Antibiotic Therapy of Bacterial Endocarditis

VI. Subacute Enterococcal Endocarditis: Clinical, Pathologic and Therapeutic Consideration of 33 Cases

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Thirty-three cases of enterococcal endocarditis encountered during the decade from January 1944 through December 1953 are reviewed. In vitro studies indicate that penicillin and streptomycin are the best antibiotic pair for bactericidal effect. Twelve of the last 14 patients were cured (86 per cent), 10 with combined therapy. The cure rate in enterococcal endocarditis now approximates that of endocarditis caused by penicillin-sensitive streptococci. A maximal number of cures is achieved by individualization of therapy. The daily dosage of penicillin and the duration of combined penicillin-streptomycin therapy should be guided by in vitro bactericidal tests employing the patient’s strain of enterococcus.

A DECADE ago enterococcal endocarditis was considered quite rare and only a limited number of such cases had been reported. In 1906 Andrews and Horder found *Streptococcus faecalis* to be the offending organism in 4 of 24 cases of “malignant endocarditis.” In 1922 Gordon noted that 3 of 24 strains of *Streptococcus faecalis* studied came from malignant endocarditis. In 1929 Dible observed that in one of six cases ulcerative endocarditis was caused by an enterococcus and in 1936 Elser and Thomas pointed out that *Streptococcus zymogenes* was not infrequently isolated from patients with bacterial endocarditis. Of the 17 strains studied, eight were obtained from the blood and six of these were from patients with endocarditis. Following Sherman’s definitive work concerning the differentiation of enterococci from other streptococci, Moran studied 20 organisms from patients with endocarditis and found that 20 per cent of them were enterococci. In 1942 Skinner and Edwards reviewed 37 cases collected from the literature and added two cases of their own. Wheeler and Foley observed that 4 of 23 patients with nongroup A streptococcal infections had enterococcal endocarditis.

MacNeal and Blevins found that in 6 of 36 patients bacterial endocarditis was caused by *Streptococcus faecalis*.

Since the foregoing reports were made, the proportion of cases of endocarditis attributable to enterococci has been variously estimated as 3 to 8 per cent, 5 to 10 per cent, and 10 to 15 per cent. In a series of 46 patients with endocarditis treated at the Mayo Clinic from October, 1950, through May, 1952, enterococci were implicated in 10 instances, a proportion of 21 per cent. This proportion approximates that found in recent publications. Today the proportion of cases of endocarditis caused by enterococci seems to be increasing. This apparently reflects a decreased prevalence of endocarditis caused by penicillin-sensitive streptococci of the salivary or viridans type.

We propose in this paper to report our experiences with enterococcal endocarditis seen at the Mayo Clinic during the first decade of antibiotic therapy for bacterial endocarditis. We wish to consider particularly some of the therapeutic problems that arise in the antibiotic therapy of this valvular infection caused by penicillin-resistant streptococci.

**METHODS***

From January, 1944, through December, 1953, 33 cases of enterococcal endocarditis were encountered.* The bacteriologic procedures in this study were performed in the Section of Bacteriology under the

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at the Mayo Clinic. These constitute an unselected consecutive series of cases and represent approximately 10 per cent of the total number of patients with endocarditis seen during this period. As a result of this experience, a definite plan of study and therapy of enterococcal endocarditis has evolved.

In vitro sensitivity tests are carried out by the plate dilution method. Uniform amounts of a pure culture which have been incubated for six hours are spread evenly over the surfaces of a series of blood-agar plates containing twofold dilutions of the antibiotic. The plates are incubated at 37 C. for 24 hours, and the sensitivity recorded represents the concentration of antibiotic which completely inhibits growth of the organism. A standard strain of *Micrococcus pyogenes* having a known degree of sensitivity to the antibiotic is used as a control. Assays for serum concentrations of penicillin are carried out by the Fleming slide cell technic. A tube dilution method using *Klebsiella pneumoniae* as a test organism is utilized to determine the serum levels of dihydrostreptomycin.

Tests were carried out to determine the bactericidal effect of penicillin, dihydrostreptomycin, chloramphenicol, oxytetracycline (terramycin) and erythromycin, singly and in combinations, on five of the strains of enterococci isolated (cases 21, 27, 29, 30 and 33). (Case numbers used in this paper correspond to those in tables 7 and 8.) The antibiotics were added to heart infusion broth containing approximately 4,000 actively growing organisms per milliliter. After incubation at 37 C. for 18 hours the organisms were subcultured on solid or semisolid media to determine the number of survivors. In each case penicillin and dihydrostreptomycin were found to be the most effective pair of antibiotics for bactericidal effect. Although the organisms were relatively insensitive to dihydrostreptomycin, the addition of this antibiotic to penicillin considerably increased the bactericidal effect over that of penicillin alone. Under the conditions of the test, killing of the organisms was complete with concentrations of the two antibiotics ranging from 2.5 units of penicillin and 2.5 micrograms of dihydrostreptomycin per milliliter to 5 units of penicillin and 5 micrograms of dihydrostreptomycin per milliliter. The addition of erythromycin or bacitracin to the penicillin-dihydrostreptomycin combination was not advantageous.

An attempt was made to gauge the probable effectiveness of antibiotic therapy by determining the bactericidal effect of the patient's serum against his own organism while he was under treatment. Serial 1:1 dilutions of the serum were made with heart infusion broth and these together with un-diluted serum were seeded with a six-hour culture of the organism to give approximately 4,000 bacteria per milliliter. After 18 hours of incubation, cultures were made from each tube to determine the number of surviving organisms. Such studies, carried out in cases 31, 32 and 33, indicated that total killing of the organism occurred in a 1:8 dilution of the serum of all three patients when they were receiving daily 20, 20 and 50 million units of penicillin respectively and 2 Gm. of dihydrostreptomycin.

**Bacteriology of Enterococci**

The enterococci belong to group D of Lancefield's classification of streptococci. They are differentiated from other streptococci by the serologic reaction of precipitation with Lancefield's group D streptococcal antiserum.11 *Streptococcus faecalis, Streptococcus liquefaciens, Streptococcus durans* and *Streptococcus zymogenes* are the four species that are classified as enterococci. For practical clinical and therapeutic purposes, the enterococci can be considered as one since they are highly resistant to penicillin. They are quite hardy, are of low virulence and grow well in ordinary laboratory media. Most enterococci are inhibited by 2 to 12 units of penicillin per milliliter.25 Rarely, strains are inhibited by 0.1 unit or less of penicillin.27 Enterococci are normally found in the human intestine and vagina, and in milk and dairy products.

The enterococci are differentiated by means of varying biochemical and physiologic characteristics but for practical purposes no attempts were made to determine the species of the strains of enterococci isolated herein; only the bacteriologic procedures necessary for the identification of the bacteria as enterococci were carried out. Of the 33 patients in this series from whom enterococci were isolated, in vitro sensitivity tests with penicillin, dihydrostreptomycin and other antibiotics were carried out on 31 (table 1).

**Pathogenesis**

Bacteremia occurring in the face of antecedent disease of or operation on the genitourinary or gastrointestinal tract should cause one to consider the likelihood of an enterococcal infection. Urologic manipulation, perforative lesions of the lower part of the intestinal tract, and septic abortion may initiate such bactere-
Table 1.—In Vitro Sensitivity of 31 Strains of Enterococci to Various Antibiotics

<table>
<thead>
<tr>
<th>Concentration*</th>
<th>0.2</th>
<th>0.4</th>
<th>0.8</th>
<th>1.6</th>
<th>3.2</th>
<th>6.2</th>
<th>&gt;6.2</th>
<th>25.0 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin†</td>
<td></td>
<td></td>
<td>1</td>
<td>6</td>
<td>15</td>
<td>12</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Dihydrostreptomycin</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>1</td>
<td></td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1</td>
<td></td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* In units per milliliter of medium for penicillin and bacitracin; in micrograms per milliliter for all others.
† Total is more than 31 since in vitro sensitivity determinations made on organisms isolated during relapses are included.

mia. Isolated bacteremia due to enterococci occurs occasionally; repeated detection of this organism in the blood stream almost invariably signifies endocarditis.

While in the majority of cases enterococcal endocarditis is associated with organic heart disease, the infection may be engrafted on normal heart valves. This aspect of enterococcal endocarditis will be commented on later.

Enterococcal endocarditis may complicate urologic instrumentation such as cystoscopy, urethral dilatation or transurethral resection. This infection has been associated with or complicated carcinoma of the sigmoid colon, so-called Blalock-Taussig operation, abortion and normal pregnancy. Periapical dental abscesses have also been implicated.

