The Natural History of Rheumatic Fever and Rheumatic Heart Disease

Ten-Year Report of a Cooperative Clinical Trial of ACTH, Cortisone, and Aspirin

A Joint report by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association.*

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THIS is the 10-year report of the United Kingdom and the United States and Canadian Cooperative Clinical Trial which was conducted in 1951-52 and designed to compare the relative merits of ACTH, cortisone, and aspirin in the treatment of rheumatic fever and their effects upon the evolution of rheumatic heart disease. Over a period of approximately a year and a half, and under closely defined diagnostic criteria, 497 children under the age of 16 were admitted to the trial in 12 centers in the United Kingdom, the United States, and Canada. They were allocated at random to one or another of the three agents under investigation and treated according to a specified plan for 6 weeks. After a further 3 weeks of detailed observation, they were followed up at defined intervals. Full details of the plan of study were given in an earlier publication.¹

Two reports at 1⁴ and at 5 years² have been published. The first report compared the three treatment groups in detail throughout the 6 weeks of treatment, 3 succeeding weeks of observation, and at the end of a further year of follow-up. It was concluded that there was no evidence that any of the three agents resulted in uniform termination of the disease and that on each agent some patients developed fresh manifestations during treatment. Treatment with either of the hormones resulted in more prompt control of certain acute manifestations but this more rapid disappearance was balanced by a greater tendency for the acute manifestations to reappear for a limited period upon cessation of treatment. Congestive cardiac failure and pericarditis each responded similarly in all three treatment groups. Treatment with the hormones was followed by a more rapid disappearance of nodules and soft apical systolic murmurs but at the end of 1 year there was no significant difference between the three treatment groups in the status of the heart.

The second report³ at 5 years showed that, on the treatment schedule used, the prognosis had not been influenced more by one treatment than another. Moreover, the very low case fatality rate on each of the three treatments indicated that the patients had done well regardless of which therapy was given. In terms of natural history, the major factor determining the prevalence of rheumatic heart disease at 5 years was the status of the heart when treatment was begun. Cases requiring retreatment for recurrence of acute rheumatic fever had had a more severe cardiac involvement at the start of treatment. A larger proportion of these retreated cases had murmurs at 5 years.

After the publication of the 5-year report, and because information was lacking on the course of rheumatic fever and rheumatic heart disease in the modern era, it was decided to extend the follow-up period to 10 years. It was, however, not possible in this 6- to 10-year interval to perform repeated scheduled examinations as in the first 5 years. Instead, an examination of each case was to be made at a date as close as possible to the tenth anniversary of the end of the original 9-week period of treatment and observation. However, the long hiatus in follow-up after the 5-year examination greatly increased the difficulty in tracing some of the cases. Thus, while the 23 deaths now reported are those known to have occurred in the interval from start of treatment up through the tenth anniversary, the 10-year period for the examined cases had to be defined more broadly. Thus, in one center a relatively large number of cases had been examined in the eighth year, and in all centers a few cases were examined in the ninth year. The difficulty in finding other cases led to their examination in the eleventh, twelfth, or thirteenth year. The 10-year follow-up of examined cases, therefore, includes a range from the eighth to the thirteenth year with

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the large majority (60 per cent) examined in the tenth year (table 1). Hereafter, with respect to the 347 examined cases in this report, the phrase "at 10 years" will refer to the period from 8 to 13 years inclusive.

### The Numbers Involved

Of the 497 cases admitted to the trial (240 U. K. and 257 U. S.), 397 (80 per cent) were known to be alive at the end of 10 years, and the status of the heart had been recorded for 347 of them. There were 23 known deaths during the 10-year period. Thus, 420 or 85 per cent of the original 497 cases had been traced at 10 years. Of the remaining 77 cases untraced at 10 years, 9 were known to be alive at the end of 7 years, 8 at the end of 6 years, 33 at the end of 5 years, and 27 were lost before the fifth year of follow-up.

The number of deaths and the number of cases successfully followed up are given in table 2, where the cases have been divided into three major groups according to the status of the heart on admission to the trial: namely, Group A, no or questionable carditis* and no pre-existing heart disease; Group B, carditis* present but no pre-existing heart disease; and Group C, definite or questionable pre-existing heart disease.

### Lost Cases

One hundred and twenty-seven or approximately one quarter of the 497 cases (table 2) were not examined "at 10 years" and lacking evidence of their heart status, must be classified as "lost." The loss of cases resulted mostly from migration, induction into the Armed Forces, change of name by marriage, or lack of patient cooperation and the proportion varied widely among the research centers (from 9 to 50 per cent). Since this large case loss might bias the conclusions presented here, an attempt was made to determine whether the cases examined at 10 years could in fact be considered a representative sample of the total group.

It had been found at 1 year, when the full effect of the treatment of acute disease could be evaluated and when there were very few lost cases, that residual murmurs were the best index of severity of disease. The proportion of cases in each cardiac category with murmurs at 1 year can therefore be used as an index to compare the relative severity of disease in the 10-year groups of examined and

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*The diagnostic criteria for admission to the study specified carditis as shown by any one of the following:

(a) Development of an organic apical systolic murmur or an aortic diastolic murmur under acceptable observation.

(b) Change of heart size of more than 15 per cent on standard x-ray film by any standard method of measurement.

(c) Pericarditis revealed by a definite friction rub or by pericardial effusion.

(d) Congestive failure, in a patient under 25 years and in the absence of other causes, and shown by one or more of the following: (1) dyspnea, (2) orthopnea, (3) enlargement of the liver, (4) basal pulmonary rales, (5) increased jugular venous pressure, or (6) edema.

In the assessment of carditis as a criterion for entry to the trial, it was assumed in patients with no known pre-existing rheumatic heart disease or history of an attack of acute rheumatic fever that previous to the current illness the patient's heart was of normal size and that there were no rheumatic murmurs. In other patients observations of changes in heart size and murmurs were used in determining carditis and recorded.
lost cases. When this is done (table 3) it is clear that in Group A and in every subcategory of Group B, the severity of disease in the examined and lost cases with minor exceptions was similar at 1 year. Therefore, as far as this measurement is concerned, the examined sample may be considered to be representative of the total group of cases.

