Long-Term Prognosis of Rheumatic Fever Patients Receiving Regular Intramuscular Benzathine Penicillin

By DOBOTHY G. TOMPKINS, M.D., BERNARD BOXERBAUM, M.D., AND JEROME LIEBMAN, M.D.

SUMMARY
The prognosis for 115 rheumatic fever patients subsequently receiving regular intramuscular penicillin prophylaxis for at least 5 years was studied. Average follow-up was 9.3 years, and 57 patients were followed for 10 years or longer. Of the 79 patients with acute mitral regurgitation, 70% lost their murmur from 4 days to 8.5 years after it was first heard. This is in contrast to those with acute aortic regurgitation which persisted in 73%. No patient developed mitral or aortic stenosis: this suggests that regular prophylaxis may prevent the development of stenosis. Congestive failure, cardiomegaly, and arrhythmia correlated closely with persistence of murmurs, but increased P-R interval, acute QRS or T-voltage variation or both, and ST-T abnormalities did not.

Additional Indexing Words:
Rheumatic valvulitis  Rheumatic prophylaxis  Rheumatic heart disease

The long-term follow-up studies of patients after acute rheumatic fever deal for the most part with patients, now adults, who never have been or are no longer receiving prophylaxis. Studies by Jones, Bland, and others were carried out prior to the advent of beta-streptococcal prophylaxis. The morbidity and mortality from acute rheumatic fever (ARF) has changed greatly owing to an unexplained decrease in severity and a reduction in the number of initial attacks and recurrences because of adequate antistreptococcal treatment and prevention. Since rheumatic fever unfortunately has not been eradicated, the prognosis for patients receiving prophylaxis and how long prophylaxis should be carried out need to be studied.

Methods
The Clinic
Patients are referred to the Rainbow Rheumatic Fever Clinic at Babies and Childrens Hospital from the staff and private inpatient services at the hospital, from other area hospitals, and from area doctors. The registry dates back for 10 years and includes many patients who began to be followed before that time as well as patients who have “graduated” to the adult cardiology clinic or to private internists. Over 90% of the patients receive 1,200,000 units of benzathine penicillin intramuscularly every 28 days. A few patients in the clinic prefer to take penicillin by mouth although intramuscular prophylaxis is advised. Some are allergic to penicillin and take a sulfa drug each day. Excellent compliance has been possible...
because of the interest and persistence of the staff. Since patients who refused to come in for prophylaxis could not be followed regularly, if at all, a controlled comparison of patients receiving prophylaxis with those not receiving prophylaxis could not be carried out. However, a few of the patients not maintained on prophylaxis have been seen intermittently and are available for comparison.

Patients periodically receive examinations, electrocardiograms (ECGs), and chest X-rays in the clinic. The frequency of the examinations depends upon the severity of the cardiac problem and the presence of other complaints. All but a few of the patients in the study were examined recently by one of us. These few were examined by an adult cardiologist.

Selection of Patients

Only patients who met the modified Jones criteria for acute rheumatic fever, who maintained regular prophylaxis with benzathine penicillin every 28 days, and had been followed for 5 years or longer after their initial episode of ARF were included in the follow-up study. Patients who had rheumatic fever elsewhere were not included unless an excellent history, detailed physical examinations, and laboratory data were available (two patients). Patients who had graduated from the clinic were included if they still received prophylaxis, and we could either call them in for examination or obtain a recent description by a cardiologist of their physical findings.

Unless the auscultatory findings were adequately described during the acute episode and during follow-up, the patient was not included in the study—that is, it had to be clear whether the murmur was one of the significant murmurs of rheumatic fever or a functional murmur. Most of the patients were examined by a cardiologist during the acute episode. A murmur heard at the lower left sternal border only or maximal at the lower left sternal border but also heard at the apex was not considered a rheumatic murmur. The patient was considered to have mitral regurgitation if there was a pansystolic murmur maximal at the apex with radiation to the axilla. Aortic regurgitation was considered to be present if an early diastolic murmur was described along the left sternal border.

