CLINICAL PROGRESS

Bacterial Endocarditis in the Antibiotic Era
With Special Reference to the Later Complications

By William L. Morgan, M.D., and Edward F. Bland, M.D.

In 1944 Loewe and his associates demonstrated the effective use of penicillin in the treatment of bacterial endocarditis. During the ensuing decade and a half, 228 patients with this disease have been treated at the Massachusetts General Hospital. The present report concerns primarily the outcome of therapy in this group with particular reference to the fate of those who survived their active disease. It also emphasizes certain syndromes and delayed complications peculiar to the healing process. As a reminder of the relentless deteriorating course that prevailed before the antibiotic era, a brief review of the earlier contributions that established this disease as a clinical entity and prepared the way for successful therapy is included.

In 1852 Kirkes first clearly attributed systemic emboli to vegetations on heart valves, but similar cases actually had been described as early as 1707 by Lancisi and later by Senac, Morgagni, and others. It was Kirkes, however, who provided the impetus to study ulcerative endocarditis at the time when pathologic investigation was foremost and bacteriology was still in its infancy.

By 1870, Winge and Heiberg had visualized microorganisms in valvular vegetations. Wilkes had associated arterial pyemia with endocarditis, pointing out that such a febrile illness might be mistaken for ague or miasmatic fever, and Lanceereaux, Leyden, and Jaecoud had each given clear clinical descriptions of the disease. By 1886, Wyssokowitsch had isolated Staphylococcus aureus from a case of ulcerative endocarditis and had produced the disease in dogs.

In 1885 appeared the important contribution of William Osler. He presented in the Gulstonian Lectures an analysis of 209 cases of malignant endocarditis and gave a description of its pathologic features. He recognized that healed rheumatic valvulitis was a frequent precursor and the presence of microorganisms in the vegetations a constant feature of this disease. Subsequently in 1908 he described the "chronic" cases and at that time called attention to the "nodosités cutanées éphémères" which bear his name.

By the turn of the century the nature of the organisms causing bacterial endocarditis had become known and the diagnostic technic of blood culture had come into use. While opinions differed as to the classification of the gram-positive cocci, Schottmüller in 1910 identified it as a streptococcus of the "viridans" type. At the same time Löhelein described the focal embolic nephritis characteristically found post mortem, which Horder had labeled the "flea-bitten kidney." A feature more fully discussed by Baehr in 1912. Libman, who is credited with having named the disease subacute bacterial endocarditis, called attention to an occasional patient whose lesions healed spontaneously.

By the end of the second decade of this century the clinical concept of this disease had been crystallized. Therapy, however, was universally unsuccessful, although Blumer predicted that "chemotherapy might in the future be developed to a degree permitting
of the elimination of these organisms from the body.'”

In the 1920’s and 1930’s clinical studies emphasized the frequency of bacterial endocarditis in rheumatic and congenital heart disease,22-27 and pathologic studies were concerned with further detailed descriptions of the cardiac and systemic manifestations28-34 and the mechanism of valvular infection.35-37

During this period an occasional encouraging instance of surgical cure was reported. Thus in 1935 Hauman and Reinhoff, by excision of an infected arteriovenous aneurysm of the external iliac, cured a case of subacute endarteritis and septicemia,38 and Touroff in 1940 described a patient with an infected patent ductus arteriosus who recovered after ligation of the ductus.39

With the advent of sulfonamide therapy in 1938, the promise of definitive treatment appeared near realization, but results proved disappointing. Lichtman’s review in 1943 of 2596 cases in the literature revealed recovery of only 4 to 6 per cent of the patients treated with sulfonamide, alone or in combination with heparin or hyperthermia.40 Prior to this therapy approximately 1 per cent of patients had recovered spontaneously. Anticoagulants which were used in conjunction with the sulfonamides in 193941 were soon abandoned because of the added risk of cerebral hemorrhage, presumably secondary to embolism.42-43

In 1944, after decades of disappointment, a new and brighter era began. Very soon after the introduction of penicillin it became apparent that nearly 3 out of 4 of the victims of this heretofore fatal disease could be rescued.44-46 Now that almost 15 years have elapsed, both the immediate and the ultimate fate of patients with bacterial endocarditis can be viewed in helpful perspective.

### Table 1.—Bacterial Endocarditis (1944-1958)

<table>
<thead>
<tr>
<th></th>
<th>Cured</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute</td>
<td>119</td>
<td>31</td>
</tr>
</tbody>
</table>

THE PRESENT STUDY

The 228 patients who form the basis for this report comprise all cases with bacterial endocarditis admitted to the Massachusetts General Hospital since 1944. The criteria for diagnosis were a clinical picture compatible with bacterial endocarditis and at least 2 positive blood cultures, or a pathologic diagnosis post mortem. There were 15 of 119 successfully treated patients who had negative blood cultures but presented the characteristic clinical features of this disease.