Additional evidence for lack of bias is to be found in the fact that death or the status of the heart among the survivors had been recorded in 68 per cent of Group A, 77 per cent of Group B, and 74 per cent of Group C. Similarly, the figures for the three treatment groups were 78 per cent for ACTH, 72 per cent for cortisone, and 73 per cent for aspirin. The corresponding figure was 80 per cent for the U. K. and 69 per cent for the U. S. It is clear that within these broad classifications no serious differential losses, which might obscure comparison, have taken place.

But, there were some differences. As might
Table 3

Proportion with Murmurs at One Year among Cases Examined and Not Examined at Ten Years

<table>
<thead>
<tr>
<th>Cardiac status at start of treatment</th>
<th>Examined at 10 years*</th>
<th>Not examined at 10 years†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases examined at 1 yr.</td>
<td>No.</td>
</tr>
<tr>
<td>Group A</td>
<td>78</td>
<td>9</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Without failure and/or pericarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Apical systolic murmur grade I, only</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>b. Apical systolic murmur grade II or III, only</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>c. Apical systolic and apical mid-diastolic murmurs</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>d. Basal diastolic murmur only</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>e. Basal diastolic and other murmurs</td>
<td>32</td>
<td>23</td>
</tr>
<tr>
<td>2. With failure and/or pericarditis</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>Group C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Without failure and/or pericarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. With failure and/or pericarditis</td>
<td>59</td>
<td>50</td>
</tr>
<tr>
<td>19</td>
<td>18</td>
<td>95</td>
</tr>
</tbody>
</table>

*Exclusive of cases absent at 1 year: 2 Group A; 3 Group B; E Group C.
†Exclusive of cases absent at 1 year: 5 Group A; 6 Group B; 1 Group C.

be expected there was a greater loss among the older cases (30 per cent of those 10 to 15 years old at start of treatment) than among the younger ones (19 per cent of those 3 to 9 years old). Since, as will be demonstrated, age analysis showed no difference in prognosis, this differential age loss is of little importance.

Although the loss of males (29 per cent) was somewhat greater than of females (21 per cent), an analysis of cases in Group A and in the subcategories of Group B revealed that murmur rates at 1 year are similar for examined and lost cases for each of the sexes separately. Thus, it is unlikely that the differential sex loss is a source of bias.

Finally, the loss rate was related to cardiac status at start of treatment with a tendency toward a greater loss among the milder cases (table 2). Thus, the unexamined cases were not evenly distributed among the subgroups of Group B. The greatest loss (40 per cent) occurred among the cases in Group B with the lowest grade of heart disease at start of treatment, i.e., those admitted with only a Grade I apical systolic murmur. The smallest loss (11 per cent) occurred among the cases originally admitted without failure or pericarditis, but with a basal diastolic and another heart murmur. In all of the other subgroups of Group B, approximately 20 per cent of the cases were not examined. Analysis of these losses revealed that they are partially dependent upon failure of cases without residual heart disease to return for examination. But, losses also vary with the type of case admitted to and the effectiveness of follow-up in individual research centers. The conclusions of this report take this factor of selection into account, since the results are presented
separately for Group A and for each subgroup of Group B.

In total, it is unlikely that the lost cases at 10 years were a source of major bias in this follow-up report.

Deaths

Of the 497 children under the age of 16 who were admitted to the study and completed the prescribed course of treatment, only 19 were known to have died from rheumatic fever or rheumatic heart disease by the end of 10 years of follow-up* (table 2). One of these deaths occurred shortly after the end of treatment and 4 more within the first year of follow-up. There was 1 death in the third year followed by 4 in the fourth year and 4 in the fifth year. Only 5 additional deaths from rheumatic fever or rheumatic heart disease occurred in the sixth to tenth years of follow-up; 1 each in the sixth, seventh, and ninth years and 2 in the tenth year. Among the 238 females admitted to the study, there were 10 deaths (4 per cent) and among the 259 males there were 9 deaths (3 per cent) of rheumatic fever and/or rheumatic heart disease. Division by treatment showed 10 among the 162 ACTH cases (6 per cent), 3 among 167 cortisone (2 per cent), and 6 among 168 aspirin cases (4 per cent).†

Death from rheumatic fever and rheumatic heart disease has been distinctly related to the cardiac status at the start of treatment. Thus, there were no deaths in the 117 Group A cases (cases with no or questionable carditis and without pre-existing heart disease), and only 6 deaths (2 per cent) among the 252 Group B cases (carditis present but no pre-existing heart disease). Of the 6 Group B deaths, 1 occurred among the 37 cases with failure and/or pericarditis at entry (3 per cent) and 5 in the remaining 215 cases (2 per cent) where these features were absent.

Most of the deaths, 13 of 19 occurred among the 128 Group C cases (with pre-existing heart disease) (10 per cent). Eight of the 13 deaths in Group C occurred in the small group of 31 cases (26 per cent) where failure and/or pericarditis was already present at the start of treatment. In other words, death occurred in 1 of every 4 of these cases as compared with 1 in 20 in the remainder of Group C.

There were more deaths from rheumatic fever or rheumatic heart disease among those whose disease was 6 weeks or more in duration when treatment was started (10 of 104 or 10 per cent) than among those treated within 6 weeks of onset (9 of 393 or 2 per cent). This difference occurred entirely in the Group C cases where the death rate was 20 per cent among late treated cases as compared with 6 per cent among those in which treatment was begun during the first 6 weeks. The death rate was not significantly lower among those treated within 2 weeks of onset (5 of 255 or 2 per cent) than among those treated at 2 to 6 weeks (4 of 138 or 3 per cent).

The very low fatality rate during the first 10 years continued the trend of favorable life expectancy noted in previous reports. As previously noted1,2 many factors may be responsible for the striking decrease in the severity of the disease. It may also be observed that the fatality rate remains remarkably low even though all three agents were given in doses smaller than those currently in use.

In addition to the deaths resulting from rheumatic fever and rheumatic heart disease, there were 4 deaths (2 males and 2 females) from unrelated causes. Two of these deaths occurred in the fourth year, 1 in the ACTH group from acute nephritis and uremia, and

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*One child given cortisone who died 20 hours after the start of treatment is not included in the 497 children or the 19 deaths. With this single exception, all the patients survived this course of treatment. The death rates following these courses can therefore be compared without the introduction of any bias due to the incidence of deaths during treatment.

