

# RHEUMATIC FEVER IN CAPE TOWN

## FOUR-YEAR FOLLOW-UP OF PATIENTS TREATED WITH SALICYLATES OR A COMBINATION OF STEROIDS AND SALICYLATES

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In spite of the ever-increasing numbers of reports on the treatment of rheumatic fever, there is still no agreement as to the most effective form of therapy. Since the introduction of steroids into the management of hypersensitivity states,<sup>1</sup> the treatment of acute rheumatic fever, particularly in childhood when it is important to try to abort the rheumatic process and thus prevent cardiac sequelae, has become more complicated, more expensive, and has acquired new risks. Dorfman *et al.*<sup>2</sup> have reviewed 25 papers since 1951 on the use of steroids in rheumatic fever. This paper adds a little more to our knowledge of this subject, and it is also a comparative study of treatment of children with acute rheumatic fever in Cape Town over a period of 4 years.

When cortisone and its related steroids were found by the Combined Cooperative Trial<sup>3</sup> not to be a panacea for rheumatic fever, two schools of thought emerged: advocates for the use of steroids and advocates for the use of non-steroids. The latter appear to be, at present, in the forefront.<sup>4</sup> However, the large amount of rheumatic heart disease in adults clamours for any preventive measures

that may be possible. It is of particular importance that a decision for or against steroids should be arrived at as soon as possible, because the cost and danger of such treatment is considerable. If it is of proved benefit, the risks and expense are justifiable.

Local conditions here do not provide for long-term care in special institutions. The children in this study were treated in hospital, then sent home to a variety of social backgrounds. The drug therapy in hospital was the only factor which could be accurately controlled, but that is the usual state of affairs in most medical therapeutic regimes, and any material benefit arising from the use of one drug must stand up to such a test or be suspect. The groups of children are small, partly because they were drawn from the hospital admissions over a short period, and partly because of the difficulty of maintaining contact with children whose homes are some distance away from hospital.

The diagnosis of rheumatic fever was made on the American Heart Association's modification of the Duckett Jones criteria.<sup>5</sup> The diagnosis of carditis, though well defined by the American Heart Association, was not always consistent since the patients were not always assessed on admission by the same observers. Figures for

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the incidence of carditis must therefore be viewed with circumspection. The series was divided into 2 groups: those treated with salicylates and those treated with steroids. The salicylate group was given salicylates only and consisted of patients admitted between September 1956 and the end of 1957. They have been followed up by the same observer for 4 years. The steroid group received salicylates plus steroids; were admitted during 1958, and have been followed up for 3 years.

## RESULTS

The clinical findings and details of the follow-up study are shown in Tables I, II and III, and some elaboration of these is needed.

TABLE I. COMPARISON OF CLINICAL FINDINGS IN THE SALICYLATE AND STEROID GROUPS

Analysis of chief findings	Salicylate group		Steroid group	
	1st attack (17 patients)	Total patients (18 patients)	1st attack (16 patients)	Total patients (28 patients)
Age-range	2-75 years to 12 years	4 years to 12 years	4 years to 12 years	4 years to 12 years
Average	7-6 years	7-5 years	7-9 years	8-3 years
Males	8 (47%)	8 (44.4%)	7 (42.5%)	14 (50%)
Arthritis	16 (94.1%)	17 (94.4%)	12 (75%)	21 (75%)
Carditis on admission	12 (70.6%)	13 (72.2%)	15 (93.7%)	27 (96.6%)
Chorea	2 (11%)	2 (11%)	1 (6%)	1 (3.5%)
Nodules	2 (11%)	2 (11%)	2 (12%)	5 (18%)
Pyrexia	14 (82.3%)	15 (83.3%)	13 (81.1%)	21 (75%)

TABLE II. DEVELOPMENT OF HEART DISEASE

	Salicylate group	Steroid group
Total patients	18	28
Murmurs on admission (total)	13 (72.2%)	27 (96.4%)
Murmurs after 3-4 years (total)	5	16
Patients in first attack with murmurs on admission	12/17 (70.6%)	15/16 (94%)
Patients in first attack with murmurs after 3 years	5/17 (29%)	4/16 (25%)
Deaths	1	0