The precipitating factors in our cases are given in table 2.

**Symptomatology**

Twenty of the 33 patients with enterococcal endocarditis in our series were men. The ages ranged from 25 to 77 years; the average age was 51 years. In 15 cases there was no knowledge of antecedent valvular disease. The remaining 18 patients were aware of heart murmurs.

The onset was gradual in 22 cases and acute in nine; in two cases it was not possible to describe the type of onset properly. The nine patients who had an acute onset were able to relate the first symptom precisely to a certain time. Headache, chills and fever, or embolization were, singly or in combination, the first symptoms of the disease.

Every patient had fever at some time during the course of the disease (table 3). In 11 cases the fever was low grade, that is, the temperature did not exceed 102 F. In the remaining 22 cases the temperature often ranged as high as 103 to 106 F. The higher spikes of fever usually were associated with chills.

Eleven patients had symptoms referable to the central nervous system. Five of these had hemiplegia; two of the latter became comatose and died, one recovered completely after two such episodes and two retained residua. Two patients complained of severe occipital headaches without definite evidence of cerebral embolism. One patient experienced homonymous hemianopsia and one had terminal and generalized convulsions.

Eleven patients complained of generalized arthralgias. Two others suffered from severe myalgias. One of these was referred because of "acute arthritis of the cervical spine"; no primary disease of the vertebrae was found to explain the complaint and the condition subsided with treatment of the endocarditis. The other of the two patients was distraught be-
TABLE 3.—Symptoms in 33 Cases of Enterococcal Endocarditis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>33</td>
</tr>
<tr>
<td>Loss of weight</td>
<td>23</td>
</tr>
<tr>
<td>Chills</td>
<td>19</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>17</td>
</tr>
<tr>
<td>Gastrointestinal—anorexia</td>
<td>16</td>
</tr>
<tr>
<td>Rheumatic—arthralgias</td>
<td>15</td>
</tr>
<tr>
<td>Genitourinary*</td>
<td>13</td>
</tr>
<tr>
<td>Sweats</td>
<td>12</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>11</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6</td>
</tr>
</tbody>
</table>

* In only 1 case were the genitourinary symptoms due to bacterial endocarditis.

TABLE 4.—Physical Signs in 33 Cases of Enterococcal Endocarditis

<table>
<thead>
<tr>
<th>Sign</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart murmur*</td>
<td>33</td>
</tr>
<tr>
<td>Apical systolic</td>
<td>19</td>
</tr>
<tr>
<td>Aortic systolic</td>
<td>13</td>
</tr>
<tr>
<td>Aortic diastolic</td>
<td>9</td>
</tr>
<tr>
<td>Apical diastolic</td>
<td>2</td>
</tr>
<tr>
<td>Roger type</td>
<td>1</td>
</tr>
<tr>
<td>Embolic phenomena</td>
<td>23</td>
</tr>
<tr>
<td>Enlarged heart</td>
<td>18</td>
</tr>
<tr>
<td>Sinus tachycardia (above 100 per min.)</td>
<td>15</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>14</td>
</tr>
<tr>
<td>Clubbing of digits</td>
<td>11</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8</td>
</tr>
<tr>
<td>Precordial thrill</td>
<td>8</td>
</tr>
<tr>
<td>Fundic hemorrhages</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
</tr>
<tr>
<td>Auricular fibrillation</td>
<td>3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2</td>
</tr>
</tbody>
</table>

* Total of breakdown is more than 33 because several patients had more than one murmur.

cause of shoulder aches which also subsided with treatment of the endocarditis. Two patients had red, hot, tender, swollen ankles.

PHYSICAL FINDINGS

The most prominent physical findings were related to the cardiovascular system. Each patient exhibited a heart murmur (table 4).

It was difficult to be certain of the etiologic types of heart disease. In 11 cases there was definite evidence of pre-existing rheumatic heart disease, in five the rheumatic origin of the heart disease was questionable and in two the heart disease was congenital. The other 15 patients probably did not have underlying heart disease.

Embolic phenomena were detected in 23 patients. Five of these had pulmonary infarction. Three patients experienced clinically substantiated embolism of the eyes and these are to be distinguished from two patients who had retinal hemorrhages that were not related to obvious embolism; two of the three patients also exhibited retinal hemorrhages. Five patients had intracranial embolism with resultant paralysis. Three had splenic infarction and two of these also had suffered from ocular embolism. One patient each apparently experienced mesenteric and coronary embolism. The remaining sites of embolism were the extremities; three of the patients with emboli elsewhere also had emboli lodge in arterial channels of the extremities. Eight patients exhibited petechiae; only two of these did not suffer from major embolism. Four patients had Osler's nodes and all of these had major embolism. No patient had so-called Janeway nodes.

Laboratory data are summarized in table 5.

PATHOLOGY*

Although the clinical picture and course of enterococcal endocarditis are similar to those

* We are indebted to Dr. Jesse E. Edwards, Section of Pathologic Anatomy, for review of the pathologic material in this series of cases.
seen in other types of nonhemolytic streptococcal endocarditis, it has been stated that enterococcal valvular infections are associated at necropsy with an increased incidence of suppurative lesions in peripheral organs and in the heart, a very low incidence of focal and diffuse glomerulonephritis, and evidence of more frequent occurrence in persons who previously had normal hearts and normal valves. With this in mind, we reviewed the clinical and postmortem data in the six cases in which necropsy was performed in this series (table 6).

These postmortem studies indicate that in five of the six cases there did not appear to be any definite evidence of pre-existing valvular disease. In each of the five, however, there were minor thickenings of the chordae tendineae and valves which were attributed to bacterial endocarditis. In cases of bacterial endocarditis in which evidence of previous valvular disease is minimal, it often cannot be stated with any certainty that any in fact existed. Some of the minimal thickening in the five cases just mentioned might conceivably have resulted from pre-existing rheumatic inflammation but if this is so then the thickening had no characteristic rheumatic features such as fusion between leaflets or shortening of the chordae.

In five cases abscess formation was absent; abscesses were noted in the lungs in case 14 (table 6) in which the endocarditis arose from the tricuspid valve. The kidneys were involved in all six cases; the findings consisted of tubular hemorrhage (three cases), gross infarctions (three cases), acute diffuse glomerulonephritis (one case), foci of fibrinoid necrosis of glomerular tuft (one case) and thickening of the basement membrane (one case).

### Table 6.—Enterococcal Endocarditis: Cardiac Findings at Necropsy in 6 Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, Sex</th>
<th>Duration of Disease</th>
<th>Cardiac History*</th>
<th>Cause of Death</th>
<th>Necropsy Data</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>48 M</td>
<td>&gt;2 mo.</td>
<td>No hist. of RF, HD or M</td>
<td>Cerebral embolism, infarct</td>
<td>Vegetations on normal mitral valve</td>
<td>See Comment, table 7</td>
</tr>
<tr>
<td>12</td>
<td>63 M</td>
<td>5 wk.</td>
<td>No hist. of RF, HD or M</td>
<td>Renal insuf.</td>
<td>Vegetations on normal mitral valve</td>
<td>See Comment, table 7. Also given 2-4.5 Gm. of chlorotetracycline for 13 da. without benefit. Total period of therapy: 40 da.</td>
</tr>
<tr>
<td>13</td>
<td>77 M</td>
<td>9 da.</td>
<td>No hist. of RF, HD or M</td>
<td>Progressive deterioration</td>
<td>Vegetations on normal mitral valve</td>
<td>See Comment, table 7. SBE suspected 1 da. before death</td>
</tr>
<tr>
<td>24</td>
<td>65 M</td>
<td>3 yr.</td>
<td>M noted 18 mo. after onset of dis. No prev. hist. of RF, HD or M</td>
<td>Cerebral embolus, infarct</td>
<td>Vegetations on bicuspid aortic valve</td>
<td>See Comment, table 8. Rectal cancer &amp; a pararectal abscess also present</td>
</tr>
<tr>
<td>31</td>
<td>38 F</td>
<td>20 mo.</td>
<td>No hist. of RF, HD or M</td>
<td>Cerebral embolus, infarct</td>
<td>Vegetations on normal mitral valve</td>
<td>See Comment, table 8</td>
</tr>
</tbody>
</table>

* See table 7 for abbreviations.
THERAPY OF ENTEROCOCCAL ENDOCARDITIS

The treatment of penicillin-resistant enterococcal endocarditis was very unsatisfactory prior to the introduction of combined penicillin-streptomycin therapy. Endocarditis caused by penicillin-sensitive streptococci had responded readily to penicillin therapy, but enterococcal endocarditis had failed to respond in most instances when penicillin was used alone. Only in the last half-decade have the results of combined antibiotic therapy for this form of endocarditis approached those of the form caused by penicillin-resistant organisms. A spontaneous cure of the infection of bacterial endocarditis occurs occasionally. Whether enterococcal endocarditis ever heals spontaneously is not known but probably it does rarely.

