding of deciduous teeth.
2 Does not include simple adjustment of orthodontic appliances.
3 Eg, ventricular septal defect, tetralogy of Fallot, aortic stenosis, pulmonic stenosis, complex cyanotic heart disease, patent ductus arteriosus or systemic to pulmonary artery shunts. Does *not* include uncomplicated secundum arterial septal defect.

4 Although cases of infective endocarditis in patients with mitral valve prolapse syndrome have been documented, the incidence appears to be relatively low and the necessity for prophylaxis in all of these patients has not yet been established.
5 Some patients with a prosthetic heart valve in whom a high level of oral health is being maintained may be offered oral antibiotic prophylaxis for routine dental procedures except the following: parenteral antibiotics are recommended for patients with prosthetic valves who require extensive dental procedures, especially extractions, or oral or gingival surgical procedures
* From American Heart Association Committee Report: Prevention of bacterial endocarditis, Circulation 55:139A-143A, 1977.

**Regimen A - Penicillin**

1. Parenteral - oral combined

*Adults:* Aqueous crystalline penicillin G (1.000.000 units intramuscularly) mixed with procaine penicillin G (600.000 units intramuscularly). Give 30 minutes to 1 hour prior to procedure and then give penicillin V (formerly called phenoxymethyl penicillin) 500 mg orally every 6 hours for 8 doses.

*Children:* Aqueous crystalline penicillin G (30.000 units/kg intramuscularly) mixed with procaine penicillin G (600.000 units intramuscularly). Timing of doses for children is the same as for adults. For children less than 60 lbs, the dose of penicillin V is 250 mg orally every 6 hours for 8 doses.

2. Oral

*Adults:* Penicillin V (2.0 gm orally 30 minutes to 1 hour prior to the procedure and then 500 mg orally every 6 hours for 8 doses.)

*Children:* Penicillin V (2.0 gm orally 30 minutes to 1 hour prior to procedure and then 500 mg orally every 6 hours for 8 doses. For children less than 60 lbs use 1.0 gm orally 30 minutes to 1 hour prior to the procedure and then 250 mg orally every 6 hours for 8 doses.)

For patients allergic to penicillin use either vancomycin (see Regimen B) or use

*Adults:* Erythromycin (1.0 gm orally 1.5-2 hours prior to the procedure and then 500 mg orally every 6 hours for 8 doses).

*Children:* Erythromycin (20 mg/kg orally 1.5-2 hours prior to the procedure and then 10 mg/kg every 6 hours for 8 doses.)

**Regimen B - Penicillin plus streptomycin**

*Adults:* Aqueous crystalline penicillin G (1.000.000 units intramuscularly) mixed with procaine penicillin G (600.000 units intramuscularly) plus streptomycin (1 gm

intramuscularly). Give 30 minutes to 1 hour prior to the procedure; then penicillin V 500 mg orally every 6 hours for 8 doses.

*Children:* Aqueous crystalline penicillin G (30.000 units/kg intramuscularly) mixed with procaine penicillin G (600.000 units intramuscularly) plus streptomycin (20 mg/kg intramuscularly). Timing of doses for children is the same as for adults. For children less than 60 lbs the recommended oral dose of penicillin V is 250 mg every 6 hours for 8 doses.

For patients allergic to penicillin

*Adults:* Vancomycin (1 gm intravenously over 30 minutes to 1 hour). Start initial vancomycin infusion 0.5 to 1 hour prior to procedure; then erythromycin 500 mg orally every 6 hours for 8 doses.

*Children:* Vancomycin (20 mg/kg intravenously over 30 minutes to 1 hour). Timing of doses for children is the same as for adults. Erythromycin dose is 10 mg/kg every 6 hours for 8 doses.

**Footnotes to Regimens**

In unusual circumstances or in the case of delayed healing, it may be prudent to provide additional doses of antibiotics even though available data suggest that bacteria rarely persists longer than 15 minutes after the procedure. The physician or dentist may also choose to use the parenteral route of administration for all of the doses in selected situations.

Doses for children should not exceed recommendations for adults for a single dose or for a 24-hour period.

For vancomycin the total dose for children should not exceed 44 mg/kg/24 hours.

For those patients receiving continuous oral penicillin for secondary prevention of rheumatic fever, alpha hemolytic streptococci which are relatively resistant to penicillin are occasionally found in the oral cavity. While it is likely that the doses of penicillin recommended in Regimen A are sufficient to control these organisms, the physician or dentist may choose one of the suggestions in Regimen B or may choose oral erythromycin.

Other indications for prophylactic antibiotics are:

1. Those patients who have had a documented previous episode of infective endocarditis, even in the absence of clinically detectable disease.

2. Those patients with indwelling cardiac catheters, especially those that reside in one of the cardiac chambers.

3. Those patients with indwelling transvenous cardiac pacemakers, even though at low risk; the dentist should consult the patient's physician, and they may choose to employ prophylactic antibiotics to cover dental and surgical procedures in these patients.

4. Those patients on renal dialysis with implanted arteriovenous shunt appliances.

5. Those patients with orthopedic joint replacements (such as total knee, total hip).

It is not possible to make recommendations for all possible clinical situations. Practitioners should exercise their clinical judgment in determining the duration and choice of antibiotic(s) when special circumstances apply. Consultation between the dentist and the patient's physician in these cases is stressed.

Since endocarditis may occur despite antibiotic prophylaxis, dentists and physicians should maintain a high index of suspicion in the interpretation of any unusual clinical events following the above procedures. Early diagnosis is important to reduce complications, sequelae, and mortality.

## Physiology of infection

A frequent cause of acute inflammation in the oral cavity and its adjacent structures is the invasion of microorganisms. The response to infection of the host follows a relatively normal pattern. Accepting this premise, one can state that the physiological response to infection is inflammation. The nature of the inflammatory reaction is dependent in turn on the site, type, and virulence of the bacteria. In addition, the physical status of the host may determine the degree of inflammation, depending on the local and systemic factors that have already been discussed.

The response of the host to infection may be local and systemic. The local reaction is inflammation, which is defined by Moore as "the sum total of the changes in the tissues of the animal organism in response to an injurious agent, including the local reaction, and the repair of the injury. If the inflammatory reaction is adequate, it minimizes the effect of the injurious agent, destroys the injurious agent, and restores the part to as near normal structure and function as possible. If it is not adequate, there is extensive destruction of tissue, invasion of the body, and somatic death." More briefly stated, one might say that inflammation is the reaction of the body to irritants, the most common of which are bacterial. The classic signs of inflammation are redness, swelling, heat, and pain. The degree and frequency of these signs vary considerably, depending on the virulence of the bacteria and their location. For example, in the oral cavity one might find a mild gingivitis, which is a minimal inflammatory reaction, and at the same time find a fulminating cellulitis of the neck caused by the same microorganisms. The different response is dependent in part on the location of the bacteria involved and may vary considerably if its environment is aerobic or anaerobic. In addition, the various body tissues respond differently to the same invading organism.

The signs and symptoms of inflammation can be explained when the tissue response to an irritant is understood. Initially a marked dilation of the vascular bed occurs, which is accompanied by a deceleration of the blood flow resulting from the greater volume of the vascular bed. The increased capillary volume is responsible for the cardinal signs of redness, swelling, and heat. As the rate of blood flow decreases, leukocytes begin to penetrate through the vessel walls into the surrounding tissues. This phenomenon is accompanied by an exuding of blood plasma through the walls, producing an inflammatory edema. The escape of the blood plasma may be caused by the toxic reaction of the capillary walls to infection or to an

increased osmotic pressure of the surrounding tissues. This tissue distention produces pressure against the neurogenic fibers and may actually cause the destruction of these fibers. This pressure phenomenon, along with the release of histamines from injured cells, plays a major role in the appearance of the fourth classical sign of inflammation - pain.