The patient had to have had a clear history of one major plus two minor or two major criteria. Joint symptoms had to be adequately described in order to determine if the patient had definite polyarthritis (objective as well as subjective joint findings). Pertinent laboratory, ECG, and X-ray data were required for the patient to be included. Over 300 charts were reviewed. After patients were excluded because of insufficient data concerning their initial episode or because of insufficient follow-up, 115 patients were included in the study.

Results

The Initial Episode of Acute Rheumatic Fever

The average age of the patients at the time of the acute attack was 8.6 years. Fifty patients were 10 years of age or older and six were 15 years or more at the time of their ARF. The average age of the patient at the first episode is similar to that of the series of 1,000 patients reported by Bland and Jones but is greater than in many series probably because the older teenager with ARF tends to be admitted to the pediatric rather than to the adult service at our hospital.

Thirty-five patients had neither the murmur of mitral regurgitation (MR) nor of aortic regurgitation (AR) with the acute episode (table 1). Of these 35, one had a transient middiastolic rumble at the apex (the Carey Coombs murmur) and 27 others had ECG changes suggesting myocarditis, such as an increased P-R interval, ST-T abnormalities, acute QRS or T-voltage changes, or both acute QRS and T changes, or an arrhythmia (table

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of pts</th>
<th>Average follow-up (yr)</th>
<th>Followed more than 10 yr (pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No murmur of MR or AR</td>
<td>35</td>
<td>7.9</td>
<td>9</td>
</tr>
<tr>
<td>MR or AR*</td>
<td>66</td>
<td>9.7</td>
<td>38</td>
</tr>
<tr>
<td>MR and AR</td>
<td>14</td>
<td>11.2</td>
<td>10</td>
</tr>
</tbody>
</table>

*Only one patient had AR without MR.
2). Thus only seven patients had no evidence of myocarditis or ECG abnormalities.

Sixty-five patients had acute MR without acute AR, one had AR only, and 14 had MR and AR. Additional findings on these patients are summarized in Table 2. The P-R interval was considered prolonged if it was greater than the 95th percentile for age. The P-R interval in all these patients but one decreased significantly and to normal while in the hospital. ST-T abnormalities included abnormal S-T-segment elevations, flat T waves, or a significant change in the mean T-wave vector. Arrhythmia as used in Table 2 refers to atrial, A-V junctional, or ventricular arrhythmia. Ten other patients who showed marked nonphasic sinus arrhythmias were not included. Acute QRS or T-voltage variations or both refer to marked change in voltage. Transient voltage variations occurred irrespective of the presence of valvulitis. Of the total 115 patients 14 did not have elevated antistreptolysin O titers. Of these 14 all but two had elevated C-reactive proteins.

Table 2

<table>
<thead>
<tr>
<th>Findings</th>
<th>No murmur (35 pts)</th>
<th>MR and/or AR (89 pts)</th>
<th>Total (115 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>31</td>
<td>89</td>
<td>42</td>
</tr>
<tr>
<td>Monoarthritis</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Polyarthralgia</td>
<td>1</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Joint symptoms, total</td>
<td>32</td>
<td>92</td>
<td>67*</td>
</tr>
<tr>
<td>Chorea, total</td>
<td>8</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>“Pure” chorea</td>
<td>4</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>3</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Pericardial friction rub</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Elevated C-reactive protein</td>
<td>32</td>
<td>91</td>
<td>72</td>
</tr>
<tr>
<td>Elevated ASO titer</td>
<td>28</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>Cardiomegaly on X-rays</td>
<td>1</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>ST-T abnormalities</td>
<td>16</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Increased P-R interval</td>
<td>12</td>
<td>34</td>
<td>41</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>6</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Acute QRS and/or T-voltage</td>
<td>4</td>
<td>11</td>
<td>20</td>
</tr>
</tbody>
</table>

*Two patients had monoarthritis and polyarthralgia.