TABLE III. FALL OF ESR

	Salicylate group (11 cases)	Steroid group (25 cases)
Normal at 1 week	0	13 (52%)
2 weeks	3 (27%)	21 (80%)
3 weeks	4 (36%)	24 (96%)
4 weeks	4 (36%)	25 (100%)

*Salicylate Group—18 Patients*

Salicylates were given in the form of soluble aspirin, gr. 1 - 1½ per pound of body weight daily (0.132 - 0.198 G./kg./d.), according to the child's tolerance. From the onset of treatment penicillin or sulphadiazine was administered in therapeutic doses, and subsequent prophylaxis maintained as far as could be established, through the entire period of study.

There were 15 non-White children in the group. 17 of them were believed to be having their first attack of rheumatic fever; one had had a previous attack.

The ESR (Westergren) was between 35 and 130 mm. in 17 of the patients on admission, and in the remaining child, who was in congestive failure, it was at first 6 mm.,

but rose to 60 mm. after digitalization and relief of the failure. For a variety of reasons it was not possible to adhere to the programme of weekly estimations, but of the 11 cases in which such a record was obtained, only 4 patients were normal within 3 weeks.

The children were seen as outpatients approximately every 2 - 6 months for the 3 - 4 years following the original observation. The child who had had cardiac failure succumbed to a further attack of rheumatic fever. There were 2 recurrences in patients who had residual damage after the first attack.

Originally, 12 (70%) of the 17 'first attack' children in this group had cardiac signs assessed as indicative of carditis, but at the end of the study only 5 of these (29%) had significant murmurs and none had developed in the remainder of the patients. In 7 instances, therefore, the apparent cardiac damage seemed to have disappeared.

*Steroid Group—28 Patients*

The therapeutic regime followed was a slight modification of that suggested by Illingworth *et al.*<sup>6</sup> Prednisolone was given orally, 60 mg. for 24 hours, 40 mg. for each of the next 4 days, 20 mg. daily for the following 16 days, followed by gradual reduction of the dose to zero by the end of the 5th or 6th week. At the same time, soluble aspirin was given exactly as in the other group. The same prophylactic and follow-up regime was also instituted.

Fifteen of the children were non-White and 13 were White. Sixteen were having a first attack of rheumatism and 12 had a history of a previous attack.

The serial weekly ESR estimations showed that 24 out of 25 children had elevated readings on admission, but 13 had returned to normal 1 week after starting on treatment. By 3 weeks only one reading remained high, and after 4 weeks of treatment all were normal.

On admission 27 patients had significant murmurs, of which 12 were found in the 12 'second attack' children. There were 15 cases of presumed carditis at the onset, in the 16 'first attack' children, i.e. 94% of them. At the end of the study period, only 4 of these latter had significant murmurs, i.e. 25% appeared to have established rheumatic heart disease. Seven relapses of rheumatic fever were reported in this group, but there were no deaths. They occurred in patients who had heart damage at the end of the initial treatment, and 4 were patients who had been seen in their second attack.

## DISCUSSION

In comparing groups in this way, the shortcomings are fully appreciated. Firstly, it is not a controlled series, but partly a retrospective comparison, and, secondly, the numbers are relatively small. No breakdown into racial groups has been attempted. However, the results are sufficiently striking to bear comment.

Rheumatic fever is a very variable disease, and in comparing small groups this characteristic must engender a cautious approach to the assessment of the results of any particular form of therapy.

It has been stated that the incidence of rheumatic fever is declining in Europe, Great Britain and America.<sup>7-12,15</sup> The probable reasons are improved social conditions in those countries<sup>12</sup> and also the widespread use of antibiotics

in the treatment of sore throats. There is also a difference in incidence based on climatic variations.<sup>13</sup> The virulence of the streptococcus may vary from year to year, especially with regard to its antigenicity for producing rheumatic fever, nephritis, scarlet fever, etc.<sup>14</sup>

The incidence of rheumatic fever in Cape Town has only been estimated by an ECG survey,<sup>42</sup> and so far as we know, no attempt has been made to determine whether it is falling or not. However, the ultimate low incidence of cardiac damage in the salicylate group makes one suspect that either the disease is not very violent, or some unrecognized but beneficial factor is at work.