The 228 patients may be divided for convenience into 3 major groups (table 1): (1) those with acute bacterial endocarditis (53 cases); (2) those with subacute bacterial endocarditis who died during hospitalization (56 cases); and (3) those with subacute bacterial endocarditis treated successfully (119 cases).

The patients with acute bacterial endocarditis were somewhat older than the subacute cases, with an average age of 55 years, ranging from 8 months to 85 years and equally divided as to sex. Staphylococcus aureus, the predominant organism, was found in 31 instances (60 per cent).*

In nearly one half (25) of the acute cases there was no apparent preexisting cardiac disease or defect. Rheumatic valvular disease was found in 18 instances, calcific aortic stenosis in 6, bicuspid aortic valve in 2, syphilitic aortitis in 1, and a ventricular septal defect in 1.

Of the 175 patients with subacute bacterial endocarditis, there were 96 males and 79 females; the ages ranged from 3 1/2 to 96 years, with an average of 42. In the 119 cured cases, rheumatic heart disease was present in 105 and congenital heart disease in 14. Strep tococcus viridans was isolated in 87 (73 per cent).† The usual treatment was parenteral

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*Staphylococcus aureus 31, Pneumococcus 9, no organism 6, Bacillus coli 2, and 1 each of B. proteus, α-hemolytic streptococci, β-hemolytic streptococci, Hemophilus influenzae, and brucella.
†Streptococcus viridans 87, Staphylococcus albus 3, β-hemolytic streptococci 2, Enterococcus 2, Staphylococcus aureus 1, Hemophilus influenae 1, diagnosis post mortem 8, and negative cultures in 15.
penicillin for at least 3, often for 4 weeks or longer and penicillin combined with other antibiotics in special instances.

Forty-eight of the 56 patients who died had postmortem examination. Twenty-nine of them were afflicted with Streptococcus viridans; in 18 patients no organism was isolated.* Rheumatic heart disease was present in 38 of the fatal cases, whereas in 8 instances there had apparently been no antecedent valvular disease as far as clinical history or postmortem examination could disclose.†

**Acute Bacterial Endocarditis**

Only 8 of the 53 patients with acute bacterial endocarditis (15 per cent) survived hospitalization. The cause of the high mortality is partially explained by the fact that the diagnosis was made during life in only 2 patients. The reasons for failure of diagnosis were as follows. In 19 instances the presence of endocarditis was masked by the signs of overwhelming infection elsewhere, notably by pneumonia, meningitis, or peritonitis (11 of these infections were postoperative). Furthermore, there were 11 patients who did not survive long enough to permit a diagnosis. Of the 21 cases in which the disease was recognized before death, therapy was inadequate, in 8, since only a few days elapsed between diagnosis and death. Of the remainder, 4 were given too low a dose by present standards, 2 died of resistant infection despite high antibiotic dosage, 1 died of a myocardial abscess with compression of a coronary artery, and 6 survived. The 2 additional patients who survived are of special interest. The acute endocarditis, unrecognized at the time in both instances, had been cured with treatment of a severe pulmonary infection, but months later postmortem examination revealed the healed bacterial endocarditis that had been unsuspected during the acute illness.


†Rheumatic heart disease 38, calcific aortic stenosis 4, tetralogy of Fallot 2, bicuspid aortic valve 2, transposition and bicuspid pulmonary valve 1, pulmonary stenosis 1, and no valvular disease 8.

**Table 2.—Fatal Complications during Bacterial Endocarditis (92 Postmortem Cases)**

<table>
<thead>
<tr>
<th></th>
<th>Acute bacterial endocarditis</th>
<th>Subacute bacterial endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic emboli</td>
<td>Cerebral</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Major coronary</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Mesenteric</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Other major</td>
<td>4</td>
</tr>
<tr>
<td>Mycotic aneurysms</td>
<td>Cerebral with rupture</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Cerebral without rupture</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Aortic root with rupture</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Aortic root without rupture</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Coronary with rupture</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mitral valve</td>
<td>1</td>
</tr>
<tr>
<td>Ruptured heart valves</td>
<td>Mitral or chordae tendineae</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Aortic cusps</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Mitral and atrial septum</td>
<td>1</td>
</tr>
<tr>
<td>Glomerulonephritis with clinical uremia</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Splenic rupture</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Postmortem examination was performed on 44 patients (table 2). In contrast to the findings in the subacute cases, many emboli were septic and the valve damage was more acute, but mycotic aneurysms and glomerulonephritis were less frequent, probably because of the shorter duration of the disease.