Transiency or Persistence of Cardiac Abnormalities

Of the 79 patients with acute MR, 70% lost this murmur anywhere from a few days to 8.5 years after it was first noted. The patient whose MR persisted 8.5 years recently had cardiac catheterization and was found to have no evidence of MR on left ventricular angiograms. In a report by Massell and associates on 484 patients followed as long as 9 years after having ARF, 247 had evidence of valvulitis on admission to the hospital. Nineteen percent lost their murmurs before discharge, and 9 years later only 35% still had their murmurs. The length of time for MR to disappear in this study is shown in Table 3. The most common time for MR to disappear was between 1 and 6 months after it was first heard, and the average duration was 1.8 years. In 20 of the total 79 patients with MR, murmurs disappeared more than 2 years, and in six more than 5 years, after the onset of ARF. All of the patients who had MR but lost the murmur have normal findings on physical examinations, ECGs, and X-rays at present.

Figure 1 illustrates the disappearance of MR. All 79 patients are included through the first 5 years. Beyond 5 years, at each point the percentage is based on the number followed to that time. The MR murmurs decreased sharply during the first year and by 9 to 10
Table 3
Length of Time for Mitral Regurgitation to Disappear

<table>
<thead>
<tr>
<th></th>
<th>&lt;1 mo</th>
<th>1-6 mo</th>
<th>6 mo-1 yr</th>
<th>1-2 yr</th>
<th>2-3 yr</th>
<th>3-5 yr</th>
<th>5-7 yr</th>
<th>7-10 yr</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts</td>
<td>6</td>
<td>17</td>
<td>3</td>
<td>9</td>
<td>4</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>%</td>
<td>11</td>
<td>31</td>
<td>5</td>
<td>16</td>
<td>7</td>
<td>18</td>
<td>5</td>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 1
Persistence of mitral regurgitation. All 79 patients who had MR with their acute episode were followed at least 5 years. At 6 years 74 patients, at 7 years 65, at 8 years 61, at 9 years 54, and at 10 years 48 patients were still being followed who had MR with their acute episode. Same abbreviations as text.

years the incidence has leveled off at 26 to 27% of the original number heard.

Correlations between findings during the acute episode and persistence of MR were made in table 4. Patients with both MR and AR acutely were not included because there were too few patients to attempt any correlation. Signs of congestive heart failure and cardiomegaly correlated most closely with the persistence of the murmur, as has been found by others. Seventy-four percent of all patients with MR and no AR lost their murmur. If no cardiomegaly was present, 84% became murmur-free; with cardiomegaly only 36% became murmur-free. The Irvington House Study classified patients according to cardiac status at the time of admission to the clinic where they received parenteral benzathine penicillin, oral penicillin, or oral sulfadiazine prophylaxis. Of those patients with MR and no AR when admitted to the clinic and a history of only one episode of ARF, 44% became murmur-free (follow-up, 4 to 7 years). If no cardiomegaly was present 60% lost their MR murmur, but if cardiomegaly was present only 25% did so. In the Joint Report
from Great Britain and the United States\textsuperscript{15} patients receiving sulfadiazine since their first known episode of ARF were followed for 5 years. If an apical systolic murmur was the only murmur during the acute episode and was not accompanied by cardiac failure, 74% were murmur-free at 5 years. Of patients with congestive failure or pericarditis, or both with the initial episode, 30% were murmur-free at 5 years. Bland and Jones\textsuperscript{6} followed 1,000 patients beginning in 1928; hence the patients did not receive prophylaxis. Of 635 patients with signs of well-defined rheumatic heart disease, at the end of 10 years 11\%, and by 20 years 16\%, had no physical signs of valvular disease. One third of their patients with only a grade II or greater systolic murmur at the apex lost their murmur by the end of 20 years. The mortality in the patients who initially had MR only was 6\% at 20 years compared to a mortality of 80% among patients who had a greatly enlarged hearts or congestive heart failure initially.