Penicillin

A number of cases have been reported in which penicillin alone or penicillin together with caronamide or probenecid (Benemid) has resulted in cure of enterococcal endocarditis. Harris in 1945 cited a cure in which 24 million units of penicillin alone over a 76-day period resulted in eradication of the infection.

In 1946, MacNeal and colleagues reported a case in which a clinical arrest of enterococcal endocarditis followed long-term therapy with a combination of enterococcal bacteriophage and penicillin. The organism in this case was very resistant to penicillin but quite sensitive to bacteriophage. Subsequent to these two communications, additional reports of cures of enterococcal endocarditis with penicillin alone or together with renal tubular blocking agents have appeared. In these cases, total doses of penicillin varying from 12.5 to 1,852 million units and given for periods ranging from 28 to 66 days proved successful. Very high blood levels of penicillin, ranging up to 100 units or more per milliliter of medium, were obtained often in these cases.

As has been previously noted, almost all enterococci are resistant to the action of penicillin. Mathews and McCoy and Mason have reported two cases of enterococcal endocarditis in which enterococci unusually sensitive to penicillin were isolated. In a recent report Baker and Pilkington cited a case of enterococcal endocarditis in which the infection was not controlled by what appeared to be adequate combined penicillin-streptomycin or chlortetracycline (Aureomycin) therapy but was controlled by large daily doses of penicillin (32 million units) and probenecid (4 Gm.) for a 59-day period.

Streptomycin

The role of streptomycin in the therapy of bacterial endocarditis has been reviewed by Hunter and by Wallach and Pomerantz. Streptomycin used alone was found to be of little value except occasionally against a streptomycin-sensitive organism. The results of therapy of enterococcal endocarditis with this antibiotic were uniformly poor. In four cases of such infection reported by Hunter streptomycin, used alone, failed. Cure was obtained in one of these cases with combined penicillin-streptomycin therapy.

Additional reports on the value of this drug in enterococcal endocarditis have appeared. In one of four cases reported by Sirota and colleagues, streptomycin gave only a temporary remission. Apparently, only two of the patients included in these reports were cured with streptomycin alone. In two other cases failure with streptomycin was followed by cure with penicillin and caronamide.

The value of streptomycin in enterococcal endocarditis lies in its supportive role to penicillin. In vitro and in vivo studies indicate that streptomycin synergizes the bactericidal action of penicillin so that endocarditis caused by penicillin-resistant enterococci is controlled in almost all cases. Further comments regarding the combined use of these two antibiotics will be made below.

Broad-Spectrum Antibiotics

Chlortetracycline. The value of chlortetracycline in the therapy of bacterial endocarditis has been reviewed recently by Friedberg and by Kane and Finn. In 2 of the 11 cases presented by Friedberg the isolated organism was an enterococcus. Chlortetracycline alone in adequate doses for an appropriate period did not control the enterococcal infection.
ditional reports, \textsuperscript{31} 57-63 most of the therapeutic results were said to be unfavorable even though only small amounts of the drug were required to inhibit the organism in vitro. Cures of one or two patients with enterococcal endocarditis have, however, been recorded by Long and co-workers,\textsuperscript{68} by Harvey and co-workers\textsuperscript{63} and by Roberts and Goldberg.\textsuperscript{60} The case reported by Glasser and Smith\textsuperscript{59} illustrates the usual response obtained with the drug. In three of the cases of enterococcal endocarditis reported by Finlay and Kane,\textsuperscript{56} 62 this drug was of no value in controlling the infection.

\textit{Oxytetracycline}. Few reports on the value of oxytetracycline in enterococcal endocarditis have appeared.\textsuperscript{63-66} Since this antibiotic and chlortetracycline parallel each other closely with regard to chemical structure, pharmacologic properties, bacteriostatic end points and actual therapy of patients, it would be supposed that their effects in endocarditis caused by enterococci would be similar. In the few cases in which oxytetracycline has been tried, the infection was arrested in only one instance.\textsuperscript{64} Oxytetracycline combined with dihydrostreptomycin was unsuccessful in two cases reported by one of us.\textsuperscript{65}

\textit{Chloramphenicol}. The use of chloramphenicol in enterococcal endocarditis is mentioned briefly in several communications.\textsuperscript{55, 56, 62, 63, 67} In most instances the drug was used in combination with other antibiotics. There have been no reports of success in the arrest of enterococcal endocarditis with this antibiotic alone. It seems to be of little or no value in this infection.

\textit{Erythromycin and Carboxymycin}

It was hoped that two recently introduced antibiotics with a penicillin-like spectrum, erythromycin and carboxymycin,\textsuperscript{69-72} would prove useful in the therapy of bacterial endocarditis. To date, only a few reports on this point have appeared.\textsuperscript{70, 72-75}

The status of erythromycin in the therapy of endocarditis has been presented in another publication.\textsuperscript{73} One of these patients had relapsing enterococcal endocarditis. Erythromycin in doses of 0.5 Gm. was given every six hours for a month. Symptomatic improvement occurred but the blood cultures never became negative. The drug merely suppressed growth of the organisms so that cultures became positive only after periods as long as 15 days. In vitro studies of these organisms did not reveal any synergistic bactericidal effects when erythromycin and penicillin were used together.

Carboxymycin in adequate dosage was found to be ineffective in two cases of enterococcal endocarditis.\textsuperscript{72} Since erythromycin and carboxymycin tend to behave like bacteriostatic antibiotics both in vitro and in the treatment of endocarditis\textsuperscript{56, 77} and since most enterococci are relatively insensitive to them, it is unlikely that these drugs either alone or in combination with other antibiotics will prove to be of much value in enterococcal endocarditis.

\textit{Penicillin-Streptomycin Combination}

Since Hunter's\textsuperscript{59} first communication concerning the cure of a patient of enterococcal endocarditis with a combination of penicillin and streptomycin, an increasing number of reports have attested to the value of this antibiotic combination for penicillin-resistant streptococcal valvular infections.\textsuperscript{17, 18, 78, 79} These reports on patients actually treated confirmed the in vitro studies of Hunter\textsuperscript{59}, Jawetz and Gunnison\textsuperscript{54} and Spicer.\textsuperscript{56} These workers had demonstrated that penicillin and streptomycin had a definite synergistic bactericidal action on the enterococcus when they were used together in the test tube. The results of in vitro studies have enabled the clinician to obtain as high a percentage of cures in cases of penicillin-resistant enterococcal endocarditis as has been obtained in cases of penicillin-sensitive endocarditis. Robbins and Tompsett\textsuperscript{15} were able to control the valvular infection in seven of nine patients to whom adequate combined therapy had been given. Hunter in more recent communications\textsuperscript{72, 78} has said that 10 million units of penicillin and 2 Gm. of streptomycin should be given daily for six weeks in order to achieve a maximum of cures.

To date, only the antibiotic combinations of penicillin-streptomycin and penicillin-bacitracin\textsuperscript{81} have been successful in controlling enterococcal endocarditis. The antibiotic
combinations of oxytetracycline-dihydrostreptomycin, 64 chlortetracycline-streptomycin, 39 penicillin-chlortetracycline, 65 chlortetracyclinechloramphenicol, 83 and penicillin-chloramphenicol 85 have failed.

Therapy in Present Series of Cases

The significant clinical features and the data concerning the treatment of the patients reported herein are given in tables 7 and 8. In table 7 are listed the patients who were treated with penicillin. Most of the 11 patients treated unsuccessfully were seen during the first half-decade (1944 to 1948 inclusive) of antibiotic therapy for bacterial endocarditis, when the efficacy of penicillin for this purpose was being determined. The daily doses ranged from 0.1 to 15 million units and the duration of treatment was from 10 to 126 days. These patients received what would now be considered inadequate therapy. Several, however, were treated with fairly large daily doses of penicillin and for long periods without success. In the seven cases in which treatment was successful the daily doses of penicillin ranged from 2 to 12 million units, and the duration of therapy ranged from 17 to 63 days.

A study of the data in this series leads to the conclusion that there is little correlation between the in vitro sensitivity of the isolated organisms and the effectiveness of therapy given. The results of the in vitro sensitivity tests were roughly similar in the two series. Unfortunately, bactericidal end points were determined in only one instance.

