Antibiotic Therapy of Bacterial Endocarditis

IV. Successful Short-Term (Two Weeks) Combined Penicillin-Dihydrostreptomycin Therapy in Subacute Bacterial Endocarditis Caused by Penicillin-Sensitive Streptococci

By Joeseph E. Geraci, M.D., and William J. Martin, M.D.

Twenty-three patients with endocarditis caused by penicillin-sensitive streptococci have received short-term treatment with penicillin and dihydrostreptomycin, combined, for two weeks. Five of the patients died from complications of their infection; 18 were living and well, at the time of this study, after an average follow-up period of more than one year. No failures in treatment or relapses have occurred. It is concluded from the study of these patients that 1,000,000 units of aqueous procaine penicillin-G and 1 Gm. of dihydrostreptomycin sulfate given intramuscularly every 12 hours for two weeks is curative for this type of endocarditis.

A PRACTICAL form of short-term therapy for subacute bacterial endocarditis would be of considerable economic and psychologic value. The importance of such short-term therapy can be appreciated if one considers the expenditure of time and money involved currently in treating a patient afflicted with the disease mentioned. In a recent paper it was estimated that the average cost of present-day treatment of a private patient with subacute bacterial endocarditis, exclusive of physicians' fees, amounted to $601. If infectious endocarditis affects the breadwinner of the family so that he is without gainful employment for several months, the economic loss and consequent psychologic effects may be very distressing.

Current concepts of the therapy of bacterial endocarditis caused by penicillin-sensitive organisms indicate that the average daily dose of penicillin should be 1 to 2 million units and that treatment should be continued for four to eight weeks. In contradistinction to this conventional duration of treatment, "short-term therapy" applies to those instances in which treatment is not given beyond two weeks. King and colleagues treated eight patients with penicillin on an intensive short-term basis. Their eight patients, seven with streptococcal and one with staphylococcal subacute bacterial endocarditis caused by penicillin-sensitive organisms (sensitivity range of 0.02 to 0.3 unit with an average of 0.1 unit per cubic centimeter of medium), were treated with 14 million units of penicillin per day for 10 days. Only the patient with the most resistant organism (sensitive to 0.3 unit per cubic centimeter) was cured. In one other of their cases, therapy with both short-term massive daily doses and with long-term conventional daily doses of penicillin was without success. The organism responsible for the endocarditis was very sensitive one, and combined therapy with penicillin and streptomycin was eventually curative.

Hamburger and Stein treated 12 patients with 15 or 16 million units of penicillin given daily for two weeks. Two of these patients had a relapse within one month and were then successfully retreated with a second course. Hunter encouraged by in vitro studies on the synergistic bactericidal effects of combined penicillin and streptomycin, treated five patients who had penicillin-sensitive streptococcal endocarditis with this antibiotic combination for 10 days and obtained satisfactory results.

From Jan. 1, 1951, through January, 1953, a 25-month period, we have treated 23 consecutive patients who had penicillin-sensitive streptococcal endocarditis. In these 23 cases...
combinations of penicillin and dihydrostreptomycin were given for a period of two weeks.

**Material and Method**

The diagnosis of bacterial endocarditis in our 23 cases was established in each instance by an average of three (range two to six) positive blood cultures. After the organism was identified and in vitro sensitivity tests carried out, the patient was given aqueous procaine penicillin G intramuscularly in a total daily amount of 1.2 to 2.4 million units; this amount was given in divided doses two, three or four times per day for 14 days. Dihydrostreptomycin sulfate was given also in a total daily amount of 1.2 to 2.4 Gm. in divided amounts either in combination with the penicillin in the same injection or as a separate injection.* Blood cultures were obtained twice a week during therapy, and several daily consecutive blood cultures were obtained after therapy was completed. Urinalyses were made and sedimentation rates were determined twice per week. Assays for the concentration of penicillin and dihydrostreptomycin were made once a week in most cases. For the penicillin assays the Fleming slide cell technic was used.† For the dihydrostreptomycin assays a tube dilution method using *Klebsiella pneumoniae* as the test organism was employed.

The organisms isolated were *Streptococcus mitis* in 20 cases, *Streptococcus salivarius* in two, and an unidentified streptococcus in one. The organisms were inhibited by 0.1 unit of penicillin or less per cubic centimeter in all instances save one. The unidentified streptococcus was inhibited by 0.2 unit per cubic centimeter. The in vitro antibiotic sensitivities of the isolated organisms were determined by the use of the agar-plate dilution method as described by Herrell and Heilman.‡ The results of the sensitivity tests were read at the end of 16 hours, or when organisms on the control plate with no antibiotic had grown well.†

In some cases, in vitro sensitivity studies were also made with Aureomycin, terramycin, dihydrostreptomycin, or erythromycin. In 13 cases the isolated organisms were inhibited by 0.39 to 3.1 micrograms (average 1.14) of terramycin or Aureomycin or both per cubic centimeter; none of these patients were treated with these drugs. In six cases the organisms were inhibited by less than 0.05 to 0.2 microgram (average 0.11 microgram) of erythromycin. In two cases each, the streptococci were inhibited by less than 0.05, 0.1 and 0.2 microgram of this drug; only two of these six patients were treated with erythromycin. Sensitivity studies for dihydrostreptomycin were made in only two of the cases; the values were 6.25 and 3.1 micrograms for organisms which were sensitive to less than 0.05 unit of penicillin.

