The Evolution of Rheumatic Heart Disease in Children

Five-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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Members of the Principal Investigators Subcommittee and United States participating centers: Dr. David D. Rutstein (Chairman) Coordinating

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This cooperative clinical trial was first proposed by Dr. John R. Mote, then assistant general manager of the Armour Laboratories. For the planning of the study, funds were provided by Armour Laboratories and Merek and Company, and space and services by the Helen Hay Whitney Foundation.

In the planning and conduct of this trial much is owed to the wise advice and guidance of the late Dr. T. Duke Jones and the late Sir James Spence.

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THE UNITED KINGDOM AND UNITED STATES cooperative clinical trial was set up in 1951-52 to compare the relative merits of ACTH, cortisone, and aspirin in the treatment of rheumatic fever and the preven-
tion 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. These patients were allocated at random to one or another of the three treatments under investigation. They were treated according to a specified plan for 6 weeks and, after a further 3 weeks of detailed observation, were followed up at defined intervals. Full details of the plan of the study have been given in an earlier publication.¹

The previous 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 on all treatments some patients developed fresh manifestations during treatment. Treatment with either of the hormones had 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. Treatment with the hormones was followed by a more rapid disappearance of nodules and soft apical systolic murmurs. At the end of 1 year, however, there was no significant difference between the three treatment groups in the status of the heart.

This second joint report records the state of the patients after a follow-up of 5 years. It is concerned with a comparison of the amount and severity of rheumatic heart disease in each of the three treatment groups at the end of this time period. It also demonstrates that the status of the heart at start of treatment is the major factor determining the condition of the heart at the end of 5 years and that no treatment can be properly evaluated if this factor is not taken closely into account.

The Numbers Involved

Of the 497 cases admitted to the trial (240 U.K. and 257 U.S.) 445 (89.5 per cent) were known to be alive at the end of the 5 years and the status of the heart had been recorded for all but 19 of them. Sixteen (3.2 per cent) were known to have died. Thus 92.7 per cent of 497 cases had been traced at 5 years. Of the remaining 36 untraced cases 9 were known to be alive at the end of 4 years, 9 at the end of 3 years, 8 at the end of 2 years, 1 at the end of 1 year, and 9 were lost before the end of the first year.

The numbers of deaths and the numbers successfully followed up are given in more detail in table 1, where the cases have been divided into three 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.*

At the end of 5 years the fact of death or the status of the heart among the survivors had been recorded in 88 per cent in Group A, 90 per cent in Group B and 88 per cent in Group C. Similarly, the figures for the three treatment groups were 91 per cent ACTH, 89 per cent cortisone and 87 per cent aspirin.

*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.
The corresponding figure was 91 per cent for the U.K. and 87 per cent for the U.S.

It is clear that within these classifications no differential losses, which might obscure comparisons, have taken place.

Deaths

Of the 497 children under the ages of 16 who were admitted to the study and completed the prescribed course of treatment only 14 had died from rheumatic fever or rheumatic heart disease by the end of the 5 years of follow-up.* One of these deaths occurred shortly after the end of treatment and 4 more within the first year of follow-up. There were no deaths in the second year and only 1 in the third, followed by 4 deaths in the fourth year and 4 in the fifth. In addition there were 2 deaths from unrelated causes, namely one in the ACTH group from acute nephritis and uremia in the fourth year and one in the cortisone group from acute intestinal obstruction in the fourth year.

Division by treatment of the 14 deaths due to rheumatic fever or rheumatic heart disease shows 7 among the 162 ACTH cases (4.3 per cent), 2 among the 167 cortisone cases (1.2 per cent), and 5 among the 168 aspirin cases (3.0 per cent). Division by cardiac status at the start of treatment (tables 1 and 9) shows no deaths at all in the 117 Group A cases (cases with no or questionable carditis and without pre-existing heart disease), 4 deaths (1.6 per cent) among the 252 Group B cases (carditis

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*One child given cortisone who died 20 hours after the start of treatment. He is not included in the 497 children or the 14 deaths. With this single exception all the patients survived the 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. 

