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# THE EVOLUTION OF RHEUMATIC HEART DISEASE IN CHILDREN
## FIVE-YEAR REPORT OF A CO-OPERATIVE 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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THE UNITED Kingdom and United States co-operative clinical trial was set up in 1951-52 to compare the relative merits of adrenocorticotrophic hormone (ACTH), cortisone and aspirin in the treatment of rheumatic fever and the prevention 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 centres 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

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The National Heart Institute of the United States Public Health Service supported the study with grants to the co-ordinating centre and to the co-operating centres in the United States and by a travel grant to the Medical Research Council of Great Britain. The Medical Research Council provided support for the six centres and for a co-ordinating registrar in the United Kingdom. The centre in Toronto received a grant from the Canadian Arthritis and Rheumatism Society. In the United States, the costs of the medical care of its patients were met by each co-operating centre, and in Great Britain by the National Health Service. The American Heart Association provided office space for the American Co-ordinating Center and a grant for statistical services.
This co-operative 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 Merck & 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. Duckett Jones and the late Sir James Spence.

TABLE I.--NUMBER OF PATIENTS TRACED AT FIVE YEARS ACCORDING TO CARDIAC GROUP—U.K., U.S.A., AND U.K. AND U.S.A.

| Cardiac group at start of treatment | Number of patients: At start of treatment | Died | Alive and heart status known | Alive but heart status unknown | Untraced | % Untraced |
|---|---|---|---|---|---|---|
| U.K. | | | | | | |
| Group A—no or questionable carditis; no pre-existing heart disease | 41 | 0 | 37 | 0 | 4 | 9.8 |
| Group B—carditis present; no pre-existing heart disease | 123 | 4* | 109 | 4 | 6 | 4.9 |
| Group C—with definite or questionable pre-existing heart disease | 76 | 7† | 61 | 3 | 5 | 6.6 |
| All groups | 240 | 11 | 207 | 7 | 15 | 6.2 |
| U.S.A. | | | | | | |
| Group A—no or questionable carditis; no pre-existing heart disease | 76 | 0 | 66 | 4 | 6 | 7.9 |
| Group B—carditis present; no pre-existing heart disease | 129 | 1 | 112 | 6 | 10 | 7.8 |
| Group C—with definite or questionable pre-existing heart disease | 52 | 4 | 41 | 2 | 5 | 9.6 |
| All groups | 257 | 5 | 219 | 12 | 21 | 8.2 |
| U.K. and U.S.A. | | | | | | |
| Group A—no or questionable carditis; no pre-existing heart disease | 117 | 0 | 103 | 4 | 10 | 8.5 |
| Group B—carditis present; no pre-existing heart disease | 252 | 5* | 221 | 10 | 16 | 6.3 |
| Group C—with definite or questionable pre-existing heart disease | 128 | 11† | 102 | 5 | 10 | 7.8 |
| All groups | 497 | 16 | 426 | 19 | 36 | 7.2 |

*1 death from acute nephritis and uræmia
†1 death from acute intestinal obstruction

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 one 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 the 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%) 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%) were known to have died. Thus 92.7% of 497 cases had been traced at 5 years. Of the remaining 36 untraced patients, 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 one 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 I. 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% in Group A, 90% in Group B

*One Canadian centre took part in the trial, but for easy reference the term "U.S." is used to include all North American centres.

*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% 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) dyspnœa, (2) orthopnœa, (3) enlargement of the liver, (4) basal pulmonary rales, (5) increased jugular venous pressure or (6) œdema.
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.

and 88% in Group C. Similarly, the figures for the three treatment groups were 91% ACTH, 89% cortisone and 87% aspirin. The corresponding figure was 91% for the U.K. and 87% 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 age 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 uræmia 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 treated with ACTH (4.3%), 2 among the 167 treated with cortisone (1.2%), and 5 among the 168 treated with aspirin (3.0%). Division by cardiac status at the start of treatment (Tables I and IX) 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%) among the 252 Group B cases (carditis present but no pre-existing heart disease), and 10 (7.8%) among the 128 Group C cases (with pre-existing heart disease). Of the Group B cases there was 1 death among the 37 patients with failure and/or pericarditis at entry (2.7%) and there were 3 deaths in the remaining 215 (1.4%) in whom these features were absent. Six of the 10 deaths in Group C were in a small group of 31 where there was already failure and/or pericarditis at the start of treatment. In other words, 1 out of every 5 of these died compared with 1 in 25 in the remainder of Group C.

