STAPHYLOCOCCAL bacteremia with or without endocarditis is as great a threat to life today as it was before specific antibacterial treatment was available. The numerous instances in which cures have been effected by the administration of one or more of the potent antibiotic drugs do not belie this statement. Soon after penicillin and other effective antistaphyloccocal drugs were put into general use, there was a dip in mortality statistics which seemed an encouraging harbinger of the expected trend. Since 1948, however, the death rate has in most clinics approached that which existed before the antibiotic era. This apparent failure of current therapy to reduce mortality appears to be due to the increased incidence of bacteremia and endocarditis in already diseased persons rather than to an alteration in the character of the organism. To appreciate the nature of the problem of staphyloccic bacteremia as an infection in older and often severely debilitated patients as well as in the young, it is necessary to consider the nature of both the organism and the patient. The purposes of this review are to re-examine the host-parasite relationship, to reconsider the important clinical aspects of bacteremia with and without endocarditis, and finally to discuss the methods of treatment that have met with greatest success.

**STAPHYLOCOCCAL BACTEREMIA**

*The Organism*

Staphylococcus aureus is responsible for more cases of endocarditis and bacteremia than any other organism save alpha and non-hemolytic streptococci. While all staphylococci may cause serious infections, some are more virulent than others. The distinguishing features of these pathogenic strains were once considered to be the appearance of a ring of hemolysis around colonies growing on blood agar, and the production of a golden pigment. These are helpful but not entirely dependable criteria. The ability of the staphylococcus to produce coagulase is now regarded as the single most important indication of pathogenicity. It is demonstrated by the development of a coagulum in fresh human plasma after several hours' incubation with organisms from a 24-hour culture. The precise relation of coagulase to pathogenicity or virulence is undefined. Rammelkamp and Lebovitz recently proposed that coagulase was of importance in modifying the host response to staphyloccocal invasion. They suggested that coagulase, in action with reacting factor, was responsible for localizing infection and observed that infants, normally deficient in reacting factor, were not so capable of discrete abscess formation as adults. It is more generally believed that coagulase enhances the virulence of staphylococci by protecting them against the action of normal serum bacteriocidins and against phagocytosis. Staphylococci that would not survive after entrance into the blood stream without coagulase can proliferate in its presence.

All pathogenic strains elaborate one or more of the many staphyloccocal toxins or enzymes. In addition to hemolysins of 4 antigenically distinct types, staphylokinase, dermonecrotic toxin, enterotoxin, erythrogenic toxin, hyaluronidase, fibrinolysin, and a leukocidin are produced. The roles of enterotoxin, erythrogenic toxin, and the dermonecrotic or lethal toxin in clinical infection are self evident.
This is not so true of the others. Their in vitro behavior is measurable but their actual mechanism of action in clinical infection is not clear. Staphylococci obtained from enclosed abscesses produce both staphylokinase and hemolysins in uniformly high titer. Coagulase-positive strains from healthy carriers in the hospital vary in toxin production but are nevertheless more toxigenic than those obtained from people outside the hospital area.\textsuperscript{5}

The more highly toxigenic strains are apparently better able to establish themselves in normal tissues than others. While coagulase productivity is a way by which pathogenic strains in general can be separated from saprophytic ones, further gradations of potential virulence can be determined by the number and amount of the specific toxins they elaborate.

Although the various toxins are antigenic, their antibodies have at best a limited protective capacity. The course of acute infection in experimental animals was altered by the administration of anticoagulase antibody but the eventual fatal outcome was only delayed. Horse serum containing antibodies against the hemolysins, the lethal toxin, and possibly others, has been used in the past to treat infection in man, with occasional cures of cases of meningitis, pneumonia, and osteomyelitis.\textsuperscript{6} There were, for example, 6 cases of meningitis with 4 recoveries. However, less favorable results have been observed by others, suggesting that antitoxins are of uncertain value in treatment of infections. Antibody formation does not occur in localized staphylococcal infections such as furunculosis in human beings, even when repeatedly due to the same strain. This has been attributed to the limited permeability of the abscess wall, which prevents the release of whole antigens into the circulation.\textsuperscript{1}

Penicillinase (perhaps a natural endowment of the organism from prehistoric times), is produced by some coagulase-positive staphylococci. As a specific penicillin-splitting enzyme, it does not account for resistance to other antibiotics; strains producing it, however, are more readily capable of acquiring resistance to other drugs.

\begin{center}
\textbf{The Epidemiology of Staphylococcal Infections}
\end{center}

Specific identification of staphylococcal strains is essential to the determination of their distribution and for tracing the source of epidemic disease. Serologic differences among pathogenic strains led to the establishment of 9 subgroups in 1940. However, a more satisfactory technic now widely employed is typing with bacteriophage.\textsuperscript{7,8} Four broad subdivisions of coagulase-positive staphylococci have been established based on reactions with 19 distinct bacteriophages. Within each of these "phage-types" are strains which are lysed by one or more specific phages. Staphylococci are identified by the specific phages that exert this effect upon them; e.g., strain 42B is lysed only by phage 42B, while 6/47 is lysed by both 6 and 47. No correlation has been established between strain types and specific diseases with 2 exceptions: staphylococcal pneumonia complicating influenza was found to be primarily of phage type 1 while food poisoning was most frequently due to type III.\textsuperscript{9}

The nose and throat of about 63 per cent of the normal population contain staphylococci of varying pathogenicity. The majority of these strains are penicillin-sensitive. The skin harbors these organisms in 20 to 30 per cent of people. Inside the hospital, however, the carrier rate in nose and throat as well as on the skin is increased by nearly 90 per cent. This is true of such hospital workers as nurses, orderlies, members of the house staff, and patients. The nares of newborn infants in hospital nurseries have been shown, in 90 per cent of cases studied, to harbor staphylococci that by phage typing were identical with the strain predominant in the hospital.\textsuperscript{10} It has also been shown that they carry these strains for as long as a year after discharge.\textsuperscript{11} The reservoir from which staphylococcal infections may be drawn is a large one, and the greatest concentration of organisms is in those areas where the most vulnerable people are to be found.