In view of previously reported studies of bactericidal tests for combined penicillin-dihydrostreptomycin activity on penicillin-sensitive streptococci, such studies were not carried out with the organisms isolated in this series of patients. 8. 11-13

**Clinical Features**

Sixteen of our 23 patients were men and seven were women. Their ages ranged from 26 to 66 years and averaged 45 years. Pre-

| Table 1.---Initial Symptoms Encountered in 23 Cases of Penicillin-sensitive Streptococcal Endocarditis |
|-------------------------------------------------|-----------------|
| Symptom                                         | Cases |
| Malaise, asthena, weakness, fatigue             | 10    |
| Low-grade fever and malaise                     | 7     |
| Chills and high fever                           | 4     |
| Headache and nausea                            | 1     |
| Anemia                                          | 1     |
| Acute organic toxic psychosis                   | 1     |
| Total                                           | 24*   |

* One patient had two attacks of the disease.

 precipitating pathogenetic factors were elicited in only nine patients; in the other 14 the history did not reveal any possible source for the valvular infection. In five cases the extraction of teeth was definitely implicated and in four an upper respiratory infection or sore throat seemed to be the determining event leading to the onset of the disease. The duration of symptoms before treatment was started by us averaged three and a half months and varied from 2 to 68 weeks.

The onset of the disease was acute, almost dramatically sudden, in five and gradual or insidious in 18 (table 1). In four of the five cases in which the onset was acute, the sudden appearance of a chill or chills and fever was the first manifestation of the disease; in the other case the sudden onset of a severe throbbing headache was the initial symptom. In eight

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* We are grateful to Eli Lilly & Company, Indianapolis, Ind., and Chas. Pfizer & Company, Inc., Brooklyn, N. Y., for supplying us with procaine penicillin G and dihydrostreptomycin sulfate combined in the same cartridge and for supplying us with combiotic.

† We are greatly indebted to Drs. Heilman, Thompson, Needham and Ulrich, of the Section of Bacteriology, Mayo Clinic, for their help in the study of these patients.
cases the patient had no previous knowledge of the presence of heart disease, in 12 the diagnosis of bacterial endocarditis had not been established before the patient came to the clinic, and in three the presence of bacterial endocarditis had been suspected at home but had not been diagnosed.

The symptoms in these cases were similar to those previously reported by other authors (table 2). In many instances a low-grade fever, malaise, anorexia, and a feeling of ill health characterized the patient's illness and were the only symptoms complained of. The presence of an associated heart murmur was the clue to the source of the patient's difficulty. Fever occurred in every case. In 13 cases the fever was of low grade all of the time and the temperature was never higher than 102 F. In nine cases the temperature on several or many occasions exceeded 102 F and reached levels as high as 105 F. Chills occurred surprisingly often. Sweats and arthralgias were prominent features. In one case the onset of the patient's illness was accompanied by the sudden onset of a very severe pain in the left sacroiliac region. Roentgenographic study of this site revealed a destructive arthritis which was felt to be of embolic origin. Both the pain and the local changes cleared up rapidly with therapy for the endocarditis. The details of this complication will be reported in a separate communication.

**Physical Findings.** The physical findings in the 23 cases are listed in table 3. Definite antecedent heart disease was established clinically in 22 of the 23 patients. Rheumatic heart disease was felt to be present in 18, and degenerative or "arteriosclerotic" heart disease in three patients. In one case syphilitic heart disease was diagnosed and demonstrated at post-mortem examination. In one case it was not possible to state whether any pre-existing heart disease was present. This patient was a 34 year old housewife in whom a minimal apical systolic murmur was present initially during therapy but was absent when she returned for reexamination one month after therapy. She had no prior knowledge of heart disease or a heart murmur.

Of the 3 patients with degenerative heart disease, one was a 59 year old man who gave a history of

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**Table 2.**—Symptoms Recorded in 23 Cases of Penicillin-sensitive Streptococcal Endocarditis Prior to Therapy

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Cases</th>
</tr>
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<tr>
<td>Fever</td>
<td>23</td>
</tr>
<tr>
<td>Malaise, asthenia, tiredness, weakness</td>
<td>22</td>
</tr>
<tr>
<td>Chills</td>
<td>14</td>
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<tr>
<td>Sweats</td>
<td>12</td>
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<td>Arthralgia</td>
<td>9</td>
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<tr>
<td>Anorexia</td>
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<td>Headache</td>
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<td>Pallor or anemia</td>
<td>6</td>
</tr>
<tr>
<td>Sore throat</td>
<td>4</td>
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<tr>
<td>Mild cough</td>
<td>4</td>
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<tr>
<td>Other central nervous system symptoms</td>
<td>4</td>
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<tr>
<td>Mild effort dyspnea</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Diarrhea</td>
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**Table 3.**—Physical Findings Noted in 23 Cases of Penicillin-sensitive Streptococcal Endocarditis on Admission and Prior to Treatment

