A Study of the Manifestations of Rheumatic Fever Following Cessation of Therapy

By Edward E. Fischel, M.D., Charles W. Frank, M.D., and Marjorie T. Bellows, M.S.

Following cessation of therapy for acute rheumatic fever manifestations of rheumatic activity frequently reappear. The incidence of these manifestations and their severity were studied during the 3-week observational period in 257 patients treated as part of the Cooperative Clinical Trial on the treatment of rheumatic fever. From the analysis of these manifestations certain concepts may be derived concerning diagnostic and therapeutic criteria.

When hormone or salicylate therapy for acute rheumatic fever is discontinued there is frequently a reappearance or persistence of manifestations of rheumatic activity. These have been variously interpreted. Exacerbation of the disease following withdrawal of salicylate therapy was described in 1876, when salicylate was introduced as an antirheumatic drug. With the use of adrenal corticoids more attention has been focused on this phenomenon. Although the manifestations of rheumatic activity are frequently transient and subside spontaneously, the benign aspects of this phenomenon have perhaps been overly emphasized. Attempts have been made to differentiate between the mild and severe exacerbations using the terms "rebound" and "reactivation." Such differentiation can be made only in retrospect. The post-therapy reactions are manifestations of rheumatic activity emerging after the discontinuation of suppressive therapy. Their severity seems to be related to the severity and duration of the preceding rheumatic attack. Study of this phenomenon may also contribute to the formulation of broader diagnostic and therapeutic concepts.

The records of 257 children treated in the United States and Canada in the Cooperative Clinical Trial of ACTH, Cortisone, and Aspirin, were made available for this analysis by agreement of the principal investigators of that study. It is thought that these data afford a unique description of the post-therapy period, inasmuch as all the children were kept in the hospital for 3 weeks following 6 weeks of therapy. Regular observations of the commonly accepted indices of rheumatic involvement were recorded.

Because the current analysis is concerned with the description of the post-therapy period, the data from all 3 treatment groups have been combined. Cardiac murmurs have not been included as indices of "activity," since changes in intensity are difficult to evaluate, and new murmurs did not occur during this period. The signs observed are listed in Table 1. Abnormal erythrocyte sedimentation rates of 20 mm. or more (uncorrected Wintrobe method) occurred in one half of the patients. Fever, defined as at least 2 consecutive days of rectal temperature over 100.3° F. or 1 day over 101.3° F., was recorded almost as frequently. The other manifestations in order of frequency were P-R interval greater than 0.18 second, joint involvement manifested by arthralgia or arthritis, erythema marginatum, congestive failure or pericarditis, nodules, and chorea.

Of the 257 children, one quarter had none of the above manifestations of rheumatic activity during the 3 weeks following therapy, and the others had 1 to 5 manifestations (Table 2).

These 8 manifestations appeared in 35 dif-
Table 1.—Incidence of Specific Manifestations

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Patients Number</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>114</td>
<td>44.4</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>130</td>
<td>50.6</td>
</tr>
<tr>
<td>P-R interval over 0.18 second</td>
<td>37</td>
<td>14.4</td>
</tr>
<tr>
<td>Joint involvement</td>
<td>23</td>
<td>8.9</td>
</tr>
<tr>
<td>Failure or pericarditis</td>
<td>10</td>
<td>3.9</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>13</td>
<td>5.1</td>
</tr>
<tr>
<td>Nodules</td>
<td>9</td>
<td>3.5</td>
</tr>
<tr>
<td>Chorea</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>No manifestations</td>
<td>67</td>
<td>26.1</td>
</tr>
<tr>
<td>Total patients</td>
<td>257</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 2.—Number of Manifestations of Rheumatic Fever per Patient

<table>
<thead>
<tr>
<th>Number of manifestations per patient</th>
<th>Number of patients</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>67</td>
<td>26.1</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
<td>35.0</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>25.3</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>9.7</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>2.7</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Total patients</td>
<td>257</td>
<td>100.0</td>
</tr>
</tbody>
</table>

ferent combinations, forming a wide spectrum of severity. Many of the combinations of signs that occur during the post-therapy period would not be specific enough to establish a diagnosis of rheumatic fever without knowledge of the earlier course. This observation suggests that inadequate or abortive initial therapy may obscure later attempts at diagnosis.

The number of manifestations exhibited during the post-therapy period varied with the cardiac status on admission, there being more manifestations with more severe initial involvement. In table 3 the 257 children are grouped according to the cardiac status at the start of therapy. The first 2 groups represent first attacks of rheumatic fever, with or without carditis. Children with prior heart disease are next listed. Finally, 33 children with failure or pericarditis are presented, three fourths of whom were in their first known attack.

There was also a great number of manifestations during the post-therapy period in those patients who were first treated 6 weeks or more after the onset of their illness (table 4). It is not known whether this increase is due to the selective factor of late therapy itself or to other factors. There is no difference between the groups treated 0 to 14 days from onset and those treated 14 to 42 days.

These data suggest several interpretations concerning the significance of the post-therapy period. The apparent relationship between the duration and severity of the rheumatic process before therapy and the frequency with which abnormalities appear after withdrawal of therapy is again indicative of the relationship of the "rebound" to the basic disease. If the "rebound" were solely a drug-induced phenomenon, unrelated to rheumatic fever, such a relationship would not be expected.