Varied types of inflammation are seen, depending on the tissue involved, the type of bacteria, and the resistance of the host. The most important are pyogenic, serous, catarrhal, fibrinous, hemorrhagic, and necrotizing inflammation.

The type of inflammation encountered most frequently in the field of oral surgery is pyogenic, meaning "pus forming". Most infections in this region, if allowed to progress without treatment, will eventually produce pus. The invasive bacteria or their toxins or both may produce several different clinical entities that will be discussed in detail in Chapter 11. They include lymphadenitis, cellulitis, abscess formation, phlegmon, and osteomyelitis. All may be either acute or chronic, and combinations of two or more of these clinical manifestations may be present. The pattern of infection is dependent on the numerous factors discussed previously, the length of time the infection has been present, and the mode of treatment.

## Systemic effects of oral infection

In all infectious diseases except the most trivial, systemic manifestations of bacterial invasions are found. The reaction may be produced by the actual destructive ability of the bacteria, as in an abscess, or by its toxins, as in diphtheria. When bacteria are present in the blood, the condition is known as "bacteremia". Most authors use the term "septicemia" when the bacteria and their toxins are found in large numbers, suggesting actual growth while in the bloodstream. Transient bacteremias are usually seen after the removal of teeth or periodontal therapy. This is generally of little consequence except when a cardiac valve deformity exists or the resistance of the host is impaired or the organism is highly virulent.

Fever is perhaps the most outstanding symptom of a systemic infection and probably results from the action of the bacterial toxins on the heat-regulating mechanisms of the brain. As one might suspect, fever may vary considerably from one individual to another, even though they may be afflicted with the same infectious process. The exact nature of temperature control is not clearly understood, but with sufficient fever, an accompanying reduction in blood volume is caused by a shift of blood fluids to the tissues and extravascular spaces. This phenomenon together with the loss of fluid caused by excessive perspiration leads to decreased urinary output (oliguria) and retention of chlorides. An increase in the nonprotein nitrogen, both in the blood and urine, results from an increased metabolism, which is also a consequence of fever. If the kidneys are functioning properly, this is not a serious problem, but if marked dehydration goes uncorrected, the patient may be in real difficulty because of the abnormal electrolyte balance and retention of nitrogenous waste products.

The elevated metabolism resulting from a fever also causes an increased pulse rate, cardiac output, and respiratory rate. These clinical symptoms of a fever are invaluable in determining the progress of the disease and the effectiveness of the therapy used. Any marked deviation of these manifestations from normal would require an alteration of the therapy and increased supportive care.

## Focus of infection

The principle of focal infection has been a controversial issue for many years. The pendulum of opinion has swung in both directions many times since the turn of the century. The modern concept of focal infection was given strong support by Billings and Rosenow so that in the 1920s considerable importance was placed on this concept. Since that time many studies have been conducted to ascertain the validity of the earlier conclusions. Some have substantiated the principle of focal infection and some have not. Today the pendulum has gradually swung back to a more conservative concept. It is generally agreed that the principle of focal infection is valid and that a focus of infection should be eliminated when possible. However, the general consensus is that a minor focus is, as a rule, not capable of producing exacerbations of unrelated disease except in specific and occasional instances.

In the last half century, many teeth have been condemned on the block of focal infection. Today with the aid of roentgenograms, vitalometer tests, and better clinical judgment the dentist is able to defend his or her position in attempting to salvage a patient's dentition. A focus of infection may act as a depot from which bacteria or their products may be disseminated to other parts of the body, or it may act as a site in which bloodborne bacteria may localize, setting up an acute inflammatory reaction.

The concept of elective localization of microorganisms is not fully understood, but it explains in part why certain bacteria have an affinity for one or more specific tissues of the body. Undoubtedly some close chemical interplay takes place between bacteria and tissues. This would explain why most apical lesions do little damage elsewhere unless the body resistance is depressed or a specific area elsewhere has been damaged. An excellent illustration of this phenomenon is the effect of the alpha hemolytic streptococcus on a previously damaged mitral valve.

The practitioner must keep these possibilities in mind when making a decision concerning the preservation of a tooth or its supporting tissues. If a tooth is infected, the infection must be removed. Little controversy exists about this basic tenet of good dental practice. This does not necessarily mean the extraction of the tooth. One can and should do root canal therapy if indicated in relation to the remaining dentition, and, in addition, a root resection should be performed if the apical lesion cannot definitely be eliminated by more conservative means. A root resection ensures a complete seal of the accessory canals and also eliminates the area of infected cementum. If the question of focal infection arises, it seems reasonable to accept the principle of root resection as being more reliable regarding the elimination of a focus of infection.

Periodontal disease of varying degrees has been accepted as a frequent site of focal infection. This disease, except for caries, is perhaps the most common chronic infectious process in man. Clinical evaluation regarding the presence of pus and inflamed gingiva is perhaps more reliable in determining if the disease is infectious than are roentgenograms. The latter may show bone loss, which may be persistent over a period of years, although the surrounding tissues show no clinical evidence of infection. When the dentition is firm even in the presence of moderate bone loss and clinical evidence of infection is absent, conservatism is justified in considering the teeth as a possible focus of infection.

As mentioned previously, specific diseases have been shown to have a direct relationship to oral foci of infection. Acute infections of the eyes, heart, kidneys, and joints have on occasion shown a direct correlation to oral infection. Some forms of optic neuritis and iritis have been traced directly to a chronic periapical or periodontal lesion. In the past it was not unusual to remove a chronically infected tooth and find a sudden exacerbation of a chronic iritis. The bacterium causing the initial eye condition, being suddenly released into the bloodstream in relatively large quantities, may produce an acute condition. Today this clinical observation does not occur as frequently, since most patients with iritis are given some supportive therapy with antibiotics prior to extractions.

Arthritic patients as a group have in the past probably lost more teeth under the guise of focal infection than all other groups combined. Arthritis is a painful and debilitating disease, and everyone associated with the case makes every effort to leave no stone unturned in the hope of finding the etiological factor. Arthritis occurs in a number of different forms, dependent on various etiological factors. In infectious arthritis (such as gonococcal and pneumococcal) and in degenerative arthritis, the etiological factors are readily established. Thus no effort is made to establish an oral focus. In rheumatoid arthritis, however, the exact etiology is unknown, although it is thought to be infectious. For this reason the dentist invariably sees the patient to eliminate any possible focus of infection. This is not an unreasonable request, since the patient is in desperate need of assistance. Any active infectious process of the oral cavity should be eliminated. Teeth that have root canals and no apical involvement and areas of condensing osteitis should not be removed unless the dentist is convinced that infection is present or unless the physician insists and has examined the patient for all other possible foci of infection. In this way it is possible to aid the patient and yet protect him in the retention of his dentition.

Studies have been reported that attempt to explain one of the disturbing aspects of focal infection. Some infectious processes in specific areas of the body are definitely believed to result from a primary focus of infection yet do not respond favorably when the primary focus is removed. These studies have shown that the secondary focus has been present long enough and the damage is of sufficient magnitude to be irreversible. The secondary site then is no longer dependent on the primary focus. This would explain the absence of dramatic results in many cases where teeth are removed as a focus of infection. An illustration of this problem as it relates to dentistry is the presence of some long-standing apical infection, which might well be the primary focus for pyelitis, bacterial nephritis, or other infectious processes. Although the apical infection is eliminated, the secondary focus will not respond, since the process is no longer reversible.

