SPECIAL ARTICLE

Staphylocoecal Infections of the Heart

By Sidney Cohen, M.D.

A SPATE of publications attest to the concern of physicians throughout the world about staphylocoecal infections. The manifold clinical problems created by these infections touch upon all medical specialties. Cardiologists, however, must be especially concerned in view of the propensity of staphylocoecal infection for secondary localization in the heart; in such cases the outcome depends principally upon the response to therapy of the cardiac infection. Furthermore, patients with acquired valvular or congenital heart disease are uniquely susceptible to cardiac infection with staphylocoeci that are in other respects virtually nonpathogenic for man.

This review will be devoted principally to the biology of staphylocoeci related to pathogenicity and to antibiotic treatment. The clinical and pathologic features of staphylocoecal infections, areas in which the state of our knowledge has not changed greatly, will be treated more summarily.

ASPECTS OF PATHOGENICITY IN STAPHYLOCOCCI

Criteria of Pathogenicity

Much experimental effort has been expended on defining reliable criteria of pathogenicity in staphylocoeci. To some extent any assessment of pathogenicity is only an approximation, for a microbe’s ability to cause infectious disease cannot be evaluated apart from the host’s ability to resist infection. Human resistance to staphylocoecal infection varies so widely that one may encounter fatal infections by staphylocoeci that are ordinarily nonpathogenic and trivial lesions caused by pathogenic staphylocoeci. Nevertheless division of staphylocoeci into these 2 groups is worthwhile, for even when infection is incited by a "nonpathogenic" staphylocoecus, the clinical and pathologic features of the resultant disease differ significantly in most cases from that caused by a typically pathogenic strain.

Staphylocoeci isolated from lesions that stamp them as being unequivocally pathogenic for man are characterized usually by golden or orange pigment and the ability to produce in vitro a remarkable array of extracellular toxic or enzymic substances; these include coagulase, at least 3 hemolysins, a leukocidin active against human leukocytes, enterotoxin, hyaluronidase, fibrinolysin, phosphatase, lipase, enzymes mediating the fermentation of mannitol, as well as other compounds. In general the more virulent staphylocoeci, as assayed in mice, produce a greater number of extracellular antigenic, and presumably toxic, substances.

The most conveniently determined and reliable evidence of pathogenicity is the production of coagulase.* This substance, in the

*The seventh edition of Bergey's Manual of Determinative Bacteriology defines the pathogenic species Staphylococcus aureus by the properties of coagulase production and mannitol fermentation, irrespective of pigment. Strains reacting negatively in these tests are classified as Staphylococcus epidermidis. The clinician who has only recently become familiar with the earlier nomenclature—Micrococcus pyogenes var. aureus and Micrococcus pyogenes var. albus—is entitled to sympathy. To avoid confusion, in this article I have used the words "aureus" and "albus" to signify only the color of the staphylocoecal colony.
presence of a co-factor found in human or rabbit plasma, induces the clotting of fibrinogen. It may be readily detected by inoculating a culture of the microorganism into a tube of diluted human or rabbit plasma. Coagulase-positive strains yield a clot usually within 3 hours, occasionally as late as 18 to 24 hours. A rapid slide test has been proposed for this purpose but it may not detect the same entity as the tube test.

The production of alpha lysin, a hemolysin relatively specific for rabbit erythrocytes, correlates very well with clinical evidence of pathogenicity. In the opinion of some investigators it is a better index of pathogenicity than coagulase production. However staphylococci produce at least 2 other hemolysins (beta and delta lysins) with maximum lytic activity against erythrocytes of other species and poorer correlation with pathogenicity for man. Specific tests for alpha-lysin production are not usually performed in clinical bacteriology laboratories. Accordingly, the common laboratory report of a "hemolytic" staphylococcus without further qualification is ambiguous, and may be misleading when taken as an index of pathogenicity.

Although more than 90 per cent of pathogenic staphylococci are yellow in color, gray or white strains of staphylococci cannot be regularly dismissed as nonpathogenic without the danger of serious error. Occasionally such strains may produce coagulase and alpha lysin and be responsible for outbreaks of highly invasive infection. Furthermore, production of yellow pigment is not a very stable property of staphylococci, as is demonstrated by the ease with which albus variants, which still produce coagulase and alpha lysin, are obtained in vitro from typical pathogenic aureus strains. By the same token aureus strains should not be regarded ipso facto as being pathogenic.

**Bacteriophage Typing**

Although the toxic products of the staphylococci are useful in defining pathogenic and nonpathogenic species, they do not provide a basis for subclassification of strains within either species. The advantages of a sharper characterization have been realized in recent years through the development of bacteriophage typing. Coagulase-positive staphylococci may be classified into 4 broad groups, I to IV, according to their susceptibility to lysis of a battery of stock bacteriophages. More specifically, the bacteriophage type of a given strain may be described by the numerical designations of the bacteriophages to which it is susceptible (e.g., 42B/80/81/52). This procedure has yielded results of great importance. Significant biologic properties have been correlated with bacteriophage groups or types. Thus, penicillinase-producing staphylococci fall most often into group III and to a lesser extent, group I. Enterotoxigenic staphylococci occur principally in group III. Staphylococci isolated from the majority of a large group of cases of impetigo in England were found to be bacteriophage type 71. Evidently this type is biologically adapted to this special variety of parasitism. Since 1954 a previously unrecognized type, 80/81, has been found to be associated frequently with virulent staphylococcal infection, particularly in hospitals and often on an epidemic scale.