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*One death from acute nephritis and uremia. 
†One death from acute intestinal obstruction.
present but no pre-existing heart disease) and 10 (7.8 per cent) among the 128 Group C cases (with pre-existing heart disease). Of the Group B cases 1 death occurred among the 37 cases with failure and/or pericarditis at entry (2.7 per cent) and 3 deaths in the remaining 215 cases (1.4 per cent) where these features were absent. Six of the 10 deaths in Group C occurred in a small group of 31 cases where there was already failure and/or pericarditis at the start of treatment. In other words death occurred in 1 out of every 5 of these cases compared with 1 in 25 in the remainder of Group C.

There were more deaths among females (9 in 238 or 3.8 per cent) than among males (5 in 259 or 1.9 per cent) but the difference might very easily be due to chance. There were also more deaths among those whose disease was 6 weeks or more in duration when treatment was started than among those treated within 6 weeks of onset (8 of 104 or 7.7 per cent compared with 6 of 393 or 1.5 per cent). The difference occurred entirely in the Group C cases where the death rate was 17.5 per cent among late treated cases as compared with 3.4 per cent in early treated cases (7 of 40 and 3 of 88 cases). In Group B the rates for late and early treated cases were 1.9 per cent and 1.5 per cent respectively (1 of 54 and 3 of 198 cases). The death rate was not significantly lower among those treated within 2 weeks of onset (3 of 225 or 1.3 per cent) than among those treated at 2 to 6 weeks (3 of 138 or 2.2 per cent).

One of the most remarkable features of this study is the very low case fatality in comparison with previous reports.2-5 In addition to the modern treatment of the disease there may, however, be a number of other factors concerned in this striking decrease in the severity of the disease. These factors could include a change in the natural history of rheumatic fever or streptococcal infection, the introduction of penicillin and sulfadiazine prophylaxis and environmental features associated with the higher standard of living. There were also six severely ill patients reported in the U.S. as being kept out of the trial of randomized treatments in addition to the one death after 20 hours of treatment (see footnote page 505). On the other hand, not included in this study are cases of rheumatic fever too mild to be admitted to the study hospital’s, a number of which limit their admissions to rheumatic fever and receive referrals from other hospitals. In other words the case fatality rate could have been biased in either direction by these selective factors.

Recurrences

The study plan specified that all cases should receive daily prophylaxis with sulfadiazine, after initial eradication of the streptococcus with a 10-day course of penicillin. In spite of this schedule, recurrences did occur and for analytical purposes were defined as the appearance, after an interval of at least 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. There were, in total, 64 such retreated recurrences in the 5 years among 56 different cases of the 497 admitted (11 per cent). In addition there were 16 retreated recurrences among 14 cases in which chorea was the only manifestation in the recurrences.

It is more informative, however, to limit attention to the cardiac groups A and B, since many cases in Group C had continuous rheumatic activity making recurrence impossible to identify. In Groups A and B there were, excluding recurrences of pure chorea, 42 recurrences in 36 cases (10 per cent of the 369 cases). Further, in these two groups the 42 recurrences and 36 cases in which they occurred were divided almost exactly among the three treatment groups. Thus, there were 16 recurrences in 12 of the 114 ACTH cases, 12 recurrences in 12 of the 128 cortisone cases, and 14 recurrences in 12 of the 127 aspirin cases. It is clear that the frequency of retreated recurrences does not bias the subsequent comparisons of the treatments used in this study.
Comparison of the Treatments

The dosage schedules of ACTH, cortisone, and aspirin were based on published studies and unpublished reports at that time (1950), the aim being to select a dosage likely to be effective over a period of administration short enough to indicate whether the acute attack had been differentially shortened by any one of the three drugs.

The schedules were as follows:* 

**ACTH**
- U.K. cases. A daily dosage in U.S.P. units of 50 for the first 4 days, 60 for the next 3 days, 40 for the second and third weeks, 30 for the fourth and fifth weeks, and 20 for the sixth week.
- U.S. cases. 120 U.S.P. units for the first 4 days, 100 for the next 3 days, 80 for the second week, 60 for the third week, 40 for the fourth and fifth weeks, and 20 for the sixth week.