Of the 33 patients in this series, 31 received antibiotic therapy; in the others, the diagnosis was made only at postmortem examination. One patient (case 10) had marked hypersensitivity to penicillin and hence could not be treated with this drug. Dihydrostreptomycin alone was given in doses beginning with 0.25 Gm. and gradually increasing to 4 Gm. per day. Therapy was given for three weeks; the patient became afebrile and the sedimentation rate dropped from 67 to 12 mm. Nevertheless, the patient deteriorated progressively and finally died. In all, 16 of the 33 patients (48 per cent) died. However, only two of the last 14 patients (14 per cent) given appropriate combined therapy (12 patients) or penicillin alone (two patients) succumbed to their disease; these two deaths were from cerebral embolism and massive cerebral infarction.

Seven of 31 patients given antibiotic therapy were cured with penicillin alone (22 per cent). Eleven of 18 patients treated with penicillin alone represented failures (61 per cent) (table 7). Table 8 presents the pertinent data on the 14 patients given combined penicillin-dihydrostreptomycin therapy. Control of the infection was achieved in 12 of the 14 patients given adequate antibiotic therapy (86 per cent); in 10 patients this was achieved with combined therapy, and in the two others with penicillin alone. Two patients died of massive cerebral hemorrhage and cerebral embolism respectively 9 and 17 days after antibiotic therapy was begun.

Ten of the 12 cured patients were given combined therapy, 6 million to 50 million units of aqueous crystalline penicillin per day by continuous intravenous drip for 4 to 10 weeks, and dihydrostreptomycin sulfate, 1 to 2 Gm. per day, was given for a similar period. In another patient (case 21), combined penicillin-dihydrostreptomycin therapy was given for 10 days and then penicillin alone (7 million units per day) was given for 60 more days. In the latter instance, bactericidal tests indicated antagonism between penicillin and dihydrostreptomycin with a grown-out seven-hour culture and a lack of additive or synergistic bactericidal effect with an actively growing two-hour culture under the conditions of the tests. The patient who was given combined therapy for only three weeks (case 20) had a relapse shortly after arriving home. Cure was achieved with 12 million units of penicillin a day for a period of eight weeks (table 7).

Relapses occurred in 5 of the 12 living patients; all five were retreated successfully (table 8). Four of the five patients were given what now is considered inadequate therapy. In the fifth patient, adequate dosage of the combined antibiotics for five and one half weeks was ineffective. One patient (case 20) was treated for only three weeks, since he insisted on going home. The infection was of one
Table 7.—Enterococcal Endocarditis Treated With Penicillin Alone

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, Sex</th>
<th>Type of Heart Disease*</th>
<th>Penicillin Sensitivity</th>
<th>Penicillin Therapy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily dose</td>
<td>Days treated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1§</td>
<td>52 M</td>
<td>RHD; apical syst. M</td>
<td>—</td>
<td>.1-.2</td>
<td>31</td>
</tr>
<tr>
<td>2§</td>
<td>48 M</td>
<td>Apical syst. M</td>
<td>1.6</td>
<td>.16-4.0</td>
<td>45</td>
</tr>
<tr>
<td>4§</td>
<td>62 M</td>
<td>Aortic syst. &amp; dias. M</td>
<td>10.0</td>
<td>0.08-0.1</td>
<td>20</td>
</tr>
<tr>
<td>5§</td>
<td>73 M</td>
<td>Apical syst. M</td>
<td>&gt;25.0</td>
<td>0.3-5.4</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>55 M</td>
<td>Apical syst. M</td>
<td>1.6-6.0</td>
<td>6.0-10.0</td>
<td>126</td>
</tr>
<tr>
<td>7§</td>
<td>63 M</td>
<td>RHD; aortic syst. M</td>
<td>3.2</td>
<td>0.3-4.0</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>25 F</td>
<td>RHD; apical syst. M</td>
<td>1.6</td>
<td>5-20</td>
<td>49</td>
</tr>
<tr>
<td>9</td>
<td>27 F</td>
<td>RHD; aortic &amp; apical M</td>
<td>&gt;3.2</td>
<td>15</td>
<td>56</td>
</tr>
<tr>
<td>10</td>
<td>57 M</td>
<td>RHD; syst. &amp; dias. aortic M</td>
<td>3.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>62 M</td>
<td>Aortic dias. M</td>
<td>3.2</td>
<td>6</td>
<td>21</td>
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</table>
Table 7.—(Continued)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, Sex</th>
<th>Type of Heart Disease*</th>
<th>Penicillin Sensitivity†</th>
<th>Penicillin Therapy†</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily dose</td>
<td>Days treated</td>
</tr>
<tr>
<td>12</td>
<td>63 M</td>
<td>Apical sys. M</td>
<td></td>
<td>1.6</td>
<td>1.2-7</td>
</tr>
<tr>
<td>13</td>
<td>77 M</td>
<td>Apical sys. &amp; dias. M</td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>53 F</td>
<td>Apical sys. M</td>
<td></td>
<td></td>
<td>10.0</td>
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</tbody>
</table>

TREATMENT CURES

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, Sex</th>
<th>Type of Heart Disease*</th>
<th>Penicillin Sensitivity†</th>
<th>Penicillin Therapy†</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily dose</td>
<td>Days treated</td>
</tr>
<tr>
<td>15</td>
<td>40 F</td>
<td>RHD; apical sys. M</td>
<td></td>
<td></td>
<td>&gt;10.0</td>
</tr>
<tr>
<td>17</td>
<td>63 M</td>
<td>Apical sys. M</td>
<td></td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>19</td>
<td>67 M</td>
<td>Apical sys. M</td>
<td></td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>20</td>
<td>75 M</td>
<td>HHD &amp; RHD; aortic sys. M</td>
<td></td>
<td>&gt;3.2</td>
<td>12</td>
</tr>
<tr>
<td>21</td>
<td>33 F</td>
<td>Apical sys. M</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Abbreviations: CHD = congenital heart disease; HD = heart disease; HHD = hypertensive heart disease; IM = intramuscular; IV = intravenous; M = heart murmur; RF = rheumatic fever; RHD = rheumatic heart disease; SBE = subacute bacterial endocarditis; sys. and dias. = systolic and diastolic; TUR = transurethral prostatic resection; VSD = ventricular septal defect.
† Penicillin in units per milliliter of medium.
‡ Dosage in millions of units.
§ Reported previously by Merritt.29
|| No history of rheumatic fever, heart disease or heart murmur before treatment at Mayo Clinic.
¶ Reported previously by Hagedorn and Scheifley.41

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Table 8.—Enterococcal Endocarditis Treated With a Combination of Penicillin and Dihydrostreptomycin