In addition to the light that it has cast on the biologic properties of certain strains of staphylococci, bacteriophage typing has become an indispensable epidemiologic tool in tracing the course of epidemic or institutional outbreaks of staphylococcal infection. In several instances it has been possible to trace series of cases of staphylococcal infection to a limited number of carriers of the bacteriophage type in question and to terminate the outbreak by removing the carriers.

**Pathogenesis of Staphylococcal Infection**

Pathogenicity implies the existence of mechanisms for microbial survival and multiplication within the host and for inflicting injury. Coagulase-positive staphylococci are able to grow in normal human serum, in which many nonpathogenic microbes including coagulase-negative staphylococci are inhibited. The resistance of coagulase-positive strains may be derived from inactivation of the serum
inhibitor by their growth products, for culture filtrates of coagulase-positive staphylococci destroy the nonspecific inhibitory properties of serum. The available evidence indicates that the effective agent is associated with coagulase.5

A basic pathogenic attribute of staphylococci is their ability to survive phagocytosis by human leukocytes. In contrast to other Gram-positive pathogenic cocci, staphylococci are readily phagocytized by human leukocytes. Coagulase-positive strains survive within leukocytes and eventually kill them. Indeed the leukocyte may serve the staphylococcus as protection and means of dissemination.6 This property may be related to a leukocidin that has been demonstrated in culture filtrates of many coagulase-positive staphylococci (but not coagulase-negative staphylococci) and which is active in high dilution upon human leukocytes.7 It appears to be formed in infections in man for antibodies to it appear in increasing titer in 80 per cent of patients with acute staphylococcal infections.8 Another staphylococcal product, delta lysin, is also toxic to human leukocytes.9 Its role in vivo is uncertain for its action is inhibited nonspecifically by proteins.

The ability of staphylococci to multiply in vivo is greatly dependent upon the tissue in which they are deposited, as is apparent from clinical observations of the distribution of staphylococcal lesions. Experimental studies of murine infections indicate that staphylococci persist in large numbers for variable periods of time in the lungs, spleen, and liver without development of lesions, while in the kidney coagulase-positive staphylococci continue to grow and form multiple abscesses.6,10 The biochemical tissue factors that determine these differences in growth patterns are obviously important but unknown.

The mechanism by which staphylococci damage tissue cells other than leukocytes is not understood. Staphylococci produce a toxin thought to be identical with alpha lysin, which causes necrosis when injected into the skin or death when injected intravenously in rabbits. It is possible that large collections of staphylococci may produce alpha lysin or other toxins in amount sufficient to damage tissues locally and to provide the systemic toxemia characteristic of very severe staphylococcal infections.

Specific antibodies fail to provide very effective defense against staphylococcal infections. They may furnish some protection, however, for agammaglobulinemic patients, who are deficient in antibodies, are prone to infections by staphylococci.

Host Factors and Resistance to Infection

The primary habitat of pathogenic staphylococci is the nasal mucosa of man from which the skin and the immediate environment are contaminated. Coagulase-positive staphylococci may be cultured from perhaps 25 to 50 per cent of normal adults and about 60 to 80 per cent of personnel in general hospitals. Accordingly, exposure to the staphylococcus is universal and especially intense in the hospital. Normal adults are highly resistant to infection. The occurrence of disease is often associated with conditions that breach epithelial barriers against the staphylococci or weaken the normal defenses against them in the tissues. Some clinically important conditions that facilitate staphylococcal infection are summarized in table 1.

Experimental, as well as clinical evidence demonstrates the potentiation of staphylococcal infection by factors that impair host resistance. In a study with subcutaneously inoculated human volunteers Elek found that the number of staphylococci required to produce purulent infection was reduced by a factor of as much as 10,000 if a silk suture was left in place with the microorganisms.11 Furthermore the infection was much more severe and extensive in the presence of the suture. These experiments confirm strikingly, clinical evidence of long standing that foreign bodies facilitate the establishment and persistence of staphylococcal infection.

In the experimental animal, appreciable and often striking changes in resistance to in-
STAPHYLOCOCCAL INFECTIONS OF THE HEART

Infection have been produced by a wide variety of procedures. Experimental staphylococcal or other microbial infections have been enhanced by quantitative or qualitative dietary deficiencies, hemorrhagic shock, the injection of polysaccharides or bacterial extracts (endotoxins), or by the administration of cortisone, thyroxine, dinitrophenol, or certain naturally occurring organic acids. The depression of resistance engendered by some of these agents is of short duration, lasting only a few hours or days, and may be followed by a period of increased resistance. The mechanisms by which resistance is affected by these diverse agents must be manifold. Irrespective of mechanism, however, it is clear that host resistance is a variable property sensitive to a wide range of stimuli.