Established rheumatic heart disease in the young adult patient can be a most serious handicap to productivity and life. The aim of all forms of treatment has been to lessen the effects of the disease on the heart. Bed rest was instituted by Sibson in 1877,<sup>16</sup> a year after salicylates had been introduced by Maclagan.<sup>17</sup> Bed rest and salicylates remained the standard form of therapy until 1949, when Hench *et al.*<sup>1</sup> introduced steroids in the treatment of rheumatic fever. There has been, however, a considerable amount of conflicting literature on the subject, varying from considerable optimism to extreme and apparently justifiable pessimism (Table IV).

TABLE IV. REPORTS ON INCIDENCE OF CARDIAC DAMAGE

Author	Cardiac damage (%)
Ash, 1948 <sup>18</sup> .. .. .	60% 9% improvement in 10 years
Bland and Jones, 1952 <sup>20</sup> .. .. .	65% (1921-1951): $\frac{1}{3}$ died in 10 years
Kusken, 1956 <sup>15</sup> .. .. .	60% before 1948 30% since 1948
Wilson, 1953, 1956 <sup>19,22</sup> .. .. .	100%
Done, 1955 <sup>21</sup> .. .. .	100% no treatment 74% salicylates 13% ACTH 17% cortisone
Cooperative Trial, 1955 <sup>3</sup> .. .. .	60% { salicylates ACTH cortisone
Illingworth, 1957 <sup>6</sup> .. .. .	72% no treatment 53% salicylates 25% cortisone and salicylates
Ferencz, 1959 <sup>23</sup> .. .. .	35% prednisolone
Wilson, 1959 <sup>24</sup> .. .. .	0 high dosage prednisolone
Bywaters and Thomas, 1961 <sup>4</sup> .. .. .	steroids no better than salicylates
Thomas, 1961 <sup>37</sup> .. .. .	steroids better when carditis no difference when no carditis
Dorfman, 1961 <sup>2</sup> .. .. .	
Present Series .. .. .	29% salicylates 25% hormone and salicylates

In an attempt to clear up some of the confusion, the Anglo-American Cooperative Trial<sup>3</sup> collected 500 cases. The conclusions of the committee were that there was no difference in the end results of the 3 forms of therapy. They did note, however, that clinical improvement and relief of symptoms was a little more rapid and that the ESR fell more rapidly in the steroid-treated patients.

Illingworth *et al.*<sup>6</sup> reported on 200 patients studied in a carefully controlled trial. Comparing the effects of 6 forms of therapy, the results showed that 28% of those with no specific therapy had no murmurs at 1 year. Of those treated with salicylates, 47% had no murmurs,

while 75% of the steroid group were normal, i.e. of those who had steroids, 25% had cardiac damage at 1 year.

Ferencz *et al.*,<sup>23</sup> Wilson and Lim,<sup>24</sup> and Dorfman *et al.*<sup>2</sup> were all favourably impressed by steroids in their series. Yet, in the recent report by Bywaters and Thomas,<sup>4</sup> it was concluded that there was no difference in the end result with either steroids or salicylates.

In the patients reported here, 29% of those treated with salicylates alone had murmurs at follow-up. This is considerably lower than most of the reported series and is comparable with some steroid therapy results. Whether this indicates that the disease is less severe in the Cape, or whether the year under review was a mild one for rheumatic fever, is not known.

Of those patients treated with steroids in the present series who were in their first attack, 4 (25%) had murmurs when reviewed 3 years later. This is much the same as was reported by Illingworth,<sup>6</sup> whose regime was followed, and is not very different from the results obtained with salicylates alone.

It would seem, therefore, that high dosage steroid therapy achieved no better results than salicylates in this series, the development of cardiac damage in both groups being low.