<table>
<thead>
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<th>Symptom</th>
<th>Cases</th>
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<td>Heart murmurs*</td>
<td>23</td>
</tr>
<tr>
<td>Apical systolic</td>
<td>16</td>
</tr>
<tr>
<td>Aortic diastolic</td>
<td>8</td>
</tr>
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<td>4</td>
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<tr>
<td>Apical diastolic</td>
<td>0</td>
</tr>
<tr>
<td>Heart enlarged</td>
<td>13</td>
</tr>
<tr>
<td>Markedly†</td>
<td>0</td>
</tr>
<tr>
<td>Moderately†</td>
<td>3</td>
</tr>
<tr>
<td>Slightly†</td>
<td>10</td>
</tr>
<tr>
<td>Size normal†</td>
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</tr>
<tr>
<td>Sinus tachycardia (rate above 100)</td>
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<tr>
<td>Auricular fibrillation</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
</tr>
<tr>
<td>Loss of weight</td>
<td>15</td>
</tr>
<tr>
<td>Embolic phenomena</td>
<td>14</td>
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<tr>
<td>Splenomegaly</td>
<td>12</td>
</tr>
<tr>
<td>Clubbing</td>
<td>9</td>
</tr>
<tr>
<td>Changes in fundus†</td>
<td>4</td>
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</table>

* Some patients had more than one murmur.
† Heart of patient became markedly enlarged during therapy.
‡ Determined in 16 cases; positive findings consisted of petechiae or small hemorrhages.
having had a myocardial infarction 10 years prior
to the development of endocarditis (case 1, table 4).
He was not aware of the presence of a murmur
before admission to the clinic. He had a systolic
murmur at the apex which was also heard to the
left of the sternum in the third intercostal space; the
size of the heart was normal. It was difficult to say
whether or not this murmur represented aortic
stenosis, mitral insufficiency of rheumatic origin, or
perhaps mitral insufficiency resulting from the
previous infarction, that is, from involvement of the
posterior papillary muscle by the infarction with
resulting incompetence of the mitral valve.

The second patient in this category was a 66 year
old man who also was without previous knowledge
of a heart murmur or heart disease prior to the
diagnosis of his endocarditis (case 9, table 4). A
minimal aortic systolic murmur appeared during the
clinic examination when the diagnosis was being
established. One year later, when the patient
returned for re-examination, no murmur was heard
and a phonocardiogram revealed no evidence of a
bruit.

The third patient was a 60 year old man who had
a minimal basal aortic murmur (case 20, table 4).
He also had strong clinical evidence of coronary
artery disease with angina pectoris. He gave no
history of a heart murmur in his youth or early adult
life. The presumptive diagnosis was aortic stenosis.

It is interesting to note (table 4) that in the
18 patients thought to have rheumatic heart
disease, only the murmurs compatible with
mitral and aortic insufficiency and occasionally
a murmur suggestive of aortic stenosis were
observed. In no case was it felt that the
endocarditis was engrafted on a mitral stenosis.
In six of these cases there was a definite history
of previous rheumatic fever, in five there was
an equivocal history and in seven there was
no history of rheumatic fever or its sequelae.
In seven cases there was the characteristic
murmur of aortic insufficiency; in four of these
patients there was no history of rheumatic
fever or heart murmur, while in three an
apical systolic murmur was also present. In the
remaining 11 patients felt to have rheumatic
heart disease, only an apical systolic murmur
of minimal to moderate intensity was heard; in
only one of these patients was aortic systolic
murmur noted also. This aortic murmur seemed
to be of the same character as the apical
murmur but much less intense. A diagnosis of
rheumatic mitral valvulitis was entertained in
these 11 cases, and it is probable that in most
of them the murmur represented mitral insufficiency.

Of the 11 cases in which a diagnosis of
rheumatic mitral valvulitis was entertained,
there was a definite history of rheumatic fever
in four, and equivocal history in four, and no
history in three. In all of these cases except one
of the last-mentioned group, there was a history
of a heart murmur of long duration prior to the
onset of bacterial endocarditis. In the case in
which the patient was without previous knowl-
edge of a heart murmur (case 14, table 4),
examination after death disclosed that involve-
ment of the mitral valve and its chordae tendineae
by previous attacks of rheumatic fever
was the substrate for the bacterial endo-
carditis. It would seem, then, that previous
damage to the mitral valve had occurred
before the onset of the bacterial endocarditis
in all 11 cases. However, the possibility that
the bacterial infection was engrafted on a
normal mitral valve in some cases cannot be
excluded. Such cases have been recorded.14
Whether some of these apical systolic murmurs
may actually have represented aortic valvular
lesions would be difficult to say. However, the
apical location of the murmur, the previous
knowledge of valvular damage, and the
presence of bacterial endocarditis would indi-
cate that the murmur was of mitral valvular
origin, and the result of rheumatic mitral
incompetence. The problem of differentiation
of apical systolic murmurs and organic mitral
insufficiency has been reviewed recently.13

Embolic manifestations occurred in 61 per
cent of the 23 cases. Petechiae were the most
frequent finding. Osler’s nodes were noted in
six cases.15 16 Janeway’s spots were noted only
once.17 Splenic infarction occurred three times,
and cerebral, coronary or pulmonary embolism
was diagnosed in one instance each. Major
arterial embolism occurred once, in the calf of
the right leg.

Laboratory Data

Anemia, noted in 15 of the 23 patients, was
mild in 12 and moderate in three (table 5). The
values for hemoglobin ranged as low
as 6.2 Gm. per 100 cc. of blood and averaged
10.3 Gm. Leukocyte and differential counts
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<thead>
<tr>
<th>Case</th>
<th>Age, sex</th>
<th>Type of heart disease*</th>
<th>Weeks of symptoms before treatment</th>
<th>Streptococcus isolated†</th>
<th>Sensitivity‡</th>
<th>Therapy¶</th>
<th>Method</th>
<th>Months followed</th>
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</tr>
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</table>

*Abbreviations: RHD, rheumatic heart disease; SHD, syphilitic heart disease; DHD, degenerative heart disease; A8, angina pectoris; Cor. Scel., coronary sclerosis; MI, mitral insufficiency; AI, aortic insufficiency; A8, aortic stenosis; SBE, subacute bacterial endocarditis; Pen, penicillin; DSH, dihydrostreptomycin; IV, continuous intravenous drip; q, every.