Despite antibiotic prophylaxis and treatment an increase in the number of postopera-
tive wound infections has been observed in many surgical wards. It was found that simple although rigidly enforced antiseptic technics in dressing wounds was followed by a significant reduction in the number of these infections.\textsuperscript{12, 13} There was also a decrease in the number of staphyloccal carriers among the attending hospital personnel, and when the antibiotic prophylaxis of clean surgery was discontinued, it was found that fewer of these staphylocci were penicillin-resistant.

Whether one is within the hospital or outside it, infection does not develop simply because the organism is present. The organism must first be introduced into healthy tissues and overcome the normal physical barriers and humoral mechanisms that oppose bacterial proliferation. The first obvious barrier against infection is the intact skin and subcutaneous tissues. If staphylocci penetrate these defenses and enter the lymphatics or blood stream, phagocytes engulf them as do the fixed reticuloendothelial cells. A variety of naturally occurring substances in human serum exert a bacteriostatic or bacteriocidal effect. The importance of phagocytic activity was illustrated by Rogers,\textsuperscript{14} who showed that the number of coagulase-positive staphylocci injected into the carotid artery of a rabbit was reduced 1000-fold within 20 minutes by trapping of bacteria within circulating phagocytes. Low grade bacteremia persisted despite this early phagocytosis because many of the organisms were not killed and were soon released. Obviously, the larger the number of organisms injected, the greater is the likelihood of continuing bacteremia. If only a small number of organisms enters the circulation, there is no particular danger to the normal person, but serious disease in the host or persistence of staphylocci at the point of entry may make even a small number dangerous.

\textit{Pathogenesis of Staphylocoecemia}

Staphylocci in a traumatized area of skin or within a localized infection of any tissue normally fail to enter the blood stream because of the activity of phagocytes or the presence of physical barriers. It has been shown that when they do so it is often by direct entrance into lymphatics.\textsuperscript{15} No bacteremia occurs even when organisms are introduced in large amounts into a freshly opened wound in an experimental animal’s extremity if the lymphatic drainage has been obstructed. There is evidence that in the presence of inflammation lymphatic channels remain patent or are actually widened. Thrombosis of small venous radicles has long been accepted as a tissue response to staphyloccal infection. Septic thrombothrombophlebitis of these vessels has been shown to provide a source for the bacteremia that may complicate minor infections.\textsuperscript{16} This intravascular focus for dissemination is an important mechanism by which emboli of organisms alone or of infected thrombin fragments enter the circulation in quantities too large to be controlled by phagocytes or serum bacteriocidins. Denuding dermatoses provide a large surface area for contamination, while sutures that hold the edges of a wound together provide a small though uncloseable portal of entry for bacteria. In addition to these, vesicular or pustular skin lesions, and the eczematosed rashes frequently evoked in children by contact with such irritants as kerosene and turpentine are also apt to be complicated by bacteremia. Ischemic ulcers in adults, particularly on the extremities of diabetic subjects, are often contaminated and may support the growth of numerous bacteria. If diabetes is poorly controlled, minor skin infections may become a serious threat to health, since even mild degrees of ketonemia interfere with the metabolic processes of granulocytes responsible for killing engulfed organisms. (The lactic acid production of neutrophilic cells has been shown to decline in the presence of ketone bodies.\textsuperscript{17}) Once disorders of the skin were the most common of the predisposing diseases complicated by bacteremia, and their incidence was 30 to 50 per cent in most series. Whereas they are still a common cause when furuncles, carbuncles, burns, and abrasions are added to the lesions already listed, the frequency with which skin lesions are now com-
Complicated by endocarditis or bacteremia is decreasing, since blood-stream invasion can usually be prevented by appropriate therapy (table 1).

Intravascular infection developing within abscesses or more diffuse parenchymal inflammatory processes has been cited as a source for bacteremia of major importance. Osteomyelitis, pneumonia, and other infections are often followed by staphylococcal contamination on this basis. Recently more attention has been focused on the possibility of this complication developing from the thrombi that form about the end of metal cannulas or plastic tubing introduced in veins through incisions for purposes of administering fluids, antibiotics, or pressor substances. Endocarditis, usually of the right heart, is a complication of the thrombophlebitis and superficial skin abscesses that develop on the arms and legs of narcotic addicts using contaminated needles and solutions for intravenous injections. In contrast to the falling incidence of bacteremia due to skin infections, the number of cases following such intravascular infections is increasing, particularly among elderly or debilitated hospitalized patients.

The underlying cause of staphylococcal bacteremia in 15 to 20 per cent of cases prior to 1940 was osteomyelitis. It is currently responsible in only 2.4 per cent (table 1). Originating from trauma, skin infection, or even from bacteremia, osteomyelitis has always been difficult to treat even when recognized early in its course. While antibiotic treatment has reduced the incidence of complicating bacteremia, cases are still observed, especially in infants and in elderly patients. The diagnosis may easily be overlooked, since painful cellulitis of the underlying skin and subcutaneous tissues often masks its symptoms. In infants, who localize staphylococcal infections poorly, widespread osteitis complicating adenitis or cellulitis may develop rapidly and lead to deformity or to death.

Pneumonia is an important cause of staphylococcal bacteremia. Its incidence is unchanging yet the death rate is climbing. The

<table>
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by bacteremia in up to 50 per cent of cases. In the hospital serious staphylococcal pneumonia terminating in death from bacteremia often represents a superinfection in patients given antibiotic prophylaxis for such noninfectious processes as heart failure.20

Schirger and his co-workers21 among others, have re-emphasized the hazard of bacteremia as a complication in the postoperative period, especially in the first few days. Thrombophlebitis, a contaminated suture, the leakage of bacteria-laden material onto exposed tissues, or the introduction of large numbers of organisms directly into the blood stream consequent to manipulation of infected tissues may lead to persisting bacteremia. In 1937 Skinner and Keefer22 noted that bacteremia often followed incision and drainage of abscesses of the skin. This is no longer so true. At present bacteremia follows prostatic surgery more often than any other operation. In Schirger’s group of 44 patients who developed staphylococcal bacteremia postoperatively 27 had had transurethral resection of the prostate. The degree of contamination of this organ, the trauma exerted in removing it, and the susceptibility of its venous plexus to thrombophlebitis are all contributing factors.