**Cortisone**
- A daily dosage of 300 mg. for the first day, 200 mg. for the next 4 days, 100 mg. for the second and third weeks, 75 mg. for the fourth and fifth weeks, and 50 mg. for the sixth week.

**Aspirin**
- A daily dosage of 60 mg. per pound of body weight or 10 Gm. (whichever was less) for the first 2 days, 40 mg. per pound or 10 Gm. (whichever was less) for the next 5 days, and 30 mg. per pound for the second to sixth weeks.

If retreatment was necessary at any time during the 3 months following the original course of therapy, then a 4-week retreatment scheme was followed using the same drug and dosage as in the first 4 weeks of initial therapy. No patient was retreated unless he demonstrated rheumatic activity sufficient to have brought him into the study initially. If, after 3 months without activity, the patient developed a new attack of rheumatic fever, he was treated as in the original course, i.e., for 6 weeks on the same drug and dosage, followed by a 3-week period of observation.

The results among cases followed for 5 years are analyzed in terms of the cardiac groups already defined.

Looking first at Group A (table 2), it will be seen that 6 of the 37 ACTH cases had a murmur at the end of 5 years (all grade I apical systolic murmurs), 1 of the 33 cortisone treated cases (a basal diastolic murmur), and 1 of the 33 aspirin treated group (a grade I apical systolic murmur). The small excess in the ACTH group is not statistically significant. The striking fact which emerges from this comparison 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 5 years of follow-up. The prognosis in cases without carditis, but otherwise meeting the criteria for the diagnosis of rheumatic fever, is so good that it would be unreasonable to expect that large-dose cortisone therapy could significantly improve it. The well recognized occasional severe toxic manifestations in large-dose cortisone therapy also militate against its use in such cases.6

In Group B (table 2), the cases are divided into 6 sub-groups according to their cardiac status, ranging from the mildest with only a grade I apical systolic murmur* to the most severe with pericarditis and/or failure. Examination of these groups shows no consistent difference in favor of any one treatment but the number of cases in each group is small. Direct comparison of the effects of treatment among the total of 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, there were more severely ill cases in the

*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.

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*Further details of the treatment schedule, including control of auxiliary therapy, can be found in the original report.*

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ACTH group and more of the milder cases in the cortisone group. There were only 5 ACTH in comparison with 19 cortisone cases in the group of mild cases with only a grade I apical systolic murmur. On the other hand, there were 16 cases with a basal diastolic and one or more other murmurs in the ACTH group compared with only 9 in the cortisone group. Also there were only 7 cases with pericarditis and/or failure in the aspirin group in comparison with 13 on ACTH and 13 on cortisone treatment.

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. Making the assumption that in each of the cardiac sub-groups the three treatments had no differential effects whatsoever, it is possible to calculate the expected outcome in Group B cases for each of the 3 treatment groups.* The expected figures may then be compared with those which actually occurred. Thus, for ACTH the expected number of cases having murmurs at 5 years was 31 as compared with 35 observed, for cortisone 31 expected versus 29 observed, and for aspirin 30 expected and 29 observed. There is no evidence in this comparison that the prognosis has been affected more by one treatment than by another.

*The proportions with murmurs at 5 years were taken separately for the U.S. and the U.K. for each of 6 sub-groups 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 6 sub-groups (U.K. and U.S. separately) to see how many in the small sub-groups would have had a murmur at 5 years if they had experienced the total rate of occurrence. The ‘expected’ numbers in each small sub-group 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 5 years.
Table 3
Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases Followed-up for Five Years and Proportion with One or More Murmurs at That Time, According to Treatment Given and Initial Cardiac Status. U.K. and U.S.