## Antibiotics

### Historical background

The antagonism of microorganisms to each other and the ability of various bacteria and fungi to produce antibacterial substances have been known since the late nineteenth century. Prior to 1938 this phenomenon was a scientific curiosity, utilized only to separate various bacterial species from one another. Since that time, however, this well-known fact has all but revolutionized modern medicine. Fleming in 1928 reported the value of penicillin in the isolation of *Haemophilus influenzae.* It was not until 1940 that a group from Oxford was

able to develop penicillin as a therapeutic agent. The investigation of Waksman and associates and Dubos and his group at about the same time led to the development of numerous other antibiotic agents suitable for clinical use. Some time earlier, in 1935, Domagk observed the therapeutic value of Prontosil in the treatment of mice with streptococcal septicemia. This was only the beginning of a new era in the treatment of infection. Countless lives have been saved by sulfanilamide and related sulfonamide drugs, although since 1944 the antibiotics have largely supplanted the sulfonamide drugs.

## General considerations

The ideal antibiotic has not yet been found. If one is ever discovered, it would have to have numerous important attributes. (1) It should be antimicrobial and therapeutically effective in vivo in concentrations that would not injure the host. (2) It should be able to attack the pathogenic organisms regardless of their location within the host. (3) It should have consistent therapeutic value. (4) It should not impair normal antibody or phagocytic activity. (5) It should not readily induce the development of resistant strains of microorganisms. (6) Its effectiveness should not be impaired in the presence of other therapeutic agents that might be administered concurrently. (7) It should be stable and easy to administer. (8) It should be inexpensive.

Before an antibiotic can be administered safely and effectively, certain factors require careful consideration.

### *Nature of the lesion*

The nature of the lesion caused by microorganisms commonly found in the field of oral surgery may fall into one of three categories. The one encountered most often in general practice is wound contamination, as in a "dry socket". Although the clinical picture is not necessarily caused by infection, wound contamination is not uncommon when teeth have been removed in the presence of oral filth and chronic infection. The blood clot is delicate, and if bacterial enzymatic action occurs before vascularization from the side walls of the wound, the clot will be destroyed. The use of unsterile instruments and materials is likely to cause wound contamination, since the bacteria are foreign to the oral flora and thus normal local tissue resistance is absent.

Abscess formation is the second most common bacterial lesion related to the oral cavity. These lesions may be chronic or acute, depending on the virulence of the bacteria, resistance of the host, and location of the infectious process. Apical abscesses are generally chronic, since the microorganisms in this location are not particularly virulent, and the normal body responses are able to build up a protective reaction as seen in a granuloma. Only when the body resistance is lowered or the environment altered to favor bacterial growth do these lesions become acute.

The third type of bacterial lesion is the invasive type of infection, which spreads through the soft tissues and usually results from an acute episode of an apical abscess. Until evidence of purulent material appears, this clinical entity is known as a cellulitis. An inflammatory reaction occurs in response to the invading microorganism or its toxins or both. In the field of oral surgery it almost invariably involves the connective tissues and muscles

adjacent to the mandible or maxilla or both, since the lesion generally results from a breakdown of the periosteum. Unless prompt measures are taken to control the infection, abscess formation with necrosis of tissue, lymphadenitis, and bacteremia will occur.

The effectiveness of antibiotic therapy has a direct bearing on the nature of the lesion. If a wound is contaminated and is on a surface where the antibiotic can be applied topically and maintained in sufficient quantity without producing sensitivity to the drug, then topical administration may be the method of choice. However, in the majority of instances an infected oral wound cannot be treated topically, since the concentration of the drug is difficult to maintain because of saliva dilution. More important, however, is the fact that the oral mucosa is highly prone to produce a drug sensitivity in the host. For this reason alone the use of topical antibiotics is to be avoided and is contraindicated except in a few instances in which the more insoluble antibiotics may be beneficial. Before any type of antibiotic therapy is effective in wound contamination, it is usually necessary to debride the area of necrotic material. This will ensure a healthy wound periphery for healing and an adequate blood supply.

Extracellular microorganisms are most often responsible for acute infections, and unless an accumulation of pus has developed they can generally be destroyed by phagocytic cells and antibiotics. The absence of normal tissue structures in an abscess deprives the leukocytes of the surface on which they operate effectively, and when deprived of oxygen, as in the case of an abscess, leukocytes become nonmobile and lose their phagocytic properties. To be effective an antibiotic must come into direct contact with the infective agent. This is not possible in many abscesses since the only contact can come through the intact capillaries at the periphery of the lesion. The larger the abscess the less effective is the antibiotic. This fact alone illustrates the necessity for continued surgical intervention when fluctuant material is within a tissue space. It has become apparent in recent years that antibiotics are only adjunctive aids in the presence of pus and that the purulent material must be evacuated surgically.

A cellulitis, on the other hand, that has not undergone sufficient degenerative changes to produce pus may be amenable to antibiotic therapy alone. The rich blood supply, characteristic of early inflammation, provides optimal transport of the antibiotic to the involved tissues. In addition, the drug tends to accumulate in the infected area because of the increased vascular bed and permeability of the vessel walls. Antibiotic therapy, therefore, must be instituted promptly if surgery is to be avoided. Before therapy is discontinued it is advisable to remove the causative factor to eliminate the possibility of a relapse.

### *Sensitivity of microorganisms*

An ever-increasing problem in the treatment of an infectious process is the response of the causative organisms to antibiotics. When the antibiotics were first introduced and as each new one was placed on the market, the manufacturer could generally predict, on the basis of laboratory data, which of the species and strains of bacteria would be sensitive. This is no longer the case. Although antibiotics are effective against certain bacterial groups, specific effectiveness is no longer the general rule. On the contrary, individual strains and species are showing wide variations in susceptibility to the same antibiotic. Making the

treatment even more complex is the fact that initial susceptibility to an antibiotic by a specific strain of bacteria may change during treatment.

It is difficult to explain why microorganisms change in their response to an antibiotic. Most investigators feel that bacteria actually undergo sufficient change to be considered mutations. Some, however, feel that an organism initially sensitive to one or more antibiotics gradually builds up a resistance and is no longer affected by the bacteriostatic or bactericidal property of the drug. The exact explanation is still controversial.

The resistance of microorganisms to antibiotics is a serious problem and promises to become even more difficult. For example, in numerous hospitals throughout the USA, strains of staphylococcus have been found that are resistant to all available antibiotics. Research installations are working overtime to produce new drugs that hopefully will be effective. Because of the numerous deaths caused by this strain, it has been necessary in some hospitals to close their operating suites for long periods of time.

One of the most effective means of determining the antibiotic sensitivity of the causative microorganism is to test it in the laboratory. It is first necessary to secure some of the purulent material. This is usually accomplished early in the treatment of oral surgery cases, since prompt incision and drainage of the abscess, as stated earlier, is generally indicated. An agar plate is inoculated with the freshly obtained material, and medicated disks, each containing a measured amount of antibiotics, are spaced over the plate. If the microorganism is sensitive to the antibiotic, it will fail to grow around the medicated disk. Resistant organisms will grow to the disk, and gradations of sensitivity or resistance may be present that can be evaluated by an experienced observer. If, however, the degree of susceptibility is important or if a mixed infection (more than one organism) is anticipated, other laboratory aids, such as the tube dilution method, are available.

It should be emphasized that although the laboratory procedures are important and should be used whenever possible, antibiotic therapy should not be delayed until results of the test are available. On the contrary, these drugs should be used and the antibiotic therapy altered if the laboratory studies warrant the change.

For more sophisticated and sensitive determinations the agar-gel dilution method may be used for each antibiotic in which the concentration of the antibiotic tested is in micrograms per milliliter.

### *Dosage and route of administration*

When use of an antibiotic is contemplated, the dosage and route of administration are important considerations. The purpose of the therapy is to produce as promptly as possible an optimum concentration of the drug at the site of infection and to maintain it at an effective level. The causative bacteria must, of course, be sensitive to the antibiotic used. Each antibiotic has its own characteristics regarding rate of absorption and excretion, which in turn are dependent on the mode of administration. For example, penicillin has a slower rate of absorption when administered orally as compared to parenteral injection, although some of the newer oral preparations have increased the rate of absorption considerably. The rate of absorption will also vary with the vehicle, whether oil or aqueous. In addition, penicillin

combined chemically with a procaine radical has a much slower rate of absorption than potassium penicillin alone.