Clinical Manifestations of Staphylococcal Bacteremia

Patients with staphylococcal bacteremia can be grouped in 5 categories on the basis of their major symptoms: (1) symptoms due to the primary infection, (2) symptoms due entirely to bacteremia, (3) symptoms due to the metastatic suppurative lesions, (4) symptoms due to a combination of the three, and finally (5) those in which all symptoms are masked by a co-existing disease or suppressed by therapy administered in treatment. The manifestations of the infections range in degree from mild to fulminant.

1. Symptoms Predominantly of Primary Infection. Patients with staphylococcal pneumonia, meningitis, osteomyelitis, or other severe though localized processes normally have, in addition to the specific symptoms of these infections, high fever, leukocytosis, and rapidly developing anemia. They are often prostrate. Bacteremia is a common complication of each of these infections and may develop silently. The temperature often rises, the pulse rate becomes more rapid, and the patient may seem more gravely ill, but there is no more than an intensification of existing signs and symptoms.

If no treatment is given, or if it is inadequate, metastatic suppuration occurs or death follows a rapidly mounting fever and falling blood pressure. Given early enough, antibiotics can prevent bacteremia as a complication, or they can reduce the incidence of sepsis secondary to it (table 2). However, during the period before either of these occurs the presence of bacteremia may go undetected unless blood cultures have been obtained. Since this early phase of blood-stream invasion may last for days before specific signs of it are detectable clinically, recognition of its likelihood during any severe though localized infection is essential for its effective treatment.

While patients of any age may develop these serious staphylococcal infections of the lungs, meninges, or bone, it is usually in the very young or very old that the time interval between the development of this complication and death is shortest, and delay in the institution of specific therapy is most often disastrous.

2. Symptoms due Primarily to Bacteremia. The majority of patients with staphylococcal bacteremia probably belong in this category. Often, the source is a minor infection or an injury with only local discomfort. The entrance of micrococci into the circulation in these cases is usually accompanied by dramatic physical changes. The course of bacteremia may be subacute, acute, or fulminating. A small number of patients in all age groups (although most are derived from the extremes of youth and age) have an explosive illness, beginning and ending in the space of only a few days. The onset may be signaled by an abrupt chill with temperatures rapidly rising to 104 degrees and higher; diffuse muscular pains often follow. Soon, sometimes in hours, the pa-
tient is prostrate, exhibiting changes in the sensorium ranging from confusion or somnolence to coma. Infants occasionally exhibit a peculiar pallor associated with rapid respiration and tachycardia. Adults, on the other hand, display either no visible color change or show marked facial suffusion. The blood pressure is at first maintained but soon falls, rarely to be revived. Terminally, purpuric lesions may appear on the skin and are found in some cases to be associated with hemorrhage in the adrenal parenchyma. Widespread lesions may be demonstrated at postmortem study in such cases, but the course of the disease is so swift that they are rarely manifested openly.

The majority of patients, though severely ill, are not so rapidly devastated. As in the preceding group the onset of bacteremia is sudden, with fever and chills or chilly sensations predominating at first. Soon afterwards, the patient feels sick and often has moderate to marked pain in the larger joints without swelling or local tenderness. There are often diffuse muscular aching pains, persistent headache, sweatiness, and loss of appetite or actual nausea and vomiting. But for the fever, there are no physical changes other than those associated with the underlying infection. Fever in this group, while characteristically high, may vary from sustained high temperatures to a swinging "septic" pattern and uncommonly is observed to be intermittent. In a number of patients symptoms may persist without change for a week and occasionally longer before other evidence of bacteremia develops.

A small group of patients have only mild symptoms and signs produced by the intermittent release of small numbers of staphylococci into the circulation. Low-grade fever with a normal diurnal curve is observed in association with milder variants of the symptoms presented above; anorexia, insomnia, and slight general discomfort without localization are also common. Symptoms of this type have been known to persist for as long as 4 or 5 months before a diagnosis could be established, even without antibiotic suppression.

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*Figures obtained from reports not specifying individual lesion observed.

Antibiotic therapy may actually convert an acute, though often undiagnosed bacteremic process into a slowly progressive, less symptomatic one of this type. When the presence of organisms in the blood stream accounts for all the symptoms the underlying infection is often relatively insignificant. Peripheral thrombophlebitis, furuncles, superficial wounds or suture infections, and pyoderma associated with an underlying dermatosis are common.
examples of the primary focus. Similarly, bacteremia complicating surgery of the prostate or elsewhere is not likely to be masked by the symptoms due to disease in the traumatized area. The variability of the response to bacteremia is such that unless the diagnosis is considered when the only major symptom is fever it will often be missed until late in its course. The presence of leukocytosis in association with fever suggests bacterial infection, but not its origin; migratory joint pains may suggest the diagnosis of arthritis. Low-grade fever may even be dismissed as unimportant if not accompanied by other evidence of disease. An example is the case of a woman who received x-irradiation for a pelvic malignancy and developed an eczematoid skin eruption over the lower abdomen. Daily fever to 100.2 degrees occurred a week later, and, in association with anorexia, represented the only symptoms of a low-grade bacteremia. The diagnosis was verified by 3 successive blood cultures obtained for evaluation of her "obscure fever." Treatment with antibiotics chosen on the basis of the organism's sensitivity resulted in a prompt decline of temperature to normal levels, sterile blood cultures, and a return of her appetite.

3. Symptoms due to Metastatic Lesions. Septic emboli that lodge in the vessels of the heart, the lungs, the central nervous system, and other organs can produce dramatic symptoms that may be the first noticeable evidence of bacteremia.

Pulmonary Symptoms. Many patients with endocarditis involving the tricuspid or pulmonic valves as well as those with bacteremia and no endocarditis have symptoms of dyspnea, chest pain, tachypnea, or hemoptysis as a first major indication of infection.

Although fever had been present for a day, sudden spiking of fever with chills and severe dyspnea were the first alarming signs that occurred in an 18-year-old girl with facial cellulitis complicating a small pimple. Her chest was clear to physical examination, but an x-ray showed many small, fluffy, nodular infiltrates throughout both lung fields. Although the staphylococcus in her blood stream was sensitive to the antibiotics employed, she succumbed to this infection, which had started under the mantle of oral tetracycline therapy given for the cellulitis. Abscesses were present in the myocardium, the liver and the spleen, but the lungs were the site of the most extensive changes. Non-fatal pulmonary infarcts with recurring episodes of fever, cough, and occasional hemoptysis may be the only early symptoms of staphylococcosis.