<table>
<thead>
<tr>
<th>Cardiac sub-group at start of treatment</th>
<th>ACTH</th>
<th>Cortisone</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>With murmurs at 5 years No. Per cent</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Group B—carditis present; no pre-existing heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) One murmur, any grade</td>
<td>26</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>2) Two or more murmurs, any grade</td>
<td>28</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>3) With failure and/or pericarditis</td>
<td>13</td>
<td>11</td>
<td>85</td>
</tr>
</tbody>
</table>

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 3). Among cases with a single murmur at start of treatment, 23 per cent of those on ACTH, 27 per cent on cortisone, and 28 per cent on aspirin still had one or more murmurs at 5 years, a negligible difference between the treatments. For those who initially had two or more murmurs, the corresponding proportions were 64 per cent ACTH, 42 per cent cortisone, and 50 per cent aspirin. For cases with failure and/or pericarditis at start of treatment the proportions were 85 per cent for ACTH, 62 per cent for cortisone, and 57 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 the start of treatment (table 2) there were 26 on ACTH, 27 on cortisone, and 27 on aspirin. At 5 years 17 (65 per cent), 21 (78 per cent), and 18 (67 per cent) had murmurs. Of the 22 Group C cases with failure and/or pericarditis 10 were treated with ACTH, 7 with cortisone, and 5 with aspirin. In every one of these cases murmurs were present at 5 years. There is once again no evidence of any significant difference between the three treatment groups.

The Evolution of Rheumatic Heart Disease

Since there is no evidence that the treatments varied in their effectiveness, the three groups can be added together for the study of the evolution of rheumatic heart disease in this particular series of patients. The essential division is the cardiac status when treatment was begun.

Cardiac Group A

Of the 103 cases in this group 12 (12 per cent) had a murmur at 1 year. At 5 years* (table 4) the figure is 8 or 8 per cent (7 with grade I apical systolic murmur and 1 with a basal diastolic murmur). It appears that the outlook is better for the 71 cases without any murmur than for the 32 with a questionabie murmur† at the start of treatment, 96 per cent with no apparent heart disease compared with 84 per cent. The difference is not formally

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*Murmurs in all cardiac groups both appeared and disappeared in the time interval between 1 and 5 years. Thus in some cases murmurs present at 1 year were absent at 5 years, while in other cases that were without murmurs at 1 year a murmur was present at 5 years.

†The questionable apical systolic murmur (P murmur) was defined differently in the United States than in the United Kingdom. This difference affects the comparison of the results between the countries and the interpretation of the natural history of the disease. In the U.S., each principal investigator was permitted to classify a doubtful apical systolic murmur as a P murmur. In the U.K., however, the Working Party agreed that each investigator make a firm decision as to the presence or absence of an apical systolic murmur at the time of admission of the cases to the study. (A few cases, 7, were called doubtful in the U.K.). In the U.K. some patients with doubtful apical systolic murmurs were unquestionably labelled 'no murmur,' others were labelled 'apical systolic murmur' and included in Group B.
significant but it appears in both countries and is in accordance, as shown later, with the general trend of the results.

The number of retreated recurrences in Group A was 10, but none of the 9 cases followed for 5 years had a murmur at that time.

In summary, the prognosis for the cases without carditis when treatment is started (Group A) is excellent. None of the patients had died and 92 per cent were without apparent heart disease 5 years later.

**Cardiac Group B**

Of the 252 cases in this category originally admitted to the study 5 had died, 10 were known to be alive although their cardiac status was unknown, and the cardiac status at 5 years had been recorded for 221. The remaining 16 had been lost (table 1). As has already been shown the group is clinically heterogeneous and for analysis of the 5-year results has been subdivided in table 5 into five sub-groups of murmurs (without failure and/or pericarditis) and one sub-group comprising cases with failure and/or pericarditis. The untraced cases were spread evenly over these sub-groups. Confining attention first of all to the total figures (U.K. and U.S.) the following results may be noted:

(1) Cases with a Grade I Apical Systolic Murmur Alone

Of the 39 cases with only a grade I apical systolic murmur at the start of treatment 14 or 36 per cent had murmurs at 1 year while at 5 years the number had fallen to 7 or 18 per cent (3 with a grade I apical systolic murmur, 1 with a grade III apical systolic murmur, 1 with apical systolic and mid-diastolic murmurs, 1 with basal diastolic, apical systolic and mid-diastolic murmurs, and 1 with apical systolic and pre-systolic murmurs). Thus 82 per cent of this group had no apparent heart disease at 5 years and none had died.

