Comparison of Large and Small Doses of Hormones in the Treatment of Acute Rheumatic Carditis


Disappearance of significant murmurs was twice as common in 47 rheumatic children treated with large doses of hormones as in a comparable group of 41 children treated with small doses of hormones. Results were also related to the duration of illness before therapy was started. The findings suggest that the divergencies of opinion regarding the efficacy of hormones in the treatment of acute rheumatic carditis may in part be explained on the basis of differences in doses of hormones, in duration of therapy, and in duration of illness before the beginning of therapy.

In the last 6 years, ever since Hench and his associates first pointed out the apparent usefulness of corticotrophin (ACTH) and cortisone in the treatment of rheumatic fever and rheumatic carditis, various investigators, both from this country and abroad, have expressed divergent opinions on the efficacy of these hormones in the treatment of rheumatic fever. The opinions range from those of the ultraoptimistic group, who believe hormones terminate the disease, to those of the over pessimistic group, who are convinced that hormones are in no way a better suppressive drug than aspirin. The report of a cooperative clinical trial, which has recently been published simultaneously in this country and in the United Kingdom, indicated that there was no consistent pattern in the response of the various manifestations of rheumatic fever in patients treated for 6 weeks with ACTH, cortisone, or aspirin, and that "no consistent difference in the behavior of murmurs present at the start of treatment was noted except that the soft apical systolic murmurs disappeared more rapidly in hormone treated groups." This clinical trial, usually referred to as the Cooperative Study, was a study in which 6 centers in the United Kingdom, 1 in Canada, and 5, including the House of the Good Samaritan, in the United States participated.

The divergencies of opinion regarding the relative efficacy of hormones in the treatment of rheumatic fever and rheumatic carditis led us to consider whether these differences could be explained, in part, on the basis of differences in dosage, in duration of therapy, and in duration of illness before starting therapy. The purpose of the study being reported here was to explore these possibilities. Heart damage being the most important effect of rheumatic fever, the results of hormone therapy in this study have been evaluated regarding data pertaining to carditis only. Furthermore, since carditis is best indicated by the presence of significant murmurs, this study has been confined to observations of the frequency with which murmurs present at the start of the treatment disappeared completely at the end of the twentieth week from the beginning of therapy.

It should be noted that the present study is not concerned with the relative merits of hormones and salicylates in the treatment of rheumatic fever nor with the toxic and other undesirable effects of these drugs.

Subjects

At the House of the Good Samaritan, Boston, between May 1949 and December 1954, a total of 160 rheumatic fever patients under the age of 17 years were treated with variable doses of ACTH and cortisone for varying lengths of time. Of these patients, 88 who were in their initial attack of rheumatic fever and who presented definite signs of carditis, in addition to other signs of active rheu-
matics fever prior to therapy, were selected for this study. Carditis was not considered to be present unless there were significant murmurs.

All of the patients with significant murmurs in this study had signs of mitral regurgitation or signs of aortic regurgitation. There were no instances of aortic stenosis or mitral stenosis. Mitral regurgitation was diagnosed on the basis of a long, blowing systolic murmur that was best heard at the apex, was of more than slight (grade II) intensity at the apex, radiated to the left axilla, and did not change appreciably with respiration or with change in the patient's position. In some instances, this significant systolic murmur was accompanied by a rumbling mid-diastolic murmur at the apex. Aortic regurgitation was diagnosed on the basis of an early diastolic blowing murmur which, even when faint, occupied more than half of diastole.

Of the 88 patients with significant murmurs prior to therapy, 41 were treated with relatively small doses of the hormones for an average of 6 weeks and 47 were treated with relatively large doses of the hormones for an average of 14 weeks. Those in the small-dose group were given intramuscularly a total of 1100 to 2400 units of lyophilized ACTH* or 4.1 Gm. of cortisone.† Those in the large-dose group were given a total of 4100 to 7000 units of ACTH-gel

* All the ACTH used in this study was donated by the Armour Laboratories. The kind that was used in the small-dose group was a water-soluble lyophilized preparation standardized in terms of USP units. The USP unit is expressed as a milligram equivalent of ACTH lot number LA-IA. That used in the large-dose group was a purified long-acting preparation in a gelatin base supplied as H. P. Aechter gel and standardized in terms of Armour units.

† All cortisone used in the study was Cortone Acetate and was donated by Merck and Co.