†Four additional deaths have been reported since the tenth year, all from rheumatic fever and rheumatic heart disease: 1 in the eleventh year (Group B male with failure and/or pericarditis treated with aspirin); 2 in the twelfth year (one Group B male with failure and/or pericarditis treated with cortisone and a Group C female with failure and/or pericarditis treated with cortisone) and 1 in the thirteenth year (a Group B female treated with ACTH).
the other in the cortisone group from acute intestinal obstruction. Two other cases died of injury: 1 in the aspirin group with burns in the sixth year; and 1 in the ACTH group of an automobile accident in the seventh year.

Evolution of Rheumatic Heart Disease

It was previously shown at 1\(^1\) and at 5 years\(^2\) that the status of the heart on entry to the trial was the major factor in the evolution of rheumatic heart disease. Moreover, there was no evidence that treatment with any of the three therapeutic agents (ACTH, cortisone, or aspirin) led to a more favorable outcome. The analysis of the data at 10 years will therefore be based upon the cardiac status of the cases when treatment was begun. But, attention will be directed almost entirely to the cases in Groups A and B, since it is difficult to evaluate the course of Group C cases with their history of pre-existing heart disease of varying and sometimes long duration. The effect of recurrences of rheumatic fever and of other factors relevant to prognosis at 10 years will be studied. A special analysis will also be made of factors affecting the development of mitral stenosis. Finally, the relationship of the original treatment to the outcome at 10 years will be examined.

Cardiac Group A

There were 117 cases with no carditis at the start of treatment (Group A). At 10 years, none had died, 80 were examined, and of 37 cases not examined 12 were known to be alive (table 2).

Among the 80 cases examined (table 4), only 5 (6 per cent) had any evidence of cardiac involvement at 10 years (3 with only a grade I apical systolic murmur,* 1 with a grade II apical systolic, and 1 with an apical systolic and a pre-systolic murmur (mitral stenosis)). Two of the 5 cases had had recurrences of rheumatic fever but the single case with mitral stenosis was a female with no history of recurrence. It is of interest that among the 9 Group A cases with recurrences, there were 2 with murmurs while there were only 3 with murmurs among the 71 cases without recurrences (4 per cent). This difference is not formally significant but as shown later is in accordance with the general trend of results.

The 32 per cent (table 2) of cases in Group A which were not examined at 10 years should not distort the conclusions reached, since at 1 year of follow-up the lost and examined cases had disease of equal severity. Thus, at 1 year, there had been 5 cases with murmurs (16 per cent) among the 32 cases not examined at 10 years (table 3), compared with 9 (12 per cent) among the 78 cases that were examined at 10 years.

In summary, the prognosis of cases without carditis when treatment was started (Group A) is excellent. At 10 years, none had died and among those examined 94 per cent were without apparent heart disease and one had developed mitral stenosis.

Cardiac Group B

There were 252 cases with carditis but without pre-existing heart disease at start of treatment (Group B). At 10 years, 7 had died, 188 were examined and of the 57 not examined 25 were known to be alive (table 2). As has already been shown, Group B is clinically heterogeneous and for analysis has been subdivided into five subgroups of murmurs among those without failure and/or pericarditis and one subgroup comprising all of the cases with failure and/or pericarditis at start of treatment.

The evolution of heart disease in the various subgroups in Group B is as follows:

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*In this study, the following grades were adopted for reporting apical systolic murmurs:

Grade O—No murmur, or a murmur considered to be “functional” on the basis of its apparent origin at the pulmonic area or along the left sternal border.

Grade P—Murmur apparently localized to the apical area, but so faint as not to be transmitted to or toward the axilla. The “P” murmurs were not considered indicative of carditis.

Grade I—Soft apical systolic murmur transmitted to or toward the axilla.

Grade II—Louder similar murmur.

Grade III—Very loud similar murmur, usually transmitted to the back.
I(a). Group B Cases with a Grade I Apical Systolic Murmur Alone

There were 45 cases with only a grade I apical systolic murmur at the start of treatment (table 2). At 10 years, none had died, 27 were examined, and of the 18 not examined 8 were known to be alive.

Of the 27 examined cases (table 4), 8 (30 per cent) had murmurs at 10 years (2 with only a grade I apical systolic murmur; 1 with a grade III apical systolic murmur; 3 with a basal diastolic murmur alone; and 2 with basal diastolic and other murmurs, including one with an apical systolic and mid-diastolic murmur and the other with an apical systolic and pre-systolic murmur (mitral stenosis)). Among the 5 cases with recurrences there were 4 with murmurs in contrast with the smaller proportion of only 4 with murmurs among the 22 cases without recurrences (18 per cent).

The large proportion of losses (40 per cent) (table 2) in this category should not distort the conclusions reached, since at 1 year of follow-up the lost and examined cases had disease of equal severity. Thus, murmurs had been present at 1 year (table 3) in 9 of the 27 cases (33 per cent) examined at 10 years, and in 5 of the 18 cases (28 per cent) not examined at 10 years.

In summary, the prognosis of cases admitted with only a grade I apical systolic murmur is quite good. At 10 years, none had died, and among those examined 70 per cent had no apparent heart disease and 1 had developed mitral stenosis.

Table 4

<table>
<thead>
<tr>
<th>Cardiac status at start of treatment</th>
<th>Cases examined at 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>No. cases</td>
</tr>
<tr>
<td>Group A</td>
<td>80</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
</tr>
<tr>
<td>1. Without failure and/or pericarditis</td>
<td></td>
</tr>
<tr>
<td>a. Apical systolic murmur grade I, only</td>
<td>27</td>
</tr>
<tr>
<td>b. Apical systolic murmur grade II or III, only</td>
<td>50</td>
</tr>
<tr>
<td>c. Apical systolic and apical mid-diastolic murmurs</td>
<td>38</td>
</tr>
<tr>
<td>d. Basal diastolic murmur only*</td>
<td>12</td>
</tr>
<tr>
<td>e. Basal diastolic and other murmurs*</td>
<td>33</td>
</tr>
<tr>
<td>2. With failure and/or pericarditis</td>
<td>28</td>
</tr>
<tr>
<td>Group C</td>
<td></td>
</tr>
<tr>
<td>1. Without failure and/or pericarditis</td>
<td>60</td>
</tr>
<tr>
<td>2. With failure and/or pericarditis</td>
<td>19</td>
</tr>
</tbody>
</table>

*See text, page 463.
1(b). Group B Cases with a Grade II or III Apical Systolic Murmur Alone

There were 68 cases with a grade II or III apical systolic murmur only at start of treatment (table 2). At 10 years, 2 had died (a female in the fourth month and a male in the fifth month, both with progressive carditis), 50 were examined and of the 16 cases not examined 6 were known to be alive.