(2) Cases with a Grade II or III Apical Systolic Murmur Alone

Of the 60 cases in this category 32 or 53 per cent had at least one cardiac murmur at 1 year. This figure had decreased considerably at 5 years to 19 or 32 per cent (6 with grade I apical systolic murmurs, 5 with grade II or III apical systolic murmurs, 5 with apical systolic and mid-diastolic murmurs, 1 with basal diastolic and apical systolic murmurs, and 2 with known but unspecified murmurs). Thus among these cases 68 per cent had no apparent heart disease at 5 years. Two additional cases originally in this group had died, both in the first year.

(3) Cases with an Apical Systolic Murmur of Any Grade Plus an Apical Mid-Diastolic Murmur

Of the 44 cases in this category 28 or 64 per cent had at least one murmur at 1 year while at 5 years the number was 23 or 52 per cent (6 with an apical systolic murmur grade I, 6 with an apical systolic murmur grade II or III, 4 with an apical systolic and an apical mid-diastolic murmur, 2 with a basal diastolic murmur and an apical systolic murmur, 3

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Table 4

<table>
<thead>
<tr>
<th>Cardiac sub-group at start of treatment</th>
<th>U.K.</th>
<th>U.S.</th>
<th>U.K. and U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>With murmurs at 5 years No. Per cent</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Group A—no or questionable carditis; no pre-existing heart disease</td>
<td>37</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>No murmur</td>
<td>30</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Questionable murmur*</td>
<td>7</td>
<td>3</td>
<td>43</td>
</tr>
</tbody>
</table>

*A murmur apparently localized to apical area but so faint as not to be transmitted to or toward axilla.

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with a basal diastolic murmur, an apical systolic, and a mid-diastolic murmur, and finally 2 with an apical pre-systolic murmur accompanied by an apical systolic murmur in the first and by an apical systolic and a basal diastolic murmur in the second). Thus, among these cases only about half (48 per cent) had no apparent heart disease at 5 years. In addition one had died during the fourth year but not from rheumatic fever.

(4) Cases with a Basal Diastolic Murmur Alone

There were only 11 cases in this category of whom 5 or 45 per cent had at least one murmur at 1 year, decreasing to 3 cases or 27 per cent at 5 years (2 with basal diastolic murmurs alone, 1 with unspecified murmurs). Thus, 73 per cent of this group had no apparent heart disease at 5 years. None had died.

(5) Cases with a Basal Diastolic Murmur and an Apical Systolic and/or a Mid-Diastolic Murmur

Of the 34 cases in this category at 5 years, 33 were reported at 1 year and of these, 22 or 67 per cent had at least one murmur at that time. The figure decreased to 18 out of 34 cases or 53 per cent at 5 years (4 with a grade II apical systolic murmur, 1 with apical systolic and mid-diastolic murmurs, 1 with an apical mid-diastolic murmur alone, 7 with a basal diastolic murmur alone, and 5 with a basal diastolic murmur and another murmur, 4 of which were apical systolic and 1 a mid-diastolic murmur). Thus, almost one half of this group (47 per cent) had no apparent heart disease at 5 years. In addition one patient had died during the fifth year.

(6) Cases with Failure and/or Pericarditis

Turning finally to the cases in Group B with failure and/or pericarditis at the start of treatment, there were 33 such cases, of which 24 or 73 per cent had at least one murmur at 1 year. At 5 years 23 or 70 per cent had a murmur (4 with a grade I apical systolic murmur, 8 with a grade II or grade III apical systolic murmur, 3 with apical systolic and mid-diastolic murmurs, 2 with a basal diastolic murmur alone, and 6 with a basal diastolic murmur and other murmurs of which 3 were apical systolic, 2 were apical systolic and mid-diastolic, and 1 was apical pre-systolic and mid-diastolic). In other words, only 30 per cent of this group were without apparent heart disease at 5 years. In addition one patient had died during the fourth year.

Comparison of the U.K. and U.S. experiences in all Group B cases (table 5) reveals no consistent pattern of advantage or disadvantage. The largest difference, which lies in the group with basal diastolic plus other murmurs, is almost entirely a function of a
Table 6
Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases Followed-up for Five Years and Numbers Expected* and Observed to Have Murmurs at Five Years According to Sex, Age, Duration from Onset, and Presence or Absence of Various Signs or Symptoms. U.K. and U.S.