Dosage is also determined by the rate of inactivation and excretion of the drug used. When administered orally, several antibiotics are destroyed readily by the lower digestive tract, whereas some are absorbed very slowly and may be excreted before therapeutic value can be obtained. At one time it was thought that the maximum tolerated dose was the only limitation on the amount given a patient. This has been found to be an erroneous conception and can cause untoward side effects in the host. The premise that if a little does some good then a lot will do better does not apply in the use of antibiotics.

Antibiotics may be administered intramuscularly, intravenously, orally, or topically. With the exception of the latter method, the antibiotics reach the area of infection by way of the bloodstream. When placed intramuscularly, the site acts as a depot from which the drug is taken slowly into the bloodstream.

Intravenous administration produces a rapid, high level of concentration in the bloodstream, but the excretion rate is even more rapid. This method of administration is generally used when an acute fulminating disease must be treated with the utmost haste. To maintain an adequate level the intravenous method is often combined with one or more other routes of administration.

Originally the oral administration of some antibiotics was necessary, since this was the only route available other than the intravenous. This is no longer true, but this mode of administration has become popular with the doctor and the patient. It is painless and convenient and particularly valuable when children are concerned. Palatable oral suspensions are most advantageous in treating children. Several disadvantages occur with the oral route of administration, the most serious being the reliability of the patient. Therapy depends on the cooperation of the patient, who is likely to be lax and forgetful about maintaining the dosage at regular intervals for as long as it is necessary. Some clinicians have taken the attitude that if a patient is ill enough to warrant an antibiotic, they would rather administer the drug themselves, thereby having the assurance that the patient receives the drug and also the added opportunity of evaluating the patient's progress more often.

One of the most controversial subjects with respect to antibiotics is the topical use of these drugs. Perhaps the greatest hesitancy has arisen because serious complications have occurred with the use of the sulfonamide preparations in topical form. It has been well established that the topical use of the sulfonamides often induces allergic reactions in the host. This has caused severe complications, even death, and is definitely contraindicated except in specific and rare instances under strictly controlled conditions.

Antibiotics have caused similar allergic responses in the host and also tend to produce resistant strains of bacteria. In addition, in the oral cavity the topical use of some antibiotics leads to partial destruction of the normal oral flora, permitting the rapid overgrowth of some of the fungi. Normal antagonisms as well as normal symbiotic associations are eliminated, and a flora that is naturally resistant to the drug becomes predominant. Thrush, cheilitis, and the production of resistant strains that can cause superinfections may be the result of the indiscriminate use of topical antibiotics.

Some antibiotics cannot be given systemically without hazard to the host because of toxic reactions to the drug. On occasion it is most beneficial to use this group topically, particularly when the offending organism is resistant to the drugs normally employed. Fortunately these agents (bacitracin, tyrothricin, neomycin, polymyxin) are rather insoluble, which is a distinct advantage when used topically, and relatively nontoxic. They seldom produce allergic manifestations and only occasionally produce resistant strains.

The therapeutic value of these drugs in the field of dentistry is still questionable except in isolated instances. Maintaining sufficient concentration for therapeutic efficacy in the oral cavity is well nigh impossible because of the constant dilution by saliva. They can be used effectively in ointment form on the lips and soft tissues outside of the oral cavity, primarily as prophylactic agents. In the presence of a chronic osteomyelitis the topical antibiotics have been found most beneficial, particularly when one can be placed in a cavity of bone and maintained there in adequate concentration. Antibiotics administered parenterally do not diffuse into infected bone in therapeutic concentrations as a result of a variety of factors, including impaired circulation and fibrous barriers. When this is the case, the practitioner must resort to any method left open to him. Parenteral therapy is indicated to prevent the spread of the infection, and topical administration is indicated in an effort to control and abort the infective process within bone.

## Indiscriminate use of antibiotics

Undoubtedly the discovery of the antibiotics as therapeutic agents must be considered among the greatest advancements of medical science, but with their discovery came the unnecessary, indiscriminate, and dangerous use of these drugs. Antibiotics have their therapeutic limitations and on occasion can produce toxic results far more serious than the initial disease for which they may have been given. On the basis of present-day knowledge the practitioner must make a new appraisal of the situation and use these drugs in a more reasonable manner.

The two most hazardous sequelae of antibiotic therapy are the toxic reactions exhibited by the host and the increasing problem of drug resistance by numerous microorganisms. Bacterial resistance can occur in two basic forms - the naturally insensitive strains, which are present to some degree in all bacterial populations, and by far the most dangerous, resistant strains developed as a result of inadequate and indiscriminate use of antibiotics. Resistance to the drugs has been shown to develop when the bacteria are exposed to suboptimal concentrations. The practicing dentist must be made acutely aware of this problem since in some locales the habit of administering antibiotics in insufficient dosage has become common practice. After removal of an impacted tooth, for example, the operator gives the patient a "shot" of penicillin as a prophylactic measure and then does not see the patient for subsequent antibiotic therapy. This procedure is to be condemned because it has little therapeutic value and can produce resistant strains of organisms that may cause the patient considerable damage.

Drug resistance is not dependent on inadequate dosage alone. Antibiotics administered therapeutically for protracted periods of time and producing excellent results for a specific organism may still cause alterations of other bacteria that can produce difficulty at a later date either for the host or by cross infection. As mentioned earlier, the problem of cross infection

has become a serious one in hospitals throughout the country because of the production of resistant strains of staphylococcus. Rigid aseptic techniques must be adhered to in the dental office for this reason alone if for no other. Most of our population has received antibiotic therapy at one time or another and may be carrier of resistant strains of bacteria. It is imperative that those associated with the healing arts, as well as the lay public, be apprised of the ever-increasing problem of drug resistance, since the incidence is related in large measure to the indiscriminate use of antibiotics.

A toxic reaction of the host to antibiotic therapy is another complicating factor in the use of these drugs. It is more prevalent when the drugs are used indiscriminately and may be produced in two ways. First, a sensitivity or allergic response of the host to the drug may be produced, and second, the alteration of certain normal physiological activities of the host may be disturbed either by a prolonged or massive dosage. The incidence of allergic responses to antibiotics is increasing primarily because of the repeated indiscriminate use of the drugs for trivial problems. As has already been pointed out, one of the best means of sensitizing a patient is by the use of topical preparations, particularly on the skin and oral mucosa. Erythemas, hives, and exfoliative dermatitis, are not uncommon and are occurring more frequently as the population becomes increasingly sensitive to the drugs. Having been forewarned by relatively minor reaction or by the patient's history, the practitioner should avoid the use of the offending drug or the results may be disastrous. Anaphylactoid reactions generally occur after the patient has had a minor reaction on a previous occasion. This reaction is characterized by the rapid onset of cyanosis, coughing, tonic spasm, a weak and thready pulse, and a marked drop in blood pressure. The incidence of serious and fatal results is increasing, and although more common after the use of penicillin, the problem cannot be ignored whenever any antibiotic is used.

Several antibiotics other than penicillin are capable of producing episodes of headaches, nausea, vomiting, and diarrhea. Most often these reactions are mild and can be controlled with adjunctive therapy, but occasionally the symptoms become acute and difficult to treat. Vertigo, nerve damage, renal disorders, blood dyscrasia, and resistant secondary infections are but a few of the additional complications that may evolve from the use of antibiotics. The specific toxic reactions and contraindications of each drug will be discussed independently.