The importance of the post-therapy exacerbation during its acute phase is dramatically apparent in those few patients, 4, who first experienced cardiac failure or pericarditis at that time. One of these patients died, despite prompt reinstitution of therapy. Six patients had a recurrence or continuation of failure and pericarditis during the period following therapy. In some instances the severity of the disease during the post-therapy period was as great or greater than at the start of treatment. In most instances, the various abnormalities subsided spontaneously. Retreatment was considered necessary for only 6 patients. It is difficult to assess the contribution of the rebound to the development of permanent valvular or myocardial damage. Under the conditions of therapy, prophylaxis, and 1 year follow-up of the Cooperative Clinical Trial, it appears that in most instances no effect could be attributed to the recurrence of inflammatory reaction after discontinuation of therapy. Nevertheless, the extent of heart damage may be related to the severity and duration of rheumatic inflammatory reaction, whether this occurs before, during, or after suppressive therapy. Just as it appears judicious to avoid recurrent attacks of rheumatic fever by prophylaxis, so it may be of value to avoid exacerbations of rheumatic in-
flammation at any time. Appropriately designed therapeutic programs may eliminate or minimize the recurrence of inflammatory reaction. This approach may be of particular importance in the management of those patients with cardiac involvement or illness of long duration, in whom a recurrence of inflammation may be more likely to occur.

From the nature of the rebound we may also deduce some of the areas in which the drugs had an effect, however incomplete. When any or all of the presenting manifestations of rheumatic activity subside during drug therapy, the effect may be attributed to several possible causes: spontaneous remission in the course of the disease, bed rest, or to the drug administered. Following cessation of therapy, the recurrence of rheumatic manifestations is ample evidence that the drug employed did not eradicate the disease. However, it is also evidence, in retrospect, that the drug had a suppressive action while it was being administered. It was widely taught that aspirin did not affect the rheumatic inflammation in the heart (and that concept has occasionally been extended to cortisone). The recurrence of heart failure or pericarditis after cessation of either drug conflicts with that view. A flare-up of the disease process would not be expected if a totally ineffective agent were discontinued.

**Summary**

The 3-week period following cessation of therapy was studied in 257 children with rheumatic fever treated for 6 weeks as part of the Cooperative Clinical Trial. Most patients exhibited some manifestations of rheumatic activity, most frequently an elevation of the erythrocyte sedimentation rate or of temperature. Occasionally more severe and complex manifestations occurred. The number of manifestations was greater in those patients with more severe manifestations on admission.

The study of the post-therapy period may provide some perspective concerning diagnostic criteria and the effectiveness of therapeutic agents in retrospect. The manifestations of the post-therapy period are sufficiently common under apparently good conditions of management. Study of this period should be included in attempts to define optimal therapy for rheumatic fever.

**Summario in Interlingua**

Durante 3 septimanas immediatamente post le cessation del tractamento, observationes esseva colligite in 257 patientes pediatric con febre rheumatic qui habeva essite tractate durante 6 septimanas como parte del Essayo Clinic Cooperative.

Le majoritate del patientes exhibiva alseva manifestationes de activitate rheumatic, le plus frequentemente un acceleration del sedimentation erythrocytic o un elevation del temperatura. In alseva casos, plus sever e complexe manifestationes esseva noteate. Le numero de iste manifestationes esseva plus gran-de in le patientes in qui le manifestationes habeva essite le plus sever al tempore de lor hospitalisation.

Le studio del periodo post-therapeutic provide possibilmente un certe perspectiva concernente le criterios diagnostic e le efficacia
del agentes therapeutic (judicate in retrospecto). Le manifestationes del periodo post-tractional es satis commun sub apparentemente bon conditiones de providentia. Le studio de iste periodo debe esser includite in tentativas de definir optimos therapeutic pro febre rheumatic.

REFERENCES

Medical Eponyms

By ROBERT W. BUCK, M.D.

De Musset Sign. The de Musset sign of aortic regurgitation was described not by a physician, but by Paul de Musset, brother of the poet, in his "Biography of Alfred de Musset" (Biographie de Alfred de Musset, sa Vie et ses Oeuvres) Paris, 1877. The quotation is from chapter 14, pages 274-275.

"The illness so well cared for by Sister Marcelline had left him with a troublesome tendency to affections of the chest...We called the doctors twice during the course of the winter; they bled him too often.

"Whatever they may say, I am convinced that their lancets caused him irreparable harm. At breakfast one morning in March, I noticed that my brother's head was bobbing involuntarily with each pulse beat. He asked my mother and me why we were looking at him with such a startled air. We told him what we saw, and he said, 'I did not think you could see it; but I will reassure you."

"He made some sort of pressure on his neck with his index finger and thumb, and in a moment his head stopped marking his pulse. ‘You see,' he then said to us, 'that this dreadful illness can be cured by simple and inexpensive means.'

"We were reassured, being ignorant, for we had just observed the first symptom of a grave malady to which he was to succumb fifteen years later."
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Circulation. 1958;18:367-370
doi: 10.1161/01.CIR.18.3.367

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