In the 8 survivors *Staphylococcus aureus* was the responsible organism in 5 instances, and a pneumococcus in 3. The latter infections were successfully eradicated by 2 to 4 million units of penicillin a day over a 3- to 4-week period. However, in the staphylococcal cases very large doses of penicillin were used, from 20 to 60 million units a day for 5 weeks, combined with other antibiotics such as chloramphenicol and erythromycin or, in the later cases, vancomycin.

Three of the survivors have subsequently died: 1, in whom a perforated mitral valve was found post mortem, after 6 months of progressive congestive failure; 1 after 17 months of progressive congestive failure; and the third 20 months after cure, with cerebral emboli complicating a mitral valvulotomy. Five patients are living at 3, 4, 17, 34, and
60 months after cure of the acute infection.

In comparison the series reported by Anderson and Keefer is of special interest. They collected from the literature, up to 1948, 116 cases of staphylococcal endocarditis treated with antibiotics. The mortality was 77 per cent. Subsequently others have recorded a slightly more encouraging outcome with approximately a 50 per cent survival rate, but the most recent report (1958) by Shubin and his collaborators indicated a 74 per cent death rate in 27 cases.

As to therapy, Finland (1958) recommends that endocarditis caused by a resistant staphylococcus be treated by 2 antibiotics to which the organism is sensitive, initially in the maximum tolerated dose by the parenteral route, with treatment continued for 6 weeks. A change to the oral route and lower dosage is advised only after bacteremia, fever, and acute symptoms have subsided. If tolerance develops, the dose should be increased to the maximum tolerated or the antibiotics should be changed.

Subacute Bacterial Endocarditis Unsuccessfully Treated

Fifty-six of the patients with subacute bacterial endocarditis died before leaving the hospital (32 per cent). Congestive heart failure was an important cause of death in 31 of these patients. It can be seen from the postmortem findings of 48 of these cases that recent severe endocardial damage superimposed on preexisting heart disease of considerable degree was usually the determining factor (table 2). The immediate cause of death in one half of the cases was an embolus to a major systemic vessel or rupture of either a mycotic aneurysm or a valve cusp. Embolic myocardial infarction occurred in 5 instances, and this together with focal myocardial injury was probably an important factor in congestive failure and death in 14 of the 48 postmortem cases.

It is possible that many of these severe complications could have been prevented by earlier and more vigorous treatment, since the diagnosis was not suspected in 25 patients and 7 other patients died within a few days after diagnosis and before therapy could be effective. In general the reasons that the diagnosis was not suspected or established were as follows: hospitalization for only a few days; mistaking a complication (such as myocardial or cerebral infarction) for the primary disease; masking of symptoms by antibiotics employed for localized infection elsewhere; negative cultures; and absence of fever. Ten patients in the early days were given too small a dose by present standards.

The experience of others has been similar to that in the present series (table 3). A mortality of 32 per cent was recorded in Anderson and Keefer's collected statistics on a series of 457 patients with non-hemolytic streptococcus endocarditis. Friedberg's mortality rate was 34 per cent in 148 patients.

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**Table 3.—Major Factors as a Cause of Death during Subacute Bacterial Endocarditis**

<table>
<thead>
<tr>
<th>Series</th>
<th>Total no. patients</th>
<th>Number dead</th>
<th>Percent dead</th>
<th>Congestive failure</th>
<th>Arterial embolism</th>
<th>Gremia</th>
<th>Cerebral or other infection</th>
<th>Resistant infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson and Keefer (1948)</td>
<td>457*</td>
<td>149</td>
<td>32</td>
<td>33</td>
<td>22</td>
<td>3</td>
<td>5</td>
<td>53</td>
</tr>
<tr>
<td>Friedberg (1950)</td>
<td>148</td>
<td>50</td>
<td>34</td>
<td>29</td>
<td>13</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Cates and Christie (1951)</td>
<td>408†</td>
<td>108‡</td>
<td>24</td>
<td>50</td>
<td>13</td>
<td>14</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Present (1958)</td>
<td>175</td>
<td>56</td>
<td>32</td>
<td>32§</td>
<td>21</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

*Cases of non-hemolytic streptococcus subacute bacterial endocarditis with one or more treatment courses, collected from various hospitals in the United States.
†Based on an analysis of 408 patients with positive blood cultures from 14 treatment centers in Great Britain.
‡Cases dying during treatment and within 1 month.
§Includes 13 with valve rupture.
In his study inadequate therapy was explained by negative cultures in 19 instances, resistant organisms in 8, and diagnostic errors in 8. The commonest cause of death in his 50 fatalities was congestive heart failure in 29, cerebral embolism in 13, uremia in 6, and persistent infection in the remainder. In a combined study of 408 patients assembled from 14 centers in Great Britain, Cates and Christie found a mortality of 24 per cent during treatment or within a month thereafter.\textsuperscript{44}

