Therapy of Severe Rheumatic Carditis
Comparison of Adrenocortical Steroids and Aspirin

By GABOR CZONICZER, M.D., FRANCISCO AMEZCUA, M.D.,
SALVATORE PELARGONIO, M.D., AND BENEDICT F. MASSELL, M.D.

ALTHOUGH adrenocortical steroid therapy has been available for 14 years, its value in acute rheumatic fever still remains controversial. The Cooperative Study failed to demonstrate any significant difference between aspirin and steroids with regard to their effect on residual heart disease. On the other hand, extensive data collected at the House of the Good Samaritan have shown that steroids in large dosage cause a considerably higher incidence of regression and disappearance of significant murmurs than does aspirin. The study of Dorfman et al., which evaluates the effect of prolonged therapy with aspirin, steroids, and the combination of both drugs, comes to the same conclusion.

Our clinical experience for some time has shown that the difference in results with steroids and aspirin therapy is especially striking in very ill patients with rheumatic carditis and that in such patients steroid therapy may be lifesaving. Because most clinicians have had the same experience, aspirin has, since the advent of steroids, rarely been used in very severe rheumatic carditis. This fact has hindered the collection of reliable data comparing the effect of aspirin with that of steroids in severe rheumatic carditis and explains why such data cannot be found in the medical literature.

In an attempt to overcome this obstacle we have reviewed our experience with very ill patients observed at the House of the Good Samaritan during the past two and a half decades. The purpose of this study is to present the results of our critical review.

Clinical Material and Methods

Table 1 shows our clinical material, which is comprised of ward patients observed at the House of the Good Samaritan from 1939 through 1962. We included in this study only patients who had severe rheumatic carditis as indicated by congestive heart failure or pericarditis.

As this table shows, we evaluated 137 cases of congestive heart failure due to active rheumatic carditis. These 137 patients include 42 who were given no antirheumatic therapy, 42 who were treated with aspirin, and 53 who were treated with steroids. The next to the last column of table 1 shows that some of the patients also had pericarditis in addition to congestive heart failure. Not included in this table are eight other patients who had pericarditis without congestive heart failure. Thus, the total number of cases evaluated is 145.

Our schedule of treatment was as follows: The patients in the aspirin group generally received 40 mg. of aspirin per pound of body weight per day for 12 weeks, but some had a somewhat shorter course. The treatment for the patients who were included in the steroid group consisted in the great majority of cases of a 12-week course of prednisone or dexamethasone, the dose being 60 mg. and 6 mg., respectively, per day for the first 3 weeks; this dose was tapered gradually during the next 9 weeks. The patients who were labeled as receiving "no therapy" were given no antirheumatic

Table 1

<table>
<thead>
<tr>
<th>Therapy</th>
<th>CHF without pericarditis</th>
<th>CHF with pericarditis</th>
<th>Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>No therapy</td>
<td>28</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Aspirin</td>
<td>27</td>
<td>15</td>
<td>42</td>
</tr>
<tr>
<td>Steroids</td>
<td>37</td>
<td>16</td>
<td>53</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>45</td>
<td>137</td>
</tr>
</tbody>
</table>

* Not included in this table are eight additional cases of pericarditis without congestive heart failure.

---

From the House of the Good Samaritan, Children's Hospital Medical Center, and the Department of Pediatrics, Harvard Medical School, Boston, Massachusetts. Supported by Grant HE 04957 from the National Heart Institute, U. S. Public Health Service, Grant 511-F from the Massachusetts Heart Association, and by a training grant (for Dr. Amezcua) from the Barnstable County Chapter of the Massachusetts Heart Association.

Circulation, Volume XXIX, June 1964
drugs at all or a minimal amount of aspirin, a dose that could not be considered as effective.