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Type of Heart Disease</th>
<th>Penicillin Sensitivity</th>
<th>Penicillin Therapy</th>
<th>Dihydrostreptomycin Therapy</th>
<th>Follow-Up</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily dose</td>
<td>Days treated</td>
<td>Total dose</td>
<td>Daily dose</td>
<td>Days treated</td>
</tr>
<tr>
<td>20</td>
<td>75</td>
<td>M</td>
<td>HHD &amp; RHD; aortic sys. &amp; dias. M</td>
<td>&gt;3.2 0.6-6 12.5 56</td>
<td>66.5 672</td>
<td>1-2 22 34.5</td>
<td>1 mo. 2 yr.</td>
<td>Failure with 3 wk. combined therapy. Further treatment refused after 3 wk. Relapse at home 1 mo. later. Cure with Pen. alone</td>
</tr>
<tr>
<td>21</td>
<td>33</td>
<td>F</td>
<td>Apical syst. M§</td>
<td>3.2 6.0 28 143</td>
<td>1 10 10</td>
<td>3 yr.</td>
<td>Combined treatment changed to Pen. Well for 4 mo. after 1st course Pen.; then reinfection? Second course: no response to oxytetracycline-DHS for 1 wk.; Pen.-DHS given only 10 da.; bactericidal tests showed Pen. more effective alone; blood Pen. levels ranged from 2-32 units (average 11) throughout treatment; probenecid given. Cure with Pen. alone</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>48</td>
<td>F</td>
<td>RHD. Aur. fib. &amp; apical sys. &amp; dias. M</td>
<td>3.2 10 42 420</td>
<td>1-2 42 55</td>
<td>&gt;1 yr.</td>
<td>Cure. Probenecid caused severe heartburn, nausea, abdominal pain. Treated for cong. heart failure 6 mo. before therapy. Pen. blood levels averaged 16 units throughout treatment</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>54</td>
<td>M</td>
<td>RHD? Aortic syst. M</td>
<td>&gt;3.2 10 38 380</td>
<td>1-2 38 52</td>
<td>2 yr.</td>
<td>Cure. Uncomplicated recovery</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>35</td>
<td>M</td>
<td>Aortic Sys. &amp; dias. M§</td>
<td>3.2 15 41 615</td>
<td>1-2 27 39</td>
<td>2½ yr.</td>
<td>Cure. Uneventful recovery. Home doctor could detect no M before admission here</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>25</td>
<td>F</td>
<td>Apical syst. M§</td>
<td>&gt;3.2 10 28 280</td>
<td>1-2 28 38</td>
<td>2 yr.</td>
<td>Cure. Uneventful recovery with 1 mo. of therapy—organism resistant to &gt;3.2 units of Pen.</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>62</td>
<td>M</td>
<td>RHD? Aortic syst. M§</td>
<td>3.2 5-6 28 156</td>
<td>1 28 28</td>
<td>1½ yr.</td>
<td>Cure. Failure with oxytetracycline-DHS initially and with 1st course of Pen.-DHS for 4 wk.; uneventful cure with 2nd course</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>38</td>
<td>F</td>
<td>Apical syst. M§</td>
<td>5.0 10-20 17 200</td>
<td>2 17 34</td>
<td>—</td>
<td>Death on 17th day of therapy as result of cerebral embolism. Temp. fell to normal day after treatment started. Subsequent cultures neg. Probenecid not tolerated</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>68</td>
<td>M</td>
<td>RHD. Aortic syst. M</td>
<td>5.0 10-20 42 580</td>
<td>1-2 42 81</td>
<td>1 yr.</td>
<td>Cure. Uneventful recovery. Pen. increased from 10 to 20 million units when bactericidal tests indicated little killing with smaller Pen. dose &amp; DHS. Probenecid given</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>30</td>
<td>F</td>
<td>RHD with aortic syst. &amp; dias. M</td>
<td>5.0 10-20 28 280</td>
<td>1-2 28 55</td>
<td>1 mo.</td>
<td>Cure. Organism not killed by 100 units of Pen. or 100 mg of DHS. 50 million units of Pen. given by IV drip for last 40 da. Probenecid not used—caused severe epigastric burning, nausea, anorexia</td>
<td></td>
</tr>
</tbody>
</table>

*§: See table 7 for definitions.
§: No history of rheumatic fever, heart disease or heart murmur before treatment at Mayo Clinic.
†: Dosage in grams.
‡: Relapse after first course of therapy.
week's duration, and the patient was afebrile and the cultures were free of growth very soon after the institution of therapy. Still, relapse occurred within a month; cure was achieved with 12 million units of penicillin daily for eight weeks. In one case (case 21) the first course of therapy was with penicillin alone. The patient did well for four months. After symptoms recurred, the in vitro sensitivity of the isolated organism was two dilutions less than that of the organism obtained initially. It would seem that the cure of this apparent reinfection was achieved by penicillin alone, since during the second course of therapy only 1 Gm. of streptomyein a day was given for 10 days together with penicillin. In the remaining three patients who had relapses, penicillin in doses of 10 to 50 million units and streptomyein in doses of 1 to 2 Gm. per day for a period of 6 to 10 weeks were needed to effect cures of these infections. Probenecid was apparently helpful in one of these five patients (case 30).

Case Reports

Pertinent problems in the antibiotic management of enterococcal endocarditis are illustrated by the following four cases.

Case 30. A 50 year old man was first admitted with a four-month history of low-grade fever (temperature up to 101°F.), occipital headaches, arthralgias, malaise, weakness, intermittent episodes of neck pain which extended into the right shoulder, and a 30-pound loss of weight. The onset had been sudden with headache, chill and rise in the temperature to 104°F. The positive findings were: rheumatic heart disease with an enlarged heart and aortic and mitral valvular involvement, the predominant lesion being aortic insufficiency; clubbing of the fingers; Osler's nodes; mild anemia; sedimentation rate of 108 mm. in one hour; minimal microhematuria; and three blood cultures positive for enterococci. In vitro sensitivity tests revealed the bacteriostatic end point to be 1.6 units of penicillin and more than 25 micrograms of dihydrostreptomycin. The patient was given 10 million units of aqueous crystalline penicillin daily by continuous intravenous drip and 2 Gm. of dihydrostreptomycin per day divided into two doses. Therapy was continued for 38 days. Total doses of 380 million units of penicillin and 65 Gm. of dihydrostreptomycin were given, and average levels of 8 units of penicillin per milliliter of blood were obtained. Relapse occurred in three months. At this time the patient was asymptomatic; the routine blood cultures were negative after two days of incubation and the organisms grew out in brain broth only after 15 days of incubation. The patient had been afebrile on admission and remained so through the additional 50 days of the second course of therapy. In vitro sensitivity tests disclosed a bacteriostatic end point at a concentration of 3.2 unit of penicillin per milliliter of medium. Treatment consisted of giving 15 million units of penicillin per day by continuous intravenous drip for 50 days, 2 Gm. of dihydrostreptomycin per day for 39 days and 1 Gm. per day for 11 days, and 2 Gm. of probenecid per day for 40 days and 4 Gm. per day for 10 days. Total doses were 750 million units of penicillin, 89 Gm. of dihydrostreptomycin and 120 Gm. of probenecid. An average concentration of 16 units of penicillin per milliliter of blood was obtained. Ten blood cultures during and after therapy were negative. The patient relapsed one and one half months after completion of the second course of therapy. The third course was with erythromycin as reported elsewhere. Symptomatic response occurred within a month but this new antibiotic served only to suppress the organisms. The blood cultures remained positive but required 12 to 15 days of incubation for the organisms to become evident. The fourth course of treatment consisted of 30 million units of penicillin per day by continuous intravenous drip, 2 Gm. of dihydrostreptomycin per day (1 Gm. every 12 hours), and 2 Gm. of probenecid per day in divided doses, all for a 70-day period. The patient was dismissed and was advised to take 2 million units of procaine penicillin and 0.5 Gm. of dihydrostreptomycin every 12 hours for an additional 30 days. Hence, total doses of 2,160 million units of penicillin, 170 Gm. of dihydrostreptomycin and 140 Gm. of probenecid were given for this fourth course. For the last eight weeks of the hospital course of therapy, the blood concentration of penicillin ranged from 32 to 128 units per milliliter and averaged 64 units almost constantly. This was 10 times the in vitro sensitivity value (6.2 units per milliliter) which had been determined before the fourth course of treatment was started. Repeated cultures during therapy were negative. The period of therapy was marred only by five brief febrile episodes resulting from phlebitis caused by the plastic needle (temperature going as high as 102°F.). Audiometric and caloric tests at the close of the 70-day course of therapy gave normal results. On the twenty-ninth day of the follow-up maintenance therapy, the patient experienced slight positional vertigo. Re-examination indicated that hearing was normal; a very slight impairment of the caloric responses was noted. The subjective and objective evidence of the dihydrostreptomycin toxicity disappeared after several weeks. When last seen the patient had been completely well for 18 months without change in heart size or auscultatory findings.
The total doses for the four courses of therapy were: penicillin 3,290 million units, dihydrostreptomycin 344 Gm., probenecid 332 Gm. and erythromycin 60 Gm.

The enterococcus from this patient was subjected to extensive in vitro studies in which more than 60 bactericidal tests with seven different antibiotics were carried out with combinations of two and three of these agents. The best combination that was relatively nontoxic on systemic administration was that of penicillin and dihydrostreptomycin, 2.5 units of penicillin plus 2.5 micrograms of dihydrostreptomycin per milliliter being totally bactericidal. Other active in vitro combinations giving a total bactericidal effect were: 2.5 micrograms of dihydrostreptomycin plus 0.312 unit of bacitracin per milliliter; 2.5 micrograms of neomycin plus 0.156 unit of bacitracin per milliliter; 1 microgram of oxytetracycline plus 1 microgram of dihydrostreptomycin plus 0.078 unit of bacitracin per milliliter; and 1 unit of penicillin plus 1 microgram of neomycin plus 0.312 microgram of oxytetracycline per milliliter.

The concentration of antibiotics required for complete killing were as follows*: penicillin and bacitracin, more than 10 units per milliliter; and streptomycin, erythromycin, oxytetracycline, neomycin and chloramphenicol, each more than 10 micrograms per milliliter.