Table 1.—Frequency of Rheumatic Fever Manifestations in Patients with Carditis

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Small-Dose Group (41 Patients)</th>
<th>Large-Dose Group (47 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Significant murmurs</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Cardiac enlargement</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Congestive failure</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Nodules</td>
<td>27</td>
<td>38</td>
</tr>
<tr>
<td>Joint pains</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Elevated sedimentation rate</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>Antistreptolysin-0 titer of 400 units or more</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>Prolonged P-R interval</td>
<td>22</td>
<td>23</td>
</tr>
</tbody>
</table>

The frequency of important clinical and laboratory signs of rheumatic fever and carditis in the 41 cases of the small-dose group is compared in table 1 with the frequency in the 47 cases of the large-dose group. Such manifestations as cardiac enlargement, joint symptoms, elevation of the sedimentation rate, elevation of the antistreptolysin-O titer, and prolongation of the P-R interval occurred with almost exactly the same frequency in the 2 groups. The incidence of pericarditis and congestive failure was slightly greater in the small-dose group, but the incidence of subcutaneous nodules and chorea was somewhat greater in the large-dose group.

Table 2.—Frequency of Complete Disappearance of all Significant Murmurs Twenty Weeks after Beginning of Therapy

<table>
<thead>
<tr>
<th>Interval in days between onset of rheumatic fever and beginning of therapy</th>
<th>Small-Dose Group</th>
<th>Large-Dose Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases with significant murmurs</td>
<td>Disappearance of murmurs</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>Per cent</td>
</tr>
<tr>
<td>1 to 7</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>8 to 14</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>15 to 42</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>More than 42</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Total cases</td>
<td>41</td>
<td>8</td>
</tr>
</tbody>
</table>

in intramuscularly or 13.0 to 15.5 Gm. of cortisone orally.

All of the patients in the small-dose group were treated prior to July 1952; all of the patients in the large-dose group were treated after that date.

The frequency of important clinical and laboratory signs of rheumatic fever and carditis in the 41 cases of the small-dose group is compared in table 1 with the frequency in the 47 cases of the large-dose group. Such manifestations as cardiac enlargement, joint symptoms, elevation of the sedimentation rate, elevation of the antistreptolysin-O titer, and prolongation of the P-R interval occurred with almost exactly the same frequency in the 2 groups. The incidence of pericarditis and congestive failure was slightly greater in the small-dose group, but the incidence of subcutaneous nodules and chorea was somewhat greater in the large-dose group.

RESULTS AND DISCUSSION

The 41 patients in the small-dose group and the 47 patients in the large-dose group were divided into subgroups according to the interval that elapsed between the onset of the rheumatic fever attack and the beginning of hormone therapy. The frequency with which all significant murmurs had completely disappeared by the twentieth week from the beginning of therapy for each sub-group is shown in table 2.

From the data in the table it is evident that, in both the small and the large-dose groups, the shorter the duration of illness prior to the start of therapy, the greater the frequency of complete disappearance of all significant murmurs. Thus, in the small-dose group the frequency of disappearance of murmurs decreased from 50 per cent for patients ill 1 to 7 days to 0 per cent for patients ill more than 42 days, and in the
large-dose group the frequency for the corresponding subgroups decreased from 73 per cent to 14 per cent.

It is also to be noted that in each duration subgroup, the frequency of complete disappearance of all significant murmurs in the large-dose group was consistently greater than the frequency in the small-dose group. Thus, for the 4 successive duration subgroups the percentages of disappearance of significant murmurs in the large-dose and the small-dose groups were respectively 73 and 50; 43 and 25; 40 and 13; and 14 and nil. For all patients, irrespective of duration of illness, the frequency of disappearance of significant murmurs was 40 per cent for the large-dose group and only 20 per cent for the small-dose group, a ratio of 2 to 1.

Statistical analysis reveals the following; in the large-dose group the difference in frequency of disappearance of murmurs in patients treated within 7 days of onset of rheumatic fever and in patients treated after an elapse of more than 42 days is significant, in that $p$ is almost .01; the frequency of disappearance of murmurs in all of the patients in the large-dose group treated within 42 days of onset (17 out of 33 cases) is significantly greater than the frequency in those treated after an elapse of more than 42 days (2 out of 14 cases), in that $p$ is approximately .02; of all the patients treated within 42 days of onset of rheumatic fever (66 cases) the frequency of disappearance of murmurs is significantly greater in the large-dose group (17 out of 33 cases) than in the small-dose group (8 out of 33 cases), in that $p$ is approximately .02.