Of the 50 examined cases in this category (table 4), 13 (26 per cent) had murmurs at 10 years (7 with a grade II or III apical systolic murmur; 3 with apical systolic and mid-diastolic murmurs; 2 with basal diastolic and other murmurs, including one with a basal systolic and the other with apical systolic and pre-systolic murmurs (mitral stenosis); and 1 case with apical systolic and pre-systolic murmurs (questionable mitral stenosis)). Among the 4 cases with recurrences, one had a murmur at 10 years as compared with 12 with murmurs among 46 cases without recurrences (26 per cent).

Once again the unexamined cases probably do not distort the conclusions. Thus, murmurs had been present at 1 year in 25 of the 50 cases (50 per cent) examined at 10 years and in 9 of the 16 cases (56 per cent) not examined at 10 years (tables 2 and 3).

In summary, the prognosis of cases with only a grade II or III apical systolic murmur is fairly good. At 10 years, 2 had died* and among those examined 74 per cent had no apparent heart disease and 1 or possibly 2 had developed mitral stenosis.

1(c). Group B Cases with an Apical Systolic Murmur of Any Grade Plus a Mid-Diastolic Murmur

There were 49 cases with apical systolic and mid-diastolic murmurs at the start of treatment (table 2). At 10 years, 3 had died (2 of rheumatic fever and rheumatic heart disease, in the seventh and tenth years; and the third of acute nephritis); 38 were examined and of the 8 cases not examined 3 were known to be alive.

Of the 38 examined cases in this category (table 4), 14 (37 per cent) had murmurs at 10 years (2 with an apical systolic grade I murmur only; 7 with an apical systolic grade II murmur only; 2 with apical and mid-diastolic murmurs (1 with mitral stenosis); 1 with a basal diastolic murmur only; 1 with a basal diastolic and apical systolic and mid-diastolic murmurs; and 1 with apical systolic and pre-systolic murmurs (mitral stenosis)). Among the 3 cases with recurrences, 1 had murmurs at 10 years as compared with 13 with murmurs among the 35 cases without recurrences (37 per cent).

In this category, only 8 cases were unexamined at 10 years (16 per cent) but the unexamined cases were possibly more severe at 1 year than were those which were examined at 10 years (tables 2 and 3). Thus, murmurs had been present at 1 year in 22 of the 36 cases (61 per cent) examined at 10 years and in 5 of 7 cases (71 per cent) not examined at 10 years.

In summary, the prognosis of cases admitted with apical systolic and mid-diastolic murmurs is uncertain. At 10 years, 2 had died of rheumatic fever and rheumatic heart disease, and among those examined 63 per cent had no apparent heart disease. It is of clinical interest that of the 38 cases admitted with apical systolic and mid-diastolic murmurs and followed for 10 years, only 2 had developed mitral stenosis.

1(d). Group B Cases with a Basal Diastolic Murmur Alone

There were 15 cases with a basal diastolic murmur only at the start of treatment (table 2). At 10 years, none had died, 12 were examined and of the 3 cases not examined 1 was known to be alive.

Of the small group of 12 examined cases in this category (table 4), only 3 had murmurs at 10 years (2 with a basal diastolic murmur only and 1 with a basal diastolic and an apical pre-systolic murmur (mitral stenosis)). However, 9 of the 12 cases in this category were reported from one center where only 1 case had murmurs at 10 years.
In contrast there were 2 cases with murmurs among 3 reported from the 11 other centers. There were no retreated recurrences in this category.

In summary, the prognosis of cases with a basal diastolic murmur only at start of treatment cannot be determined. However, none had died and one case had developed mitral stenosis.

1(e). Group B Cases with a Basal Diastolic Murmur and an Apical Systolic and/or Mid-Diastolic Murmur

There were 38 cases with a basal diastolic murmur together with an apical systolic and/or mid-diastolic murmur at the start of treatment (table 2). At 10 years, 1 had died, 33 were examined, and of the 4 cases not examined 3 were known to be alive.

Of the 33 examined cases (table 4), 15 (45 per cent) had murmurs at 10 years (4 with an apical systolic grade II murmur only; 5 with a basal diastolic murmur only; 6 with a basal diastolic and other murmurs, including 3 with an apical systolic murmur, 1 with an apical mid-diastolic murmur, 1 with a basal systolic and apical systolic and mid-diastolic murmurs, and 1 with an apical pre-systolic murmur (questionable mitral stenosis)). However, 24 of the 33 cases in this category were reported from one center where only 8 (33 per cent) had murmurs at 10 years. The number of cases and proportion with murmurs in this center is in sharp contrast with the 7 cases with murmurs among only 9 reported from the 11 other centers. Furthermore, there was but 1 recurrence (without murmurs) among the 24 cases in the one center compared with 5 (4 with murmurs) among the 9 cases in the other 11 centers. It is therefore impossible to determine the effect of recurrence on the murmur rate in this category.

The follow-up of cases had been most successful in this category with only 4 cases (11 per cent) not examined at 10 years (table 2).

In summary, the prognosis of cases admitted with a basal diastolic and other murmurs was the most serious of all the categories of Group B cases without failure and/or pericarditis, with almost half (45 per cent) having heart disease at 10 years. In addition, 1 had died and among those examined none or possibly 1 had developed mitral stenosis.

2. Group B Cases with Failure and/or Pericarditis

Turning finally to this most severe category of the Group B cases, there were 37 cases with failure and/or pericarditis at the start of treatment (table 2). At 10 years, 1 had died, 28 were examined, and of the 8 cases not examined 4 were known to be alive.

Among the 28 examined cases (table 4), there were at 10 years 19 (68 per cent) with murmurs (1 with an apical systolic grade I murmur only; 5 with an apical systolic grade II or III murmur only; 3 with apical systolic and mid-diastolic murmurs (one with mitral stenosis); 3 with basal diastolic murmurs alone; 5 with basal diastolic and other murmurs, including two with basal systolic and apical systolic murmurs, two with basal systolic and apical systolic and mid-diastolic murmurs, and one with an apical mid-diastolic murmur. In addition, there was 1 with only an apical pre-systolic murmur (mitral stenosis). Finally, 1 case had subacute bacterial endocarditis at the time of examination, having had only a grade I apical systolic murmur at the last examination at 5 years.