Table 2 shows the comparability of the 137 congestive failure cases with regard to several features that possibly might have influenced the course of their disease. Such features, listed in table 2, are as follows: age of the patient, severity and duration of congestive heart failure, additional penicillin treatment, and whether the patient was treated during a first attack or during a recurrence. The severity of congestive heart failure was graded on a scale of 1 to 4. The average grade of severity was about the same for each of the three groups, and there is no significant difference in the time interval that elapsed between the onset of congestive heart failure and the beginning of treatment in the aspirin and in the steroid group. There is no appreciable difference in the average age of the patients either, since only patients under 17 years of age were included in all three groups. However, the groups differ with regard to the proportion of patients observed in their initial attack of rheumatic fever and the proportion treated with penicillin in addition to an antirheumatic drug. It is evident that there are relatively more first attacks and more penicillin-treated patients in the steroid group, a fact that makes comparison somewhat difficult.

Results

To evaluate the results we have taken into consideration the behavior of the congestive heart failure—that is, whether it subsided or worsened—and the death rate in the aspirin and in the steroid group within the first year after onset of therapy.

Table 3A shows the results of the different therapeutic approaches. The proportion of cases in which congestive heart failure subsided was only 36 per cent in the nontreated, 43 per cent in the aspirin-treated, but 92 per cent in the steroid-treated group. Almost half (47 per cent) of the patients who were not given antirheumatic therapy died during hospitalization. In contrast, there were only two deaths (4 per cent) in the group of 53 patients treated with steroids, and of these two deaths, only one was actually due to rheumatic fever; the other was caused by complicating hemorrhagic chickenpox. In the group of 42 patients treated with aspirin there were nine deaths—a death rate of 21 per cent. Although this rate is definitely less than that for the nontreated group, it is well above the 4-per cent rate for the steroid-treated patients. Statistical analysis shows that the differences for this table are highly significant ($p<0.0001$). Thus it is evident from this table that steroid therapy was definitely superior to aspirin therapy in this series of patients with severe rheumatic carditis.

Because we were especially interested in the...
difference in the effect of aspirin versus steroids, we analyzed the figures for these two drugs alone, excluding the group that was given no therapy (table 3B). A chi-square test showed that the differences here also are highly significant (p<0.01).

Table 2 shows that there were more penicillin-treated cases in the steroid group than in the aspirin group. In order to obviate the effect of penicillin on results, both the aspirin and the steroid groups were divided into two subgroups: one subgroup comprised patients given penicillin in addition to aspirin or steroids (table 4); the other subgroup was made up of patients who were not given penicillin (table 5).

Tables 4 and 5 show that the steroid-treated patients responded definitely better than did the aspirin-treated patients, whether or not additional penicillin was given. Of the patients receiving penicillin (table 4), the percentage of cases that improved was only 48 in the aspirin group, but 88 in the steroid group; the death rate was 17 per cent in the aspirin group and only 5 per cent in the steroid group. The difference is also evident in the patients who were not given penicillin (table 5); in this subgroup there was 100-per cent improvement in the steroid-treated patients and only 37-per cent improvement in the aspirin-treated patients. The differences are highly significant for both tables 4 and 5 (p<0.01).

A second possible factor in addition to penicillin treatment, which was considered in evaluating results, is whether the patients were treated during a first attack or during a recurrence of rheumatic fever. The proportion of first attacks was slightly greater in the steroid group than in the aspirin group. Therefore, we compared the results of aspirin and steroid treatment separately in patients with first attacks (table 6) and in patients with recurrences (table 7).

It is obvious that here too the steroid-treated patients did better than those treated with aspirin. When only first attacks were analyzed (table 6), the percentage of patients who improved was only 47 in the aspirin group in contrast to 91 in the steroid-treated group (p<0.01). In the table including only those patients who were treated during a recurrence (table 7) the difference between the effect of aspirin and that of steroids is not statistically significant if we consider the three grades of effect (i.e., “subsided,” “worsened,” and “died”) separately. However, if we combine the group of patients whose congestive heart failure worsened with the group of deaths (last two columns) and compare this new group with the group of patients whose congestive heart failure subsided during treatment, the difference in effect of aspirin versus steroids becomes significant (p<0.05).