STAPHYLOCOCCAL ENDOCARDITIS

Clinical Features

Endocarditis is the commonest and most important type of staphylococcal infection of the heart. Also, staphylococci are the cause of about 20 per cent of bacterial endocarditis. This relatively high frequency of staphylococcal endocarditis is the result mainly of reduction in the incidence of other forms of bacterial endocarditis due to effective antibiotic treatment of the primary infections.

Current concepts of the pathogenesis of bacterial endocarditis imply that microbes circulating in the blood during transient bacteremias settle in certain specially vulnerable areas of endocardium or vascular endothelium where they grow and produce vegetations. The increased susceptibility to bacterial endocarditis conferred by anatomic abnormalities of the heart valves has been demonstrated in dogs with experimentally induced aortic insufficiency. In these animals endocarditis has been produced regularly by a single intravenous injection of staphylococci or streptococci. However, another factor, perhaps related to the workload of the heart, may also be important in the pathogenesis of bacterial endocarditis. In dogs with large peripheral arteriovenous fistulas, bacterial endocarditis occurs frequently upon normal valves without the deliberate injection of bacteria. Also, by prior exposure to the cardiovascular stress of living under conditions simulating high altitude, rats may be rendered highly susceptible to the development of endocarditis following intravenous injection of bacteria.

The clinical setting in which staphylococcal endocarditis occurs is very variable. In some patients with acquired valvular or congenital heart disease, but otherwise in good health, endocarditis may begin without any obvious primary source of infection and without contact with hospital strains of staphylococci. Usually, the diagnosis is not difficult and the likelihood of success in treatment may be rel-

<table>
<thead>
<tr>
<th>Table 1.—Conditions Affecting Susceptibility to Staphylococcal Infection</th>
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<tbody>
<tr>
<td>A. Factors facilitating the entry of the staphylococcus</td>
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<tr>
<td>a. Break in the integrity of skin or mucosa, e.g., surgery, trauma, childbirth, cystoscopy.</td>
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<tr>
<td>b. Indwelling intravenous catheters.</td>
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<tr>
<td>c. Intravenous injection of nonsterile solutions, e.g., heroin addicts.</td>
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<tr>
<td>d. Dermatoses.</td>
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<tr>
<td>e. Antibiotics ineffective against the staphylococcus. By reducing the normal microbial populations these agents permit the proliferation of staphylococci on body surfaces to a degree permitting invasion and disease, e.g., staphylococcal enterocolitis and superinfections.</td>
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<tr>
<td>B. Factors reducing ability of the host to dispose of staphylococci within the tissues.</td>
</tr>
<tr>
<td>a. Foreign bodies.</td>
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<tr>
<td>b. Neonatal state.</td>
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<tr>
<td>c. Influenza, e.g., staphylococcal pneumonia.</td>
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<tr>
<td>d. Systemic disease.</td>
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<tr>
<td>(1) Diabetes mellitus.</td>
</tr>
<tr>
<td>(2) Leukemia, lymphoma, Hodgkin's disease, myeloid metaplasia.</td>
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<tr>
<td>(3) Cirrhosis of the liver, especially in advanced cases.</td>
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<tr>
<td>(4) Arterial insufficiency.</td>
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<tr>
<td>(5) Advanced neoplastic disease.</td>
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<tr>
<td>e. Valvular or congenital heart disease.</td>
</tr>
<tr>
<td>f. Mediation.</td>
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<tr>
<td>(1) ACTH and glucocorticoid hormones.</td>
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<tr>
<td>(2) Hematopoietic toxins, e.g., 6-mercaptopurine, folic acid antagonists, nitrogen mustard.</td>
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<tr>
<td>(3) Ionizing radiation.</td>
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</table>
atively good. In other patients, more often without obvious cardiac disease, but with some of the predisposing factors cited earlier, endocarditis may make its appearance secondary to staphylococcal infection at other sites. The illness is often contracted in the hospital environment and the attendant problems of antibiotic resistant strains of staphylococci and underlying disease make treatment more difficult and recovery less likely. In a third group of patients endocarditis may be only one of multiple metastatic foci in severe bacteremic staphylococcal infection and indeed may be an incidental and relatively unimportant terminal event. Accordingly, the term staphylococcal endocarditis does not define a uniform clinical entity. Questions of prognosis, prevention, and treatment cannot be treated meaningfully without reference to the clinical substrate in which the disease has occurred.

Staphylococcal endocarditis is usually a rapidly progressive typically acute endocarditis, but milder, more prolonged illnesses similar to subacute bacterial endocarditis are also seen usually with strains reported as Staphylococcus albus which may be inferred to be coagulase-negative in most cases. Infection by coagulase-negative strains almost always takes places on an existing cardiac deformity, whereas 40 per cent of cases of coagulase-positive staphylococcal endocarditis begin on a previously normal valve. An additional difference is that infarcts resulting from embolism in coagulase-negative staphylococcal endocarditis are usually bland in contrast to the septic infarcts characteristic of endocarditis caused by coagulase-positive organisms.