† Numbers in parentheses represent positive blood cultures.
‡ In vitro sensitivity to penicillin in the indicated concentration (units per cubic centimeter). See text for in vitro sensitivity values for other antibiotics.
§ Numbers represent millions of units of penicillin and grams of dihydrostreptomycin given intramuscularly except where otherwise stated.
were abnormal in only a few cases. The highest leukocyte count noted on admission was 16,800 per cubic millimeter, and this was the only reading above 15,000. Reticuloendothelial cells without evidence of phagocytosis, phagocytic reticuloendothelial cells, and phagocytic monocytes without reticuloendothelial cells were noted in four cases, 2 cases and one case, respectively, of the 15 cases in which this examination was carried out. These figures are somewhat lower than were found by Cole.18

The sedimentation rates (Westergren method) ranged from 30 to 70 mm. in 1 hour in 12 cases, and from 71 to 100 in seven cases; in two cases the rates were greater than 100 mm., and also in two cases the rates could be considered normal. Persistent hematuria was noted in only nine cases. Roentgenograms were interpreted as showing some enlargement of the heart in only 13 cases.

| TABLE 5.—Significant Laboratory Data Obtained on Admission in 23 Cases of Penicillin-Sensitive Streptococcal Endocarditis |
|---------------------------------------------------------|----------------|
| Anemia (hemoglobin less than 12 Gm., erythrocytes less than 4 million) | 15 |
| Leukocytosis (neutrophils more than 10,000) | 4 |
| Leukopenia (neutrophils less than 5,000) | 4 |
| Differential count (20 cases) | 5 |
| Neutrophils more than 80 per cent | 15 |
| Normal | 21 |
| Blood smears (15 cases) | 4 |
| Reticuloendothelial cells without phagocytosis | 2 |
| Phagocytic reticuloendothelial cells | 1 |
| Phagocytic monocytes | 9 |
| Elevated sedimentation rate (above 30) | 3 |
| Erythrocytes persistently in urine | 3 |
| Increased blood urea (on basis of 18 cases) | 3 |

* In the other 2 cases the rates were 20 and 23 mm. respectively.

Results of Treatment

In this series of 23 cases there were five deaths, giving a mortality rate of 22 per cent. Eighteen patients (78 per cent) have remained in good health during follow-up periods varying from 3 to 24 months. The average follow-up period was one year. No treatment failures and no relapses have occurred in the living patients. In 21 of the 23 cases the response to treatment was good and prompt. The temperature fell to normal on the day of, or the day following, the start of therapy, and continued normal throughout the remainder of the period of treatment except for an occasional brief febrile response arising from embolization. The blood cultures promptly reverted to negative and remained so during therapy and the follow-up period. In one case a low-grade fever persisted for 12 days while the blood cultures were persistently negative. In another case the initial temperature of 103 F., noted before the onset of therapy, gradually fell to normal over a four-day period. Follow-up studies of the living patients have revealed little or no change in their exercise tolerance and little or no change in cardiac size or auscultatory findings.

Deaths. Data on the five patients who died are given in table 6. It will be noted that in the three cases in which the cause of death was congestive heart failure the underlying valvular lesion was aortic insufficiency. Postmortem examinations were obtained (at the clinic) in two cases in which death occurred on the eleventh day of therapy and in a third case in which death occurred (at home) three weeks after treatment had been concluded. Cultures were obtained from the involved valves in only one of the three cases, and the results of these were negative. A résumé of the two cases in which necropsy was performed at the clinic follows.

A 32 year old white woman (case 14, table 6) gave a history of chronic febrile illness of four months' duration. Her disease had a gradual onset about a week following the extraction of several teeth. The initial symptoms of a "cold," dry cough, fever and anorexia were followed by the appearance of the nephrotic syndrome about 10 days later which lasted for approximately two weeks. The patient then had intermittent hematuria, weakness and tiredness, recurrent febrile episodes with the temperature rising as high as 104 F. and loss of weight until admission to the clinic.

Examination revealed a normal-sized heart with a moderately loud apical systolic murmur, sinus tachycardia, mild clubbing of the fingers, and splenomegaly. The laboratory findings were:
moderate anemia, leukopenia, phagocytic reticuloendothelial cells in the peripheral blood smear, elevated sedimentation rate, microhematuria, increased concentration of blood urea, and three blood cultures positive for *Streptococcus mitis*.

Therapy was complicated by the appearance of moderately severe epigastric pain on the third day, which was followed by enlargement and tenderness of the liver, jaundice, and elevation of temperature to 100.6 F. This episode lasted about four days. The patient was then afebrile and the blood cultures were negative until death, which resulted from cerebral embolism with massive infarction and hemorrhage into the left frontotemporoparietal lobes of the brain on the eleventh day of treatment.

Necropsy revealed a normal-sized heart weighing 315 Gm. The chordae tendineae were slightly thickened and shortened. The mitral valve was the only one involved. At the posterior medial commissure and in the adjacent portions of the anterior and posterior leaflets of the mitral valve, there was an erosive lesion involving the valvular tissue. This caused a moderate excavation of the involved tissue. Small thrombi were deposited upon the surface of the lesion.