The results presented in tables 4 to 7 show

### Table 3B

**Results of Therapy in 95 Cases of Acute Rheumatic Fever with Congestive Heart Failure Treated with Aspirin or Steroids**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of cases</th>
<th>Subsided</th>
<th>Worsened</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>42</td>
<td>18 (43%)</td>
<td>15 (36%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>Steroids</td>
<td>53</td>
<td>49 (92%)</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>67</td>
<td>17</td>
<td>11</td>
</tr>
</tbody>
</table>

### Table 4

**Results of Therapy in 66 Patients with Severe Rheumatic Carditis to Whom, in Addition to Anti-rheumatic Therapy, Penicillin Was Given**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of cases</th>
<th>Subsided</th>
<th>Worsened</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>23</td>
<td>11 (46%)</td>
<td>8 (35%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Steroids</td>
<td>43</td>
<td>38 (88%)</td>
<td>3 (7%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

### Table 5

**Results of Therapy in 29 Patients with Severe Rheumatic Carditis to Whom No Penicillin Was Given**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of cases</th>
<th>Subsided</th>
<th>Worsened</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>19</td>
<td>7 (37%)</td>
<td>7 (37%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Steroids</td>
<td>10</td>
<td>10 (100%)</td>
<td>0 0</td>
<td>0</td>
</tr>
</tbody>
</table>
clearly that the superior effect of steroids over aspirin, demonstrated by this study, cannot be attributed to the fact that there were more penicillin-treated patients and slightly more first attacks in the steroid group than in the aspirin group.

There is another factor, however, that should be taken into consideration when we are comparing the effect of the two drugs. We are referring to the theory that the pattern of acute rheumatic fever is changing and that this disease has decreased in severity during the last four decades.\(^4\)\(^5\) To exclude the influence of this factor we evaluated separately the cases which were treated in the time period between January 1953 and December 1962. These 36 patients, of whom 16 were given aspirin and 20 were given steroids, were quite comparable in every aspect.

Table 8 shows that there was a 90-per cent improvement in the steroid group in contrast to a 56-per cent improvement in the aspirin group. There were two deaths in the aspirin group but no deaths in the steroid group. Although the number of cases in Table 8 is small, statistical evaluation of these cases shows that the \(p\) value for this figure is 0.05. This means that the difference between the effect of aspirin and that of steroids is probably significant even when we include in our evaluation only cases treated in the same period of time. It seems reasonable to infer that the presumed changing pattern of acute rheumatic fever cannot be a determining factor in the superior result of steroids in this series of severe rheumatic carditis.

Still another factor that may have influenced our results is the appearance of recurrent acute rheumatic fever during the course of therapy. It is well known that recurrences have a serious effect on the prognosis of valvular disease. Hence, if the distribution of recurrences were to be uneven in the three groups, this fact should be taken into consideration when evaluating the effect of therapy. To be able to make this evaluation, we reviewed all the cases in our study regarding recurrences. It turned out that there were definitely more recurrences in the so-called “no therapy” group than in the other two groups. This fact could be partly responsible for the high death rate in the “no therapy” group. However, we have found only one patient who had a recurrence of rheumatic fever during aspirin treatment and who died. If we excluded this one patient from the study, the percentage of deaths would drop so slightly (from 21 per cent to 19 per cent) that it would not influence the evaluation of our results. Hence, the inferior effect of aspirin cannot be attributed to the influence of rheumatic fever recurrences.

Table 9 shows the results of steroid and aspirin therapy in pericarditis, especially the effects on the pericardial friction rub. The last column of this table shows that there were 11 deaths in the total group of 53 patients with
pericarditis. Six of these deaths occurred in 17 patients given no antirheumatic drugs, and four of the deaths occurred in 16 patients treated with aspirin. In the group of 20 patients with pericarditis who were treated with steroids, there was only one death.