Masking of the true clinical entity is another complication of the indiscriminate use of antibiotics. When a patient has symptoms that suggest infection, treatment must not consist of antibiotic therapy alone. It is equally important to establish the diagnosis before treatment is instituted. For example, if a patient gives symptoms of infection in the maxillary arch, an acute sinusitis and even a malignancy of the maxillary sinus might be masked if antibiotics are given on the premise that an acute apical abscess is the causative factor. Once the drug has been administered it is conceivable that the acute symptoms may subside and lie dormant only to arise again at some later date with more serious consequences. Antibiotics administered in the presence of pus may also complicate the problem. Surgery is still the best means of treating a fluctuant infected area, and it should be borne in mind that antibiotic therapy is only adjunctive therapy. Failure to evacuate pus might well produce what is known as a "sterile abscess", and although dormant for awhile, it will be activated again with increased virulence.

## Specific antibiotics

New antibiotics and modifications of old ones are being released frequently by various pharmaceutical houses. This is a natural by-product of active and competitive research and is to be encouraged. It is necessary if the increasing number of resistant strains and incidence of superinfections are to be combated. The antibiotics of today may be useless or outmoded tomorrow, although the ones that are to be discussed have stood the test of time reasonably well.

Recent laboratory investigations suggest that there may be some previously undetected anaerobic bacteria that may be causing some severe infections of dental origin. Until recently most cultures have been only for aerobic bacteria. The penicillin-resistant, anaerobic bacteria may require dentists to alter their choice of antibiotics. More research is in progress.

An effort has been made to discuss the antibiotics on a generic basis rather than by proprietary names.

### *Penicillin*

Although the oldest antibiotic, penicillin is still the most widely used. Penicillin is a selective inhibitor of bacterial cell wall synthesis in multiplying bacteria because of its capacity to inhibit formation of the cross linkages in the mucopeptide lattice. The inhibiting of cell wall synthesis may not in itself be lethal, but under the osmotic conditions in body fluids, which are normally hypotonic in relation to the interior of the bacteria, lysis of the organisms results. Penicillin is effective against gram-positive streptococci and staphylococci, which are of particular interest to the oral surgeon. It is also effective against several gram-negative cocci, notably meningococci and gonococci, but most gram-negative rods are naturally resistant. In addition, most spirochetes are sensitive, making penicillin the drug of choice in syphilis. With the exception of those infections in which resistant organisms and some gram-negative organisms are present and those patients in which allergic responses occur, penicillin is still the desirable drug for the treatment of oral infections.

**Preparation and dosage.** Penicillin is available in numerous preparations for intramuscular, oral, and intravenous use and is combined with various chemical radicals and carrying agents to produce short or long effective doses.

**Intramuscular.** Because of the recent increase in allergic reactions to penicillin, some clinicians have discontinued the use of intramuscular penicillin except when the patient is hospitalized. Treatment of allergic manifestations after intramuscular injection is more difficult than treatment of those reactions resulting from the oral route.

1. Procaine penicillin G is the preparation most frequently used today as a prophylactic and therapeutic drug. One milliliter contains 300.000 units, and the recommended dose is 600.000 units a day for moderately severe infections, with a reduction in dosage toward the end of treatment. When the patient requires hospitalization, it is practical and desirable to administer the drug every 12 hours.

2. Crystalline potassium penicillin G in aqueous suspension was one of the original preparations, but because of its rapid absorption, it is used in combination with procaine penicillin G, except in intravenous therapy. The combining of these two penicillin preparations (referred to as fortified) permits a rapid, high blood level (30 to 60 minutes) with a maintenance level. The usual dosage is 1 mL (300.000 units of procaine penicillin and 100.000 units of crystalline potassium penicillin) given every 12 or 24 hours, depending on the severity of the infection.

3. Benzathine penicillin G is a long-acting preparation that has found favor with those who feel the need for a prolonged blood level in their patient. The average dose is 300.000 to 600.000 units every 10 days. Like procaine penicillin it can be combined with aqueous penicillin, thus giving a high level for 24 hours and then sustaining a low blood level. Its most frequent use in oral surgery is as a prophylaxis against secondary infection or in treatment of a systemic condition such as rheumatic fever. It is not generally used in the treatment of acute infections and should not be used if the patient is sensitive to iodides.

4. More recently the semisynthetic derivatives methicillin, oxacillin, and nafcillin have become available. As noted previously, the indiscriminate use of antibiotics can produce resistant strains, and many infections today are caused by resistant penicillinase-producing staphylococci. These new semisynthetic penicillins may be used for this type of infection, in which resistant strains such as those of hospital-acquired infections are suspected. However, sensitivity of the bacterium should be determined by in vitro tests when possible.

Penicillinase-resistant drugs should be restricted to treatment of resistant staphylococcus infections, since extensive or indiscriminate use of these drugs may produce more resistant strains of bacteria.

The intramuscular dosage and frequency of administration for the new semisynthetic penicillins vary from 250 mg to 1.5 Gm every 4 to 6 hours, depending on the drug used, size and age of the patient, and severity of infection. Before the dosage is established, all pertinent factors should be evaluated and a review of the prescribed dosage studied.

**Oral.** The more recent preparations of oral penicillin have an excellent absorption rate in the bloodstream. When one is assured of a cooperative patient, these preparations are effective even for serious infections. It should be emphasized that the oral penicillins should be taken when the stomach is empty, to minimize gastric retention, and preferably with an antacid.

1. Penicillin G, as an oral preparation, has been available for some time, but some hesitancy has prevailed about its use because the degree and rate of absorption are variable. In addition, one must depend on the patient to take the drug exactly as prescribed, since a high blood level is not sustained for any length of time. When used, the average dose is 250 mg (250.000 units) given four times a day. This is believed to be equal in effectiveness to one injection of 300.000 units intramuscularly.

2. Penicillin V (pheneticillin) is a more /// recent and popular development and is being used rather extensively for the oral administration of penicillin. This drug has been found to be reliable in its rate of absorption and effective blood level. It is also compatible

with penicillin G, which may have been given during the acute phase of an infectious process. It is generally administered three or four times a day and is available either in tables or capsules containing from 125 to 300 mg (200.000 to 500.000 units). Oral suspensions containing 125 mg per teaspoonful are available for children.

3. Penicillin therapy should be discontinued at the first sign of allergic symptoms to the drug, including minor reactions such as itching and redness at the site of injection.

4. When penicillin is administered intramuscularly, extreme care should be taken to avoid an accidental intravenous injection.

5. If used intramuscularly, it is preferable to administer penicillin in the deltoid or triceps of the arm so that a tourniquet may be applied if the patient gives any indication of an anaphylactoid reaction.

### *Erythromycin*

Erythromycin has a bacterial spectrum similar to that of penicillin, and because of its unequaled safety record it is used by many clinicians in preference to penicillin, particularly for oral infections. It is active against the gram-positive cocci and a few of the gram-negative rods. It has also been reported to be effective against some of the viruses, rickettsiae, and certain strains of the diphtheria bacilli. Like penicillin, it may be either bactericidal or bacteriostatic, depending on the concentration of the drug and the organisms involved. Strains of *Staphylococcus aureus* that are insensitive to penicillin may be susceptible to erythromycin. This drug has its chief usefulness in the management of infections produced by staphylococci or other penicillin-resistant gram-positive organisms.

Erythromycin is indicated for treatment of a large variety of infections caused by a wide spectrum of susceptible microorganisms. Indications include cases in which use of other antibiotics is limited by undesirable or serious side effects. In cases in which organisms have become resistant to other antibiotics, particularly penicillin, erythromycin is often the drug of choice.

Side effects from the administration of erythromycin are rare. The oral administration may occasionally cause mild gastrointestinal disturbances, but the withdrawal of the drug is rarely necessary, since the symptoms disappear promptly.

Serious complications are extremely rare, but several proprietary preparations should be used cautiously when liver function is impaired.