There were more deaths among females (9 in 238, or 3.8%) than among males (5 in 259, or 1.9%) but the difference might very easily be due to chance. There were also more deaths among those whose disease was six weeks or more in duration when treatment was started than among those treated within six weeks of onset (8 of 104, or 7.7%, compared with 6 of 393, or 1.5%). The difference was entirely in the Group C cases where the death rate was 17.5% among patients treated late as compared with 3.4% in patients treated early (7 of 40 and 3 of 88 cases). In Group B the rates for late and early treatment were 1.9% and 1.5% respectively (1 of 54 and 3 of 198 cases). The death rate was not significantly lower among those treated within two weeks of onset (3 of 255, or 1.2%) than among those treated at 2 to 6 weeks (3 of 138, or 2.2%).

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 sulphadiazine prophylaxis, and environmental features associated with the higher standard of living. There were also six severely ill patients reported in the U.S.A. who were kept out of the trial of randomized treatments in addition to the one who died after twenty hours of treatment (see footnote). On the other hand, not included in this study are patients with rheumatic fever too mild to be admitted to the study hospitals, 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 patients should receive daily prophylaxis with sulphadiazine, after initial eradication of the streptococcus by a 10-day course of penicillin. In spite of this schedule, there were recurrences which, for analytical purposes, were defined as the appearance, after an interval of at least 3 months' freedom from rheumatic activity, of manifestations that would have originally qualified the patient for admission to the trial. An analysis was made of all case reports in which there was retreatment 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%). In addition there were 16 retreated recurrences among 14 cases in which chorea was the only manifestation in the recurrence.

It is more informative, however, to limit attention to the cardiac groups A and B, since many patients in Group C had continuous rheumatic activity which made recurrence impossible to identify. In groups A and B there were, excluding recurrences of pure chorea, 42 recurrences in 36 cases (10% 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 treated by ACTH, 12 recurrences in 12 of the 128 treated by cortisone and 14 recurrences in 12 of the 127 treated by aspirin. It is clear that the frequency of retreated recurrence

*One child given cortisone who died 20 hours after the start of treatment 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.

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. patients. A daily dosage in U.S.P. units of 80 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. patients. 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 lb. of body weight or 10 g. (whichever was less) for the first 2 days, 40 mg. per lb. or 10 g. (whichever was less) for the next 5 days, and 30 mg. per lb. for the second to sixth weeks.

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

*Further details of the treatment schedule, including control of auxiliary therapy, can be found in the original report.[1]

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

Looking first at Group A (Table II), it will be seen that 6 of the 37 patients treated by ACTH had a murmur at the end of 5 years (all were grade I apical systolic murmurs), 1 of the 33 treated by cortisone (a basal diastolic murmur) and 1 of the 33 treated by aspirin (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 patients 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]

TABLE II.—NUMBER OF PATIENTS FOLLOWED UP FOR 5 YEARS AND PROPORTION WITH ONE OR MORE MURMURS AT THAT TIME, ACCORDING TO TREATMENT GIVEN AND INITIAL CARDIAC STATUS—U.K. AND U.S.A.

| *Cardiac group at start of treatment* | *ACTH* | | | *Cortisone* | | | *Aspirin* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | |
| | | *No.* | *%* | | *No.* | *%* | | *No.* | *%* |
| Group A—no or questionable carditis; no pre-existing heart disease | 37 | 6 | *16* | 33 | 1 | *3* | 33 | 1 | *3* |
| Group B—carditis present; no pre-existing heart disease | | | | | | | | | |
| (1) Apical systolic murmur grade I, only | 5 | 0 | *0* | 19 | 3 | *16* | 15 | 4 | *27* |
| (2) Apical systolic murmur grade II or III, only | 18 | 4 | *22* | 17 | 7 | *41* | 25 | 8 | *32* |
| (3) Apical systolic *and* apical mid-diastolic murmurs | 12 | 9 | *75* | 15 | 6 | *40* | 17 | 8 | *47* |
| (4) Basal diastolic murmur only | 3 | 2 | *67* | 5 | 1 | *20* | 3 | 0 | *0* |
| (5) Basal diastolic *and* other murmurs | 16 | 9 | *56* | 9 | 4 | *44* | 9 | 5 | *56* |
| (6) With failure and/or pericarditis | 13 | 11 | *85* | 13 | 8 | *62* | 7 | 4 | *57* |
| Group C—with definite or questionable pre-existing heart disease | | | | | | | | | |
| (1) Without failure and/or pericarditis | 26 | 17 | *65* | 27 | 21 | *78* | 27 | 18 | *67* |
| (2) With failure and/or pericarditis | 10 | 10 | *100* | 7 | 7 | *100* | 5 | 5 | *100* |