Of the 28 examined cases, 10 were reported as having had a retreated recurrence but in this severely ill group it is certain that some of the cases had continual rheumatic activity. Among the 10 cases with recurrence, heart murmurs were present at 10 years in 7, which is not different from the 12 cases with murmurs among the 18 cases not specifically treated for a recognized recurrence.

In this category the lost cases were less severely ill at 1 year than were those examined at 10 years. Thus, murmurs had been present at 1 year in only 2 of 7 cases not examined at 10 years in contrast with 22 of the 28 cases (79 per cent) examined at 10 years (table 3).

Even allowing for the possible loss of less severe cases, the prognosis in this most severely ill category of cases, admitted to the study

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with failure and/or pericarditis in the first attack of rheumatic fever, remains very serious. At 10 years, 1 had died* and among those examined only about one third had no apparent heart disease and two had developed mitral stenosis.

Recurrences in Groups A and B. The study plan specified that all cases were to receive daily prophylaxis with sulfadiazine after initial eradication of the streptococcus with a 10-day course of penicillin. Nevertheless, some recurrences did occur. It is, however, not possible to come to any conclusions as to the effectiveness of prophylaxis, since this investigation was not designed to evaluate it and the records do not include the necessary detailed information on the faithfulness with which the regimen was followed. It is, however, clear that in many cases, particularly those not seen between the 5- and 10-year examinations, prophylaxis was discontinued.

For analytical purposes, recurrences were defined as the appearance after an interval of 3 months of freedom from rheumatic activity, of manifestations that would have originally qualified the patient for admission to the trial. An analysis was made of all cases retreated for such a recurrence, but it is more informative to limit attention to cases in the cardiac Groups A and B. Many cases in Group C had continual rheumatic activity, making recurrence impossible to identify.

In Groups A and B there were, excluding recurrences of pure chorea, at least one or more retreated recurrences in 37 (14 per cent) of the 268 cases examined at 10 years (table 4). Furthermore, these 37 cases were divided almost exactly among the three treatment groups, viz., 12 of 86 ACTH, 12 of 89 cortisone, and 13 of 93 aspirin cases. It is clear that the frequency of such recurrences does not bias the subsequent comparisons of the treatments used.

In the 5-year report it was noted of those with retreated recurrences that "the cardiac status at start of treatment among these cases was on the average more severe than in the remainder of Group B cases." At 10 years on the other hand, there is no tendency for the proportion of cases retreated for recurrences to increase with severity of disease among the cases in Group A (9 in 80) and the subgroups of Group B without failure and/or pericarditis (18 in 160) (table 4). The increased proportion of retreated Group B cases with failure and/or pericarditis (10 in 28) may be due at least in part to the presence of continual rheumatic activity in many of them. Moreover, the effect of lost cases cannot be measured. Therefore, no conclusions can be reached at 10 years concerning the effect of the initial severity of disease on the subsequent rate of recurrences as defined in this study.

It can be noted, however, that among the 37 cases in Groups A and B with retreated recurrences, 30 had had only one recurrence while the remaining 7 cases had suffered 23. These cases with multiple recurrences were of varying severity at start of treatment being distributed throughout Group A and the subgroups of Group B.

The analysis of cases in Group A and in the individual subgroups of Group B (table 4) makes it clear that, as in the 5-year report, retreated recurrences of rheumatic fever, particularly in the less severe cases where their effect is easier to evaluate, are a major factor in worsening the prognosis at 10 years.

Most important, the 37 cases with retreated recurrences include 19 cases with murmurs at 10 years, and 8 of these were reported as having no heart disease prior to the retreated recurrences. Thus, cases surviving an initial attack of rheumatic fever without residual heart disease do develop heart disease following a retreated recurrence.

Cardiac Group C

There were 128 cases (table 2) with pre-existing definite or questionable heart disease prior to the attack which brought the case into the study (Group C). At 10 years, 16 had died (13 from rheumatic fever and rheumatic heart disease and 3 from other causes),
Table 5

Proportion with Murmurs among All Males and Females Examined at Ten Years and among Those without Retreated Recurrences

| Cardiac status at start of treatment | All examined cases | | | Cases without retreated recurrences | | |
| | Males | | | Females | | |
| | No. cases | No. | Per cent | No. cases | No. | Per cent | No. cases | No. | Per cent |
| Group A | | | | | | |
| Group B | | | | | | |
| 1. Without failure and/or pericarditis | | | | | | |
| a. Apical systolic murmur grade I, only | 12 | 4 | 33 | 15 | 4 | 27 | 8 | 1 | 12 | 14 | 3 | 21 |
| b. Apical systolic murmur grade II or III, only | 21 | 3 | 14 | 29 | 10 | 34 | 18 | 2 | 11 | 28 | 10 | 36 |
| c. Apical systolic and apical mid-diastolic murmurs | 17 | 2 | 12 | 21 | 12 | 57 | 15 | 2 | 13 | 20 | 11 | 55 |
| d. Basal diastolic murmur only | 4 | 0 | 0 | 8 | 3 | 38 | 4 | 0 | 0 | 8 | 3 | 38 |
| e. Basal diastolic and other murmurs | 21 | 11 | 52 | 12 | 4 | 33 | 17 | 8 | 47 | 10 | 3 | 30 |
| 2. With failure and/or pericarditis | 11 | 7 | 64 | 17 | 12 | 71 | 6 | 4 | 67 | 12 | 8 | 67 |
| Group C | | | | | | |
| 1. Without failure and/or pericarditis | 27 | 16 | 59 | 33 | 20 | 61 | 19 | 9 | 47 | 25 | 14 | 56 |
| 2. With failure and/or pericarditis | 12 | 11 | 92 | 7 | 6 | 86 | 11 | 10 | 91 | 7 | 6 | 86 |
79 were examined and of the 33 not examined 13 were known to be alive. For analysis the group has been divided into two subgroups—those with and those without failure and/or pericarditis at start of treatment.

Among the 60 cases examined at 10 years without failure and/or pericarditis at start of treatment, 36 (60 per cent) (table 4) had heart disease at 10 years, including 6 with mitral stenosis. This is to be compared with 17 (28 per cent) with heart disease, including 4 with mitral stenosis among the 19 cases with failure and/or pericarditis at start of treatment.

Of the 13 deaths from rheumatic fever and rheumatic heart disease, 5 occurred in the 97 cases without and 8 in the 31 cases with failure and/or pericarditis at start of treatment. (The remaining deaths were 2 from injury and 1 from intestinal obstruction.)