Microscopic examination of the mitral valve at the site of involvement showed the remnant of valvular tissue. This was thickened by vascular fibrous tissue in which cells, predominately macrophages, were present in moderate numbers. Hemoglobin granules were present in some of these infiltrating cells. No neutrophils, leukocytes or bacteria were identified histologically. On the surface of the involved portion of the valve, endothelial cells could be identified. Bland thrombotic material was deposited upon the surface of the valve but no evidence of active inflammation could be found. Cultures from the involved portions of the leaflets were negative (figs. 1 and 2).

It was concluded that the mitral valve was the site of healed bacterial endocarditis.

![Table 6](image-url)

*To be reported in detail elsewhere.

The second patient (case 15, table 4) was a 53 year old white man, whose first symptoms of bacterial endocarditis appeared to be the visual, auditory and paranoidal delusions of an acute organic toxic psychosis of some two or three months' duration. The history regarding the symptoms of his valvular infection was difficult to elicit. A diagnosis of syphilitic heart disease with aortic insufficiency had been made three years earlier. The patient had been treated for congestive heart failure in the interim between this diagnosis and his final illness. Examination revealed enlargement of the heart, an aortic diastolic murmur which indicated free aortic regurgitation, and splenomegaly. The laboratory...
findings of significance were: moderate anemia, phagocytic reticuloendothelial cells in the peripheral blood smear, greatly elevated blood sedimentation rate (116 to 131), microhematuria, blood flocculation, and deposition of thrombi on the surface of the altered portion of the valve.

![Image](image_url)

**Fig. 1.** Case 14. a. Mitral valve showing erosion in the vicinity of the posteromedial commissure and deposition of thrombi on the surface of the altered portion of the valve.

In the thoracic aorta there were stellate medial scarring, perivascular lymphocytic infiltration of the adventitia, and intimal atherosclerosis.

The pathologic picture was that of an unusual combination of syphilitic aortitis and bacterial endocarditis of the aortic valve. On histologic grounds, the endocarditis appeared active, with destructive and acute inflammatory features.

reaction for syphilis positive on several occasions, and blood cultures positive for *Streptococcus mitis* on five occasions. The patient died rather suddenly on the eleventh day of therapy. During the last two or three days before death he experienced several episodes of thoracic pain and dyspnea that were suggestive of pulmonary or coronary embolization.

Postmortem examination revealed syphilitic aortitis and valvulitis. The heart was enlarged, weighing 610 Gm. (normal 315 Gm.), and there was considerable left ventricular hypertrophy. The coronary arteries appeared to be normal. Scattered throughout the myocardium, particularly in the left ventricle, were many 1 to 2 mm. areas of redness and softening that represented small focal myocardial infarctions. The mitral, tricuspid and pulmonary valves were normal. The thoracic aorta was unusually wide. At the aortic valve, widening of the commissures and narrowing of the ostia of the coronary arteries were readily apparent. In addition, friable gray-brown vegetations were deposited on the luminal aspect of the aortic valve. These were concentrated at the commissure between the right and posterior leaflets, at the commissure between the posterior and left leaflets, and on the left aortic leaflet.

Microscopic examination of representative lesions showed that the vegetations were composed of fibrin and colonies of cocci. Similar organisms in large numbers were present within the valvular tissue, which simultaneously was the site of necrosis with abscess formation and fibroblastic proliferation associated with ingrowth of capillaries (figs. 3 and 4).
existing. On morphologic grounds it is impossible to state whether the bacteria observed had been viable or not at the time of the patient's death. Unfortunately, cultures of the valve were not obtained.

**Fig. 3.** Case 15. Aortic valve showing the gross characteristics of syphilitic aortitis and of bacterial endocarditis.

**Fig. 4.** Case 15. Aortic valve showing vegetations which, through artefact, have come away from the surface of the cusp. The cusp is thickened by the presence of bacteria and the cellular infiltration described in the text (hematoxylin and eosin; X4.5).

**Other Data.**

In 2 of the 23 cases the period of therapy was 20 days (table 4). A longer period of treatment and a larger daily dose of penicillin in one of these two cases were decided upon for the following reasons: the organism was an unidentified streptococcus, and the in vitro sensitivity test revealed that minimal inhibition of the organism was produced by 0.1 to 0.2 unit of penicillin per cubic centimeter of medium; also, the duration of symptoms was felt to be close to 18 months; in addition, the patient exhibited considerable debility and loss of weight. In the other case the patient had had the disease for nine months or more and was in a greatly debilitated and wasted state when therapy was started. In this case a splenic infarction also developed on the third day of treatment with a rise of temperature to 103.8 F, for 48 hours. However, the initial response to therapy in both cases was excellent, and it seems likely in retrospect that 2 million units of penicillin and 2 Gm. of dihydrostreptomycin per day for 14 days would have been adequate.

In three cases (cases 7, 8 and 10, table 4) penicillin-sensitive streptococcal endocarditis had also occurred three, four and five years respectively prior to the episodes of endocarditis recorded herein. Conventional therapy with penicillin alone for 30, 42 and 23 days respectively had effected a cure in each instance; daily doses of 1, 0.6 and 0.4 million units of penicillin were given respectively. In an additional case (case 9, table 4) a reinfection occurred one year after cure with short-term combined penicillin-dihydrostreptomycin therapy; *Streptococcus salivarius* was isolated in each instance, and the sensitivity to penicillin was the same on both occasions. However, on the second occasion the organism was sensitive to less than 0.05 microgram of erythromycin per cubic centimeter of medium, and it was decided to treat the patient with this new drug. 16, 19 A half gram of erythromycin was given every six hours for two weeks. All subsequent cultures have been negative and the patient has remained well.