In addition we noted in our study that only 40\% of the patients with MR and an arrhythmia lost their murmur. This has not been noted in previous studies. The acute transient QRS or T-voltage changes, or both, in the ECG showed a less significant correlation with the persistence of the murmur and an increased P-R interval or ST-T abnormalities showed no correlation.

In patients with persistent MR, clinically the regurgitation seemed to regress. Four patients still have marked MR with cardiomegaly, and three have moderate MR with slight cardiomegaly. All others have normal-sized hearts on X-rays and are symptom-free and unrestricted in activity. In no patient did the mitral valve disease seem to worsen. No patient in our series developed mitral stenosis. In Thomas\textsuperscript{17} follow-up of 198 patients, all patients who developed mitral stenosis (MS) had recurrences of ARF.

Aortic regurgitation was less likely to disappear than MR, as has been previously shown.\textsuperscript{1, 14} Of the patients with AR, 73\% still had the murmur; however, in all but one the murmur had become fainter. No patient developed aortic stenosis.

There were no deaths from rheumatic heart disease among the patients maintained on prophylaxis during the past 10 years, whether or not they met the criteria for the study and were among the 115 reported. (The charts of over 300 patients were reviewed.) The only cardiac deaths occurred in patients who failed to maintain prophylaxis and had recurrent rheumatic fever or subacute bacterial endocarditis, or both.

**Table 4**

<table>
<thead>
<tr>
<th>Phenomenon associated with MR</th>
<th>Persistence of murmur at follow-up in patients in whom phenomenon was present*</th>
<th>Absent†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomegaly on X-rays</td>
<td>9/14 (64%)</td>
<td>8/51 (16%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>9/15 (60%)</td>
<td>8/50 (16%)</td>
</tr>
<tr>
<td>Acute QRS and/or T-voltage variations</td>
<td>6/15 (40%)</td>
<td>11/50 (22%)</td>
</tr>
<tr>
<td>ST-T abnormalities</td>
<td>13/41 (32%)</td>
<td>4/24 (17%)</td>
</tr>
<tr>
<td>Increased P-R interval</td>
<td>9/33 (27%)</td>
<td>8/32 (25%)</td>
</tr>
</tbody>
</table>

\*Present at acute episode.
†Absent at acute episode.

**Subacute Bacterial Endocarditis and Recurrences of Rheumatic Fever**

No patient receiving benzathine penicillin developed bacterial endocarditis. Three patients not in the study, one maintained on sulfadiazine and two on oral penicillin, developed this complication.

One patient who had a recurrence of acute rheumatic fever was known to have received her benzathine penicillin every 28 days. She had MR for 7 months after the onset of the initial episode. The murmur disappeared for 1 year and then she again developed definite
acute rheumatic fever with MR and chorea. The MR persisted for 15 months after the second episode and has not been heard for the past 10 years. Four patients were known to have had acute glomerulonephritis some time before their episode of ARF.

Discussion

The Acute Episode and Prevention of Acute Rheumatic Fever

The clinical and laboratory findings during the acute episode were comparable to those in other studies. Erythema marginatum and subcutaneous nodules, manifestations which are usually late, were more common in our patients with negative C-reactive protein in the serum than in those with positive C-reactive proteins. The lack of "good fidelity" which has been noted by others and by the director of our rheumatic fever clinic prompted the urging of all patients to come in every 28 days for intramuscular penicillin prophylaxis. Because of the interest and persistence of the clinic personnel this has been highly successful. Only one patient receiving benzathine penicillin had a recurrence of rheumatic fever although she had received her penicillin on schedule. A few patients receiving intramuscular prophylaxis did develop streptococcal infections as has been known to occur.