In Group B (Table II), the cases are divided into 6 subgroups according to the cardiac status, ranging from the mildest of only a grade I apical systolic murmur* to the most severe of pericarditis

*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.

and/or failure. Examination of these groups shows no consistent difference in favour of any one treatment, but the number of cases in each group is small. Direct comparison of the effects of treatment among 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, there were more severely ill cases in the 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 which had only a grade I apical systolic murmur. On the other hand, there were 16 cases in which there were 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 of pericarditis and/or failure in the aspirin group in comparison with 13 in the group receiving ACTH and 13 in the cortisone-treated group.

ment and those with two or more murmurs at that time (Table III). Among patients who had a single murmur at start of treatment, 23% of those receiving ACTH, 27% receiving cortisone and 28% receiving aspirin still had one or more murmurs at 5 years, a negligible difference between the treatments. For those who initially had 2 or more murmurs, the corresponding proportions were ACTH 64%, cortisone 42% and aspirin 50%. For cases with failure and/or pericarditis at start of treatment the proportions were 85% for ACTH, 62% for cortisone and 57% 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 patients without failure and/or pericarditis at the start of treatment (Table II) there were 26 receiving ACTH, 27 receiving cortisone and 27 receiving aspirin. At 5 years, 17 (65%), 21 (78%) and 18 (67%) had murmurs.

TABLE III.—CARDIAC GROUP B (CARDITIS PRESENT; NO PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS FOLLOWED UP FOR 5 YEARS AND PROPORTION WITH ONE OR MORE MURMURS AT THAT TIME, ACCORDING TO TREATMENT GIVEN AND INITIAL CARDIAC STATUS—U.K. AND U.S.A.

| | *ACTH* | | | *Cortisone* | | | *Aspirin* | | |
|---|---|---|---|---|---|---|---|---|---|
| *Cardiac subgroup at start of treatment* | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | |
| | | *No.* | *%* | | *No.* | *%* | | *No.* | *%* |
| Group B—carditis present; no pre-existing heart disease | | | | | | | | | |
| (1) One murmur, any grade | 26 | 6 | *23* | 41 | 11 | *27* | 43 | 12 | *28* |
| (2) Two or more murmurs, any grade | 28 | 18 | *64* | 24 | 10 | *42* | 26 | 13 | *50* |
| (3) With failure and/or pericarditis | 13 | 11 | *85* | 13 | 8 | *62* | 7 | 4 | *57* |

It is possible, however, to allow for this unequal distribution of cases of varying degrees of clinical severity among the 3 treatment groups and thus make a valid evaluation of treatment within the entire Group B. Assuming that in each of the cardiac subgroups the three treatments had no differential effects whatsoever, we can calculate the expected outcome in group B cases for each of the three 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.

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 III). Among patients who had a single murmur at start of treatment, 23% of those receiving ACTH, 27% receiving cortisone and 28% receiving aspirin still had one or more murmurs at 5 years, a negligible difference between the treatments. For those who initially had 2 or more murmurs, the corresponding proportions were ACTH 64%, cortisone 42% and aspirin 50%. For cases with failure and/or pericarditis at start of treatment the proportions were 85% for ACTH, 62% for cortisone and 57% 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 patients without failure and/or pericarditis at the start of treatment (Table II) there were 26 receiving ACTH, 27 receiving cortisone and 27 receiving aspirin. At 5 years, 17 (65%), 21 (78%) and 18 (67%) had murmurs. Of the 22 patients in Group C with failure and/or pericarditis 10 were treated by ACTH, 7 by cortisone and 5 by aspirin. In every one, 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%) had a murmur at 1 year. At 5 years* (Table IV) the figure was 8, or 8% (7 with a grade I apical systolic murmur and 1 with a basal diastolic murmur). It appears that the outlook is better for the 71 patients without any murmur than for the 32 with

*The proportions with murmurs at 5 years were taken separately for the U.S.A. and the U.K. for each of 6 subgroups in Group B *for all 3 treatments combined.* These proportions were applied to the actual number of patients *on each treatment* and in each of the 6 subgroups (U.S.A. and U.K. separately) to see how many in the small subgroups would have had a murmur at 5 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 five years.