Following our preliminary experiences with combined therapy, particularly in this case, we decided to gauge the effectiveness of our therapy in future cases with in vitro bactericidal tests employing the patient’s serum against his organisms. Our last three patients were handled in this way. In each instance, the in vitro studies performed during treatment with 10 to 15 million units of penicillin by continuous intravenous drip and 2 Gm. of dihydrostreptomycin per day led to a more effective regimen of therapy and two of these three patients were cured. The other patient died, after 20 months of active valvular disease and on the seventeenth day of therapy, from cerebral embolism and massive cerebral infarction. Resumes of these cases follow.

Case 31. A woman, 38 years of age, was admitted with a 20-month history of active enterococcal endocarditis. She had had two months of combined therapy with penicillin and oxytetracycline without cure. Her symptoms consisted of intermittent chills and a temperature ranging up to 104°F., weakness, anorexia, and a 40-pound loss of weight. Sixteen months prior to admission, she had had a cerebrovascular lesion with hemiplegia. This cleared up for the most part. Nine months before admission she had had a myotic aneurysm in the right forearm which had been excised. Findings consisted of a loud apical systolic murmur, clubbing of the fingers, splenomegaly, moderate anemia, phagocytic reticuloendothelial cells in the blood smear, elevation of the sedimentation rate, and blood cultures that were positive for enterococci. Initial in vitro sensitivity tests revealed that the organisms were inhibited by 5 to 10 units of penicillin and 0.39 microgram of oxytetracycline per milliliter. The patient was given 10 million units of aqueous crystalline penicillin by continuous intravenous drip and 2 Gm. of dihydrostreptomycin per day. Bioassays of the blood for penicillin and dihydrostreptomycin revealed values of 8 units and 64 micrograms per milliliter respectively. In vitro bactericidal tests performed with the patient's serum and organisms disclosed total bactericidal effect only in the undiluted serum and inhibition in a dilution of 1:2. Although the patient was afebrile and the cultures were free of growth, it was felt that the penicillin dosage was inadequate and hence this was increased to 20 million units per day. Bactericidal tests repeated on this altered combined regimen showed inhibition of growth at a dilution of 1:16 and a total bactericidal effect at a dilution of 1:8. With this degree of killing effect on the patient’s organisms, it was felt that the antibiotic program was adequate and it was hoped that cure would be achieved eventually. However, three days after this altered program was begun the patient died from cerebral embolism and massive cerebral infarction.

Case 32. A 68 year old man gave a two-year history of gradually failing health, low-grade fever (temperature up to 101°F.), night sweats, anorexia, loss of weight, and intermittent dysuria and hema-turia. The findings consisted of a moderate aortic systolic and a minimal aortic diastolic murmur, clubbing of the fingers, splenomegaly, elevation of the sedimentation rate, and enterococci in the blood cultures. In vitro sensitivity tests indicated that 5 units of penicillin, 1.5 micrograms of oxytetracycline and 1.6 micrograms of erythromycin per milliliter inhibited the organisms. The patient was started on treatment with 10 million units of aqueous crystalline penicillin-G by intravenous drip and 2 Gm. of dihydrostreptomycin per day. This was given for 21 days. Bioassays of the blood for penicillin and dihydrostreptomycin gave levels of 8 units and 16 micrograms respectively. The dose of penicillin was increased to 15 million units. The antibiotic assays remained the same on the new regimen, and this dose was given for 10 days before a change to 20 million units of penicillin per day was made. Bactericidal tests with the patient’s serum while he was getting this last dosage of penicillin revealed

* Other combinations of antibiotics with erythromycin and giving total bactericidal effect are reported elsewhere.74
bacteriostasis in a dilution of 1:16 and total bactericidal effect in a dilution of 1:8. The dihydrostreptomycin had been replaced by a combination of dihydrostreptomycin and streptomycin and these had been continued in doses of 2 Gm. per day. Twenty million units of penicillin per day was given for 11 more days, and the total duration of therapy was 6 weeks. Probenecid in a daily dose of 2 Gm. was given for the last four weeks of treatment. Total doses of 580 million units of penicillin, 81 Gm. of streptomycin-dihydrostreptomycin and 56 Gm. of probenecid were given. No eighth-nerve toxicity was detected. Follow-up at the end of one year indicated that the patient was well.

Case 83. A 30 year old woman was admitted with a three-month history of joint pains, chills and fever, the temperature going as high as 104 F. One week before the sudden onset of chills and fever, she had had a hemmorhoidectomy. The positive findings were as follows: rheumatic heart disease with cardiac enlargement, aortic stenosis and insufficiency; mild anemia; leukocytosis; elevated sedimentation rate; and four blood cultures positive for enterococci. In vitro sensitivity tests revealed inhibition of the organism by 5 units of penicillin, 1.6 micrograms of erythromycin, and more than 50 micrograms of dihydrostreptomycin.

The patient was given 10 million units of aqueous crystalline penicillin-G by continuous intravenous drip and 2 Gm. of dihydrostreptomycin divided into two doses per day. The temperature fell to normal within 48 hours and remained so until the third week of therapy when the temperature spiked to 104 F. Recurrent spikes to 104 F. occurred daily for six days during therapy. The administration of penicillin was discontinued and the temperature was normal in 48 hours. Total doses of 280 million units of penicillin and 56 Gm. of dihydrostreptomycin were given over a 28-day period. Bactericidal tests with the patient's own serum drawn one hour before and one hour after the 1 Gm. dose of dihydrostreptomycin and employed against the patient's organism gave a total bactericidal effect only in the undiluted serum.

The patient remained well for one month when chills, temperatures up to 103 F., and positive blood cultures recurred. The temperature, however, was normal on admission and remained normal throughout the period of treatment. In vitro sensitivity tests revealed no change from the previous findings. Treatment with 15 million units of penicillin by continuous intravenous drip and 2 Gm. of dihydrostreptomycin was started and continued for 10 days when the dose of penicillin was increased to 30 million units per day. This dose was given for three weeks. Finally, the penicillin was increased to 50 million units per day. The dihydrostreptomycin was replaced by combined streptomycin-dihydrostreptomycin in the same dosage during the first week and this treatment was given for an eight-week period. Total dosages of 2,780 million units of penicillin and 126 Gm. of combined streptomycin-dihydrostreptomycin were given over the 10-week period of treatment. Probenecid could not be tolerated by the patient; the drug caused severe epigastric distress and heartburn, loss of appetite, and nausea and vomiting. The patient had remained well when last heard from six months later.

Therapy in this case was guided by numerous in vitro bactericidal tests in which the patient's serum containing the antibiotics was employed against the patient's organism. Although in vitro sensitivity studies revealed a bacteriostatic end point of 5 units of penicillin, a bactericidal test indicated that the end point was more than 100 units for complete killing of the organisms. This perhaps explains why the first course of therapy was unsuccessful, when, with the antibiotic dosage employed, a total bactericidal effect was obtained only in the undiluted serum.

Probenecid was used in six cases. It was of apparent value in elevating the blood level penicillin in three of these cases. In the other three, use of the drug had to be discontinued after several days because of severe epigastric distress and heartburn, nausea and vomiting, and loss of appetite. In each of these three instances, the drug was given again after several days of freedom from symptoms; the same severe gastrointestinal distress recurred. The drug was given orally in doses of 0.5 Gm. every six hours.

**Comment**

Value of Combined Penicillin-Streptomycin Therapy. The clinical and experimental data presented by Hunter and Jawetz and Gunison and Robbins and Tompsett have indicated that penicillin and streptomycin in combination are the best antibiotic pair for the cure of enterococcal endocarditis in most instances. The data obtained from our study and from a review of the pertinent literature are in agreement with this concept. In vitro bactericidal tests with five of the strains of enterococci isolated in our cases indicated that the addition of bacitracin and erythromycin or other antibiotics to this combination is of little added value. Recent studies with the newer antibiotic, erythromycin, indicate that it is
essentially a bacteriostatic agent for most organisms and is bactericidal only for organisms very sensitive to its action\textsuperscript{76, 77}; in combination it behaves very much like the broad-spectrum antibiotics. Bacitracin, on the other hand, is a predominantly bactericidal antibiotic and has been of value in the therapy of penicillin-resistant streptococcal and enterococcal endocarditis.

Inasmuch as the bactericidal antibiotics, penicillin and streptomycin, in combination, are very effective in the treatment of enterococcal endocarditis, the broad-spectrum antibiotics of the tetracycline group and chloramphenicol, erythromycin and carbenicillin should not be used in the therapy of enterococcal endocarditis except in those rare instances in which they may enter into synergistic combination with a bactericidal antibiotic or pairs of antibiotics.