Acute rheumatic fever is well known to occur in adulthood. Gordis and associates reported that 18% of all patients hospitalized in Baltimore for ARF between 1960 and 1964 were adults. Grant's follow-up of 1,000 rheumatic fever patients included 97 with mitral stenosis. More than half of these 97 reported that they had had recurrences of ARF during adulthood. Leonard and Winger recommended long-term prophylaxis in their study of 577 patients followed an average of 7 years after ARF. Of 265 without carditis initially, 7.2% had recurrences 1 to 18 years later, and of 312 with carditis, 4.2% had recurrences 1 to 20 years later. Because initial episodes were noted up to age 36 and recurrences were noted through the twentieth year after the initial episode, these authors recommended long-term prophylaxis for patients who had no initial evidence of carditis as well as those with carditis.

Regression of Heart Disease

The disappearance of 70% of the MR murmurs and lack of increase in severity of MR in any patient could be expected if further damage to the valve by recurrent rheumatic fever is prevented. In Bland and Jones series of 1,000 patients followed before the era of prophylaxis only 20% of patients with MR alone lost their murmur by 10 years, contrasting with 70% in our series.

Thomas followed 198 rheumatic fever patients for 5 years or more, 106 of whom did not have recurrences of rheumatic fever. Of those with slight carditis who did not have recurrences, none developed serious heart disease, and at 5 years 76% had lost their murmurs.

The decreased likelihood of MR to disappear in patients with cardiomegaly or an arrhythmia during the acute episode presumably reflects the more severe nature of cardiac involvement in these patients. The relatively benign course of MR, even if the patient did have cardiomegaly, contrasts sharply with the follow-up studies before the time of prophylaxis and with the follow-up of patients with recurrent attacks. Bland and Jones in their follow-up of 1,000 patients found that after 20 years 30% had died; 80% of the deaths were from rheumatic heart disease, and 10% were from bacterial endocarditis. Thomas, in a more recent study, found that "deterioration occurs with more than one recurrence or with histories of previous attacks"; 10 of 15 patients who deteriorated or died had three or more attacks of ARF. Thus, it appears that rheumatic heart disease frequently disappears clinically, usually regresses, and seldom worsens in the first 10 to 20 years if recurrences of ARF or episodes of SBE are prevented.

Lack of Development of New Heart Disease

Before the time of prophylaxis Bland and Jones found that a significant number of rheumatic fever patients initially free of
carditis had developed murmurs on later follow-up. Of 347 patients who "recovered unscarred" from their original episode of ARF, 83 (24%) at the end of 10 years and 154 (44%) at the end of 20 years had developed MS. It is unclear whether any of these patients had murmurs during the acute episode which disappeared before discharge from the hospital.

Feinstein and co-workers\textsuperscript{24} in a later study found that all of the patients who were initially free of carditis during acute rheumatic fever remained free of rheumatic heart disease. Follow-up was up to 11 years (mean, 7.8) and all patients received parenteral benzathine penicillin, oral penicillin, or oral sulfadiazine prophylaxis. Our study confirms this finding and also includes some patients followed more than 15 years. Feinstein's group, however, attributed the lack of development of new heart disease to greater interest in diagnosis and follow-up of ARF since prophylaxis and rheumatic fever clinics have become widespread. He stated "rheumatic heart disease develops insidiously de novo, therefore, in the medically undetected patient with carditis, but not in the patient examined during the acute attack and judged to be free of carditis." That is, patients who develop "new" heart disease on later follow-up actually had carditis which was undetected during the acute episode. Thomas\textsuperscript{17} found that, if patients have no heart disease in the hospital, they will have none at follow-up over periods of 5 to 10 years if there are no recurrences.