In summary, the Group C cases had a very grave prognosis. At 10 years, 13 died of rheumatic fever and rheumatic heart disease. Among those examined only 40 per cent of the cases without and 11 per cent of the cases with failure and/or pericarditis at start of treatment had no apparent heart disease and 10 cases had developed mitral stenosis.

Other Factors Possibly Affecting Prognosis

An analysis was made of factors which might have prognostic effects. These factors included sex, age, duration between onset and start of treatment, and presence or absence at start of treatment of polyarthritis, nodules, chorea, and prolonged P-R interval.

Only one of these factors—sex—clearly affected prognosis at 10 years (table 5). Among the milder cases without recurrence the proportion with murmurs at 10 years is consistently greater for females than for males, viz., Group A—11 per cent for females and 0 for males; Group B with an apical systolic murmur grade I only—21 per cent and 12 per cent; with an apical systolic murmur grade II or III only—36 per cent and 11 per cent; with apical systolic and mid-diastolic murmurs—55 per cent and 13 per cent; with basal diastolic murmurs only—38 per cent and 0.

This more serious prognosis for females is not apparent among the more severe cases, namely, the Group B cases with a basal diastolic and other murmurs, those with failure and/or pericarditis at start of treatment, the cases in Group C, and any category of cases in which recurrences took place. This difference in prognosis can also be seen in the disappearance of murmurs in the two sexes in cases without a history of recurrence examined at 1, 5 and 10 years (table 6). Clearly, murmurs disappeared more rapidly in males than in females.

Thus, at 10 years, rheumatic fever in its milder grades had a worse prognosis for females than for males. Mitral stenosis in this study, as will be indicated later, was also more common among females. But, severe rheumatic fever has a serious prognosis for both sexes and the death rate for females (4 per cent) was in the same range as that for males (3 per cent).

There would appear to be a borderline relationship at 10 years between earlier treatment and a more favorable outcome (p = 0.05). There are, however, many selective factors affecting severity of disease which are involved in determining the date of admission of early and late cases to treatment centers. Since these factors cannot be evaluated, it is not possible to differentiate between this sampling effect and the effect of early treatment on the outcome of rheumatic fever. Furthermore, the relationship between early treatment and more favorable outcome occurs only among females (table 7). This early treatment effect in females does not, however, explain the sex differences among the milder cases, since the less favorable outcome for females is also evident among the early treated cases. Thus, at 10 years, among milder cases in Group B (apical systolic murmur grade I alone, apical systolic murmur grade II or III alone, apical systolic and mid-diastolic murmurs, and basal diastolic murmurs alone) treated in the interval from 1 to 14 days, three of 22 males had murmurs compared with eight of 31 females.

Analysis of the remaining factors (table 7)
### Table 6

Proportion with Murmurs at One, Five, and Ten Years among Males and Females without Retreated Recurrences Examined at Ten Years

<table>
<thead>
<tr>
<th>Cardiac status at start of treatment</th>
<th>Cases examined at 10 years*</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>Males</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>With murmurs</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>43</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Without failure and/or pericarditis</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Apical systolic murmur grade I, only</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Apical systolic murmur grade II or III, only</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Apical systolic and apical mid-diastolic murmurs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Basal diastolic murmurs only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Basal diastolic and other murmurs</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. With failure and/or pericarditis</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Without failure and/or pericarditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. With failure and/or pericarditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Exclusive of cases absent at 1 and/or 5 years: Males—0 Group A; 6 Group B; 1 Group C Females—2 Group A; 5 Group B; 1 Group C.
Table 7

Number of Observed and Expected* Murmurs among Males and Females in Group B without Retrodced Recurrences, Examined at Ten Years According to Possible Prognostic Factors at Start of Treatment

<table>
<thead>
<tr>
<th>Status at start of treatment</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>No. with murmurs at 10 yr.</td>
<td>Expected</td>
<td>No. of cases</td>
<td>No. with murmurs at 10 yr.</td>
</tr>
<tr>
<td>3-9 years of age</td>
<td>38</td>
<td>10</td>
<td>10</td>
<td>47</td>
<td>20</td>
</tr>
<tr>
<td>10-15 years of age</td>
<td>30</td>
<td>7</td>
<td>7</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>0-14 days from onset</td>
<td>32</td>
<td>8</td>
<td>8</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>15-42 days from onset</td>
<td>22</td>
<td>8</td>
<td>7</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>43+ days from onset</td>
<td>14</td>
<td>1</td>
<td>2</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>P-R .18+</td>
<td>16</td>
<td>4</td>
<td>4</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>P-R &lt; .18</td>
<td>52</td>
<td>13</td>
<td>13</td>
<td>72</td>
<td>31</td>
</tr>
<tr>
<td>With joint involvement</td>
<td>24</td>
<td>7</td>
<td>6</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Without joint involvement</td>
<td>44</td>
<td>10</td>
<td>11</td>
<td>59</td>
<td>23</td>
</tr>
<tr>
<td>With nodules</td>
<td>14</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Without nodules</td>
<td>54</td>
<td>13</td>
<td>14</td>
<td>80</td>
<td>35</td>
</tr>
<tr>
<td>With chorea</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Without chorea</td>
<td>63</td>
<td>17</td>
<td>16</td>
<td>74</td>
<td>32</td>
</tr>
</tbody>
</table>

*Expected numbers take account of differences in the initial severity of cardiac involvement among groups being compared. They were calculated, separately for males and for females, in the following manner: The proportions of cases with murmurs at 10 years were taken separately for each of the six subgroups in Group B. These proportions were applied to the actual number of cases in each cardiac subgroup of the categories listed above to see how many in these small subgroups would have had a murmur at 10 years if they had experienced the total rate of occurrence. The "expected" numbers in the subgroups were added to get the total number expected in each category.

showed no correlation with the status of the heart at 10 years.

Mitral Stenosis

At 10 years, mitral stenosis was definitely diagnosed in 1 of 80 examined cases in Group A, 7 of 188 in Group B, and 10 of the 79 in Group C. It was also diagnosed in 7 of the 19 deaths from rheumatic fever and rheumatic heart disease, all but 1 in Group C. Mitral stenosis was not present in any of the 4 cases dying from other causes. Thus, a total of 25 cases of mitral stenosis is recorded at 10 years and comprises 9 males and 16 females. This is in sharp contrast with the findings at 5 years when mitral stenosis was so uncommon as not to be included in the report.* 2

Analysis shows that failure and/or pericarditis was present at start of treatment in 6 of the 9 male cases but in only 5 of the 16 female cases. Among the 8 diagnoses of mitral stenosis in examined cases in Groups A and B, the 7 female cases had not had a treated recurrence. The 1 male case had continual rheumatic activity.