*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 without murmurs at 1 year a murmur was present at 5 years.

TABLE IV.—CARDIAC GROUP A (NO OR QUESTIONABLE CARDITIS; NO PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS FOLLOWED UP FOR 5 YEARS AND PROPORTION WITH ONE OR MORE MURMURS AT THAT TIME—U.K., U.S.A., U.K. AND U.S.A.

| *Cardiac subgroup at start of treatment* | *U.K.* | | | *U.S.A.* | | | *U.K. and U.S.A.* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | |
| | | *No.* | *%* | | *No.* | *%* | | *No.* | *%* |
| Group A—no or questionable carditis; no pre-existing heart disease | 37 | 6 | *16* | 66 | 2 | *3* | 103 | 8 | *8* |
| No murmur | 30 | 3 | *10* | 41 | 0 | *0* | 71 | 3 | *4* |
| Questionable murmur* | 7 | 3 | *43* | 25 | 2 | *8* | 32 | 5 | *16* |

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

a questionable murmur* at the start of treatment, 96% with no apparent heart disease compared with 84%. The difference is not formally 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 nine patients followed up for 5 years had a murmur at that time.

TABLE V.—CARDIAC GROUP B (CARDITIS PRESENT; NO PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS FOLLOWED UP FOR 5 YEARS AND PROPORTION WITH ONE OR MORE MURMURS AT THAT TIME—U.K., U.S.A., AND U.K. AND U.S.A.

| *Cardiac subgroup at start of treatment* | *U.K.* | | | *U.S.A.* | | | *U.K. and U.S.A.* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | |
| | | *No.* | *%* | | *No.* | *%* | | *No.* | *%* |
| Without failure and/or pericarditis | 97 | 36 | *37* | 91 | 34 | *37* | 188 | 70 | *37* |
| (1) Apical systolic murmur grade I, only | 14 | 4 | *29* | 25 | 3 | *12* | 39 | 7 | *18* |
| (2) Apical systolic murmur grade II or III, only | 28 | 10 | *36* | 32 | 9 | *28* | 60 | 19 | *32* |
| (3) Apical systolic *and* apical mid-diastolic murmurs | 24 | 11 | *46* | 20 | 12 | *60* | 44 | 23 | *52* |
| (4) Basal diastolic murmur only | 6 | 1 | *17* | 5 | 2 | *40* | 11 | 3 | *27* |
| (5) Basal diastolic *and* other murmurs | 25 | 10 | *40* | 9 | 8 | *89* | 34 | 18 | *53* |
| With failure and/or pericarditis | 12 | 10 | *83* | 21 | 13 | *62* | 33 | 23 | *70* |

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

### CARDIAC GROUP B

Of the 252 patients 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 to follow-up (Table I). As has already been shown, the group is clinically heterogeneous and for analysis of the 5-year results has been subdivided (Table V) into five subgroups of murmurs (without failure and/or pericarditis) and one subgroup comprising patients with failure and/or pericarditis. The number of untraced cases was spread evenly over these subgroups. From the total figures (U.K. and U.S.A.) the following results may be noted:

1. *Patients with a grade I apical systolic murmur alone*

Of the 39 patients with only a grade I apical systolic murmur at the start of treatment, 14, or 36%, had murmurs at 1 year, while at 5 years the number had fallen to 7, or 18% (3 with a grade I apical systolic murmur, 1 with a grade II 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% of this group had no apparent heart disease at 5 years and none had died.

2. *Patients with a grade II or III apical systolic murmur alone*

Of the 60 patients in this category 32, or 53%, had at least one cardiac murmur at 1 year. This figure had decreased considerably at 5 years to 19, or 32% (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 patients 68% had no apparent heart disease at 5 years. Two additional patients originally in this group had died, both in the first year.

*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.A., 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.

3. *Patients with an apical systolic murmur of any grade plus an apical mid-diastolic murmur*

Of the 44 patients in this category 28, or 64%, had at least one murmur at 1 year, while at 5 years the number was 23, or 52% (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 and 3 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 patients only about half (48%) had no apparent heart disease at 5 years. In addition one had died during the fourth year, but not from rheumatic fever.