<table>
<thead>
<tr>
<th>Status at start of treatment</th>
<th>Number of cases</th>
<th>Number with murmurs at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>104</td>
<td>41 44</td>
</tr>
<tr>
<td>Females</td>
<td>117</td>
<td>52 49</td>
</tr>
<tr>
<td>Under 10 years of age</td>
<td>119</td>
<td>55 54</td>
</tr>
<tr>
<td>10-16 years of age</td>
<td>102</td>
<td>38 39</td>
</tr>
<tr>
<td>0-14 days from onset</td>
<td>102</td>
<td>38 39</td>
</tr>
<tr>
<td>15 + days from onset</td>
<td>119</td>
<td>55 54</td>
</tr>
<tr>
<td>P-R &gt;.18</td>
<td>54</td>
<td>15 20</td>
</tr>
<tr>
<td>P-R &lt;.18</td>
<td>167</td>
<td>78 73</td>
</tr>
<tr>
<td>With joint involvement</td>
<td>76</td>
<td>26 30</td>
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<tr>
<td>Without joint involvement</td>
<td>145</td>
<td>67 63</td>
</tr>
<tr>
<td>With nodules</td>
<td>38</td>
<td>20 17</td>
</tr>
<tr>
<td>Without nodules</td>
<td>183</td>
<td>73 76</td>
</tr>
<tr>
<td>With chorea</td>
<td>30</td>
<td>8 11</td>
</tr>
<tr>
<td>Without chorea</td>
<td>191</td>
<td>85 82</td>
</tr>
</tbody>
</table>

*Expected numbers take account of differences in the severity of cardiac involvement among the groups being compared. They were calculated in the following manner: The proportions of cases with murmurs at 5 years were taken separately for the U.S. and the U.K. for each of the six cardiac sub-groups in Group B. These proportions were applied in the U.S. and U.K. separately to the actual number of patients in each cardiac sub-group of the categories listed above to see how many in the small sub-groups would have had a murmur at 5 years if they had experienced the total rate of occurrence. The "expected" numbers in the sub-groups were added to get the total number expected in each category for the U.S. and U.K. combined.

differing standard of interpretation, since the U.K. figure is derived from one center only. Thirty of the total 31 U.K. cases with a basal diastolic murmur at start of treatment whose status was known at 5 years were reported from this center. The basal diastolic murmurs in cases at this center were soft and 25 of the 30 disappeared.

An analysis was made of other factors which might have prognostic effects. These included sex, age, duration from onset, and presence or absence at start of treatment of polyarthritis, nodules, chorea, and prolonged P-R interval. None of these individually appeared to affect the evolution of rheumatic heart disease as measured by the presence of murmurs at 5 years (table 6). Cardiac enlargement as measured by a cardiothoracic ratio on the telerointenogram of 0.60 or greater was present at start of therapy in 16 Group B cases. In 13 of these at least one murmur was present at 5 years. This serious prognosis is explained by the large number of such cases (11 of 16) that had cardiac failure and/or pericarditis at start of treatment, practically all of which (10 of 11) had at least one murmur at 5 years.

Retreated recurrences occurred in 25 Group B cases. The cardiac status at start of treatment among these cases was, on the average, more severe than in the remainder of Group B cases (table 7). At 5 years these retreated patients had a larger proportion with murmurs than those without retreated recurrences. However, the relationship between cardiac status at start of therapy and at 5 years still held even though retreated attacks had occurred in the interim. Among Group A cases there were no murmurs at 5 years in 9 cases with retreated recurrences; in Group B cases with a single murmur at start of treatment 3 out of 8 cases had murmurs at 5 years as compared with 9 out of 9 in cases with two or more murmurs and 7 out of 8 cases with failure and/or pericarditis.