**Preparation and dosage.** The usual mode of administration of erythromycin is orally, but it is available for intramuscular or intravenous use if the infection is of sufficient magnitude. It is supplied in enteric-coated tablets of 100 and 250 mg. The usual dosage for an adult is one or two tablets every 6 hours, depending on the severity of infection. Pediatric oral suspensions are available that contain 100 mg per teaspoonful (5 mL) and should be given every 4 to 6 hours.

### *The tetracyclines*

The tetracyclines are a group of antibiotics that has been developed over the past several years, and although they differ slightly chemically, their pharmacological and therapeutic actions are essentially the same. The most notable of this group are chlortetracycline, oxytetracycline, and tetracycline. Although they are dispensed under numerous proprietary names, they will be discussed together.

The tetracyclines belong to the so-called broad-spectrum antibiotics because they are effective against many gram-positive and gram-negative bacteria. They are primarily bacteriostatic in their action and normally are effective against all pathogenic organisms arising from the oral cavity. They are also effective in the treatment of some rickettsiae infections. These drugs are of considerable importance in that many gram-positive organisms resistant to penicillin and some of the gram-negative organisms resistant to streptomycin are susceptible to the tetracyclines.

Like most antibiotics, these drugs produce resistant strains, but fortunately the susceptible organisms do not develop resistance rapidly, with the exception of certain gram-negative strains.

**Preparation and dosage.** The tetracyclines are generally administered orally, but intravenous preparations are available if desired. The standard oral regimen for the average acute infection is 0.25 to 0.5 gm (250 to 500 mg) every 6 hours for a total dose of 1 to 2 gm. For children this dosage is reduced to 100 mg every 6 hours. Most of the proprietary preparations are available in oral suspension in which 5 mL (1 teaspoonful) contains 100 mg of the antibiotic. This is a particularly effective mode of administration for children who are unable to tolerate a capsule. When the infection is of sufficient magnitude, the drug may be prescribed every 4 hours instead of every 6. Interestingly enough, increasing the antibiotic intake by increasing the dose is of little value, since the use of a dosage beyond the optimum amount fails to produce proportionately higher blood levels because of some limiting factor in the ability of the intestinal mucosa to absorb the antibiotics.

Intravenous preparations are available for those patients who require a rapid high blood level as a result of the severity of the infection. In instances in which the patient cannot take oral medications, this mode of administration is most acceptable. Unconsciousness, trismus produced by infection, and mechanical immobilization of the mandible are several instances that would warrant the use of the intravenous preparations. The dosage will vary from 500 to 1.000 mg administered with 5% glucose intravenous solution every 12 hours. Injecting these antibiotics in concentration should be done with some hesitancy because they can produce a thrombus within the vessel. Intramuscular and subcutaneous injections are not recommended, since they are painful and may cause tissue damage associated with their irritating action. Several new preparations have eliminated this problem.

Topical preparations have been withdrawn from the market by the Food and Drug Administration. In dentistry, topical preparations have been used in the past to treat various manifestations of periodontal disease and postextraction wounds. Some clinical evidence has supported their use, but systemic administration is undoubtedly more effective and less likely to produce resistant strains and host sensitivity.

**Precautions.** Signs that indicate discontinuance of the tetracyclines include the following:

1. Perhaps the most frequent untoward reaction of the host to the tetracyclines is the occurrence of nausea and diarrhea. Should the diarrhea continue unabated the drug must be discontinued immediately to avoid severe complications. Discontinuing the drug will usually permit the gastrointestinal flora to return to normal, thus aborting a possible fatal outcome.

2. Glossitis, stomatitis, and skin eruptions are not unusual after the administration of one of the tetracyclines, particularly when a topical preparation has been employed. The appearance of these relatively minor allergic manifestations warrants the prompt discontinuance of the drug - they may be a warning of more serious manifestations of drug sensitivity.

3. Prolonged use of the tetracyclines may permit the overgrowth of organisms that are not susceptible to the antibiotic. The overproduction of *Candida albicans,* for example, can produce symptoms that are painful and persistent. Oral discomfort and anal and vaginal itching are common manifestations of moniliasis and may be very difficult to treat. The drug should be discontinued promptly if these symptoms arise.

4. When an infectious organism fails to show any clinical sensitivity to one of the tetracyclines, it is most unlikely that it will respond to any in the group. Similarly, a patient with an allergic response to one is likely to have the same response to any of the tetracyclines.

5. Of particular interest to dentists is that the tetracyclines are deposited in calcifying areas of bones and teeth and may cause a yellow to gray discoloration. The discoloration of the teeth was first noted by Schwachman and associates during assessment of long-term tetracycline therapy in children with fibrocystic disease. The phenomenon has been confirmed by many investigators since then, and long-term therapy with tetracycline in children is to be strongly discouraged because the cosmetic effect on the dentition can be severe.

### ***Streptomycin***

Streptomycin and dihydrostreptomycin are effective against a number of gram-positive and gram-negative organisms. These antibiotics interfere with bacterial protein synthesis, and it is postulated that this effect may account for their bactericidal activity. These drugs are ineffective in syphilis and in infections caused by clostridia, fungi, and rickettsiae. Because of their toxic side effects and the relative ease with which microorganisms become resistant, their general use for infections about the oral cavity is not recommended except as a last resort.

**Preparation and dosage.** Intramuscular injection of streptomycin (or dihydrostreptomycin) is the only effective means of administering the drug. Dosage ranges from 1 to 3 gm daily in divided doses of 0.5 gm.

**Precautions.** The following complications may accompany the use of these two drugs and must be watched for carefully. These drugs should be discontinued immediately if untoward symptoms appear.

1. The topical use of streptomycin is contraindicated because of the high degree of sensitization.

2. Both streptomycin and dihydrostreptomycin have been reported as producing vestibular and auditory damage even in small doses. Recovery of vestibular function may occur after the drug is withdrawn, but auditory damage may be irreversible.

3. Renal complications may occur after the use of these drugs, and when renal malfunction is present, the drug is contraindicated.

### *Chloramphenicol*

Chloramphenicol is a broad-spectrum antibiotic and is effective against most pathogenic organisms associated with the oral cavity. In addition, the rickettsiae and some viruses respond to this drug. It is a specific therapeutic agent for typhoid fever. The spectrum is not unlike that of the tetracyclines, and chloramphenicol is bacteriostatic in its action. Its molecular weight is lower than that of the other broad-spectrum antibiotics, and thus it is capable of producing a rapid, high blood concentration, which is advantageous in severe infections. The drug's high diffusibility results in effective concentration in the cerebrospinal fluid. This attribute makes the drug particularly valuable in treatment of severe maxillary fractures complicated by cerebrospinal rhinorrhea. It is effective against many microorganisms that have developed a resistance to the older, more frequently used drugs. Chloramphenicol, like all antibiotics, produces resistant strains, and its indiscriminate use, particularly in minor infections, should be avoided, or its present advantage will probably be dissipated.

**Preparation and dosage.** The average adult daily dose of chloramphenicol is 1 to 2 gm in divided dosage, either four times during the day or every 6 hours, depending on the necessity of a constant blood level. The drug is dispensed for oral administration in 50, 100, and 250 mg capsule form. For children an oral suspension is available that provides 125 mg per teaspoonful (5 mL).

For the average infectious process the oral administration is preferred, but when indicated, chloramphenicol may be administered intravenously or intramuscularly. The adult dose for intravenous administration is 0.5 gm every 6 to 12 hours, either with a physiological sodium chloride solution or 5% dextrose in normal saline solution. This mode of administration should be discontinued as soon as the patient can take oral medication.

Chloramphenicol also may be administered intramuscularly in 1 gm doses and because of its repository quality can be given only every 12 to 24 hours. This generally sustains an adequate blood level to combat most infections.

**Precautions.** Continuing and careful study of the patient who is taking this drug is necessary. Chloramphenicol should not be used when other and less potentially dangerous agents will be effective.