As table 9 shows, in not one instance did we observe the appearance of a pericardial friction rub during steroid treatment. However, a friction rub appeared during observation in four of 17 patients who did not receive any antirheumatic drugs and in three of 16 patients during aspirin administration. From this experience we are inclined to infer that pericarditis—a severe manifestation of rheumatic fever—is more effectively suppressed by steroids than by aspirin.

**Discussion**

As we have mentioned in the introduction, the relative value of aspirin and steroids in the treatment of acute rheumatic fever is controversial. Some of the studies—such as the Cooperative Study and the Combined Rheumatic Fever Study—failed to demonstrate any significant difference in effect between the two drugs when the disappearance of murmurs was used as a measure of efficiency. On the other hand, data collected in the House of the Good Samaritan and in the study of Dorfman et al. have shown a considerably higher incidence of regression and disappearance of significant murmurs in steroid-treated patients than in aspirin-treated patients.

All the above-mentioned studies have been concerned with the entire scale of acute rheumatic fever cases, from very mild to very severe. However, we have noticed for some time that the superior effect of steroids is especially striking in cases of severe rheumatic carditis with congestive heart failure and that this drug, unlike aspirin, may be lifesaving in such cases. Nevertheless, we could not find data in the medical literature comparing the effect of these two drugs exclusively in very severe rheumatic carditis, i.e., in cases in which the difference in effectiveness may be the most evident.

The studies that encompass the entire scale of acute rheumatic fever are not suitable for evaluation of the effectiveness of aspirin and steroids in patients with severe rheumatic carditis. Thus in the Cooperative Study the distribution of cases with congestive heart failure among the three groups was uneven; to the aspirin group—evidently by chance—there were allotted relatively fewer patients with congestive heart failure (3.8 per cent) than to the ACTH and cortisone groups (12.5 per cent and 10 per cent, respectively).

The study of Markowitz and Kuttner shows clearly the excellent effect of cortisone in severe rheumatic carditis. This study, however, has the defect that it is limited to cases treated with steroids and does not include a comparative group treated with aspirin. Accordingly, the conclusion of the authors of this study is the statement that “further studies based on large series of cases with adequate controls are needed to establish the value of this (cortisone) regimen.”

Moreover, in the Combined Rheumatic Fever Study, set up especially for the purpose of finding out whether the more potent drug in the treatment of acute rheumatic fever is aspirin or steroids, all five patients with severe congestive heart failure who were included in this study were treated with prednisone. Two of these patients were originally in the steroid group; however, the medication of the three remaining patients, who originally were allotted to the aspirin group, was changed to steroids because “the chief investigator decided that acute symptoms of these critically ill patients might be controlled more effectively with prednisone than with aspirin.” It is evident that under such circumstances this study also cannot be used to evaluate which of the two drugs is more effective in severe rheumatic carditis.
This example shows clearly that the comparison of the effect of steroids versus aspirin in severe rheumatic carditis has been hindered by the fact that most investigators think as we do—namely, that it is not suitable to treat with aspirin a patient who is in congestive heart failure due to acute rheumatic carditis. This is the reason why, since the advent of steroids, so few patients with severe rheumatic carditis have been treated with aspirin and why random selection of drugs in severely ill patients has been generally thought to be contraindicated.

To offset these circumstances we had to attempt to compare cases that were not randomly selected. In our study, whereas all the steroid-treated cases were observed after 1949, approximately half of the aspirin-treated patients were observed prior to that year. This difference in the time period in which our patients were treated makes it understandable that the characteristics of our groups are not similar; there are relatively more penicillin-treated patients and relatively more first attacks in the steroid group than in the aspirin group.

This difficulty could be overcome only by regrouping our cases and by building smaller groups which were comparable. As tables 4 to 7 show, it turned out that the superiority of steroids in the management of severe carditis is so evident that the difference between the effect of aspirin and that of steroids proved to be significant even if we compared these new, smaller groups of patients.