The clinical features of staphylococcal endocarditis are well known and require no elaboration. They include fever, often with chills and evidence of severe toxicity. Signs of cerebral damage are common, including stupor, coma, nuchal rigidity, and hemiparesis. Petechiae, skin rashes, splenomegaly, and obvious peripheral embolization are relatively uncommon in patients seen reasonably early in their illness. Murmurs adequate to suggest the presence of heart disease, most often rheumatic valvular disease, may be heard in from 50 to 75 per cent of cases. Marked change in the character of a murmur or the appearance of a new murmur is a most helpful but relatively infrequent sign. Laboratory findings usually include a normocytic, normochromic anemia, slight to moderate polymorphonuclear leukocytosis, albuminuria, and microscopic hematuria.

Blood culture is the essential test to establish the diagnosis. Fortunately the blood culture is almost invariably positive in untreated staphylococcal endocarditis. However it may be negative after inadequate treatment, even though clinical signs of active disease persist. If the diagnosis is strongly suggested by clinical features, 6 blood cultures should be taken at 3-hour intervals before treatment is begun. In critically ill patients, where immediate treatment is indicated, it is desirable to take at least 3 blood cultures within a period of perhaps 1 to 2 hours. Excessive numbers of cultures add little to the likelihood of establishing a diagnosis. Each culture should be inoculated into at least 2 types of liquid media and, where possible, pour plates should be made with a sample of blood to permit enumeration of the bacteria in the blood. Contaminated blood cultures, often with coagulase-negative staphylococci, may be a source of confusion. They may be avoided by rigidly aseptic venipuncture and inoculation of the blood into the culture flask. Thorough sterilization of the antecubital skin with alcohol or tincture of iodine before the venipuncture goes far toward eliminating contaminated blood cultures.

Bone marrow cultures or arterial blood cultures add nothing to conventional venous blood cultures.

In the presence of positive blood cultures it may be difficult to decide whether the patient has endocarditis or uncomplicated bacteremia. Suspicion of endocarditis must be high, for 50 to 65 per cent of patients with staphylococcal bacteremia prove to have endocarditis.
also. With rare exceptions staphylococcal bacteremia in a patient with valvular or congenital heart disease signifies endocarditis. Even in the absence of signs of heart disease, bacteremia persisting for several days, or recurrent bacteremia after antibiotic treatment should suggest endocarditis. Changing murmurs or peripheral emboli strongly support the diagnosis.

The spectacular development of cardiac surgery has brought in its train the hazard of postoperative endocarditis, almost invariably caused by staphylococci. Bacterial endocarditis after cardiac surgery often begins insidiously with low-grade fever and malaise. It may be easily confused with the postvalvulotomy syndrome with resulting delay in correct treatment. Early recourse to blood culture is important for correct diagnosis. In a series of 1,889 cardiac operations, 20 cases of postoperative endocarditis were detected, of which 11 were diagnosed within 3 months of surgery. In 45 per cent of cases the infecting organism was Staphylococcus albus coagulase-negative. Similar findings are reported by others. It is possible that aortic valve surgery, whether in consequence of the nature of the procedure or the location of the lesion, may entail special risks of postoperative endocarditis. Six cases of endocarditis were reported after operations on 150 cases of aortic stenosis and 4 cases following 33 operations on patients with aortic insufficiency.

The striking influence of foreign bodies upon the establishment and persistence of staphylococcal infection has been demonstrated in the heart. Five cases have been reported of postoperative infection in relation to silk sutures in the heart or great vessels. Antibiotic therapy was unsuccessful but removal of the sutures was followed by prompt recovery.

Cardiac surgery is rapidly becoming more complex and prolonged. Devices for extracorporeal circulation and plastic prostheses present new potential avenues for entrance of infection. Under these circumstances it seems probable that postoperative staphylococcal endocarditis will continue to be a source of concern to the cardiac surgeon.

Staphylococcal endocarditis of the right side of the heart has certain distinctive clinical features. In a recent survey, 50 per cent of cases of right-sided bacterial endocarditis were caused by staphylococci. The important predisposing factors have been surgical operations, cutaneous infection, indwelling intravenous plastic catheters or intravenous injections from nonsterile equipment by heroin addicts. The disease most commonly attacks the previously normal tricuspid or, less often, the pulmonic valve where it rarely induces murmurs. Right-sided endocarditis may also occur in patients with patent ductus arteriosus, intraventricular septal defect, or other congenital lesions, and in these cases the usual murmurs are to be expected. Clinical and roentgenographic signs of pulmonary embolism and infection are common. Systemic embolization is naturally infrequent but may occur secondary to pulmonary vein thrombosis at the site of a pulmonary infarct.