Two types of pulmonary lesions are observed. One as in the cited case history, is composed of numerous miliary abscesses producing widespread changes easily visible on chest x-rays as softly outlined, rounded infiltrations. Associated with these focal parenchymal abscesses is the generalized inflammatory reaction that accounts for the degree of dyspnea. Purulent bronchitis and pulmonary edema are frequently found at autopsy. The other important type of lesion is pulmonary thrombophlebitis. Suddenly developing chest pain, cough, and occasionally hemoptysis may follow the lodging of emboli, but it is seldom that such manifestations are the dominant initial symptoms of bacteremia without endocarditis. In the presence of endocarditis, large emboli may occur and not infrequently produce major pulmonary infarction.

Central Nervous System Symptoms. Weakness associated first with fever and later with unresponsiveness were the principal manifestations in an elderly man with mild diabetes and a few furuncles. Blood cultures yielded *Staphylococcus aureus*. It was shown at autopsy several days later that he had succumbed to "brain purpura" characterized by extravasated blood and necrosis in pericapillary and perivenular areas (pericapillary encephalorrhagia). Many different neurologic syndromes arise as a result of cerebral vascular occlusion. Common among the first signs are sudden hemiplegias or cranial nerve palsies, personality changes, and psychotic behavior. Combined brain and cord disturbances may occur. A man with chronic lung disease developed headache, fever, and diplopia followed by weakness in both lower extremities that progressed upward to involve
the chest. The presence of a sensory level and the weakness suggested a cervical epidural abscess. Myelography demonstrated an obstructive lesion at the level of the second cervical vertebra. Decompressive laminectomy was carried out with immediate though transient relief of symptoms. The spinal fluid, which had been xanthochromic, became purulent within hours when the obstruction was relieved allowing communication of intracranial with lumbar intrathecal cerebrospinal fluid reservoirs. He was found to have had a subdural abscess that had produced, by extension of inflammatory edema, compression of the cervical cord. The signs of the verified staphylococcal bacteremia were entirely masked by the central nervous system disorder. Specific, intensive antibiotic therapy in this case was of no avail.

The importance of considering the possibility of bacteremia in cases of obscure febrile central nervous system disorders can for this reason scarcely be overstated. Diagnoses of "encephalitis," or "aseptic meningitis," or even of "subarachnoid hemorrhage," particularly in the young, should be regarded with suspicion and cultures of the blood obtained to ensure that bacteremia be not overlooked.

**Symptoms Related to the Cardiovascular System.** Endocarditis, with its pathogenesis and clinical manifestations, will be discussed separately below. The symptoms of cardiac involvement may dominate the bacteremic syndrome in many cases. Discrete abscesses of the myocardium and interstitial myocarditis may occur without endocardial localization but do not necessarily produce functional aberrations. Although the commonest and most important signs produced by these lesions are those associated with heart failure, whether these are due more to intrinsic cardiac damage than to concomitant fever, tachypnea, and pneumonia is difficult to assess.

Pericarditis often mimics pneumonia. Fever, cough, and dyspnea are coupled with moist rales and a friction rub. Enlargement of the area or cardiac dullness, alteration in the configuration of the heart shadow on x-ray, and electrocardiographic abnormalities all help in the diagnosis. In some, an urticarial rash, hepato-splenomegaly, and dyspnea are the presenting symptoms. Signs of constriction or tamponade may appear if the effusion develops rapidly, even when the total amount of fluid is small. Pericardial fluid may be sterile or purulent. While generally regarded as a serious complication, it is of interest that recovery from purulent pericarditis with tamponade has been known to follow treatment consisting only of transfusion, pericardial aspiration, and small doses of a soluble sulfonamide. Pericarditis of nontuberculous origin is most commonly produced by staphylococci, and while it more commonly follows pneumonia than bacteremia, it is still an important complication of the latter.

Mesenteric thrombosis, popliteal aneurysm, and axillary thrombosis are examples of the peripheral vascular complications of staphylococcal bacteremia.

4. Symptoms from a Composite of Initial Lesion, the Bacteremia and the Metastatic Suppuration. Patients in this category have usually had for a short time a localized infection without constitutional signs and develop suddenly major symptoms of fever and chills coincidentally with the appearance of a varying number of embolic manifestations. Often the first or primary infection is regarded as unimportant, as in the case of a pimple or small furuncle. Occasionally the local symptoms obscure the nature of the initial process as when pain is the only sign of a deeply situated supplicative process. An example of this is the case of a 40-year-old woman with hip pain for a week who developed within 48 hours fever, chest pain, headache, and a vesicular skin eruption. The disease, from which she recovered, consisted of a supplicative arthritis, menigitis, pulmonary infarction, and embolic lesions of the skin.

Another example is a boy who injured his neck while wrestling. In the next week, he developed spiking fevers, delirium, diarrhea, headache, and a swelling near the site of injury. At the time of admission to the hospital he had a swollen, red, and tender left ankle. There was a lymphocytic pleocytosis
of the spinal fluid, a peripheral leukocytosis and a systolic murmur without evidence of cardiomegaly. Blood cultures yielded Staphylococcus aureus. He was placed on antibiotic therapy and the mass in his neck, which became fluctuant, was drained. He recovered, but before treatment was concluded it was demonstrated that he had cervical osteomyelitis (presumably a complication of the abscess), suppurative arthritis of the left ankle, and a nonsuppurative parameningitis, but no evidence of endocarditis. The time interval separating the development of each of these metastatic lesions was so short that each contributed to the general constitutional reaction.

5. Presence of Bacteremia Masked by Therapy Directed at an Underlying Disease. Attention has been drawn to the peculiar danger in patients treated with adrenal steroids that have denuding skin diseases such as exfoliative dermatitis. Already deprived of the important skin barrier against the entrance of surface staphylococci, their jeopardy is increased by steroid treatment, which both impairs local tissue defenses and suppresses the constitutional response that heralds invasion of the blood stream. The administration of tetracyclines prophylactically in these cases has been shown to enhance rather than to reduce the likelihood of staphylococcal infections by eradicating other organisms and increasing the number of staphylococci.