**Subacute Bacterial Endocarditis Successfully Treated**

Of the patients with subacute bacterial endocarditis 119 (68 per cent) were treated successfully and were discharged from the hospital clinically well. If the 25 cases are excluded in which the disease was not recognized before postmortem examination, 79 per cent recovered of those actually treated. All 119 cured patients have been followed up to the present except for a single patient treated in 1948 who is "lost." The present state of health in each instance has been determined by hospital examination or by consultation with the patient or his physician. Figure 1 indicates the fate and duration of follow-up of the 119 survivors, and Table 4 presents the detailed statistical analysis of the clinical data based on the method of Merrell and Shulman.\textsuperscript{52} It can be seen that 60 patients have been followed for 5 years with a 70 per cent survival rate, and 23 patients for 10 years with a 50 per cent survival. The annual death rate in the present study averages 5 to 6 per cent.

These findings are in accord with those of Cates and Christie in their 4-year follow-up survey of collected cases, in which they found that after the first 6 months there was a low death rate of 4 per cent per annum. Several recent reports have presented follow-up data on patients with treated bacterial endocarditis, but as yet very few series include patients followed 10 years or longer,\textsuperscript{44, 46, 52-61} Thus in over 700 of these patients from the literature described as successfully treated, only 52 have been followed 5 or more years and only 17 to 10 or more years.

**The Fate of Patients with Healed Bacterial Endocarditis**

It has become increasingly clear with continued observation that even though therapy has been successful, a variety of delayed complications may occur in subsequent years. In
particular, further valve deformity associated with the healing of bacterial endocarditis may play a determining role in the patient’s later course.

There were 50 patients who survived subacute bacterial endocarditis but later succumbed, and a considerable number of patients were never quite well again. The prime cause of disability and death appeared to be slowly progressive heart failure in 21 instances, sudden death complicating severe aortic regurgitation in 4, cerebral vascular accident in 4, pulmonary embolism in 3, uremia in 3, subsequent acute bacterial endocarditis in 2, unassociated disease in 3; it was unknown in 10 cases.

The pathologic findings in 17 of the 50 patients who were successfully treated but later died serve to emphasize the importance of certain delayed clinical syndromes (table 5). Twelve of these patients showed severe valvular deformity, principally from healed subacute bacterial endocarditis which in turn resulted in slowly progressive congestive heart failure. Two patients revealed no recognizable residual vegetations, and 3 others had only small healed vegetations. The noteworthy features of healed endocarditis in this series are as follows:

Limitation of Activity. There are 68 living patients: 4 have been in congestive failure and 4 others have minor limitation; the remaining 60 are normally active. If all the cases that survived subacute bacterial endocarditis are considered, 42 of the 119 were ultimately in congestive heart failure (36 per cent). Kerr likewise has estimated that of the patients surviving treatment, one-sixth to one-third will have residual impairment.62

Recurrence of Bacterial Endocarditis. Ten patients had a recurrence of bacterial endocarditis 6 months to 10 years after the initial episode (table 6). All were readmitted to the hospital with 2 or more positive blood cultures and were successfully treated, except for 2 patients with *Staphylococcus aureus* endocarditis who died. One of these fatal cases had acute vegetations at the perforation site (presumably old) of an aortic cusp, and the other developed acute bacterial infection following mitral valvulotomy. This recurrence figure of 8.5 per cent is higher than that in the literature, which is quoted as 2 to 4 per cent,44, 46 but the longer duration of follow-up here, as compared with earlier reports, seems an adequate explanation for this discrepancy.

Severe Aortic Incompetence. Sixteen of the 119 cured patients had severe aortic incompetence characterized clinically by free regurgitation. In 8 instances subacute bacterial endocarditis either caused or aggravated the degree of valvular insufficiency. Nine patients are living at the latest follow-up, 5 of whom are well compensated. Four of the 16 have angina pectoris on effort, and 5 have undergone surgery with insertion of a Hufnagel valve. Four patients came to postmortem examination, and the findings indicated a severe degree of aortic incompetence attributed largely to the healed bacterial endocarditis. This hazard of further aortic valve damage and increased insufficiency at the time of subacute bacterial endocarditis is now well recognized.60, 61, 63, 64