Blood cultures are positive in more than 90 per cent of cases of staphylococcal right-sided endocarditis, in contradistinction to the lower incidence of positive blood cultures in cases due to alpha hemolytic streptococci.

The rapid development of important complications, often before treatment can be instituted, is in large measure responsible for the distressingly low rate of cure in staphylocoecal endocarditis. Aggravation of valvular deformity often leads to congestive heart failure, which may be fatal in spite of bacteriologic cure. Grossly destructive lesions of the valves including perforation of valve cusps are common. They lead to rapid development of signs of valvular incompetence with correspondingly changing murmurs. Intractable congestive failure follows.

Erosive lesions developing from aortic valvular vegetations may produce aneurysms of the sinus of Valsalva that may perforate through the interventricular or interatrial septum or cause rupture of the heart, usually in the anterior wall of the left ventricle.
TABLE 2.—Nature of Action of Antibiotics upon Staphylococci

<table>
<thead>
<tr>
<th>Bacteriostatic</th>
<th>Bactericidal</th>
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<tr>
<td>Tetracyclines</td>
<td>Penicillin</td>
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<tr>
<td>Chloramphenicol</td>
<td>Streptomyein</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Bacitracin</td>
</tr>
<tr>
<td>Oleandomycin</td>
<td>Neomycin</td>
</tr>
<tr>
<td>Spiramycin</td>
<td>Kanamycin</td>
</tr>
<tr>
<td>Novobiocin</td>
<td>Vancomycin</td>
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<tr>
<td>Ristocetin</td>
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Abscesses may occur in the fibrous structure of the valve rings. These lesions communicate by a narrow tract with a valvular vegetation. They may be readily overlooked at autopsy if the valve rings are not carefully dissected. As Sheldon suggests, such lesions may well be responsible for certain otherwise inexplicable failures of treatment.26

Embolism to the brain accounts for the high frequency of neurologic signs in this disease and is a common cause of death. Coronary arterial embolism is the cause of the many focal necrotic and inflammatory myocardial lesions found so commonly at autopsy in staphylococcal endocarditis. Occasionally a large coronary embolism is acutely fatal.

Antibiotic Treatment

The aim is rapid killing of the infecting staphylococci. In view of the wide variation of antibiotic sensitivity of staphylococci an in vitro determination of antibiotic sensitivity is essential in each case, preferably by a quantitative tube-dilution method. Also, it is desirable that the test should assess the bactericidal capabilities of the antibiotic.27 However, even without specific bactericidal tests, a satisfactory course of treatment may be selected from a simple sensitivity test and knowledge of the properties of the available antibiotics. A classification of antibiotics in terms of their typical modes of action upon sensitive strains of staphylococci is given in table 2.

Many factors difficult to duplicate in vitro may affect the lethality of an antibiotic agent under conditions prevailing in vivo. Obviously the antibiotic must be delivered to the microbe at the site of infection in appropriate concentration and for an adequate time without imposing the risk of excessive toxicity to the patient. This may be delayed in staphylococcal infections because of the lack of circulation in necrotic foci and in vegetations. Bacteria that are not multiplying, as may be the case in phagocytized organisms or in focal necrotic lesions, are not readily killed by antibiotics of any kind. Such "resting" organisms, however, may still synthesize toxins and enzymes, such as penicillinase, which may contribute to persistence or extension of the disease. Occasional organisms may survive in tissues under antibiotic treatment sufficient to kill virtually all their fellow organisms. Such "persisters" are not genetically more resistant than the original stock and the reasons for their survival are unknown.28 It is possible that this phenomenon may play a part in the difficulty of achieving cure in certain cases of staphylococcal infection. Finally biochemical factors difficult to duplicate in vitro may affect the action of antibiotics. Among these may be pH, partial pressure of oxygen, organic compounds, and salt concentrations. For these reasons, although in vitro antibiotic sensitivity tests are of great importance in screening out inefficient antibiotics and suggesting those that may be effective in treatment, the response in an individual case is subject to other factors that make each case almost a new clinical trial.

Treatment must be prompt to minimize permanent valvular damage.

The sensitivity of staphylococci to antibiotics is closely related to the nature of the population from which they are obtained. Representative data are cited in table 3. Staphylococci cultured from persons exposed to the hospital environment, whether from carriers or from infections acquired in the hospital, are highly likely to be resistant to penicillin, streptomycin, and tetracyclines. Resistance to erythromycin may be detected in 15 to 50 per cent of strains, varying to some degree according to the extent of its use. Staphylococci cultured from infections or carriers without obvious contacts with hos-
hitals may be sensitive to penicillin in 50 per cent and to streptomycin and tetracyclines in 75 per cent of cases.

To some extent resistance is a relative term, in that strains classified as resistant may be inhibited by high concentrations of the antibiotic in question. With the possible exception of penicillin, however, toxicity to the patient prevents the uses of other antibiotics in amounts large enough to achieve clinically worthwhile results in infections by resistant strains.