In one other case (case 7, table 4) erythromycin was used. The organism isolated was *Streptococcus mitis* which was sensitive to less than 0.05 unit of penicillin and to 0.2 microgram of erythromycin per cubic centimeter of medium. This constituted a reinfection endo-
carditis some three years after an initial infection. A half gram of erythromycin was given every six hours for four weeks. The initial response to treatment was excellent. The temperature dropped from 102 F. to 97 F. in a period of 12 hours and remained normal until the twenty-third day of treatment. The blood cultures rapidly became negative in the same period and remained negative until low-grade fever reappeared 23 days later. The streptococci isolated at this time were found to have the same sensitivity to penicillin, that is, they were sensitive to less than 0.05 unit per cubic centimeter of medium but the organisms were highly resistant to erythromycin, not being inhibited by more than 200 micrograms per cubic centimeter of medium. The patient was then treated with combined penicillin and dihydrostreptomycin on a short-term basis (two weeks). Two million units of aqueous crystalline penicillin G by continuous intravenous drip (the patient requested intravenous therapy) and 2 Gm. of dihydrostreptomycin sulfate in divided doses of 0.5 Gm. every six hours was given over a 24-hour period. The temperature and blood cultures again promptly became normal, and the patient made an uneventful recovery. It should be noted that during therapy with erythromycin, blood levels ranged from 2 to 16 micrograms per cubic centimeter of medium and averaged 7 micrograms. The blood levels of erythromycin in this case throughout most of the period of therapy with this antibiotic were 10 or more times greater than the amount of drug found to inhibit the organism in vitro.

As can be seen in table 4, various dosage schedules were employed. The last six patients (cases 1 to 5 and 7) have been given 1 million units of procaine penicillin G and 1 Gm. of dihydrostreptomycin sulfate every 12 hours as separate intramuscular injections, since there has been, so far, no preparation available with both these amounts of antibiotics in the same cartridge. These slightly different dosage schedules have given the same results.

The patients in this study were not asked to take their temperature after therapy was completed. However, in two cases in which a low-grade fever (temperature up to 102 F.) was observed in the first few days after dismissal of the patient, the febrile reactions were apparently not due to a relapse or reactivity of the valvular infection. Daily blood cultures during and subsequent to the elevation of temperature were repeatedly negative. The febrile response disappeared rapidly with rest in bed, and it was felt to be related to ambulation and activity following two to three weeks of almost complete rest in bed during the period of treatment and observation.

Bio-assays for the serum levels of penicillin and dihydrostreptomycin were performed in 14 cases. In 13 of these there was no evidence of renal insufficiency and the penicillin levels ranged from 1 to 16 units and averaged just above 2 units per cubic centimeter. The dihydrostreptomycin levels ranged from 4 to 64 micrograms and averaged slightly more than 16 micrograms. In one case in which the levels of blood urea averaged more than 80 mg. per 100 cc., the values for penicillin and dihydrostreptomycin in the serum were, on two occasions, 8 and 16 units per cubic centimeter for penicillin and 32 and 64 micrograms per cubic centimeter for dihydrostreptomycin. In the patients without renal insufficiency who received 2 million units of penicillin and 2 Gm. of dihydrostreptomycin per day intramuscularly in two divided doses every 12 hours, the serum levels were noted to be as high as 16 units and 64 micrograms and as low as 1 unit and 4 micrograms respectively. The higher values for penicillin and dihydrostreptomycin were found an hour or two after the administration of the antibiotics; the lower values were found one to two hours before the injections.

**Sedimentation Rate.**

The sedimentation rate was elevated before therapy in all but two cases, and it became elevated also in these with treatment. During therapy the sedimentation rate rose rather than fell in a significant number of cases. In 13 cases it rose an average of 25 mm., the range being from 10 to 56 mm.; the initial readings in these cases averaged 60 mm. with a range of 20 to 84 mm. In only two cases were the rises correlated with embolic phenomena or an observable change in the patients'
clinical status. In both instances rises of 41 and 56 mm. were associated with splenic infarction and a corresponding febrile reaction.

In six cases the sedimentation rate remained grossly unaltered, and during therapy it did not rise or fall more than 10 mm. The average initial readings in these cases ranged from 23 to 123 mm. with an average of 62 mm. In only four cases did the sedimentation rate fall with therapy. The average fall was 24 mm. with a range of 10 to 38 mm. The initial readings in these cases averaged 78 mm. and ranged from 40 to 136 mm.

In 19 cases the initial sedimentation rates were as high as or higher than the readings obtained at completion of therapy. In most cases the values had decreased to normal when the patients were re-examined after a month or two. A rise in the sedimentation rate has been noted also with the therapy of other types of bacterial endocarditis. One can only speculate on the significance of these findings.

**Comment**

For practical clinical and therapeutic consideration, cases of subacute streptococcal endocarditis can be divided into two large groups: those in which the organism is penicillin sensitive and those in which it is penicillin resistant. In the first category are the cases of subacute bacterial endocarditis caused by streptococci such as *Streptococcus mitis*, *Streptococcus salivarius*, and related organisms. These streptococci have been found to be uniformly sensitive to penicillin; occasionally one is encountered which is resistant to penicillin particularly when much previous unsuccessful penicillin therapy has been given.\(^5\) Penicillin-resistant streptococcal endocarditis is rather uniformly caused by the enterococci, most commonly *Streptococcus faecalis*. We have not been concerned with the latter patients in this paper, since long-term combined penicillin-dihydrostreptomycin therapy for six weeks with large daily doses of penicillin is usually indicated in such cases.\(^6\) Enterococcal endocarditis will be considered in a separate communication.