1. Chloramphenicol is a potent therapeutic agent, and certain blood dyscrasias have been associated with its administration, although to a lesser degree of frequency than was originally thought when the drug was first introduced. Depression of the bone marrow may result in neutropenia, agranulocytosis, or, in extreme cases, aplastic anemia. Prolonged administration is to be avoided, and blood studies (complete blood count (CBC) and differential) should be made every 48 hours during treatment. It has been suggested that chloramphenicol not be administered longer than 10 days to an adult and 7 days to a child.

2. Like the tetracyclines, chloramphenicol is capable of producing nausea and diarrhea, but the latter complication occurs much less often since this antibiotic does not suppress the intestinal flora as readily. This is explained on the basis that it is absorbed more rapidly in the upper intestinal tract and does not reach the large bowel in any quantity.

3. Moniliasis, which occurs with the use of most of the antibiotics, may also result from prolonged or topical use of this drug.

### *Novobiocin*

Novobiocin is an antibiotic that has been found to be effective in treating infections caused by both gram-positive and gram-negative bacteria. It has been effective against some strains of *Staphylococcus aureus* and is also used in infections caused by hemolytic streptococcus, *Diplococcus pneumoniae*, and *Proteus vulgaris.*

**Preparation and dosage.** The recommended dosage in adults is 500 mg every 12 hours or 250 mg every 6 hours, continued for at least 48 hours after the temperature has returned to normal and all evidence of infection has disappeared. In particularly severe infections it may be desirable to double the average dosage. The route of administration is orally in the form of capsules and a syrup for children. The syrup contains 125 mg per teaspoonful.

**Precautions.** Novobiocin is not recommended for treatment of any infection because of frequency of cholestatic jaundice, allergic reactions, gastrointestinal disturbance, neonatal hyperbilirubinemia, and fatal blood dyscrasias.

### *Lincomycin*

Lincomycin has an antibacterial spectrum similar to that of erythromycin. In vitro it inhibits the growth of many gram-positive organisms, especially staphylococci, including penicillinase-producing staphylococci, pneumococci, and some streptococci. It appears to have little effect on enterococci, meningococci, and gonococci, and it is inactive against gram-negative bacilli.

Favorable responses have been reported from its use in cases of osteomyelitis. Lincomycin is useful in the treatment of infections caused by sensitive organisms when resistance to penicillin or erythromycin has developed or when these drugs cannot be used because the patient is allergic to them. The drug may be administered in combination therapy with other antimicrobial agents when indicated.

**Preparation and dosage.** Lincomycin is adequately absorbed either by the oral or intramuscular route. The oral dosage for adults is 500 mg given three or four times daily. The intramuscular dosage is 600 mg every 12 hours or more frequently in severe infections. Oral dosage for children is based on weight (15 to 30 mg per pound).

**Precautions.** Since lincomycin is a relatively new drug, patients must be observed carefully for the appearance of unforeseen reactions. Patients receiving treatment for longer than 1 or 2 weeks should have liver function tests.

1. Because of the lack of adequate clinical data, use of the drug is not indicated in those patients with preexisting kidney, liver, or metabolic diseases.

2. Evidence of moniliasis or monilial infection necessitates prompt discontinuance of the drug.

3. Minor gastrointestinal disturbances such as nausea, vomiting, abdominal cramps, and diarrhea have been reported.

### *Clindamycin*

Clindamycin phosphate is produced from the same synthetic group as lincomycin. Although clindamycin phosphate is inactive in vitro, rapid in vivo hydrolysis converts the compound to the antibacterially active clindamycin, and orally it is more rapidly absorbed from the gastrointestinal tract than lincomycin. Recent studies seem to indicate that clindamycin is more potent than lincomycin.

It is believed that this drug is effective against *Staphylococcus aureus* and *S. epidermidis,* streptococci, and some anaerobic organisms such as the *bacteroides* species. Clindamycin is widely distributed in body fluids and tissues, including bone, and for this reason is found to be effective when treating chronic bone infections of dental origin such as osteomyelitis.

**Preparation and dosage.** Clindamycin may be administered intravenously, intramuscularly, or orally, with about the same effectiveness, except for severe infections. When administered parenterally the usual dosage is from 600 to 1.200 mg daily divided into two, three, or four equal doses. Oral administration is usually 150 mg every 6 hours but may be increased to 300 mg per dose without any untoward reactions.

**Precautions.** The following factors are to be considered for the safe use of clindamycin.

1. Clindamycin is contraindicated in those patients who may have exhibited a hypersensitivity to lincomycin.

2. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed because transient neutropenias and transient liver abnormalities have been noted.

3. Gastrointestinal symptoms, such as nausea and vomiting, occasionally occur with the oral administration of clindamycin.

### *Kanamycin*

Kanamycin sulfate is the salt of an antibiotic derived from strains of *Streptomyces kanamycetius.* The antibacterial activity is similar to that of neomycin. It is active against many aerobic gram-positive and gram-negative bacteria. This drug is indicated for the treatment of serious infections caused by susceptible organisms. When osteomyelitis, bacteremias, and soft tissue have shown resistance to conventional antibiotics, kanamycin may be used if the causative bacteria have been shown to be sensitive by in vitro studies.

**Preparation and dosage.** Kanamycin may be administered by the intramuscular, intravenous, or oral route. The oral administration of the drug should be reserved for those patients with gastrointestinal problems, since the drug is poorly absorbed from the gastrointestinal tract and therefore not too effective in systemic problems. The intramuscular route is generally the route of choice, and the dosage is calculated not to exceed 0.7 mg per pound of body weight in two or three divided doses.

**Precautions.** As noted previously, kanamycin should be reserved for infections resistant to other antibiotics. Patients should be carefully evaluated during the administration of the drug and probably should be hospitalized.

1. The major toxic effect of parenterally administered kanamycin is its action on the auditory portion of the eighth nerve. Excessive dosage seems to be a factor, and use of the drug should not be prolonged unnecessarily. Deafness may be partial or complete, and in most cases it has been irreversible.

2. Renal irritations frequently occur in those patients with prior kidney problems or in those patients who are not well hydrated.

### *Cephalosporins*

The cephalosporins are bactericidal by inhibition of cell wall synthesis. They are not hydrolyzed by penicillinase, and there is little or no cross resistance with penicillins. They have a broader spectrum than penicillins but are less active against gram-positive organisms. Resistance can develop by cephalosporinase production. In distribution, 55% to 65% of the drug is bound to plasma protein. From 70% to 80% is excreted unchanged in the urine.

Dosage types are as follows: cephalexin monohydrate (Keflex) is oral, cephaloridine (Loridine) is parenteral, and cephalothin (Keflin) is parenteral; the last two are nephrotoxic in high doses.

Toxicity is low compared to penicillins. Adverse effects include skin rashes and occasional allergic reactions and cross allergenicity to penicillins. In addition, gastrointestinal disturbance occurs occasionally with cephalexin monohydrates, and rare hepatic dysfunction occurs with cephaloridine and cephalothin.

### *Polymyxin B*

Polymyxin B has its principal effect on gram-negative bacteria (except proteus species) and should be reserved for this group. It has been used primarily as a topical drug, but the incidence of gram-negative strains has forced clinicians to resort to polymyxin B for systemic use.

Topical polymyxin is usually nontoxic and nonsensitizing. It has been combined in complex preparations for use as troches and ointments.

Systemic administration must be carefully controlled, since the drug may induce nephrotoxic or neurological disturbances (dizziness, facial paralysis) or both. The problems are not pronounced when the recommended dosage range is not exceeded.

**Preparation and dosage.** The suggested route of administration is by intramuscular injection at intervals of 8 hours. The total daily dose is from 1.5 to 2.5 mg per kilogram of body weight. The maximum dosage must not exceed 200 mg.