The most difficult task was to eliminate the influence of the supposed changing pattern of acute rheumatic fever. If the supposition is valid that acute rheumatic fever is a less severe disease today than it was two or three decades ago, the cases treated with steroids 20 to 25 years ago are not comparable to the cases treated with steroids during the last 10 years. We tried to overcome this difficulty, too, by comparing exclusively the course of 12 aspirin-treated patients and 16 steroid-treated patients, all of whom were observed during the same period, namely, within the last 7 years, and whose characteristics were all similar.

Since the effect of steroids was significantly better than that of aspirin, even in these patients, we can state that the supposed changing pattern of acute rheumatic fever did not enter into our results in this group of patients. Thus, when the supposed influence of the time factor can be excluded, steroids would seem definitely superior to aspirin in the treatment of severe rheumatic carditis.

Another reason why in the studies mentioned above the superiority of steroids could not be demonstrated may be that the usual method for evaluating the effect of an antirheumatic drug cannot be used in cases with severe carditis. In all of these studies evaluation was made by taking into consideration the percentage of patients who lose their murmurs within 1 to 5 years after onset of therapy. This method, which is effective in cases with moderately severe carditis, is not feasible in patients with congestive heart failure. This is true because the murmur indicating rheumatic valvulitis disappears in only a small percentage of all patients who also had congestive heart failure, whether they were given aspirin or steroids. Thus the superior effect of steroids cannot be demonstrated if we use the disappearance of murmurs as an indicator.

In our study, therefore, it was not the disappearance of significant murmurs that was used for evaluation but rather the behavior of congestive heart failure and the death rate within the first year after onset of treatment with aspirin and steroids, respectively.

Conclusions

The data presented show that in our series of 145 patients with severe rheumatic carditis steroids had a definitely better therapeutic effect than aspirin. This conclusion is evident from the markedly lower death rate and from the faster and higher recovery rate in our steroid-treated group and also from the fact that not one of our patients developed a pericardial friction rub while on steroids. Appearance or worsening of congestive heart failure occurred also much more rarely during steroid therapy than during aspirin treatment.

There are many variables that may have in-
fluenced these excellent results: additional penicillin therapy, the supposed changing pattern of acute rheumatic fever during the last decades, recurrence of rheumatic fever during treatment, and the question of whether we are dealing with a first attack or with a recurrence. Although the distribution of our patients regarding these factors was uneven in the aspirin and in the steroid group, we were able to show (through regrouping of our cases) that the superior effect of steroids cannot be attributed to uneven distribution.

In spite of the fact that treatment in this series could not be determined by random selection, the observations collected during this study strongly support our clinical experience that steroids in large dosage are the treatment of choice in severe rheumatic carditis with congestive heart failure or pericarditis.

Acknowledgment

The authors are most grateful to Dr. Hugo Muench for assistance in the statistical analysis of the data presented in this study.

References


Reports of Medical Cases, with Reference to Morbid Anatomy

Preface by Richard Bright—1827

The morbid appearances which present themselves on the examination of those who have died with dropsical effusion, either into the large cavities of the body or into the cellular membrane, are exceedingly various: and it often becomes a matter of doubt how far these organic changes are to be regarded as originally causing or subsequently aiding the production of the effusion, and how far they are to be considered merely as the consequence either of the effusion or of some more general unhealthy state of the system. If it were possible to arrive at a perfect solution of these questions, we might hope to obtain the highest reward which can repay our labours,—an increased knowledge of the nature of the disease, and improvement in the means of its treatment.—Original Papers of Richard Bright on Renal Disease. Edited by A. Arnold Osman. London, Oxford University Press, 1937, p. 1.
Therapy of Severe Rheumatic Carditis: Comparison of Adrenocortical Steroids and Aspirin

GABOR CZONICZER, FRANCISCO AMEZCUA, SALVATORE PELARGONIO and BENEDICT F. MASSELL

Circulation. 1964;29:813-819
doi: 10.1161/01.CIR.29.6.813

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/29/6/813.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/