Patients with penicillin-sensitive streptococcal endocarditis have in the past made up the bulk of most series of those with this infection; the proportion has been variable but has run as high as 80 to 90 per cent or more of the cases. In recent years, with the widespread use of penicillin and broad-spectrum antibiotics, this proportion seems to have dropped to figures closer to 60 per cent.\(^3\) This decrease in penicillin-sensitive streptococcal endocarditis seems to be an absolute one and also seems to be related to the widespread use of penicillin and other antibiotics in patients with any and all types of fever regardless of cause. That this may be so is illustrated by a case encountered recently at postmortem observation at the clinic and reported below, and by other patients seen at the clinic.

In January 1947, a 60 year old man came to the Mayo Clinic because of low-grade fever and malaise. A presumptive diagnosis of lymphoblastoma was made after repeated blood cultures were negative; x-ray therapy was given over the liver and spleen, since these organs were enlarged. A month later the patient returned because of increasing malaise, anorexia, loss of energy and strength, fever, and chills. The admission temperature was 104.8 F. Many blood cultures were negative after two days of incubation. On the sixth day of hospitalization, treatment with penicillin was given empirically; 120,000 units were administered daily for the first three days and then 320,000 units a day for the next seven days, for a total of 2.6 million units for the 10 days. The temperature fell to normal on the fourth day of treatment, and was still normal at the time of dismissal 19 days later. Only one of the many blood cultures obtained before the onset of therapy became positive—an anaerobic streptococcus was grown after 12 days of incubation. Many blood cultures obtained after therapy was started were negative. Six months later the patient began to have symptoms of congestive heart failure. Improvement followed conventional therapy. Bouts of congestive heart failure then recurred for the next four years until death supervened. Postmortem examination revealed organic mitral insufficiency with a healed mitral bacterial endocarditis.

The foregoing case illustrates the ease with which penicillin-sensitive streptococcal endocarditis can be cured in some cases, and the very small doses of penicillin that may be curative. There must be many similar cases in which fever is the chief manifestation of bacterial endocarditis and in which cure is obtained without a definite diagnosis being made.
prior to treatment. This case is to be contrasted with that reported by King and colleagues, in which both short-term treatment (10 days) with daily massive doses of penicillin and long-term treatment (six weeks) with conventional daily doses of penicillin were without success for a very penicillin-sensitive streptococcal endocarditis (organism inhibited by 0.02 unit of penicillin per centimeter of medium). Combined therapy with penicillin and streptomycin was curative. These two cases illustrate the relative extremes of therapy that may be curative for penicillin-sensitive streptococcal endocarditis, and indicate the difficulty that is encountered occasionally in the treatment of such patients.

A number of in vitro studies have been carried out relative to the synergistic effect of penicillin and dihydrostreptomycin on penicillin-sensitive *Streptococcus viridans* organisms. Hunter studied the effects of a combination of penicillin and dihydrostreptomycin on several strains of penicillin-sensitive viridans streptococci in vitro and found enhanced bactericidal activity. Spicer studied six strains and found that the combination of antibiotics had a greater bactericidal action than did penicillin alone on two of the organisms and the same effect as did penicillin alone on four others. Spicer, and Eagle have noted that even when sensitive strains of streptococci are studied in vitro with large doses of penicillin, a residue of viable organisms remains. These organisms were killed when exposed to streptomycin. Javetz has also studied several penicillin-sensitive strains of *Streptococcus viridans* for synergism and noted this effect in a number of instances. The efficacy of this antibiotic combination or penicillin-sensitive viridans streptococci has been further demonstrated in vivo by scattered reports of cases in which penicillin alone in adequate dosage for a prolonged period resulted in failure, but cure occurred when streptomycin was used together with penicillin. It would seem that penicillin and streptomycin in combination have a greater bactericidal effect than penicillin alone for most strains of penicillin-sensitive viridans streptococci, having either a more rapid and greater killing effect or only a greater killing effect on the organisms. In all instances the combination seems to be as effective as penicillin alone; no instance of antagonism has been recorded when this combination has been used against these organisms.

Further study of these penicillin-sensitive streptococci for antibiotic synergism between penicillin and streptomycin and other antibiotic combinations is indicated. Further observation and combined antibiotic treatment of patients with penicillin-sensitive streptococcal endocarditis may indicate that an even shorter period of therapy, of 10 days' duration, as suggested by Hunter, may be adequate. Because of the greater bactericidal effect of the penicillin-dihydrostreptomycin combination against these sensitive streptococci, further in vitro and clinical experience may perhaps show that daily doses of 2 million units of penicillin, as suggested herein, or larger doses, with or without benemid, together with dihydrostreptomycin may be curative for a shorter period of time, such as one week. Only further clinical study will reveal what is the optimal ideal therapy for these patients.