Mitral Valve Aneurysm. In 2 instances in the 17 postmortem cases aneurysms of the anterior leaflet of the mitral valve were found. In 1 (patient F.G.) the size of the aneurysm probably obstructed the mitral orifice until its perforation later resulted in severe mitral regurgitation and congestive failure.65 Saphir and Leroy demonstrated 5 true aneurysms of the mitral valve in 12 hearts from patients with bacterial endocarditis seen between 1943 and 1946, but they had encountered none in a comparable series before the penicillin era.66 The lesion occurs most frequently on the anterior mitral leaflet, especially in the presence of aortic regurgitation, and it has been found post mortem in a patient as long as 5 years after bacterial endocarditis.67

Valve Perforation. Eight patients had perforation of a cusp of the mitral or aortic valve not related to aneurysm formation. All but 1 showed severe progressive congestive failure leading to death. Although it is often
### Table 5. Pathologic Findings in "Healed" Subacute Bacterial Endocarditis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Type of heart disease</th>
<th>Interval between cure of SBE and death</th>
<th>Concomitant heart failure</th>
<th>Valve lesion</th>
<th>Myocardium</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 H.D.</td>
<td>47</td>
<td>M</td>
<td>rheumatic</td>
<td>1 mo. yes</td>
<td>small aortic vegetations with bacteria*</td>
<td>focal interstitial fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 M.D.</td>
<td>43</td>
<td>F</td>
<td>rheumatic</td>
<td>2 mo. yes</td>
<td>perforation aortic cusp</td>
<td>focal fibrosis</td>
<td>died with coronary embolus and infarction</td>
<td></td>
</tr>
<tr>
<td>3 H.Y.</td>
<td>46</td>
<td>M</td>
<td>rheumatic</td>
<td>2 mo. yes</td>
<td>perforation aortic leaflet mitral valve</td>
<td>focal fibrosis</td>
<td>died with coronary embolus and infarction</td>
<td></td>
</tr>
<tr>
<td>4 A.F.</td>
<td>50</td>
<td>M</td>
<td>calcific aortic stenosis</td>
<td>5 mo. yes</td>
<td>perforation aortic valve</td>
<td>large areas fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 A.R.</td>
<td>57</td>
<td>F</td>
<td>calcific aortic stenosis</td>
<td>6 mo. yes</td>
<td>calcified nodules aortic valve perforation mitral valve sinus Valsalva aneurysm</td>
<td>patchy fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 A.S.</td>
<td>35</td>
<td>F</td>
<td>rheumatic</td>
<td>8 mo. yes</td>
<td>perforation aortic cusp</td>
<td>fibrosis Aschoff bodies</td>
<td>nephritis with uremia</td>
<td></td>
</tr>
<tr>
<td>7 A.K.</td>
<td>35</td>
<td>M</td>
<td>rheumatic</td>
<td>9 mo. no</td>
<td>perforation aortic cusp, acute endocarditis on mitral valve</td>
<td>focal fibrosis and abscesses</td>
<td>endocarditis twice; Staph. aureus on recent mitral valveulotomoty site</td>
<td></td>
</tr>
<tr>
<td>8 G.C.</td>
<td>68</td>
<td>M</td>
<td>rheumatic</td>
<td>11 mo. yes</td>
<td>small healed mitral valve vegetations</td>
<td>interstitial fibrosis</td>
<td>died with pulm. emboli and recent myocardial infarct</td>
<td></td>
</tr>
<tr>
<td>9 P.E.</td>
<td>32</td>
<td>M</td>
<td>rheumatic</td>
<td>1 yr. no</td>
<td>free aortic regurgitation with marked scarring aortic valves and ring</td>
<td>occasional fibrotic areas</td>
<td>angina; died at time of Hufnagel valve insertion</td>
<td></td>
</tr>
<tr>
<td>10 Z.F.</td>
<td>65</td>
<td>F</td>
<td>rheumatic</td>
<td>1 yr., 10 mo. yes</td>
<td>small calcified aortic vegetations</td>
<td></td>
<td>died from metastatic carcinoma ovaries</td>
<td></td>
</tr>
<tr>
<td>11 E.R.</td>
<td>58</td>
<td>F</td>
<td>rheumatic</td>
<td>2 yr., 1 mo. yes</td>
<td>no definite residual vegetations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 B.O.</td>
<td>24</td>
<td>F</td>
<td>bicuspid aortic valve</td>
<td>6 yr. yes</td>
<td>free aortic regurgitation perforation aortic cusp mitral valve aneurysm</td>
<td>patchy fibrosis</td>
<td>endocarditis twice; Staph. aureus perforation site aortic valve; infected thrombus in Hufnagel valve</td>
<td></td>
</tr>
<tr>
<td>13 T.C.</td>
<td>23</td>
<td>M</td>
<td>rheumatic</td>
<td>7 yr. no</td>
<td>free aortic regurgitation with scarring aortic valves</td>
<td>small areas of fibrosis</td>
<td>died 1 month after Hufnagel valve, ? arrhythmia</td>
<td></td>
</tr>
<tr>
<td>14 W.H.</td>
<td>41</td>
<td>M</td>
<td>rheumatic</td>
<td>8 yr., 8 mo. yes</td>
<td>no definite residual vegetations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 L.R.</td>
<td>30</td>
<td>M</td>
<td>rheumatic</td>
<td>9 yr. no</td>
<td>free aortic regurgitation with severely scarred aortic cusps</td>
<td></td>
<td>died suddenly—no evidence prior rheumatic heart disease</td>
<td></td>
</tr>
<tr>
<td>16 S.H.</td>
<td>80</td>
<td>M</td>
<td>rheumatic</td>
<td>10 yr. yes</td>
<td>shortening post. mitral valve cusp</td>
<td>fibrous scars</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 F.G.</td>
<td>36</td>
<td>M</td>
<td>rheumatic</td>
<td>10 yr., 1 mo. yes</td>
<td>mitral aneurysm with perforation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Gram-positive organisms were found post mortem microscopically in healing vegetations, indicating probable incomplete cure.
difficult to determine the time of rupture, in 4 patients failure appeared shortly before death and months after cure of the infection. As with ruptured mitral valve aneurysms, the abrupt appearance of a new and loud murmur followed by otherwise unexplained heart failure may signal this event (fig. 2).