Treatment may be defeated by development of antibiotic resistance by staphylococci. Resistant strains appear readily from spontaneously occurring resistant mutants in patients treated with streptomycin or erythromycin or novobiocin. The emergence of resistant strains may be delayed if each of these agents is given only in combination with another agent, which in the concentration employed, is inhibitory to the staphylococcus. During treatment with penicillin, tetracyclines and, as far as experience go as, with vancomycin, ristocetin, and kanamycin resistant strains rarely, if ever, emerge from sensitive strains. However, where an opportunity exists for contamination of a lesion from external sources, resistant strains of exogenous origin may replace the original sensitive strain.

Choice of Antibiotics

Penicillin is the agent of choice in infections by penicillin-sensitive staphylococci (i.e., staphylococci that produce no penicillinase). These strains are usually inhibited by 0.5 unit of penicillin per milliliter. Recommended treatment is 1 million units of soluble penicillin intramuscularly every 2 to 3 hours for 6 weeks with probenecid 500 mg. orally every 6 hours. Some strains of staphylococci that are both penicillin and streptomycin-sensitive may be killed more rapidly if streptomycin is added; 0.5 Gm. of streptomycin should be given intramuscularly every 6 hours. If signs of vestibular or auditory toxicity appear, the dose should be reduced to 0.5 Gm. every 12 hours.

### Table 3—Antibiotic Sensitivity of Staphylococcus Aureus According to Site of Origin

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Extrahospital strains</th>
<th>Intrahospital strains</th>
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<tbody>
<tr>
<td></td>
<td>Carriers*</td>
<td>Carriers†</td>
</tr>
<tr>
<td></td>
<td>(Per cent of sensitive strains)</td>
<td>Infec-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tions†</td>
</tr>
<tr>
<td>Penicillin</td>
<td>66</td>
<td>49</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>—</td>
<td>87</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>97</td>
<td>78</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Novobiocin</td>
<td>97</td>
<td>90</td>
</tr>
<tr>
<td>Bacitracin</td>
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The place of penicillin in the treatment of infections by strains of staphylococci moderately or highly resistant to penicillin is subject to differences of opinion. These strains are resistant by virtue of their production of the enzyme penicillinase that inactivates the antibiotic. However, when exposed in small numbers to penicillin they still are killed by concentrations as low as 1 to 2 units per ml. In theory, if these concentrations could be maintained in the immediate vicinity of penicillin-resistant staphylococci for an adequate time, treatment with penicillin should be successful. Whether or not this can be achieved with appreciable frequency in patients is still in doubt. However, several clinical investigators have reported cures of penicillin-resistant staphylococcal endocarditis with very large doses of penicillin, usually in combination with another antibiotic, such as erythromycin. If high-dosage penicillin treatment is considered the treatment of choice, one may give from 50 to 150 million units per day by continuous intravenous drip together with probenecid orally. In addition to penicillin, another antibiotic should be used, either erythromycin, novobiocin, or chloramphenicol, to which the staphylococcus should be sensi-
Vancomycin appears to be the agent of choice for treatment of penicillin-resistant staphylococcal endocarditis, on the basis of admittedly scanty clinical data. This antibiotic is effective against virtually all staphylococci. The bactericidal concentration is not more than twice the bacteriostatic level and readily attained in therapy without significant toxicity. Resistant strains have not been developed by treatment in man nor are they readily obtained in vitro. Toxic manifestations appear to be restricted to occasional pyrogenic reactions, thrombophlebitis, and, rarely, impairment of hearing when high dosage or impaired renal function permit the accumulation of undesirably high blood levels. Geraei and his colleagues have reported bacteriologic cure with vancomycin in 5 of 6 cases of staphylococcal endocarditis.27 Recommended dosage is 0.5 Gm. intravenously diluted with saline or glucose solution every 4 to 6 hours for 4 to 6 weeks.

Vancomycin, one of the newer antistaphylococcal antibiotics, is related chemically to neomycin, with which it exhibits reciprocal cross-sensitivity and resistance. Bactericidal concentrations are readily attained in the blood after intramuscular injection. Clinical reports are inadequate to evaluate its effectiveness in staphylococcal endocarditis. Careful clinical trial is warranted in staphylococcal infections of the heart in which penicillin or vancomycin is either contraindicated or ineffective. Kanamycin is significantly toxic to the kidneys and the auditory nerve. Damage to these organs may be encountered even on therapeutic dosage, particularly if it is prolonged or if renal disease causes the accumulation of high blood levels. Recommended dosage is 0.5 Gm. intramuscularly 4 to 6 times daily.30

Similarly the place of another new antibiotic, ristocetin is still undetermined. It has been reported to have been effective in many staphylococcal infections, including a few cases of endocarditis. However some investigators have found it to be ineffective in some cases of severe systemic staphylococcal infection even without endocarditis.31 Concentrations that would be bactericidal for staphylococci are higher than can be attained in serum. Marked, but reversible leukopenia and, to a lesser extent, thrombocytopenia have accompanied its use in a variable proportion of patients. Additional evidence is necessary before it can be recommended for use in staphylococcal endocarditis.