Steroid therapy is certainly not without its dangers, especially with high doses and prolonged therapy.<sup>26,27</sup>

Even salicylates are not completely innocuous, and recently there have been renewed reports on gastro-intestinal bleeding as a result of aspirin therapy.<sup>28</sup> Bywaters and Thomas<sup>4</sup> feel that salicylates can be dangerous, and report on 2 patients with rheumatic fever deteriorating after the institution of therapy. It is interesting to note that Maclagan<sup>17</sup> noted toxic effects of salicylic acid in his first report on the use of salicin in 1876.

In one of the patients of the present series treated with steroids and salicylate, treatment was terminated at 4 weeks as a result of salicylism. This occurred in one of the first patients treated. Moon-face and abdominal fullness occurred in most patients, but was not very marked. Hypertension was not noted.

In the 12 patients of the present series treated with steroids, who had a previous history of rheumatic fever, there was no significant difference in the murmurs at the onset of the second attack as compared with review one year later. They all improved symptomatically as quickly as the children who were having a first attack. This is the experience of other workers as well.<sup>4,24,29-31</sup> Symptoms were rapidly relieved and no further cardiac damage was noted.

In the present series, the ESR was very slow in falling in the salicylate group: in 11 cases the ESR was still elevated after 3 weeks in 45% of patients. One patient who was in hospital for 7 weeks had an ESR of 35 mm. Westergren at 6 weeks.

On the other hand, 89% of cases treated with steroids had a normal ESR in 3 weeks. All were normal after 4 weeks. This is virtually the same finding as others have reported on cortisone therapy.<sup>2,3,5,21,30,32,33</sup> The rapid fall is probably a manifestation of the marked anti-inflammatory action of cortisone in the rheumatic process. In this series this fact did not appear to affect the ultimate prognosis.

The control of any beta-haemolytic streptococcal in-

fection is as important as steroids or salicylate. It is quite possible that the relatively low rate of cardiac damage in both groups of children was, in this study, partly due to prolonged suppression of the allergen. The first attack of rheumatic fever may be prevented by the effective treatment of Group A beta-haemolytic streptococcal infections.<sup>34,35</sup> Sulphonamides were first used successfully in rheumatic fever prophylaxis by Thomas and France<sup>36</sup> in 1939. Although penicillin or sulphonamide may not prevent recurrences entirely, the recurrence rate is much lower when there is effective prophylaxis.<sup>37</sup> Although it has been shown that rheumatic fever recurrences are sometimes mimetic,<sup>38</sup> i.e. a patient who did not have carditis with the first attack is not likely to develop carditis with the second, this is not always so, and because the development of carditis is unpredictable, prophylaxis is an essential and most important aspect of treatment<sup>39</sup> in the paediatric age group.

Prolonged bed rest, once regarded as the mainstay of treatment of rheumatic fever since the days of Sibson,<sup>16</sup> has now come under review, and it is claimed that it is of doubtful value<sup>40,41</sup> and is probably necessary only for the first 14 days. In the present series, the duration of bed rest was strictly limited by the perpetual need to clear all possible bed space at the earliest possible moment.

#### Summary and Conclusions

The effects of salicylates alone and a combination of high-dosage steroids plus salicylate on 46 children with rheumatic fever were studied.

The follow-up after 3-4 years has shown that, of patients in their first attack, 29% in the salicylate group and 25% in the steroid group had established heart disease.

It is concluded that steroids have no advantage over salicylates so far as the ultimate prognosis is concerned, but that they are of value in curtailing the time of recovery; the recent trend of opinion in the literature confirms this. A brief review of the literature is given.

The most suitable treatment to date is considered to be penicillin, limited bed rest, and salicylates for symptomatic relief. Steroids should be used in the most severe cases only.

It may have been unfortunate that both penicillin and the steroids became generally available about the same time, since it now appears probable that the really important aspect of the treatment of acute rheumatic fever in childhood is to treat the first attack, according to the needs of the moment, and to institute at once and maintain for an undetermined period an effective prophylaxis against streptococcal throat infection. Con-

centration on anti-streptococcal measures is likely to be a really critical part of the therapeutic programme of the future, especially since prevention is better than cure.

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