Steroid therapy of leukemia, chronic obstructive emphysema, nephrosis, rheumatoid arthritis, and allergic disorders increases the danger of bacterial infection, although the peculiar vulnerability to staphylococcal invasion seen in those with skin disease is not present. Because of the nature of the underlying disease, however, the prognosis is far worse should infection develop. In leukemia, for example, even so benign an infection as pharyngitis may be complicated by bacteremia.

Incidence of Specific Signs and Symptoms of Staphylococcal Bacteremia

It is of interest to review the incidence with which the various signs of the disease are encountered based on many reports from the years before and including the antibiotic epoch (table 3).

Metastatic Infections Associated with Staphylococcal Bacteremia

The outcome of persisting staphylococcal bacteremia in untreated cases is almost always death. In some there may not be time for
the development of metastatic lesions; in others bacteremia may actually clear after metastatic suppuration is established and, rarely, both bacteremia and distant infections are cleared and there is recovery. If survival is long enough, metastatic infection is almost inevitable; of 122 cases assembled before 1942 (22), 100 developed suppurative lesions in parts remote from the point of origin of the bacteremia. The incidence of metastatic sepsis has been reduced since that time, presumably by antibiotic treatment (table 2). It can be seen that once one metastasis has been produced, others are far more likely to occur. The primary sites of infection from which most metastatic lesions are derived are the heart valves, bone, and the lungs.

Central Nervous System Involvement

The localization of organisms in the brain, the cord, or in their investing membranes is a serious complication. Mycotic aneurysms occur less often than in streptococcal viridans infections,26 but focal miliary abscesses are quite common. The ability of staphylococci to invade normal tissues, to proliferate in them and to produce destructive lesions without the necessity of platelet and fibrin plugs to protect them against phagocytic action probably accounts for the many suppurative infarcts.

In brief, 4 specific alterations arise when staphylococci enter the cerebral circulation:27 simple vascular occlusion from masses of platelets, fibrin, and organisms; vascular occlusion due to focal intimal infiltration; pericapillary and perivenular hemorrhage ("brain purpura"); and localized or diffuse suppuration in the form of miliary abscesses along the course of the blood vessels or as a subdural empyema or meningitis.

The over-all incidence of lesions within the brain and its investments in cases of bacteremia was 20 per cent prior to antibiotic therapy and 3.6 per cent thereafter. In cases of endocarditis the incidence as reported by Thayer28 in 1926 in a series of 24 cases was 83 per cent. Not all of these lesions were symptomatic, many being small localized abscesses discovered at necropsy. Only 2, (8 per cent) had meningitis. After antibiotic therapy became available, there were more survivors of endocarditis and among them it is impossible to estimate the true incidence of clinically inapparent abscesses. The reported over-all incidence of central nervous system involvement is 24 per cent (table 2).

Respiratory Tract Involvement

The lungs are at once the site of primary staphylococcal infection, a repository for organisms spread by the blood stream, and a source for the dissemination of emboli to other tissues. The frequency of pulmonary embolizations large enough to produce symptoms or radiologic signs is far less than the actual incidence of lesions demonstrable at autopsy.

The commonest event is pulmonary embolism with the development of abscesses ranging upward from microscopic size. Infarction of significantly large segments of lung is less often observed. Before antibiotic therapy, the incidence of demonstrable changes of all types in the lung was nearly the same in cases of bacteremia with endocarditis as in those without endocarditis.26, 29 There were only 3 cases among 109 antibiotic-treated patients with bacteremia.21

Involvement of the Kidney

Renal lesions are commonly associated with bacteremia, and the presence of gross or microscopic hematuria is regarded as a valuable laboratory aid to its diagnosis. Focal embolic glomerulonephritis produced either by the presence of small but obstructive emboli, or by an intrinsic fibrinoid reaction of renal vessels is not a complication observed during the course of endocarditis due to staphylococci; it is common, on the other hand, in endocarditis due to pneumococci, gonococci, and to hemolytic streptococci. In his description of glomerular lesions associated with endocarditis, Bell30 pointed out that it was uncommon to find focal embolic lesions before 6 weeks had elapsed. Staphylococcie valvulitis usually terminated fatally before this.

Involvement of the Heart

Cardiac involvement complicating bacteremia is a serious complication primarily be-
cause of an increased frequency of metastatic suppurative lesions and only secondarily because of the injury to that organ or its valves.

In addition to endocarditis, suppurative inflammatory changes occur in the pericardium and in the myocardium (both as interstitial myocarditis and focal abscesses). It is likely that the myocardial changes are in some cases responsible for congestive failure or pulmonary edema, particularly when associated with pneumonia. Acutely developing ventricular aneurysm is another complication. In some instances the clinical evidence of cardiac metastasis is limited to electrocardiographic alterations termed by some as "toxic myocarditis." The actual incidence of myocarditis of this type is uncertain because of the failure to obtain electrocardiograms routinely in all cases of bacteremia.

Pericarditis was not observed by Mendell in his series of 35 patients with untreated bacteremia, but was demonstrated in 5 out of 24 cases of endocarditis reported in 1926. A single case of pericarditis was observed out of 109 treated cases of bacteremia while there were 3 cases out of 38 treated cases of endocarditis.

**Involvement of the Bones and Joints**

Transient though often severe joint pains have been mentioned as one of the manifestations of acute bacteremia. When sequestration of staphylococci within the articular spaces or the narrow cavity of long bones occurs, destruction of cartilage in the joint may lead to permanent deformity. X-ray evidence of localization may appear within 24 hours. Actual osteomyelitis is uncommon. However, in infants under the age of 1 year, osteitis characterized by periosteal prolifera-

tion, and absence of sequestration and involvement of more than one bone may develop rapidly and poses an important threat to the future development of the involved extremity.

**Involvement of the Skin**

It is difficult to determine the incidence of petechiae, vesicles, and furuncles associated with bacteremia because they are not commonly mentioned in reports of series of cases. Of recent studies, the most detailed description of the skin lesions was provided by Wilson et al. in a review of 55 cases of both bacteremia and of endocarditis. They noted a wide variety including scarlatinal, urticarial, morbilliform, and purpuric rashes. Erythema multiform and nodose lesions were also encountered. More typical of staphylococcal bacteremia than these are subcutaneous and superficial abscesses. In some, these lesions resemble the rash of chickenpox, having a red base and a central vesicle filled with only a slightly cloudy fluid. They do not always contain organisms, and in healing may leave a shallow black eschar. These lesions are the result of capillary and venular thrombosis similar to that seen in the Schwartzman reaction.