**Precautions.** In those patients who exhibit any impairment of renal function, the use of polymyxin should be avoided. If the patient has normal renal function, the nephrotoxic effects of the drug may become evident on the fourth or fifth day of treatment, but these can generally be controlled if the recommended dosage is not exceeded. The same is true regarding the neurological disturbances.

It should be emphasized that polymyxin B must be reserved for those patients afflicted with an infection caused by organisms proved to be sensitive to the drug.

### *Local antibiotics*

Antibiotics that are not normally used as systemic drugs because of their toxicity but have some benefits when used topically are referred to as local antibiotics. Used systemically they produce untoward complications and are therefore contraindicated except under dire circumstances. One common characteristic is their ability to be used topically with allergic reactions held to a minimum. These agents do have a place in dentistry, but it should be borne in mind that the concentrations employed are insufficient to control the infection and should be used as adjunctive therapy. These local antibiotics have been prepared commercially in various combinations and concentrations. Only a brief résumé of their specific characteristics seems indicated.

**Bacitracin.** Bacitracin is active against fusiform bacilli and some spirochetes and has a range similar to that of penicillin. Because of this relationship in activity it may be effective when employed with systemic penicillin in combating Vincent's infection. The effectiveness of bacitracin is not altered by serum, pus, or necrotic tissue. This characteristic makes it valuable in the treatment of osteomyelitis when the infected area can be approached directly and an adequate concentration maintained. To be effective the drug must be in contact with the pathogenic organisms.

**Neomycin.** Neomycin is bactericidal in vitro against both gram-negative and gram-positive organisms. Although occasionally administered parenterally, it has no general application because of the toxic effect on the kidneys and on the eighth nerve. Topically it is effective in skin infections and has been combined with other local antibiotics in the preparation of troches and ointments. The troches have been of value in controlling secondary local infection, particularly in those persons who are allergic to a number of the parenteral antibiotics.

**Tyrothricin.** Tyrothricin, like bacitracin, is particularly effective against the gram-positive organisms. It is made up principally of two active ingredients, gramicidin and tyrocidine. It is most effective when in direct contact with the offending microorganisms. Applied in compress form to open wounds it has been effective, and infected bone lesions have responded favorably when the drug, in solution, is carried directly to the injured part. The usual concentration is 0.01% to 0.05% in isotonic solution irrigated directly into the wound through a drain two or three times daily. Tyrothricin is also prepared in troche form, particularly to combat streptococcal oral infections.

## Sulfonamides

As a group the sulfonamides have been replaced by the antibiotics primarily because of the dramatic effect of the newer agents and the toxicity of the older drug. Now, however, the antibiotics are producing resistant organisms that can be treated with the sulfonamides, and improvements have been made in these drugs that make them less toxic.

The primary toxic complication of the sulfonamides when they were first introduced was crystalluria, resulting in renal shutdown. Drug fever, dermatitis, and alterations in the blood-forming organs, with resultant hemolytic anemia, leukopenia, and agranulocytosis, were additional complications. Most of these complications have been eliminated or at least minimized by proper controls during administration and by the combination of three of the sulfonamides into one medication. The combination of sulfadiazine, sulfamerazine, and sulfamethazine into a triple sulfonamide preparation has reduced toxic reactions considerably. Sulfisoxazole and sulfadimetine are also well tolerated when properly administered and controlled.

Triple sulfonamides are prepared in 0.5 gm tablets, and the dosage is generally 2 gm initially to be followed by 1 gm every 6 hours. Oral suspension for children is also available in concentrations of 0.5 gm in each teaspoonful. Dosage for a child is usually one-half the adult dose. Most authorities recommended that an equal amount of sodium bicarbonate be given with each dose of the sulfonamides. This will reduce the incidence of urinary tract complications.

**Precautions.** The following factors are considered in the safe use of the drugs:

1. A history of previous sulfonamide sensitivity would normally contraindicate the further use of these drugs unless the exact sensitizing drug could be ascertained.

2. Daily supervision of the patient and constant observation for signs of toxicity are imperative in sulfonamide therapy.

3. High fluid intake is mandatory to avoid renal complications, and urinary output should be above 1.200 mL per day.

4. Measurement of sulfonamide blood concentrations is indicated in severe infections to maintain a sufficient therapeutic level.

5. CBC and urinalysis should be done every other day to ascertain any early toxic reaction.

6. Patients should be advised to avoid any unnecessary exposure to ultraviolet rays, since photosensitivity may result.

## Adjunctive Therapy

In the use of antibiotics the practitioner is often confronted with the necessity of using other drugs as supportive therapy or to combat the complications of the antibiotic. To discuss the relative merits and defects of each drug would be impossible but an awareness of what agents are available seems appropriate.

## Vitamins

Vitamins are well established as an effective group of drugs in the treatment of dental problems; they have been useful in treating gingival disorders, cheilitis, and impaired healing. When antibiotics are used, vitamins are valuable in supplementing the dietary intake, particularly when the antibiotics are administered orally. Several of the broad-spectrum drugs cause a decrease in the intestinal flora, which may produce an avitaminosis. Numerous vitamins are dependent on the intestinal bacteria for their production, and, in the prolonged use of antibiotics, supportive vitamins should be administered. A therapeutic vitamin preparation that includes the B complex, ascorbic acid, and various minerals is usually adequate. A recent indicated that tetracycline therapy is more effective and rapidly induced with minimum dosage when administered with ascorbic acid. The recommended dosage is 500 mg of ascorbic acid for every 250 mg of the tetracyclines.

## Antihistamines

Allergic reactions to antibiotic therapy make it imperative to have some effective means of treating these untoward manifestations. The antihistamines are useful in treating urticaria, itching, allergic rhinitis, serum sickness, and angioneurotic edema. Penicillin is undoubtedly the antibiotic that produces most of the local reactions, and should mild symptoms appear, antihistamine therapy is indicated to keep the reaction to a minimum. Prompt therapy will make the patient more comfortable and may prevent more serious complications.

Many antihistamines are available in the form of elixirs, tablets, and nasal sprays and in combinations with other drugs. Intravenous and intramuscular preparations are also available when a rapid high level is necessary. Most of these drugs currently available may produce drowsiness or vertigo in some patients. Less frequently encountered is nausea. The advantages, disadvantages, and dosage of each antihistamine are not within the scope of this

text. A pharmacology reference provides an excellent source in the selection of the proper drug and dosage.

Cortisone, hydrocortisone, and epinephrine are used when the allergic manifestations become marked. Administered in suitable formulations and by the appropriate route, these drugs usually give dramatic relief. They should be used judiciously and in consultation with the patient's physician if the symptoms are severe or therapy is prolonged.

## Penicillinase

An enzyme, penicillinase, has been introduced for the specific purpose of combating allergic reactions to penicillin. It catalyzes the hydrolysis of penicillin to penicillinoic acid, which is nonallergenic. Whereas the antihistamines and steroids treat the effects of an allergic response to penicillin, this specific enzymes counteracts the cause of the reaction by neutralizing the penicillin itself.

The drug is administered intramuscularly as soon as signs and symptoms of a reaction appear. It may be repeated daily if needed and should be given intravenously in the presence of an anaphylactoid reaction to penicillin.

## Sequelae

The use of antibiotics as a prophylaxis against possible infectious complications has become fairly common practice. It is now clear on the basis of recent studies that in most situations such prophylaxis is of no value and in many cases superinfections result. It appears that the unnecessary and prolonged use of antibiotics may induce, rather than prevent, infection. One recent assessment on a general surgical service showed that when antibiotics were used arbitrarily the incidence of infections in the group receiving systemic prophylactic antibiotics after clean surgery was three times higher than in the group receiving none.

These findings do not preclude the necessity of administering antibiotics in selected cases, giving them to the patient with rheumatic fever or severe facial injuries, but one should develop a cautious approach to the use of these drugs.