The bacteriostatic antibiotics erythromycin, novobiocin, the tetracyclines, chloramphenicol, and the relatively toxic agents bacitracin and neomycin, for the most part given in various combinations, are not notably effective in staphylococcal endocarditis although occasional cures have been reported. Directions for their use in staphylococcal endocarditis are available and will not be repeated here.19 It should be noted that recent observations bring into question the advisability of using the common combination of erythromycin and chloramphenicol. Barber has reported, in confirmation of older observations, that staphylococci resistant to erythromycin may concomitantly show partial resistance to chloramphenicol. She recommends erythromycin plus novobiocin as a more desirable combination.32

If treatment must be begun on the basis of strong clinical suspicion of staphylococcal endocarditis but before results of blood cultures are available, vancomycin is the preferable agent. A second choice would be penicillin in high dosage plus erythromycin or novobiocin depending on the local pattern of resistance of staphylococci.

As in other serious infections, the use of compounds with glucocorticoid hormonal activity as an adjunct to effective antibiotic therapy has found favor in some quarters. Most students of infectious disease believe that the risks of potentiating the original infec-
tion or of inducing superinfection outweigh the benefits, which appear to be superficial and symptomatic.

The use of anticoagulants in bacterial endocarditis has been abandoned generally.

Criteria of Therapeutic Efficacy

Even with properly selected therapy patients with endocarditis may continue to exhibit fever, embolization, leukocytosis, elevated sedimentation rate, and other signs of infection for several days to weeks. Presumably these signs reflect the period of time necessary to sterilize the lesions and to organize vegetations. These clinical signs are not sufficient indication to change a critically selected course of treatment. The sole urgent indication for change in antibiotics is a persistently positive blood culture. To check this point, blood cultures should be taken repeatedly during early stages of treatment and at any time that the clinical picture becomes worse. Any changes in therapy should be made on the basis of tests to guard against changes in antibiotic sensitivity. If fever, toxicity, and positive blood cultures persist in spite of treatment that should be adequate, localized suppurative complications should be looked for, especially in the kidneys, spleen, bones, lung, and brain.

Results of Treatment

Taken as a whole the results of treatment in recent years of staphylococcal endocarditis have been poor, with the possible exception of the very limited experience with vancomycin. When the staphylococcal endocarditis is a complication of major surgery or advanced systemic disease, especially low recovery rates prevail. Patients who are free of illness other than valvular deformity who acquire their endocarditis in their home (i.e., nonhospital) environment appear to have a better chance of recovery. This factor may have played a part in the recovery of 8 of a total of 9 patients reported by Melton and Logue. Even in the most apparently favorable case, however, embolism or heart failure from valvular damage inflicted prior to treatment may be unexpectedly fatal. Average recovery rates in larger recent series of patients are about 30 to 50 per cent. No consistent difference in recovery rates is apparent between infections by coagulase-positive and negative strains of staphylococcus.

Prevention

Probably more than 50 per cent of cases of staphylococcal endocarditis are the result of infections acquired in hospitals. Insofar as the rate of hospital-acquired staphylococcal infection can be reduced, the incidence of endocarditis should also decline. Recommendations to this end are numerous and entail many administrative complexities. Among the simpler steps that may be of value are (1) rigorous aseptic technic in surgery, (2) restriction of intravenous catheterization and “cut downs” to the minimum, coupled with careful protection of the site from infection, (3) protection of the inordinately susceptible group of patients by isolation from the general hospital population, (4) meticulous, bacteriologically controlled hospital housekeeping.

Gould has suggested that the high prevalence of penicillin-resistant staphylococci in hospitals is due to the continuous fall-out of penicillin aerosol derived from the widespread use of the antibiotic. If this hypothesis is correct, limitation of contamination of the environment by antibiotics may be an additional step in prevention.

The benefit to be expected from prophylaxis by antibiotics against staphylococcal infection is open to question in view of the high proportion of antibiotic-resistant strains. Where it has been possible to arrange a controlled test of more or less blanket prophylaxis, the results have not disclosed significant benefit. It is possible, however, that prophylaxis against bacterial endocarditis may depend upon the ability to eradicate a small number of infectious organisms from the blood stream or the endocardial surface and hence may be specially feasible. Geraci recommends 1 million units of aqueous procaine penicillin and 1 Gm. of a streptomycin-dihydrostreptomycin mix-
ture 12 hours and again 1 or 2 hours before surgery, dental extraction or endoscopy, with repeated doses for 12 hours to several days afterward. He has not observed endocarditis with this regimen.\textsuperscript{27} In contrast, in a controlled study of prophylaxis with chloramphenicol no effect was observed on infections after transurethral prostatectomy.\textsuperscript{36} Indeed one patient who received chloramphenicol contracted staphylocoecal endocarditis.