The skin lesions do not as a rule confuse the diagnosis, although I have seen 2 cases of bacteremia in which the initial diagnoses were measles and chickenpox.

**Involvement of the Blood Vessels, Liver, and Spleen**

In addition to the embolic phenomena in various organs, the major vessels of the extremities as well as in the viscera may be involved. Peripheral gangrene of the nose has been described, as well as thrombosis of the axillary artery and mycotic aneurysms of the popliteal artery. There were 5 significant vascular lesions in a group of 38 cases of endocarditis.

Metastatic sepsis or emboli are not limited in their distribution to the organs already mentioned. Focal abscesses or zones of necrosis have regularly been observed in the liver, and mesenteric thrombosis and splenic infarcts may occur. Perisplenitis may produce
a friction rub and pain in the left upper quadrant of the abdomen.

The involvement of the liver is usually inapparent and detectable only at necropsy. Although jaundice is occasionally an early manifestation of bacteremia as a result of massive hemolysis, I have seen it develop during the second week of treatment for bacteremia associated with chemical evidence of parenchymal damage indicated by elevated alkaline phosphatase, cephalin flocculation, and thymol turbidity.

**Staphylococcal Endocarditis**

"Acute infective" or "ulcerative endocarditis," usually the result of staphylococcal valvulitis, connotes a rapidly progressing destructive lesion on the heart valve with acute onset of fever and even prostration, and an early fatal outcome. Occasionally staphylococcal infections of the endocardial surfaces may be quite slow in their evolution and produce few symptoms other than occasional fever for periods of months. The acute disease may be converted by suppressive antibiotic therapy into a subacute process.

Two features of staphylococcal endocarditis are of particular importance, i.e., the propensity of the organism to invade normal heart valves, and the frequency with which only the right side and particularly the tricuspid valve is involved. While antibiotics are responsible for reducing the incidence of pneumococcal or gonococcal endocarditis, both of which may involve undamaged valvular surfaces, they have not so affected the incidence of staphylococcal infection.

**Pathogenesis of Endocarditis**

Bacteremia from any site may lead to endocarditis. Bacteremia need not be prolonged as in prostatic surgery complicated by endocarditis, nor need it be massive; pharyngitis may be complicated by bacteremia and endocarditis, particularly if there are underlying valvular deformities.

In the presence of focal deformities of the heart valves, septa, or immediate outflow tract, there may be abnormal turbulence and associated endocardial fibrosis which enhance the likelihood of bacterial sequestration. This may effectively reduce the length and intensity of exposure necessary to produce endocarditis.

Over half the reported cases of staphylococcal endocarditis occurred on previously damaged valves (table 4). The type of deformity varies somewhat with the age of the patient; thus congenital lesions are far more likely to be present in younger patients, while as age increases the incidence of rheumatic heart disease, arteriosclerosis, and syphilitic aortitis becomes greater. The mean age of patients with underlying congenital heart disease was 20 years, and for patients with rheumatic heart disease, 44 years. In a series of 173 cases of all ages the incidence of congenital lesions was 6.9 per cent.

Table 5 shows the frequency with which each valve was involved. Rightsided endocarditis among narcotic addicts rose sharply after 1940, especially among users of heroin who often used it mixed with other contaminated materials.

**Clinical Manifestations of Endocarditis**

Over 30 years ago Thayer called endocarditis a "mere incident in the course of a generalized septicopyemia." He was not belittling the importance of the valvular lesion, but considering its relative importance as a cause of death. Of the 26 patients he studied,
TABLE 6.—Embolie Complications Associated with Staphylococcal Endocarditis (from Thayer)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number</th>
<th>Incidence</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocarditis</td>
<td>14 (of 20)</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Myocardial abscess</td>
<td>11 (of 20)</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>5</td>
<td>19.2</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11</td>
<td>48.2</td>
<td></td>
</tr>
<tr>
<td>Nephritis</td>
<td>8</td>
<td>30.7</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>6</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>Petechiae</td>
<td>4</td>
<td>16.0</td>
<td></td>
</tr>
<tr>
<td>Cerebral emboli</td>
<td>2</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>2</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>21</td>
<td>80.7</td>
<td></td>
</tr>
</tbody>
</table>

17 died of overwhelming infection, while only 1 died as a specific result of endocardial involvement. The remainder succumbed either to emboli to the brain or lungs or to other severe underlying diseases. The importance of Thayer’s description is in its emphasis that the majority of the signs and symptoms of endocarditis are those associated with bacteremia and it is often not until late in the course of the infection that the specific valvular lesions produce recognizable abnormalities. One result of antibiotic therapy, even when unsuccessful in salvaging life, has been to prolong the course of the disease long enough for these abnormalities to develop.

While the major clinical features of endocarditis are similar to those already cited for bacteremia, certain of them suggest the diagnosis of endocarditis. There are also important differences between this type of endocarditis and that produced by such less invasive organisms as *Streptococcus viridans*.

The onset of symptoms of infection may antedate changes due to valvular involvement for as short a period as a day or for as long as several weeks or even months. Important manifestations, however, may appear quite rapidly. Suddenly appearing fever followed quickly by heart failure and the development of an aortic diastolic murmur is not infrequent in endocarditis. Earlier writers have stressed the importance of a pericardial friction rub and embolic phenomena in the skin, joints, or lungs as important evidence of endocarditis, but none of these complications depends on the presence of valvular infection for its production. As with any kind of endocarditis, the most important diagnostic criteria are the development of a murmur of any type (including the addition of new heart murmurs), embolic suppurition, and the demonstration of bacteremia. Anemia and splenomegaly are usually not present at first, but either may develop rapidly. Clubbing of the fingers does not occur.

It has been observed that a peculiar syndrome frequently suggests the diagnosis of endocarditis in infants. It consists of pallor with tachycardia, intermittent cyanosis and fever without evidence of pulmonary disease or obstruction sufficient to account for these changes. Pallor alone, of course, has been observed in infants with staphylococcal pneumonia or other overwhelming infections.