It must be kept in mind that these data cannot define the total natural history of mitral stenosis. There is no representation of cases which occur in adults without a previous history of acute rheumatic fever. In this study, mitral stenosis has evolved in cases in which there has been at least one clear-cut documented attack of rheumatic fever.

In summary, mitral stenosis, uncommon at 5 years, was definitely diagnosed in 18 of the

*Actually, on review of the case records mitral stenosis was present at 5 years in 1 Group B cases (1 case lost at 10 years) and in 5 Group C deaths.

The latter were characterized by a prolonged history of rheumatic fever and rheumatic heart disease prior to admission to the study.
347 cases examined at 10 years and in 7 of the 19 deaths from rheumatic fever and rheumatic heart disease. The prevalence of this complication increased with the severity of the cardiac status at start of treatment but was not influenced by retreated recurrences. The sex distribution is consistent with the long-standing clinical impression that mitral stenosis is more common in females in whom it develops following the milder as well as after the more severe grades of acute rheumatic fever.

Comparison of the Treatments

The dosage schedules of ACTH, cortisone, and aspirin were based on published studies and unpublished reports at the start of this study in 1950 and are presented in detail in previous reports.1,2 The results among cases followed for 10 years are analyzed in terms of the cardiac groups already defined.

Looking first at Group A (table 8), murmurs were present at the end of 10 years in 3 (11 per cent) of 28 ACTH cases (1 with an apical systolic murmur grade I only; 1 with an apical systolic murmur grade II only; and 1 with apical systolic grade II and pre-systolic murmurs (mitral stenosis)); in none of 26 cortisone cases and in 2 (8 per cent) of the 26 aspirin cases (both apical systolic grade I only). Moreover, 2 cases—the ACTH case with an apical systolic grade II murmur and an aspirin case with an apical systolic grade I murmur at 10 years—were free of murmurs at 5 years and developed these murmurs during the 6- to 10-year interval following a retreated rheumatic fever recurrence. Thus, there is no significant difference in the cardiac status of Group A cases at 10 years among the three treatment groups.

Table 8

<table>
<thead>
<tr>
<th>Cardiac status at start of treatment</th>
<th>ACTH</th>
<th></th>
<th></th>
<th>Cortisone</th>
<th></th>
<th></th>
<th>Aspirin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases</td>
<td>No. with murmurs at 10 yr.</td>
<td>No.</td>
<td>Per cent</td>
<td>No. cases</td>
<td>No. with murmurs at 10 yr.</td>
<td>No.</td>
<td>Per cent</td>
</tr>
<tr>
<td>Group A</td>
<td>28</td>
<td>3</td>
<td>11</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>26</td>
<td>2</td>
</tr>
</tbody>
</table>

Group B
1. Without failure and/or pericarditis
   a. Apical systolic murmur grade I only
      4 | 1 | 25 |
   b. Apical systolic murmur grade II or III, only
      14 | 2 | 14 |
   c. Apical systolic and apical mid-diastolic murmurs
      10 | 3 | 30 |
   d. Basal diastolic murmur only
      4 | 1 | 25 |
   e. Basal diastolic and other murmurs
      14 | 7 | 50 |

2. With failure and/or pericarditis
   12 | 11 | 92 |

Group C
1. Without failure and/or pericarditis
   20 | 13 | 65 |
2. With failure and/or pericarditis
   9  | 9  | 100 |
The striking fact which emerges, however, is the exceedingly small proportion of Group A cases treated at these dosage levels of ACTH, cortisone, and aspirin in which there is evidence of heart disease at the end of 10 years of follow-up. As indicated in the 5-year report, the prognosis in cases initially without carditis but otherwise meeting the criteria for diagnosis of rheumatic fever is so good that it would be unreasonable to expect that large-dose cortisone therapy, with its well-recognized occasional severe toxic manifestations, could significantly improve it.

Examination of the subgroups of Group B at 10 years (table 8) shows no consistent difference in favor of any one treatment, but the number of cases in each group is small. Direct comparison of the total cases in Group B is not valid because of the unequal distribution of cases of different degrees of clinical severity among the three treatment groups. For example, the ACTH group is more heavily weighted with initially severely ill cases than the other two treatment groups. Thus, there are only 4 ACTH cases in comparison with 12 cortisone and 11 aspirin cases in the group of mild cases with only a grade I apical systolic murmur. On the other hand, in the groups of basal diastolic and other murmurs, and of failure and/or pericarditis, the number of ACTH cases is greater than that in the cortisone and aspirin groups.

It is, however, possible to allow for this unequal distribution of cases of varying degrees of clinical severity among the three treatment groups and thus make a valid evaluation of treatment within the entire Group B. On the assumption that in each of the cardiac subgroups the three treatments had no differential effects whatsoever, it is possible to calculate the expected outcome in Group B cases for each of the three treatment groups.* The expected figures can then be compared with those which actually occurred. Thus, for ACTH the expected number of cases having murmurs at 10 years was 24 as compared with 25 observed, for cortisone 25 expected and 26 observed, and for aspirin 23 expected and 21 observed. There is no evidence that the prognosis of Group B cases of all degrees of severity was affected more by one treatment than by another.

An alternative analysis of this important Group B can also be made by comparing separately all cases with a single murmur at the start of treatment and those with two or more murmurs at that time (table 9). Among cases with a single murmur, 18 per cent of the ACTH, 33 per cent of the corti-

*The proportions with murmurs at 10 years were taken separately for the males and the females for each of six subgroups in Group B for all three treatments combined. These proportions were applied to the actual number of patients on each treatment and in each of the six subgroups (males and females separately) to see how many in the small subgroups would have had a murmur at 10 years if they had experienced the total rate of occurrence. The "expected" numbers in each small subgroup were then added to give the total number of Group B cases expected to have murmurs. The numbers expected can then be compared with the observed numbers of cases with murmurs at 10 years.