Valve Distortion. In 2 cases the pathologist suspected that unusually severe distortion of the valve had been caused by the endocarditis. In the first instance there was extensive scarring and shortening of the posterior leaflet of the mitral valve leading to mitral incompetence of high degree, and in the other case there were extensive calcium deposits on the aortic valve, the character and distribution of which probably indicated the site of the healed endocarditis.

Myocarditis. The most frequent finding in the myocardium post mortem was widespread focal fibrosis, which probably represented healed myocardial involvement secondary to bacterial endocarditis. Aschoff bodies were found in the routine sections only once. Saphir and others have emphasized the importance of the varied myocardial lesions encountered in bacterial endocarditis, which include focal and diffuse myocarditis, micro- abscesses, perivascular cellular infiltration, and multiple minute areas of infarction.68-70

Late Embolism. There were 9 instances of embolism following cure of endocarditis, but in only 1 patient was death clearly attributed to the embolus. This patient (H.Y., table 5) died 2 months after hospital discharge following the sudden onset of a coronary embolus and acute myocardial infarction.71 Although neither late cerebral embolism nor ruptured systemic aneurysm was found in the postmortem cases, either condition may occur

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Interval between attacks of endocarditis</th>
<th>Type of heart disease</th>
<th>Organism</th>
<th>1st attack</th>
<th>2nd attack</th>
<th>Living duration of follow-up</th>
<th>Dead duration of follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.K.</td>
<td>35</td>
<td>M</td>
<td>6 mo.</td>
<td>RHD - AR, MS</td>
<td>a-strep.</td>
<td>Staph. aureus</td>
<td></td>
<td>Died in hospital. At p.m. healed S.B.E. aortic and mitral valve</td>
<td></td>
</tr>
<tr>
<td>D.D.</td>
<td>33</td>
<td>M</td>
<td>1 yr.</td>
<td>RHD - AS, AR</td>
<td>a-strep.</td>
<td>a-strep.</td>
<td>1 yr., 1 mo.</td>
<td>7 mo. (no autopsy)</td>
<td></td>
</tr>
<tr>
<td>P.C.</td>
<td>61</td>
<td>M</td>
<td>1 yr., 2 mo.</td>
<td>RHD - MR</td>
<td>a-strep.</td>
<td>a-strep.</td>
<td></td>
<td>4 yr., 9 mo.</td>
<td></td>
</tr>
<tr>
<td>M.C.</td>
<td>27</td>
<td>F</td>
<td>4 yr., 5 mo.</td>
<td>RHD - MR, AR</td>
<td>a-strep.</td>
<td>a-strep.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.S.</td>
<td>25</td>
<td>M</td>
<td>4 yr., 8 mo.</td>
<td>RHD - AS, AR</td>
<td>Staph. albus</td>
<td>a-strep.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.D.</td>
<td>25</td>
<td>F</td>
<td>6 yr., 6 mo.</td>
<td>PDA - bicuspid aortic valve</td>
<td>a-strep.</td>
<td>B-strep.</td>
<td>4 yr., 1 mo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.R.</td>
<td>59</td>
<td>F</td>
<td>6 yr., 7 mo.</td>
<td>RHD - MR</td>
<td>a-strep.</td>
<td>a-strep.</td>
<td></td>
<td>2 yr., 9 mo. (no autopsy)</td>
<td></td>
</tr>
<tr>
<td>F.C.</td>
<td>16</td>
<td>M</td>
<td>7 yr., 8 mo.</td>
<td>RHD - MR, AR, MS</td>
<td>a-strep.</td>
<td>Staph. albus</td>
<td>3 yr., 1 mo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.K.</td>
<td>37</td>
<td>F</td>
<td>10 yr., 7 mo.</td>
<td>RHD - MR</td>
<td>Enterococcus</td>
<td>a-strep.</td>
<td></td>
<td>10 mo.</td>
<td></td>
</tr>
</tbody>
</table>