Occasionally, specific metastatic complications of endocarditis help in making the diagnosis. Arterial obstructive lesions in such major vessels as the axillary or popliteal arteries, or in such smaller ones as the dorsalis pedis, indicate large emboli probably from the heart. Massive pulmonary infarcts or repeated small ones suggest, though less reliably, embolization from the right heart. Cockayne described a woman who was perfectly well until chest pain and vomiting suddenly occurred and were followed within the next seven days by arterial emboli to a foot, one hand, and the nose. She died on the seventh day because of a pulmonary infarct, and had a large aortic vegetation. There was nothing in her history to suggest where the disease had actually started or even from what point bacteremia had developed. Another patient was a young woman sent to the hospital with signs suggesting a pericardial effusion who died very shortly thereafter with a massive pulmonary infarction and a vegetation on a congenitally unicuspid pulmonary valve. Multiple embolic lesions also suggest endocarditis, even without an audible heart murmur. Representative of the frequency of various embolic lesions is the incidence compiled in the study by Thayer (table 6).
STAPHYLOCOCCAL BACTEREMIA AND ENDOCARDITIS

Whereas pulmonary emboli with sterile blood cultures have been considered a dominant feature of right-sided endocarditis, this was not true in the experience of Bain et al.23 in a study of 21 autopsied cases. Pulmonary abscesses or infarctions were present in 80 percent and a similar percentage had positive blood cultures during life. It is likely that the organisms found in the systemic circulation arose from the many small abscesses found within the lung substance. Bacteria but not embolic fragments may easily pass through the pulmonary circulation. It would appear, then, that there are 2 possible explanations for peripheral bacteremia in cases of tricuspid endocarditis. Bacteria may enter the circulation by passing through the lung filter, or if trapped there, may be disseminated from resultant focal pulmonary infection. The importance of an assiduous effort to isolate organisms from the blood stream in cases of suspected infection of the tricuspid or pulmonic valve is thus emphasized. The reward is the immeasurable advantage of identifying the causative organism and its sensitivity, and of establishing with greater certainty a diagnosis of endocarditis, which otherwise is easily missed because of the inconstancy of murmurs. The tricuspid valve is involved more often than the pulmonic valve in cases of staphylococcal endocarditis, and when murmurs are produced, they are frequently overlooked or regarded as the product of fever and tachycardia. Pulmonic murmurs are more accurately ascribable to the proper valve, and the proper diagnosis is more readily made.

According to Thayer,29 subacute staphylococcal endocarditis was associated with albus strains only. Since 1926, however, infections of this type due to Staphylococcus aureus have been observed. The clinical course of the infection does not differ from that produced by Streptococcus viridans or other organisms of poor invasive potentialities, but it may rapidly be converted into a fulminating one. In 1 case reported by Geraci and Martin39 the illness was protracted over a period of 4 months with low-grade fever and malaise as the major symptoms; then sudden spiking fevers with chills appeared, an aortic diastolic murmur was heard, and despite carefully planned therapy, death occurred from a cerebral embolus. The importance of the proper interpretation of staphylococci appearing in the blood cultures is here emphasized. "Saprophytic" strains in the blood stream of patients with a disease bearing any resemblance to endocarditis must be regarded seriously.

The Treatment of Staphylococcal Bacteremia and Endocarditis

Many new antibiotics have been marketed recently for therapy of staphylococcal infections and particularly for cases in which resistance to better known agents has been demonstrated. Too short a period of time has elapsed to assess either their value or their undesirable side reactions. Persistence of the high mortality rate in treated cases is in part due to the increasing number of patients in whom bacteremia represents a terminal complication of a severe underlying disorder and for whom the antibacterial activity of the drugs used is not enough to effect a cure. There are, nevertheless, many cases in which cure is possible because of new antistaphylococcal agents.

The factors that determine the plan of therapy are numerous, but the most important is that the drug or combination of drugs chosen be the one to which the organism is most likely to be sensitive. Of great importance too is the selection of agents least likely in themselves to be of danger to the patient if given for prolonged periods of time.

It is generally agreed that penicillin represents the most satisfactory antistaphylococcal agent when the organism is sensitive to it. Its current wide usage has reduced its value in hospital-acquired infections, since the majority of staphylococci in this area are no longer sensitive to clinically attainable concentrations. So high is its therapeutic index, however, that in many cases penicillin can be used even when, by some criteria, the organism is considered a resistant one. Thus the fact that greater than 10 units per ml of penicillin may fail to suppress staphylococcal
growth on a blood agar plate does not mean that the agent cannot be used, since it is possible by giving large amounts to obtain blood levels in excess of 50 units per ml. Disk-sensitivity determinations employ concentrations no greater than 10 units of the drug and may be quite misleading, therefore, and it is often necessary to use the cumbersome but more accurate tube-dilution technic, which can define the precise amount of drug needed to exert bacterioidal or bacteriostatic activity in vitro. Such information, however, is not as a rule available at the time treatment is begun, and the initial choice of drugs must often be made without recourse to sensitivity tests of any type.

Penicillin is the drug of first choice for management of infections developed outside the hospital in the absence of specific knowledge of the organism's sensitivity because 90 per cent of the strains thus acquired are susceptible. It should not be used in the treatment of hospital-acquired infections, however, unless it can be shown that the infecting strain is one of the susceptible 10 to 20 per cent among the hospital population of organisms. If penicillin is used, it must be given either intramuscularly or intravenously, and the aqueous crystalline benzyl salt either of sodium or potassium should be employed. It is important in choosing the penicillin preparation to remember that there is a gram of either potassium or sodium chloride in every 10 million units.

The dose of penicillin and the frequency with which it should be given depend on the age and size of the patient and the nature of the process. For a superficial skin infection with bacteraemia and no endocarditis, 2 to 4 million units of an aqueous crystalline benzyl penicillin G daily are adequate. This can be given by intramuscular injection every 4 to 6 hours or it can be given by hypodermolysis with aliquots of the daily dose diluted in saline being delivered at the appropriate time intervals. If the underlying infection is more deeply situated, larger doses of penicillin should be given to ensure adequate tissue levels at the site of localization. Depending on the severity of the infection as determined by the constitutional response and the extent of involvement, from 4 to 20 million units a day may be necessary. In overwhelming infections it is wise to use more than one drug. One important reason for this is to reduce the chance of encountering a strain resistant to the agent employed, and another is that the bacteriocidal activity of the drugs combined may be greater than that of either one alone, regardless of the dose used. Streptomycin, uncommonly used in treating staphylococcal infections, is apt to be an exceedingly good agent in both respects. It is used in full therapeutic doses of 20 to 30 mg./Kg. every day.