**Staphylocoecal Pericarditis**

With the decline in frequency of extensive pneumococcal and streptococcal infections, staphylo cocci have become the leading cause of acute pyogenic pericarditis. Of 27 cases in patients under 20 years of age occurring between 1937 and 1956, 15 were of staphylocoecal etiology.\textsuperscript{37}

Staphylocoecal pericarditis is usually an incident in severe, bacteremic staphylocoecal infection in infants and children. Rarely it appears as a relatively isolated metastatic focus from a mild or inapparent primary infection. Exceptionally it may be a complication of staphylocoecal endocarditis.

The clinical manifestations differ in no way from those of acute pyogenic pericarditis due to other organisms; they comprise precordial pain, dyspnea, friction rub, cardiac enlargement, and signs of tamponade. However, symptoms may not be detectable in patients acutely ill with generalized staphylocoecal infection. Bacteriologic diagnosis must be established by paracentesis.

The immediate aims of treatment should be the prevention of tamponade by judiciously timed paracentesis and the control of generalized staphylocoecal infection by antibiotic treatment along the lines described for endocarditis. Some additional benefit may be obtained by the local instillation of solutions of nonirritating antibiotics, e.g., bacitraein 200 units per ml or kanamycin 2.5 mg. per ml at the time of paracentesis. Surgical drainage was formerly considered to be an indispensable element in treatment. Although it is still advocated in all cases by some authorities, current experience suggests that some patients may be cured by antibiotic treatment alone. If the effusion recurs or evidence of infection persists under treatment, surgical drainage is indicated.

The results of treatment of staphylocoecal pericarditis are determined in large measure by the response of the serious infections with which it is associated. The mortality in a series of patients treated with penicillin between 1944 and 1956 was close to 50 per cent.\textsuperscript{37}

There are indications that healed staphylocoecal pericarditis may produce the syndrome of constrictive pericarditis. Rigorous proof, however, is still wanting.\textsuperscript{38}

**Staphylocoecal Myocarditis**

In fatal cases of uncontrolled staphylocoecal bacteremia the myocardium is usually peppered with miliary abscesses ranging from microscopic to grossly visible size. Whether they produce clinical signs or symptoms is unknown. In line with the suggestion made for the milder myocardial lesions of subacute bacterial endocarditis, they may contribute to the vascular collapse that often accompanies staphylocoecal bacteremia.\textsuperscript{39}

Solitary abscess of the myocardium is exceedingly rare. Among 7 cases reviewed by Weiss and Wilkins, at least 1 was caused by *Staphylococcus aureus*.\textsuperscript{39} The primary site from which the myocardial lesion arises is rarely apparent. The abscess is unaccompanied by signs of infection and manifests itself for the first time when it ruptures into the pericardium. In the few reported cases, the symptoms have been sudden precordial pain followed by signs of tamponade and death from hemopericardium within a few hours.

**Summary**

The basic problems of staphylocoecal infections do not seem near to solution. Possibly an effective and safe antibiotic will be found to which resistant, pathogenic staphylocoecal mutants will not appear. This may not be an overly sanguine hope. Had it not been for the ability of the staphylocoecus to synthesize
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penicillinase, this goal would have been achieved already, for staphylococcal mutants pathogenic to man and intrinsically resistant to penicillin (i.e., without the production of penicillinase) have not been reported. Even with better antibiotics grave problems would remain, however, for the staphylococcus often inflicts severe or even irremediable damage, especially in the heart, before the disease can be diagnosed.

Prevention is the crucial problem. Refinements in isolation technics and hospital sanitation may improve the protection of the patient in the operating room and the newborn infant in the nursery. Nevertheless, the hard core of infections in debilitated or otherwise susceptible medical patients will probably remain. To help them it will be necessary to learn to restore the mechanisms of normal host resistance that have been depleted by disease.

SUMARIO IN INTERLINGUA

Il non pare que le solution del problemes fundamental de infectiones staphylococcal es imminente. Il es possible que un efficace e innocente antibiotic va esser trovate sin que mutantes resistente del staphylococcos pathogene va disveloppar se contra illo. Iste spero es forsan non troppo promittente. Si le staphylococos non habeva le capacitate de synthetisar penicillinase, ille objectivo esserea jam attingite, proque mutantes staphylococcal que es pathogene pro humanos e que possede un resistentia intrinsee contra penicillina—i.e. un resistentia non dependente del production de penicillinase—ha non ancora essite reportate. Tamen, mesmo si melior antiboticos esseva cognoscite, grave problemas remanerara, proque le staphylococcos infilge frequentemente sever o mesmo irreparabloe injurias, specialmente in le caso del corde, ante que le morbo pote esser diagnosticate.

Le problema critic es le prevention. Le raffinamento del technicas de isolation e del sanitation hospitalari va possibilmente meliorar le protection del paciente in le sala de operation e le neonato in le nursery. Nonostante, un residuo irreducibile de infectiones

in debilitate o alteremente susceptibile patientes medical va probablemente permaner. Pro adjuvar tal patientes, il va esser necessari trovar methodos pro restaurar le mechanismos del normal resistentia del organismo le quales ha essite deteriorate per le processo pathologicie.

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