Increasing experience by others and our own observations in the antibiotic therapy of bacterial endocarditis indicate that combined therapy is being used in an increasingly greater percentage of all cases, particularly for infections resistant to penicillin and other individual antibiotics. Whether combination treatment will mean a shortening of the period of therapy in types of endocarditis other than those due to penicillin-sensitive streptococci can be determined only by further study and experience. Further in vitro testing, in vivo animal experiments and the actual treatment of the disease in man with combinations of antibiotics will eventually clarify this highly fascinating problem in the field of antibiotic therapy. In vitro and in vivo testing for antibiotic synergism with combinations of antibiotics will assume an ever-increasing importance in the management of bacterial endocarditis, especially in those cases in which the infection is caused by antibiotic-resistant organisms.

The average duration of the valvular in-
fection in our 23 cases was very close to four months. This seems to be a surprisingly long time when one considers that these patients had symptoms and considered themselves ill all of this time. In view of the availability of very effective antibiotic therapy for patients with penicillin-sensitive streptococcal endocarditis, it is interesting to speculate on what the therapeutic results and the percentage of living patients would have been in this series had the diagnosis of infectious endocarditis been made in the early weeks of the disease.

The major problem today is not so much the actual antibiotic treatment and the control of the infection as the making of an early accurate diagnosis. By this we mean the isolation and proper identification of the etiologic organism and the reliable determination of in vitro sensitivity. It is well known that active bacterial endocarditis of many months' duration leads to much valvular damage which in turn compromises cardiac function and leads to the complication of congestive heart failure, the most frequent cause of death in such cases.28

In all five cases in which death occurred in our series the disease had been present for several months (table 6). In case 15 it is likely that the disease was present for a much longer period than the recorded two months. In this case the onset and history of the disease were obscured by the presence of an organic toxic psychosis apparently of endocarditic origin. Thus it seems probable that the complications of the endocarditis causing death in these cases might not have occurred if an early diagnosis had been made and early adequate antibiotic therapy had been given. In the two cases in which death occurred on the eleventh day of the disease and in which postmortem examination was carried out at the clinic, there was considerable healing of the valvular lesions.

The evidence from this clinical study indicates that penicillin-sensitive streptococcal endocarditis is completely controlled by the short-term treatment described. It seems reasonable to conclude that early diagnosis should result in cure of the infection and ensure a living patient in 100 per cent of cases except when prolonged active valvular infection from delay in diagnosis or when previous extensive cardiac damage leads to congestive heart failure, cerebral embolism or renal insufficiency.

In only three cases of this series did any toxic reactions develop from the antibiotics used, and these reactions were mild. One patient gave a history of severe allergic sensitivity to penicillin G, so that penicillin O was used for the two-week period of therapy. Cross sensitivity must have existed, because a maculopapular rash developed over most of the areas of the body with eventual exfoliation of the skin of the fingers and hands. Successful two-week curative therapy was, however, carried out with penicillin O and dihydrostreptomycin. This case has been reported in greater detail elsewhere.29 Two patients exhibited very mild toxic reactions to dihydrostreptomycin. One had a slight transient numbness of the fingertips following the first few injections of dihydrostreptomycin; the other had numbness and paresthesias circumurally and peripherally in the tips of the fingers and toes which persisted unchanged with continuation of treatment until death from cerebral embolism on the eleventh day. No eighth-nerve toxicity from the dihydrostreptomycin was exhibited by any of the 23 patients given this drug in 2 Gm. doses for a two-week period.

Summary and Conclusions

Twenty-three consecutive patients with penicillin-sensitive streptococcal endocarditis seen during a 25 month period have been treated with a combination of penicillin and dihydrostreptomycin on a short-term basis (two weeks). Eighteen patients (78 per cent) have remained well during follow-up periods of 3 to 24 months. No treatment failures or relapses have occurred in the living patients.

Five deaths (22 per cent) occurred. Four of the deaths were due to complications of the endocarditis and the underlying heart disease, namely congestive heart failure and cerebral embolism, while the fifth was due to coronary occlusion with myocardial infarction.

The clinical features in the 23 cases are presented and the cardiac findings discussed. Rheumatic heart disease was present in 18 cases, degenerative or "arteriosclerotic" heart
ANTIBIOTIC THERAPY OF BACTERIAL ENDOCARDITIS

disease in three, and syphilitic heart disease with syphilitic aortic insufficiency in one; in one case no diagnosis of underlying heart disease could be made.

It is concluded on the basis of this study that 1 million units of aqueous procaine penicillin G and 1 Gm. of dihydrostreptomycin sulfate given intramuscularly every 12 hours for two weeks represents adequate and curative treatment for subacute bacterial endocarditis caused by penicillin-sensitive streptococci.

SUMARIO ESPAÑOL

A veinte y tres pacientes con endocarditis causada por estreptococos penicilino-sensitivos se le dió un tratamiento corto de dos semanas con penicilina y dihidroestreptomicina. Cinco de los pacientes murieron a consecuencia de complicaciones de la infección; 18 aún vivían y mantenían buen estado de salud hasta la fecha de este estudio luego de un tiempo pro medio de vigilancia de más de un año. No ocurrieron fracasos en el tratamiento o re caídas. Se concluye de el estudio de estos pacientes que 1,000,000 de unidades de procaína penicilina-G acuosa y 1 gramo de sulfato de dihidroestreptomicina administrado intramuscularmente cada 12 horas por dos semanas es curativo para esta variedad de endocarditis.

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Antibiotic Therapy of Bacterial Endocarditis: IV. Successful Short-Term (Two Weeks) Combined Penicillin-Dihydrostreptomycin Therapy in Subacute Bacterial Endocarditis Caused by Penicillin-Sensitive Streptococci

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_Circulation_. 1953;8:494-509
doi: 10.1161/01.CIR.8.4.494
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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