If infection had developed in the hospital, it is not safe to assume that either of these 2 drugs will be effective, and others must be employed. Presently, the majority of hospital strains are sensitive to chloramphenicol and erythromycin. Of the 2, erythromycin is the better agent and the addition to it of other drugs does not enhance its bacteriostatic activity. However, staphylococci may exhibit increasing resistance to erythromycin when this agent is used by itself. Chloramphenicol suppresses the rate with which this occurs. The dose of the two is the same (50-75 mg. per Kg.). Both should be given parenterally to ensure adequate tissue concentrations. In the prostrate patient oral administration is often less satisfactory as judged by clinical observation.

When infection has developed during antibacterial therapy or prophylaxis, it must be assumed, in the absence of knowledge of its drug sensitivity, that none of the agents previously given the patient will be of value. Potent but often toxic agents such as bacitracin and neomycin can be used under these circumstances.

Among the more recently developed antibiotics that have good antistaphylococcal properties are novobiocin, vancomycin, kanamycin, and ristocetin. All are new enough in the treatment of staphylococcal infection that sensitivity to them can often be safely assumed. Overwhelming infections have been
cured under treatment with each of these drugs. The decision as to which of these agents should be employed is necessarily based on determination of in vitro sensitivity of the organisms. Not enough experience has yet been collected to determine which of these antibiotics is superior. Both vancomycin and kanomycin have theoretic advantages in that bacteriocidal activity has been demonstrated in each. Only extensive clinical trial will decide whether this is an important advantage or not.

Surgical drainage of enclosed abscesses is an extremely important part of therapy as indicated by the fact that before antibiotics the majority of survivors of severe staphylococcal infections were patients with enclosed lesions that could be drained.

Once the disease is controlled, the duration of the therapy is determined by the nature of the infection. If the initial lesion is a superficial one and bacteremia occurs without endocarditis only 2 to 3 weeks may be required. When bacteremia complicates a more deeply situated infection, treatment must be continued longer. If osteomyelitis, suppurrative arthritis or endocarditis is present, 4 to 6 weeks or even more are usually necessary. The period of treatment is best dated from the time when clinical response is first observed rather than from the actual onset of therapy.

**Summary and Conclusions**

Staphylococcal bacteremia and its complication, endocarditis, are discussed from several viewpoints. A delineation of the factors that determine virulence of the organism and of those that determine host susceptibility is undertaken, and the manifestations of staphylococemia as they are encountered in practice are classified with an analysis of the incidence of its signs and symptoms.

Staphylococcal bacteremia and endocarditis have been thrust into a position of prominence by the advent of successful therapy for other bacterial infections. A decline in their incidence among young people with localized staphylococcal infections has been balanced by an increase among elderly, debilitated, or very young patients within the hospital. Antibiotic therapy is responsible for the prevention of staphylococcal in a significant number of cases on the outside, but for a variety of reasons it has not been so effective in the management of hospitalized patients. Staphylococcal infections contracted within the hospital are almost always caused by the organisms harbored there. These strains have survived exposure to many of the antibiotics used in the individual hospital. The majority of them are coagulase positive and elaborate one or more of the specific toxins and are, therefore, the ones most capable of producing serious infections. This infelicitous concentration of virulent microorganisms in areas where the most susceptible people are cared for accounts in part for the frequency of complicating staphylococcal infection.

What differences there are in the prognosis of hospital and home acquired infections are accounted for by the character of the organism in these 2 locations and by the type of patient, particularly with respect to age and the presence of other disease.

The protection of hospitalized patients by rigid antiseptic technic and early and intensive treatment of staphylococcal infections in all patients can do much to reduce their danger, but the solution to the problems of the continued high mortality rate depends at least as much on a better knowledge of the factors that determine virulence within the organism and susceptibility within the patient as it does on the development of new and potent antibiotics.

**Acknowledgment**

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**Summario in Interlingua**

Bacteremia staphylococcal et su complication, endocarditis, es discutite ab plure punctos de vista. Es interprende un delineation del factores que determina le virulentia del organismo e del factores que determina le sus-
ceptibilitate del hospite. Le manifestaciones de staphylococeemia, in tanto que illos es incontrate in le practica, es classificate como bas de un analyse del incidentia de su signos e symptomas.

Bacteremia staphylococeal e endocarditis occupa un position de prominentia deposi le advento de efficace terapias pro altere form de infection bacterial. Un reduction de lor incidentia in juvene patientes, qui contrahate localisate infections staphylococeal es balanciate por un augmento in debilitate patientes de etate avançate e in juvenissime patientes inle hospital. Therapia a antibioticos es responsabile pro le prevention de staphylococeemia in un numero significative de casos al exterior, sed varie rationes existe pro explicar que le antibioticos ha essite minus efficace in le tractamento de patientes hospitalisate. Infectiones staphylococeal que es contrahi inle hospital es quasi semper cause per le organismos que es "domiciliate" in le hospital. Isto significa que le racias de staphylococecos in le hospital ha supervivite al effectos del numerose antibioticos que es usate in le hospital individual. Le majoritate de iste racias es positive pro coagulase e illos produce un o plures del specific toxinas. Assi illos es etiam le racias que es le plus capac a causal serie infectiones. Iste infelice concentration de virulente micro-organismos in areas ubi le plus susceptibile individuos es albergate explica in parte le frequentia de infection staphylococeal como complication nosocomial.

Le differentias que existe inter le prognose de infectiones acquirite al hospital e le prognose de infectiones acquirite al domicilio es explicable per caracteristicas del organism in le 2 ambientes e per le typos de patiente, specialmente con respecto al etate e al presentia de altere morbos.

Le protection de hospitalisate patientes per rigide technicas antiseptic e per le precoce e intense tractamento de omne cases de infection staphylococeal es apte a reducer grandemente le pericul del situation, sed le solution del problema del continuatemente alte mortalitate depende al minus tanto de un meliorate comprension del factores que determina le virulentia intra le organismos e le susceptibilitate intra le paciente como del disveloppamento de nove e potente antibioticos.

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STAPHYLOCOCCAL BACTEREMIA AND ENDOCARDITIS

Staphylococcal Bacteremia and Endocarditis

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