4. *Patients with a basal diastolic murmur alone*

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

5. *Patients with a basal diastolic murmur and an an apical systolic and/or a mid-diastolic murmur*

Of the 34 patients in this category at 5 years, 33 were reported at 1 year, and of these, 22, or 67%, had at least one murmur at that time. The figure decreased to 18 out of 34 cases, or 53%, 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%) had no apparent heart disease at 5 years. In addition one patient had died during the fifth year.

6. *Patients with failure and/or pericarditis*

Turning finally to the patients in Group B with failure and/or pericarditis at the start of treatment, we find 33 of whom 24, or 73%, had at least one murmur at 1 year. At five years 23, or 70%, 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% 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.A. experiences (Table V) 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 differing standard of interpretation, since the U.K. figure is derived from one centre only. Thirty of the total 31 U.K. patients with a basal diastolic murmur at start of treatment whose status was known at five years were reported from this centre. The basal diastolic murmurs in cases at this centre were soft and 25 of the 30 disappeared.

TABLE VI.—CARDIAC GROUP B (CARDITIS PRESENT; NO PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS 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.A.

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

*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.A. and the U.K. for each of the six cardiac subgroups in Group B. These proportions were applied in the U.S.A. and U.K. separately to the actual number of patients in each cardiac subgroup of the categories listed above to see how many in the small subgroups would have had a murmur at five 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 for the U.S.A. and U.K. combined.

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 VI). Cardiac enlargement as measured by a cardiothoracic ratio on the teleoroentgenogram 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 patients (11 of 16) who had cardiac failure and/or pericarditis at start of treatment, practically all of whom (10 of 11) had at least one murmur at 5 years.

Twenty-five patients in Group B whose cardiac status at start of treatment was, on the average,

TABLE VII.—CARDIAC GROUP B (CARDITIS PRESENT; NO PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS WITH AND WITHOUT RETREATED RECURRENCES, AND PROPORTION WITH ONE OR MORE MURMURS AT 5 YEARS—U.K. AND U.S.A.

| *Cardiac subgroup at start of treatment* | *Without retreated recurrences* | | | *With retreated recurrences* | | |
|---|---|---|---|---|---|---|
| | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | |
| | | *No.* | *%* | | *No.* | *%* |
| Group B—carditis present; no pre-existing heart disease | | | | | | |
| (1) One murmur, any grade | 102 | 26 | *25* | 8 | 3 | *38* |
| (2) Two or more murmurs, any grade | 69 | 32 | *46* | 9 | 9 | *100* |
| (3) With failure and/or pericarditis | 25 | 16 | *64* | 8* | 7 | *88* |

*Excludes one case with retreated recurrence which was not traced at 5 years.

more severe than in the other patients of Group B were retreated for recurrence (Table VII). At 5 years these retreated patients had a larger proportion of murmurs than those without retreated recurrences. However, the relationship between cardiac status at start of therapy and at five years still held despite retreated attacks in the interim. Among Group A cases there were no murmurs at 5 years in 9 patients with retreated recurrences; of Group B patients with a single murmur at start of treatment 3 out of 8 had murmurs at five years as compared with 9 out of 9 in patients with two or more murmurs and 7 out of 8 with failure and/or pericarditis.

From a summary of the cases in which there was carditis but no 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% in those with a grade I apical systolic murmur to 70% 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.A., we find that 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.

### CARDIAC GROUP C

There were 102 patients of known cardiac status at 5 years who had definite or questionable pre-existing heart disease at the start of their treatment (Table VIII). Of the 80 without failure and/or pericarditis at that time, 70% 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 1 death from other causes in the group without failure or pericarditis.

In Table IX all of the cases in the study in which there was follow-up for 5 years are listed in order of increasing severity of heart disease at start of treatment. It is abundantly clear that the range from 96% with normal hearts to 0%, 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

TABLE VIII.—CARDIAC GROUP C (DEFINITE OR QUESTIONABLE PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS FOLLOWED UP FOR 5 YEARS AND PROPORTION WITH ONE OR MORE MURMURS AT THAT TIME—U.K., U.S.A., AND U.K. AND U.S.A.

| *Cardiac subgroup at start of treatment* | *U.K.* | | | *U.S.A.* | | | *U.K. and U.S.A.* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | | *No. of cases* | *With murmurs at 5 years* | |
| | | *No.* | *%* | | *No.* | *%* | | *No.* | *%* |
| Without failure and/or pericarditis | 45 | 36 | *80* | 35 | 20 | *57* | 80 | 56 | *70* |
| With failure and/or pericarditis | 16 | 16 | *100* | 6 | 6 | *100* | 22 | 22 | *100* |