Summarizing the cases with carditis but without pre-existing heart disease (Group B), it is clear that prognosis is directly dependent on the amount and severity of cardiac involvement at the start of treatment, the proportion with a murmur at 5 years varying from 18 per cent in those with a grade I apical systolic murmur to 70 per cent among those with pericarditis and/or failure. Excluding the group with basal diastolic murmurs for the reason given above and because of the relatively few cases in this category in the U.S., this trend holds when the figures are examined individually for each country. In addition, the proportion of all Group B cases with murmurs is remarkably similar in the two countries.
Table 7
Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases with and without Retreated Recurrences Followed-up for Five Years and Proportion with One or More Murmurs at That Time. U.K. and U.S.

<table>
<thead>
<tr>
<th>Cardiac sub-group at start of treatment</th>
<th>U.K. Without retreated recurrences</th>
<th>U.S. Without retreated recurrences</th>
<th>U.K. and U.S. Without retreated recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>With murmurs at 5 years</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Group B—carditis present; no pre-existing heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) One murmur, any grade</td>
<td>102</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>2) Two or more murmurs, any grade</td>
<td>69</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>3) With failure and/or pericarditis</td>
<td>25</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 8
Cardiac Group C (Definite or Questionable Pre-existing Heart Disease). Number of Cases Followed-up for Five Years and Proportion with One or More Murmurs at That Time. U.K., U.S., U.K. and U.S.

<table>
<thead>
<tr>
<th>Cardiac sub-group at start of treatment</th>
<th>U.K.</th>
<th>U.S.</th>
<th>U.K. and U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>With murmurs at 5 years</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Without failure and/or pericarditis</td>
<td>45</td>
<td>36</td>
<td>80</td>
</tr>
<tr>
<td>With failure and/or pericarditis</td>
<td>16</td>
<td>16</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 9
Prognosis in Relation to Cardiac Status at Start of Treatment. U.K. and U.S.

<table>
<thead>
<tr>
<th>Cardiac status at start of treatment</th>
<th>No. of cases observed for 5 years</th>
<th>Per cent with no murmur at 5 years</th>
<th>No. of deaths in 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No carditis</td>
<td>71</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>Questionable carditis</td>
<td>32</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical systolic murmur grade I, only</td>
<td>39</td>
<td>82</td>
<td>0</td>
</tr>
<tr>
<td>Apical systolic murmur grade II or III, only</td>
<td>60</td>
<td>68</td>
<td>2</td>
</tr>
<tr>
<td>Apical systolic and apical mid-diastolic murmurs</td>
<td>44</td>
<td>48</td>
<td>1†</td>
</tr>
<tr>
<td>Basal diastolic with or without other murmurs</td>
<td>45 (15)*</td>
<td>53 (27)*</td>
<td>1†</td>
</tr>
<tr>
<td>Failure and/or pericarditis</td>
<td>33</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>Group C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing heart disease without failure and/or pericarditis</td>
<td>80</td>
<td>50</td>
<td>5‡</td>
</tr>
<tr>
<td>Pre-existing heart disease with failure and/or pericarditis</td>
<td>22</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

*Excluding one U. K. center.
†Death from acute nephritis and uremia.
‡Includes 1 death from acute intestinal obstruction.
Cardiac Group C

There were 102 cases with known cardiac status at 5 years who had definite or question-able pre-existing heart disease at the start of their treatment (table 8). Of the 80 without failure and/or pericarditis at start of treatment, 70 per cent had heart disease at 5 years and of the 22 with failure and/or pericarditis, all had heart disease. It may also be recalled that in addition 4 and 6 deaths from rheumatic fever had taken place respectively in these two groups and one death from other causes in the group without failure or pericarditis.

* * * *

In table 9 all of the cases in the study followed for 5 years are listed in the order of increasing severity of heart disease at start of treatment. It is abundantly clear that the range from 96 per cent to 0 per cent with normal hearts at 5 years is much more striking than differences reported here or ascribed elsewhere to the effects of treatment. Thus, in the prevention of rheumatic heart disease no evaluation of therapy of acute rheumatic fever can be valid unless this major factor is taken into account in the design of the study or the analysis of the data. This conclusion is reinforced by the occurrence of most of the deaths from rheumatic fever (10 of 14) among cases with pre-existing heart disease, and the absence of deaths among the cases without heart involvement at start of treatment.