Although the lack of development of MS in patients without earlier evidence of carditis may be due to failure to detect carditis earlier, as Feinstein and associates\textsuperscript{24} discussed, the lack of development of MS in patients with a known history of carditis in our study needs further investigation. MS has been said to take 2 to 20 years to develop after an episode of ARF.\textsuperscript{5, 25} We had 79 patients with known mitral involvement and 29 others with evidence of carditis followed 5 years or longer. Forty-eight of the patients with mitral valve disease were maintained on good prophylaxis and followed 10 years or longer. Since the few patients who refused prophylaxis did not attend the clinic, we have no "control" group of patients not receiving prophylaxis. We do know, however, of six patients not receiving prophylaxis who were seen intermittently at this hospital during this period who did develop MS. Four of these six were known to have had recurrent rheumatic fever.

Thomas\textsuperscript{17} found that MS developed only in patients who had had three or more attacks of rheumatic fever. Feinstein’s group\textsuperscript{24} noted that patients with mitral systolic and diastolic murmurs were more likely to have signs of residual mitral valvular damage if they had recurrent attacks of rheumatic fever than were patients without recurrent attacks. In the Irvington House Study\textsuperscript{14} of this same group of patients, three had MS on admission to the clinic and five later developed it. It is unclear what type of prophylaxis these patients received, whether they maintained regular prophylaxis, and whether they had more than one episode of ARF.

Bland and Jones\textsuperscript{6} found that only one third of their rheumatic fever patients who developed MS had clear evidence of recurrent activity. Walsh and associates\textsuperscript{6} in another study, however, reported on 81 young persons with pure MS. All had definite rheumatic fever at the start of the follow-up study, but the authors emphasized that only one had severe symptoms with the initial episode. Eighty-five percent had definite recurrences. Seventeen percent of the recurrences were manifested by chorea only, 71% were mild rheumatic fever, and 12% were severe rheumatic fever. The authors emphasized that the patients who developed pure MS seem to be those who had mild initial episodes and mild recurrences. Because we found no patient who developed MS if he had received prophylaxis since the initial episode of ARF, and because of the findings that stenosis develops without previous carditis or a clear history of mild or severe recurrences after ARF, we believe that perhaps MS develops only after recurrences, some of which may be subclinical.

Margarey\textsuperscript{20} had discussed the pathologic findings in the mitral valve when it has
become stenotic. Approximately 70% of the mitral valves made stenotic from rheumatic fever had fibrin deposits. "Deposits of fibrin . . . become covered with endothelium extending from the contiguous surface of the cusp and fibroblasts from the pre-existing tissue gradually replace the plaque of fibrin by a layer of firm fibrous tissue. Some sections of thickened valves show this process to have been recurrent, the deeper layers of fibrin being in a more advanced stage of organization than the superficial . . . This repeated fibrin deposition followed by replacement with fibrous connective tissue leads not only to thickening of the cusps but also to gradual narrowing of the valve orifice by a silting-up process."

Whether new layers of fibrin are laid down in the absence of recurrences of ARF cannot be ascertained since the process cannot be observed in vivo. Some think that recurrences are not necessary for the "silting-up" process, but others suggest that it takes more than one attack to cause the valve to become stenotic. Gould and Guttmann27 reported the pathologic findings in the mitral valve of a patient who developed recurrent MS after commissurotomy. At the second operation the "gross anatomic and histologic appearance of the resected fragments of valve tissue with verrucae suggest that we are dealing with a chronic fibrosing rheumatic valvulitis with recrudescence of the rheumatic activity" despite the lack of symptomatic recurrence. If MS develops only after recurrent rheumatic activity, the repeated episodes could explain the "silting-up" process with new layers of fibrin being deposited with recurrent episodes.

We, therefore, suggest that regular prophylaxis should be continued through adulthood. This is based on the following: (1) ARF not uncommonly occurs in adulthood, (2) MS probably develops only after recurrent rheumatic fever which may be subclinical, and (3) MS has not been found to develop in patients who maintained regular prophylaxis. Since prophylaxis in adulthood is not generally advised, an answer could come if a control study were carried out in which patients who have been receiving good prophylaxis are divided into two groups when they reach adulthood. One group would continue to receive intramuscular benzathine penicillin prophylaxis every 28 days, the other would not.

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