Hunter\textsuperscript{22} has said that high doses of penicillin and streptomycin, 10 to 20 million units and 1 to 2 Gm. respectively per day, given in combination for a six-week period will usually cure most patients who have enterococcal endocarditis. He has stated succinctly the problem of the therapy of this valvular infection: “Ideally, the determination of the optimum treatment in penicillin-resistant infections should be based upon studies of the infecting organism recovered from each patient and these studies should include procedures which measure the bactericidal effects of the antibiotic tested.” With this concept, we agree completely. Inasmuch as most enterococci are resistant to penicillin and since there is no way of knowing which patient with enterococcal endocarditis will respond to the above-mentioned program of therapy, it is perhaps wise to study each strain of enterococcus isolated from each patient. Each patient treated for enterococcal endocarditis represents a tremendous investment in time and money and work by a trained team of medical personnel. Since life may depend on a cure of the valvular infection with the first course of therapy, it would seem mandatory that therapy in these patients be guided by appropriate bacteriologic studies.

Value of Bactericidal Tests. Because of our experiences in a case of relapsing enterococcal endocarditis, we have attempted to correlate our therapeutic program in the last three cases with the results obtained from bactericidal tests employing the patient’s organism and his serum containing the given antibiotics (cases 31, 32 and 33). In each instance, the daily dosage of penicillin was adjusted so that the penicillin-dihydrostreptomycin combination provided a bactericidal effect against the patient’s infecting organism. Doses of 20, 20 and 30 million units of penicillin per day respectively, by continuous intravenous drip for these three patients together with 1 Gm. of dihydrostreptomycin every 12 hours gave a total bactericidal effect in dilutions of the patient’s serum up to 1:8. We do not feel that this degree of bactericidal effect need be obtained in all treated patients. Adequate daily dosage of penicillin together with 2 Gm. of dihydrostreptomycin per day to provide a total bactericidal effect in the undiluted and the 1:2 dilution of serum should be curative in almost all instances when given for a six-week period. Too few patients with enterococcal endocarditis have been studied and treated in this manner to permit any final conclusions; however, it is quite possible that with a high degree of bactericidal effect during the entire course of therapy it may be possible to shorten the period of treatment for this type of valvular infection. Only further clinical trials with such bactericidal tests can indicate the optimal therapy for these patients.

Study of the results of penicillin therapy in this series of cases indicates that there is little correlation between the results of the in vitro inhibition tests and the outcome of treatment. It is unfortunate that the bactericidal end points were not obtained for all of the tested strains of enterococci as were the bacteriostatic end points. These data would have given us objective evidence of this lack of correlation. However, other studies\textsuperscript{82} have indicated the marked differences between bacteriostatic and bactericidal end points for different strains of enterococci when penicillin is used. These differences undoubtedly account for failures of therapy when apparently adequate doses of penicillin are used and for instances of relapsing enterococcal endocarditis. This informa-
Antibiotic therapy of bacterial endocarditis

Antibiotic therapy of bacterial endocarditis necessitates the study, by means of bactericidal tests, of each strain isolated from patients with enterococcal endocarditis.

Current Program of Therapy. Use of Penicillin.—Our policy at present is to begin therapy, after the patient has been studied thoroughly, with 10 million units of aqueous penicillin G by continuous drip per day through a plastic catheter. The next morning, the patient’s serum is obtained to study the bactericidal effect of penicillin alone. Then treatment with dihydrostreptomycin, 1 Gm. every 12 hours, is started and the following morning, one hour after the injection of dihydrostreptomycin, serum is obtained for study of the combined effect of the two antibiotics. If a total bactericidal effect is obtained with a 1:2 or 1:4 dilution of the serum, then therapy is continued with the same dose of penicillin. If not, the penicillin is increased 10 or 20 million units and the bactericidal tests repeated. A maximal number of cured enterococcal valvular infections will be obtained in this way if the dose of penicillin is increased in amounts of 10 to 20 million units until a total bactericidal effect is obtained in a dilution of 1:2 or 1:4, regardless of what bacteriostatic or bactericidal end points are obtained in the in vitro tests.

Use of Streptomycin.—Treatment is started with 2 Gm. of dihydrostreptomycin since this is a moderately effective dose and can be continued for a reasonable period before signs of eighth-nerve toxicity appear. In case 30, 2 Gm. of dihydrostreptomycin was given for 10 weeks without any eighth-nerve impairment. In the last three patients treated, distrycin (a combination of equal parts of streptomycin and dihydrostreptomycin) was used with success. In case 31, it was used for 17 days without signs of toxicity. In case 32, we gave dihydrostreptomycin for three weeks, then instead of decreasing the dose to 1 Gm. per day as had been our custom, we gave distrycin for another three weeks for a total of six weeks of therapy without toxicity. In case 33, 2 Gm. of dihydrostreptomycin per day for nine days and 2 Gm. of distrycin per day for an additional 54 days for a total of nine weeks of therapy induced only slight loss of hearing and slight vestibular damage. Since distrycin apparently can be given for longer periods than either streptomycin or dihydrostreptomycin alone before toxicity appears, it should be the drug of choice in the long-term treatment of these individuals. It is quite possible that most patients will be able to take combined streptomycin-dihydrostreptomycin in doses of 2 Gm. a day for six weeks with a minimum of eighth-nerve toxicity.

There is laboratory evidence to indicate that it would be preferable to continue the 2 Gm. dose of dihydrostreptomycin for the duration of therapy, barring any significant eighth-nerve damage. In vitro bactericidal tests in which the serum of patients receiving fixed amounts of penicillin but varying amounts of dihydrostreptomycin was tested against the same organism have shown that a greater bactericidal effect is obtained with the larger doses of dihydrostreptomycin. The decision to continue distrycin in the 2 Gm. dose for a full six weeks or longer will depend on the patient’s clinical response to therapy, the presence or absence of eighth-nerve symptoms and the results of audiometric and caloric tests.

Use of Probenecid.—Probenecid has been shown to increase the blood levels of penicillin significantly and is said to be of a low order of toxicity. In enterococcal endocarditis in which large doses of penicillin need to be given to effect a cure, the use of this drug may contribute significantly to the elevation of the blood levels of penicillin and thus reduce the cost of therapy. In case 30, in which penicillin was given at the rate of 30 million units daily for 10 weeks, the blood levels of this antibiotic were almost constantly 64 units when checked from week to week, and occasionally varied from 32 to 128 units when 2 Gm. of probenecid was given in divided doses four times per day. No toxicity appeared from the prolonged use of the drug in this case. However, in three of the six patients in whom this drug was used, such pronounced and persistently severe gastrointestinal irritation occurred that the use of this medication was precluded.

With the use of probenecid we have obtained penicillin levels of as high as 256 units per milliliter of blood when 50 million units has
been administered daily by continuous intravenous drip to a patient without renal insufficiency. With the ability to obtain such high levels of penicillin, the outlook for the patient with active enterococcal endocarditis should never be considered hopeless, barring death from incurable complications of the infection, even if many previous courses of therapy have been given. Additional courses of treatment, prefaced by appropriate bactericidal tests and with increasing doses of penicillin, together with probenecid, should be given these patients until a cure is achieved or death intervenes.

Prognosis. The average duration of the disease in these patients before antibiotic therapy was given at the clinic was six to seven months (range: one week to three years). This contrasts with active disease of three to four months' duration in penicillin-sensitive streptococcal endocarditis before effective therapy was given. Among the 15 patients seen in the last three years, there have been four deaths. In all four of these cases, active disease had been present 7 to 36 months.

Prognosis is definitely related to the duration of active endocarditis before adequate antibiotic therapy is given. With effective and curative bactericidal antibiotics for the treatment of enterococcal endocarditis and with early diagnosis, this valvular infection should be arrested in almost all cases, and mortality from active disease and its ensuing complications ought to be at a minimum. Within the short span of a decade, a seemingly hopeless infection carrying a high mortality rate even with penicillin therapy has been brought under control. The rate of cure of enterococcal endocarditis now approximates that obtained with endocarditis caused by the penicillin-sensitive "viridans" streptococci. The total cure rate for the group made up of our last 16 patients was 75 per cent; the corrected cure rate, calculated on the basis of 14 patients who were treated adequately for an appropriate interval, was 86 per cent.