### Table 9

<table>
<thead>
<tr>
<th>Cardiac status at start of treatment</th>
<th>ACTH</th>
<th>Cortisone</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases</td>
<td>No. at 10 yr.</td>
<td>No. cases</td>
</tr>
<tr>
<td>1. One murmur, any grade</td>
<td>22</td>
<td>4%</td>
<td>30</td>
</tr>
<tr>
<td>2. Two or more murmurs, any grade</td>
<td>24</td>
<td>10%</td>
<td>21</td>
</tr>
<tr>
<td>3. With failure and/or pericarditis</td>
<td>12</td>
<td>11%</td>
<td>12</td>
</tr>
</tbody>
</table>

*Circulation, Volume XXXII, September 1965*
sone, and 27 per cent of the aspirin cases still had one or more murmurs at 10 years. For those which initially had two or more murmurs, the corresponding proportions were 42 per cent for ACTH, 48 per cent for cortisone, and 35 per cent for aspirin. For the small groups of cases with failure and/or pericarditis at start of treatment, the proportions were 92 per cent for ACTH, 50 per cent for cortisone, and 50 per cent for aspirin. In short, in the Group B cases there is no pattern in these results to indicate any advantage for one or another of the forms of treatment.

Finally, of the Group C cases without failure and/or pericarditis at start of treatment (table 8), there were with murmurs at 10 years 13 of 20 ACTH, 11 of 20 cortisone, and 12 of 20 aspirin cases. Of those with failure and/or pericarditis murmurs were present at 10 years in all of 9 ACTH, 5 of 7 cortisone, and all of 3 aspirin cases. Once again, there is no significant difference among the treatment groups.

Among all of the examined cases at 10 years in Groups A, B, and C, mitral stenosis was diagnosed in 7 of 115 ACTH cases, 6 of 116 cortisone cases, and 5 of 116 aspirin cases. Mitral stenosis was also diagnosed among 4 of 10 ACTH, 1 of 2 cortisone, and 2 of 6 aspirin cases that died. The evolution of mitral stenosis at 10 years was therefore not affected by the agent used in the treatment of the acute disease.

In a therapeutic trial, factors existing prior to treatment and affecting outcome must be closely taken into account in any comparison of therapeutic results. In this study, three factors significantly affected outcome—the status of the heart at start of treatment (table 4), the sex of the patient (table 6), and recurrences of rheumatic fever justifying retreatment (table 4). Indeed, insofar as the status of the heart at start of treatment is concerned, it is abundantly clear that the range of 94 per cent down to 11 per cent with no heart disease at 10 years (table 10) is much more striking than differences reported here or ascribed elsewhere to the effects of treatment. Moreover, the large majority of the deaths (13 of 19) occurred among cases with pre-existing heart disease (Group C) and none among the cases without heart involvement at start of treatment (Group A).

The need to take all of these three factors into account implies that future clinical trials attempting to measure the effectiveness of a drug in the treatment of rheumatic fever will demand as in the trial here reported a large number of carefully defined and randomly assigned cases in a prospective study.

**Summary**

1. A study has been made 10 years after the end of treatment of the 497 children who were admitted to the U.K./U.S. cooperative clinical trial of the relative merits of ACTH, cortisone, and aspirin in the treatment of acute rheumatic fever.

2. Three hundred and ninety-seven of the cases (79.9 per cent) were known to be alive at 10 years and the status of the heart was known for 347 of them. In addition, 23 (4.6 per cent) had died, 19 from rheumatic fever and rheumatic heart disease, and 77 (15.5 per cent) were untraced. The very low fatality rate is striking.

3. At the end of 10 years, there is no evidence that, on the treatment schedule used in this study, the prognosis has been influenced more by one treatment than another. This confirms the findings reported at 1 year and at 5 years.

4. The most important factor in determining the prevalence of rheumatic heart disease at the end of 10 years is the status of the heart at the time treatment was begun. For cases initially without carditis the prognosis was excellent, since in 94 per cent there was no residual heart disease.

In cases initially with carditis but without pre-existing heart disease, the proportion without residual heart disease was 70 per cent for those with only a grade I apical systolic murmur, and 74 per cent for those with only a grade II or III apical systolic murmur. The proportion without heart disease decreased to
Table 10

Prognosis in Relation to Cardiac Status at Start of Treatment

<table>
<thead>
<tr>
<th>Cardiac status at start of treatment</th>
<th>Number of cases examined at 10 years</th>
<th>Per cent with no murmur at 10 years</th>
<th>Number of deaths in 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>80</td>
<td>94</td>
<td>0</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Without failure and/or pericarditis |                                     |                                     |                             |
   a. Apical systolic murmur grade I, only | 27                                  | 70                                  | 0                           |
   b. Apical systolic murmur grade II or III, only | 50                                  | 74                                  | 2                           |
   c. Apical systolic and apical mid-diastolic murmurs | 38                                  | 63                                  | 3†                          |
   d. and e. Basal diastolic with or without other murmurs | 45 (12)*                            | 60 (25)*                            | 1 (0)*                      |
2. With failure and/or pericarditis | 28                                  | 32                                  | 1                           |
Group C                             |                                     |                                     |                             |
1. Without failure and/or pericarditis | 60                                  | 40                                  | 8‡                          |
2. With failure and/or pericarditis | 19                                  | 11                                  | 8                           |

†Three deaths not rheumatic fever—acute intestinal obstruction; auto accident; burns.
*Excluding one U.K. center.
‡One death not rheumatic fever—acute nephritis.

32 per cent for those initially with failure and/or pericarditis.

In cases with pre-existing heart disease, the prognosis was poor. Forty per cent of those initially without pericarditis or failure and only 11 per cent of those with pericarditis and/or failure were without heart disease at 10 years.

5. Mitral stenosis, uncommon at 5 years, was definitely diagnosed in 18 of the 347 cases examined at 10 years and in 7 of the 19 deaths from rheumatic fever and rheumatic heart disease. The prevalence of this complication increased with the severity of the cardiac status at start of treatment and was greater in females than in males.

6. Retreated recurrences of rheumatic fever in cases without pre-existing heart disease worsened the prognosis but did not increase the prevalence of mitral stenosis. Patients surviving an initial attack of rheumatic fever without residual heart disease do develop heart disease following a retreated recurrence. The effect of initial cardiac status on the recurrence rate could not be determined.

7. Sex affected the outcome at 10 years. Rheumatic fever in its milder grades had a worse prognosis, and mitral stenosis was more common in females than in males.

8. These results make clear that the status of the heart of the patients at the start of treatment, the rate of recurrence of acute rheumatic fever, and the sex of the subjects must all be taken closely into account in the evaluation of any treatment of acute rheumatic fever.
References


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