*Follow-ups are from the time of the second attack.
RHD, rheumatic heart disease; PDA, patent ductus arteriosus; MS, mitral stenosis; MR, mitral regurgitation; AS, aortic stenosis; AR, aortic regurgitation; A.B.E., acute bacterial endocarditis; S.B.E., subacute bacterial endocarditis.
BACTERIAL ENDOCARDITIS IN THE ANTIBIOTIC ERA

Fig. 2. Perforation of anterior leaflet of the mitral valve by subacute bacterial endocarditis. The infection was arrested by antibiotics, but the patient succumbed 4 months later with intractable congestive failure. (Case Records of the Massachusetts General Hospital, no. 43321, New England J. Med. 257: 279, 1957.)

despite successful eradication of the infection. In the living patients an iliac mycotic aneurysm was found in 1 patient 9 months after discharge and was successfully excised, and an aneurysm, possibly mycotic, was found beyond the site of aortic coarctation at operation 2 years after bacterial endocarditis. Likewise, in Cates’ and Christie’s series late embolism occurred up to 70 days after treatment in 15 patients who were bacteriologically cured, and a mycotic cerebral aneurysm ruptured in 7 cases from 1 to 22 months after therapy; in 2 other cases a peripheral aneurysm developed after successful therapy.

Chronic Renal Damage. Although uremia was more frequently noted prior to the antibiotic era (in 14 per cent of Bell’s 108 cases), only 5 patients on long-term follow-up have evidence of permanent renal insufficiency. In 2 of these 5 patients there was evidence of glomerulonephritis at postmortem examination, in one without clinical impairment (patient L.R.) and in the other with a history of progressive uremia with the serum protein nitrogen rising to 150 mg. per cent (patient A.S.). This strikingly lower incidence since the introduction of antibiotics has been emphasized by others as well.

SUMMARY

Since the introduction of penicillin therapy for bacterial endocarditis in 1944 there have been 228 patients with this disease at the Massachusetts General Hospital. In 53 instances it was of the acute form, and in 175 it was subacute. The immediate outcome and the ultimate fate of these patients have been studied.

Acute bacterial endocarditis remains an ominous and often fatal disease. In only 21
patients was the presence of an acute bacterial infection on the heart valve recognized before death; 8 of these survived. Even when the disease was recognized clinically, death often ensued before an adequate antibiotic program could be instituted.

In the subacute group 119 patients (68 per cent) recovered and 56 (32 per cent) died. Postmortem examination in 48 of the 56 revealed that the principal cause of death in one half the cases was either rupture of a mycotic aneurysm or valve cusp or an embolus to a cerebral or coronary vessel. In the postmortem group the presence of bacterial endocarditis was unsuspected in 25. Therefore the "cure rate" in those actually treated was 79 per cent.

Of the 119 patients who recovered, 60 patients have been followed for 5 years with a 69 per cent survival rate, and 23 for 10 years with 49 per cent survival. Only 1 patient has been "lost." The principal cause of death in the years after cure of bacterial endocarditis has been congestive failure.

In the 119 original survivors, 16 had a high degree of aortic regurgitation, clearly augmented by their disease in 8 instances and necessitating a Hufnagel valve in 5. Embolic episodes unrelated to active infection occurred later in 9 patients, and arterial aneurysms were found at a later date in 2. A recurrence of bacterial endocarditis from 6 months to 10 years after the original infection occurred in 10 patients (8.5 per cent), 8 of whom again had *Streptococcus viridans* infection and were rescued, whereas 2 had *Staphylococcus aureus* and succumbed.

Postmortem examination was done in 17 patients with healed bacterial endocarditis who later died. In 12 of the 17 cases a severe degree of structural damage was found to be the result of the healing process. These alterations were responsible for a variety of special syndromes now recognized as peculiar to the antibiotic era. Notable in this group was aortic regurgitation of unusually high degree, frequently associated with left ventricular failure and angina pectoris. In other instances the abrupt onset of congestive failure heralded the rupture of a weakened valve cusp. Some patients were never well again, and their insidious decline and ultimate death resulted from one or more factors including valve distortion, diffuse myocardial injury, and occasionally a reactivation of rheumatic fever. Finally, in a few instances a fatal embolus occurred.