TABLE IX.—PROGNOSIS IN RELATION TO CARDIAC STATUS AT START OF TREATMENT—U.K. AND U.S.A.

| *Cardiac status at start of treatment* | *No. of cases observed for 5 years* | *% with no murmur at 5 years* | *No. of deaths in 5 years* |
|---|---|---|---|
| Group A | | | |
| No carditis | 71 | *96* | 0 |
| Questionable carditis | 32 | *84* | 0 |
| Group B | | | |
| Apical systolic murmur grade I, only | 39 | *82* | 0 |
| Apical systolic murmur grade II or III, only | 60 | *68* | 2 |
| Apical systolic *and* apical mid-diastolic murmurs | 44 | *48* | 1† |
| Basal diastolic with or without other murmurs | 45/15)* | *53(27)** | 1 |
| Failure and/or pericarditis | 33 | *30* | 1 |
| Group C | | | |
| Pre-existing heart disease without failure and/or pericarditis | 80 | *30* | 5‡ |
| Pre-existing heart disease with failure and/or pericarditis | 22 | *0* | 6 |

*Excluding one U.K. centre.
†Death from acute nephritis and uræmia.
‡Includes 1 death from acute intestinal obstruction.

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 facts that most of the deaths from rheumatic fever (10 of 14) were of patients with pre-existing heart disease, and that there were no deaths among those without heart involvement at start of treatment.

No comparisons have been made with the conflicting reports of results obtained with large-dose hormone therapy,[7-11] 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 similarly taken into account.

SUMMARY

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. co-operative clinical trial of the relative merits of ACTH, cortisone and aspirin in the treatment of acute rheumatic fever.

Of the 497 children, 445 (89.5%) were followed up for the complete 5 years, and the status of the heart was known for 426 of them. Only 16 (3.2%) had died, 14 of them from rheumatic heart disease; 36 (7.2%) were untraced. The very low fatality rate is striking.

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

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 patients without carditis initially, the prognosis was excellent, since in 96% there was no residual heart disease. In patients with carditis initially, but without pre-existing heart disease, the proportion without residual heart disease decreased progressively from 82% for those with only a grade I apical systolic murmur to 30% for those with failure and/or pericarditis. In patients with pre-existing heart disease, the prognosis was poor. Only 30% of those without pericarditis or failure and none of those with pericarditis and/or failure were without heart disease at 5 years.

Patients with carditis and without pre-existing heart disease who had recurrences which required retreatment during the follow-up period had on the average severer cardiac involvement at start of treatment than did those without recurrences requiring retreatment. At 5 years a larger proportion of these retreated patients had murmurs.

Treatment of acute rheumatic fever cannot be properly evaluated unless the status of the heart of the patients at the start of treatment is closely taken into account.

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# MODERN TRENDS IN ACUTE RHEUMATIC FEVER*

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TWENTY YEARS ago rheumatic heart disease was the major cardiac problem in the pædiatric age group. This has changed over recent years for several good reasons: one is related to the slow but steady decline in the incidence of streptococcal disease, probably associated with the widespread use of antibiotics. Another is the improved social and economic conditions of the population, with less crowding in homes. A third is related to the changing times and our increased awareness of the large number of cases of congenital heart disease, it being fully realized for the first time that they are approximately ten times as common as heart disease of rheumatic origin in childhood.

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## INCIDENCE

In 1941, the author summarized the incidence of rheumatic heart disease from numerous previous studies. At that time, it was generally considered that rheumatic heart disease occurred in approximately 2% of the school population. More recent reviews indicate that the incidence is now lower. Sampson (1945)[1] found it to be 0.38% in one group of school children and 2% in another group. Wedum (1945)[2] reported the incidence as 1.6%, Quinn (1946)[3] as 1%, Packard (1952)[4] as 0.32%, Quinn (1956)[5] as 2.2%, and Saslaw (1956)[6] as 0.3%.

In the cardiac registry for the city of Toronto (1948-1949) Gardiner and Keith[7] found an incidence of less than 0.3% (see Fig. 1). A diminishing incidence of rheumatic fever and rheumatic heart disease is reflected in the group shown in Fig. 2. A large number of patients were seen in the 1930's, but there has been a distinct falling off in the last 15 years. Hitchins (1958)[8] reports a similar drop in Cardiff, Wales, from the year 1931 to 1950.