No comparisons have been made with the conflicting reports of results obtained with large-dose hormone therapy7-11 the most recent of which shows no advantage in a well controlled study.11 A firm decision on the efficacy of large-dose hormone treatment of rheumatic fever will depend on controlled studies of adequate size in which the status of the heart is taken into account.

Summary

1. A study has been made 5 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, corticosterone, and aspirin in the treatment of acute rheumatic fever.

2. Four hundred and forty-five of the cases (89.5 per cent) were followed for the complete 5 years and the status of the heart was known for 426 of them. Only 16 (3.2 per cent) had died, 14 of them from rheumatic heart disease; 36 (7.2 per cent) were untraced. The very low fatality rate is striking.

3. At the end of 5 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.

4. The major factor in determining the incidence of rheumatic heart disease at the end of 5 years is the status of the heart at the time treatment was begun. For cases without carditis initially the prognosis was excellent, since in 96 per cent there was no residual heart disease. In cases with carditis initially but without pre-existing heart disease the proportion without residual heart disease decreased progressively from 82 per cent for those with only a grade I apical systolic murmur to 30 per cent for those with failure and/or pericarditis. In cases with pre-existing heart disease the prognosis was poor. Only 30 per cent of those without pericarditis or failure and none of those with pericarditis and/or failure were without heart disease at 5 years.

5. Cases with carditis and without pre-existing heart disease which had recurrences demanding retreatment during the follow-up period had on the average a more severe cardiac status at start of treatment than did those without recurrences requiring retreatment. At 5 years a larger proportion of these retreated cases had murmurs.

6. These results make clear that treatment of acute rheumatic fever cannot be properly evaluated unless the status of the heart of the patients at the start of treatment is taken closely into account.

Summario in Interlingua

1. Esserva studiate 5 annos post le completione de tratamento del 497 juveniles includite in le essayo clinico cooperative del Regno Unite e del Status Unite
relative al meritos comparative de ACTH, cortisona, e aspirina in le tractamento de acute febre rheumatic.

2. Quatro centos quaranta-cinque del casos (89,5 pro cento) essave observate durante le complete periodo de 5 annos, e le stato del corde eseva cogno-site in 426. Solmente 16 (3,2 pro cento) habeava morite, con morbo rheumatic del corde como causa mortal in 14. Treenta-sex (7,2 pro cento) mom poteva esser trattate. Le bassissime mortalitate es frappante.

3. Al fin de 5 annos, le datos non indica que—sub le condizioni de tractamento usate in iste studio—le prognose eseva influentiate plus mareatemente per un del formas de tractamento que per le alters. Isto representa un confirmation del constatationes al fin del prime anno.

4. Le plus importante factor de determination pro le incidentia de morbo cardic rheumatic al fin del 5 annos es le stato del corde al tempore quando le tractamento eseva initiate. Pro casos sin carditis al initio, le prognose eseva excellent, proque in 96 pro cento de istos il habeava nulle residue morbo cardic. In casos con carditis al initio sed sin pre-existente morbo cardic, le proportion del disparition complete de morbo cardic declinava progressivemente ab 82 pro cento in le gruppo con solmente un murmure apico-systolique de grado 1 a 30 pro cento in le gruppo con disfallimento e/o pericarditis. In casos con pre-existente morbo cardic le prognose eseva mal. Solmente 30 pro cento del subgruppo sin pericarditis o disfallimento e nullo del subjectos in le gruppo con pericarditis e/o disfallimento eseva libere de morbo cardic al fin del 5 annos.

5. Le cases con carditis e sin pre-existente morbo cardic le quales habeava recurrentias que requireva un retractamento durante le periodo de observation habeava habite—a generalmente parlar—un plus grave stato cardic al initio del tractamento que le casos sin recurrentias a character requirente re-tractamento. Al fin del 5 annos, murmures eseva presente in un plus grande proportion de ille cases retractate.

6. Iste resultatos rende clar que le tractamento de acute febre rheumatic non pote esser evalutate ade-quatemente si le stato del corde del patiente al comenciamento del tractamento non es prendite in consideratio in omne su aspectos.

References
The Evolution of Rheumatic Heart Disease in Children: Five-Year Report of a Cooperative Clinical Trial of ACTH, Cortisone, and Aspirin

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