In concluding this survey of bacterial endocarditis in the antibiotic era, 3 special features remain for further study and clarification. First in importance is the prevention of rheumatic and possibly of congenital heart disease, thereby eradicating the cardiac lesions most susceptible to bacterial invasion. Second, the protection of patients with these lesions during dental and other surgical procedures is vital; although the currently recommended programs for this purpose seem adequate in the majority of instances, the optimal antibiotic dosage and the duration of administration remain to be settled. Third, the emergence in recent years of increasing numbers of organisms resistant to presently available antibiotics poses a most serious and urgent problem.

**SUMMARIO IN INTERLINGUA**

Depost le introduction de therapia a penicillina in endocarditis bacterial in 1944, 228 patientes con iste morbo ha essite tracitate al Hospital General Massachusetts. In 53 casos le morbo esseva acute, in 175 subacute. Le resultatos immediate e le ultime fato de iste patientes ha essite studiate.

Acute endocarditis bacterial remane un morbo de mal augurio que se termina frequentemente con le morte del paciente. In solmente 21 del casos, le presentia de un acute infection bacterial del valvula cardiae esseva recognoscite ante morte. In 8 de iste 21 casos le paciente superviveva. Mesmo in le casos in que le morbo esseva recognoscite clinicamente, le morte occurreva frequentemente ante que un adequate programma antibiotic poteva esser instituie.

In le grupo del casos subacute, 119 patientes se restabiliva e 56 moriva (i.e. 68 e 32 pro cento respectivamente). In 48 del 56 mortes, examines necroptic revelava que le causa principal del morte (in un mediate
del casos) espe guerra de un aneurisma mycotic o de un cuspide valvular o un embolo de vaso cerebral o coronari. In le grupo de casos studiate necroticamente, 25 habeva endocarditis bacterial non previamente suspicite. Assi le proportion de eurationes in casos de facto tractate esseva 79 pro cento.

Ex le grupo de 119 patientes qui se restabilita, 60 esseva tenite sub observation durante 5 annos, con un supervivencia de 69 pro cento, e 23 durante 10 annos, con un supervivencia de 49 pro cento. Le causa principal de morte durante le annos post le euration de endocarditis bacterial esseva disfallimento congestive.

Inter le 119 superviventes original, 16 habeva un alto grado de regurgitatio aortic, claramente augmentate per le morbo in 8 casos e requirente un valvula de Hufnagel in 5. Episodios embollic non relationate a infections active esseva trovate subsequentemente in 9 patientes, aneurysmas arterial in 2. Re-currentia de endocarditis bacterial, a periodos de inter 6 menses e 10 annos post le infection original, occurreva in 10 patientes (8,5 pro cento). Octo de iste esseva inficite per Streptococcus viridans; illes esseva salvate. Duo habeva Staphylococcus aureus; illes moriva.

Examines necrotic esseva effectuate in 17 patientes con curate endocarditis bacterial qui moriva subsequemente. In 12 del 17 un grado sever de dannification structural esseva recognoscite como resultato del proceso curative. Iste alterationes esseva responsabile pro un varietate de syndromes special que es hodie considerate como peculiar al era del antibioticos. Notabile in iste grupo esseva regurgitatio aortic de grado inusualmente alte e frequentemente associate con disfallimento sinistro-ventricular e angina de pector. In altere cases le declaration abrupte de disfallimento congestive precedeva le ruptura de un debile cuspide valvular. Plure patientes nunquam se retrovava completely ben, e lor insidiose declino e lor ultime morte resultava ab un o plures in un series de factores que includeva distorsion valvular, diffuse lesiones myocardial, e a vices un re-activation de febre rheumatic. Finalmente, in plure casos un embolo mortal occurreva.

Pro conclude iste revista de endocarditis in le era del antibioticos, il remane 3 aspectos special que require un studio e un clarification additional. Le plus importante es le prevention de morbo cardiace rheumatic e possibilemente etiam congenite, con le objectivo de eradicar le lesiones cardiaques que es le plus vulnerabile per invasiones bacterial. Secundo, le protection de patientes con iste lesiones durante interventiones dental e alteremente chirurgic es vitalmente importante. Ben que le programas currentemente recommandate pro iste objectivo pare esser adequate in le majoritate del casos, le mejor dosage de antibiotic e le duration del administration remane a fixar. Tertio, le emergentia, in recente annos, de crescente numeros de organismos resistente al nune disponibile anti-bioticos pone un seriosissime e urgentissime problema.

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