Infections on Normal Valves. In this series it was possible to establish the nature of the underlying heart disease in about half of the cases. There was a definite history of rheumatic fever in 10 cases and a questionable history of this disease in another case. There was a history of a heart murmur before the onset of bacterial endocarditis in 18 cases. In the remaining 15 cases of the series, however, there was no history of rheumatic fever or chorea, heart disease or a heart murmur prior to the time the valvular infection was acquired. In at least 6 of these 15 cases, cardiac examinations by the home physician (three cases) and previous examinations at the Mayo Clinic (3 cases) had not revealed any evidence of heart disease or a heart murmur. In one patient (case 19) there apparently had been active endocarditis for some 10 months without a history of fever or chills before admission to the clinic; the patient was afebrile and without a heart murmur for the first two weeks of hospitalization, but then a heart murmur became obvious and led to the diagnosis of endocarditis.

In 16 cases it was felt that rheumatic heart disease was the determinative background for the valvular infection, and in two cases a congenital cardiac lesion was present. In nine of the cases, it was difficult to say whether the mitral or aortic valve was involved; loud systolic murmurs were heard over most of the left precordial area, these murmurs often being loudest at the apical area. While in most instances these murmurs would turn out to be the result of mitral valve involvement, on a statistical basis a few would probably be found to be aortic in origin.

In none of the six cases in which necropsy was performed was there a history of previous heart disease or heart murmur prior to the onset of the endocarditis. In one of these cases necropsy revealed a bicuspid aortic valve, while in the other five there was no apparent underlying cardiac lesion except the vegetations and changes attributable to bacterial endocarditis. These limited data suggest that in most of the 15 cases in which there was no previous history of heart disease or heart murmur the infection probably attacked previously normal valves. Support for this thesis is obtained by a review of the reported cases of enterococcal endocarditis in which necropsy was performed and a definite statement was made regarding the presence or absence of underlying
A_ntibiotic Prophylaxis. Half of the enterococcal infections in our series of cases resulted from transurethral operations or instrumentation. In half of these, in turn, there was no antecedent history of heart disease or heart murmur. Since enterococcal endocarditis may develop after urologic operations or instrumental manipulation in patients with or without heart murmurs, antibiotic prophylaxis assumes a very important role in their management. Since enhanced bactericidal effect is observed with combined penicillin-streptomycin for most strains of nonhemolytic streptococci, it would seem that this combination would constitute the best prophylactic therapy for patients who are to undergo urologic operations. We have employed 2 million units of penicillin and 2 Gm. of dihydrostreptomycin per day given in divided doses every 12 hours beginning the day before operation and continuing postoperatively until one day after the urethral catheter has been removed. One million units of penicillin and 1 Gm. of dihydrostreptomycin are administered one or two hours before the surgical procedure in order to give maximal antibiotic blood levels at the time of operation. We have not seen enterococcal or other forms of endocarditis develop when this antibiotic prophylactic program has been carried out preoperatively in patients with or without a heart murmur.

It has been recommended that larger doses of penicillin combined with 2 Gm. of dihydrostreptomycin be given prophylactically to patients who are to undergo transurethral prostatic resection.62 No evaluation of this antibiotic combination for prophylaxis before urologic operations has yet been published, but it would seem that the smaller doses recommended above would be adequate. Studies are under way to determine the value of antibiotic prophylaxis in connection with transurethral prostatic resection.69

S_ummary and C_onclusions

Thirty-three unselected cases of enterococcal endocarditis encountered during the first decade (January, 1944, through December, 1953) of antibiotic therapy for bacterial endocarditis are reported. Sixteen patients were seen in the last three years of this period. Thirty-one of the 33 patients were treated with antibiotics. Sixteen patients (48 per cent) died from their infection or from complications of active endocarditis. Seven of the treated patients (22 per cent) were cured with penicillin alone. Of the 16 patients seen in the last three years, four died, giving a cure rate of 75 per cent. However, two of these patients died without antibiotic therapy and two died from cerebral embolism while they were under adequate combined antibiotic therapy. Hence, the corrected cure rate was 86 per cent (12 of 14 patients). Ten of these patients were cured with combined penicillin-dihydrostreptomycin therapy and two with penicillin alone. The cure rate in enterococcal endocarditis now approximates that obtained in endocarditis caused by penicillin-sensitive streptococci.

Probenecid was helpful in three of six patients who received combined therapy. However, in three patients, severe epigastric distress and heartburn necessitated the stopping of treatment with the drug.

In vitro bactericidal tests performed with five strains of enterococci isolated from these patients indicated that penicillin and dihydrostreptomycin constituted the most effective pair of antibiotics for bactericidal effect. The addition of erythromycin or bacitracin to the penicillin-dihydrostreptomycin combination did not give any greater killing effect.

Therapy of enterococcal endocarditis should be individualized. The daily dosage of penicillin and the duration of therapy should be governed by the results of bactericidal tests in which the
patient's serum containing the antibiotics is employed against the patient's strain of enterococcus. A greater number of cures will be achieved in this way.

Inasmuch as enterococcal endocarditis follows urologic procedures quite frequently, it is recommended that all such patients with or without a heart murmur be given a million units of penicillin and 1 gm. of streptomycin or dihydrostreptomycin every 12 hours beginning the day before operation and continuing postoperatively until the day after the urethral catheter has been removed. We have not known enterococcal endocarditis to complicate urologic manipulation when this antibiotic prophylactic program has been followed.

The data indicate that in more than half the cases of enterococcal endocarditis the infection apparently attacked a normal heart valve. Further clinical and postmortem studies are needed to clarify this finding.

**SUMARIO Español**

Treinta y tres casos no seleccionados de endocarditis enterocócica encontrados durante la primera década (Enero, 1944 hasta Diciembre, 1953) de terapia antibiótica para la endocarditis bacterial son informados. Treinta y uno de los 33 pacientes fueron tratados con antibióticos. Diez y seis (48 por ciento) murieron de la infección o de complicaciones de la endocarditis activa. Siete de los pacientes tratados (22 por ciento) fueron curados con penicilina solamente. De los 16 pacientes vistos en los últimos tres años, 4 murieron, produciendo un promedio de 75 por ciento de curas. Sin embargo, 2 de estos pacientes murieron sin terapia antibiótica y 2 murieron de embolismo cerebral mientras estaban bajo terapia antibiótica combinada. Así es que el promedio de casos curados corregido fue de 86 por ciento (12 de 14 pacientes). Diez de estos pacientes fueron curados con combinaciones de penicilina-dihidrostreptomicina y 2 con penicilina solamente. El promedio de cura en la endocarditis enterocócica ahora se aproxima al de endocarditis causada por estreptococos penicilino-sensitivos.

La probencida fue provechosa en tres de seis pacientes que recibieron terapia combinada. Sin embargo, en tres pacientes, malestar severo epigástrico y pirosis impidió la continuación del uso de la droga. Pruebas bactericidas en vitro hechas en cinco cepas de enterococos aislados en estos pacientes indicaron que la penicilina y dihidrostreptomicina constituyeron el par de antibióticos más efectivo en cuanto a efecto bactericida. La adición de la eritromicina o bacitracina a la combinación de penicilina-dihidrostreptomicina no produjo un aumento en el efecto bactericida.

La terapia de la endocarditis enterocócica se debe de individualizar. La dosis diaria de penicilina y la duración de la terapia debe ser gobernada por los resultados de pruebas bactericidas en las cuales el suero del paciente conteniendo los antibióticos se emplea contra la cepa de enterococo. Un mayor número de curas se puede obtener de esta manera.

Como la endocarditis enterocócica frecuentemente complica procedimientos urológicos, se recomienda que todos estos pacientes con o sin soplos cardíacos se les administre un millón de unidades de penicilina y 1 gramo de estreptomicina o dihydrostreptomicina cada 12 horas empezando el día antes de la operación y continuando postoperatorivamente hasta el día después de haberse removido el catéter uretral. Nosotros no hemos tenido conocimiento de endocarditis enterocócica complicar procedimientos urológicos cuando este programa antibiótico profiláctico ha sido instituido.

Los datos indican que en más de la mitad de los casos de endocarditis enterocócica la infección aparentemente atacó una válvula cardíaca normal. Más estudios clínicos y de autopsia se necesitan para clarificar este hallazgo.

**REFERENCES**


ANTIBIOTIC THERAPY OF BACTERIAL ENDOCARDITIS


21 —: Unpublished data.


41 Hagedorn, A. B., and Scheifley, C. H.: Cardiac clinics. CX.X. Subacute bacterial endocarditis:


73 Geraci, J. E., and Martin, W. J.: Antibiotic therapy of bacterial endocarditis. V. Thera-