It is to be noted that the patients in the small-dose and large-dose groups were not treated concurrently. Furthermore, the number of cases in each duration subgroup is relatively small. Hence, we hesitate to attach great weight to statistical evaluation. Nevertheless, the consistent difference between the small-dose and the large-dose groups in regard to frequency of disappearance of murmurs within each duration subgroup is impressive. Furthermore, the relation of frequency of disappearance of murmurs to duration of illness follows a similar pattern in the small-dose and in the large-dose groups.

In regard to the apparent relation of frequency of disappearance of murmurs to duration of illness, consideration must be given to the possibility that, through natural selection, variation in severity of disease entered into the picture and influenced results. As previously pointed out, patients with mild rheumatic fever may not have continued to have active disease long enough to be included in the groups of long duration, which, in contrast to those of short duration, may therefore have been weighted with more severe cases of rheumatic fever. On this basis alone, the cases of long duration might be expected to show a higher frequency of persistent murmurs.

On the other hand, all of the patients in this study presented signs of definite heart disease at the time therapy was started; therefore they cannot be considered to be cases of mild rheumatic fever. Furthermore, the difference in frequencies of disappearance of murmurs among those ill for a relatively short period and among those ill for a long period is so striking that it is difficult to accept natural selection as the only explanation. Finally, natural selection alone would not account for the differences in the frequency of disappearance of murmurs for those patients treated with large doses of hormones and those treated with small doses.

From the foregoing discussion, it is evident that final conclusions are not yet justified. Nevertheless, the data presented here suggest that results of hormone therapy in rheumatic fever are related to the time allowed to elapse before treatment is started, to the dosage of the hormone, and to the duration of therapy. The data also emphasize the importance of taking into consideration duration of illness, dosage of drugs used, and duration of treatment in any study aimed at comparing therapeutic agents in rheumatic fever.

**Summary**

Of 100 rheumatic fever patients under the age of 17 years who were treated with variable doses of ACTH or cortisone for varying lengths of time, 88 patients were in their initial attack of rheumatic fever and had definite signs of carditis.

The frequency of complete disappearance of
significant murmurs in 41 patients treated with relatively small doses of hormones was compared with that in 47 patients treated with relatively large doses of hormones. Results were related to the duration of illness prior to beginning of therapy.

In both the small-dose and the large-dose groups, the shorter the duration of illness prior to start of therapy the greater the frequency of disappearance of all significant murmurs. It was also noted that the frequency of disappearance of significant murmurs in the large-dose group was consistently greater than that in the small-dose group.

Data presented here suggest that results of hormone therapy in rheumatic carditis are related to the time allowed to elapse before treatment is started, to the dosage of the hormones, and to the duration of therapy.

**SUMMARIO IN INTERLINGUA**

In un serie de 100 patientes de febre rheumatic—omnes de etates de infra 17 annos e omnes tractate con ACTH o cortisona in varie doses e durante varie periodos—88 habeva lor attacco initial de febre rheumatic e monstrava definite signos de carditis.

Le frequentia del disparition completa de significative murmures in patientes tractate con relativemente basse doses del hormones (41 casos) eseva studiate in comparation con le frequentia del disparition completa de tal murmures in patientes tractate con relativemente alte doses del hormones (47 casos). Le resultatos eseva relationate al duration del morbo ante le institution del therapia.

In ambe gruppos—illo a bassa e illo a alte doses—il eseva constatate que quanto plus breve eseva le duration del morbo ante le institution del therapia, tanto plus alte eseva le frequentia del disparition de omne murmures significative. Essea etiam notate que le frequentia del disparition de murmures significative eseva regularmente plus alte in le grupo a grande doses que in le grupo a parve doses.

Le datos hic presentate pare indicare que le resultatos del hormonotherapia in carditis rheumatic depende (1) de tempe passate ante le initiation del tractamento, (2) del dosage de hormones administrate, e (3) del duration del curso therapeutic.

**REFERENCES**


Withering’s introduction of the use of the foxglove for treating patients with congestive heart failure must be regarded as one of the great milestones of scientific medicine. Decoctions and infusions of the leaves and of the roots of various flowering plants had been in vogue since prehistoric times, and folk remedies were as numerous as the communities into which human beings had divided themselves. Mandrake leaves were used in ancient China to relieve pain. Tea came into vogue as a stimulating beverage at the beginning of the seventeenth century. As a specific remedial agent there is only one other with which digitalis can be compared—the alkaloid derived from cinchona bark which had a checkered career for three hundred years before digitalis was discovered, but unfortunately cinchona during that long interval had no dispasionate Withering to espouse its cause.—John F. Fulton. The Place of William Withering in Scientific Medicine. J. Hist. Med. & Allied Sc., 8: 10, 1953.
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