

RHEUMATIC FEVER TREATED WITH PENICILLIN IN BACTERICIDAL DOSAGE FOR SIX WEEKS

REPORT OF A SMALL CONTROLLED TRIAL

BY

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No drug has yet been found which prevents or conclusively decreases cardiac damage in established rheumatic fever, but from time to time such claims are advanced.

Mortimer *et al.* (1959) attempted to determine the effect of eliminating group A haemolytic streptococcus organisms from patients with acute rheumatic fever, penicillin being the therapeutic agent. They used large doses on the grounds that the maintenance of high blood levels for a prolonged period might be necessary to eradicate streptococci from sites such as the endocardium. The results of a controlled trial on 97 adult and juvenile patients in the University of Chile hospitals indicated that, although penicillin had no beneficial effect on the symptomatology, signs, and laboratory abnormalities occurring during the acute phase of illness, the cardiac state at the end of one year was significantly better in those treated with penicillin. In view of these findings it was decided to run a trial at the Rheumatism Research Unit, Taplow, along similar lines.

Present Trial

During 1959 and 1960 all admitted patients suffering from a first known attack of rheumatic fever were considered for the trial, provided that the duration from onset was less than two months, and that hormone therapy had not been used in the present illness. Patients admitted to the trial were still in the active phase of rheumatic fever as judged by an E.S.R. of over 20 mm./hr. at the time of admission. Modified Duckett Jones criteria were used for the diagnosis of rheumatic fever, as given in the Further Report of the Rheumatic Fever Committee of the Royal College of Physicians in 1957; but for the purpose of this trial patients with chorea only, and those with a previous history of rheumatic fever or established rheumatic heart disease were excluded.

Two treatment groups were defined:—(1) Test group: penicillin in bactericidal dosage for six weeks followed by oral prophylactic penicillin, with salicylates in moderate dosage for a minimum of six weeks; and (2) control group: salicylates in moderate dosage for a minimum of six weeks and oral prophylactic penicillin.

In order to spare the younger children from painful injections the test group was subdivided according to age, and dosage and administration of penicillin varied as follows:

Age 0-10 years:—Loading dose first day, one injection into each buttock of (a) 800,000 units of benzathine penicillin, and (b) 800,000 units of procaine penicillin; six

subsequent days, 1.6 megaunits of oral penicillin; five subsequent weeks, 1.2 megaunits of oral penicillin; and oral penicillin 200,000 units twice daily as prophylaxis for the next five years at least.

Age 11 years and over:—First five days, 2 megaunits of crystalline penicillin intramuscularly (500,000 units q.d.s.); nine subsequent days, 1.2 megaunits of procaine penicillin intramuscularly (600,000 units b.d.); and four subsequent weeks, 1.2 megaunits of oral penicillin followed by prophylactic penicillin as above.

The test and control groups were subdivided into those patients with and without carditis on admission to the trial, and allocation to treatment groups was assigned in a random fashion.

Murmurs were graded 1-3, grade 1 being soft and grade 3 louder and longer.

Carditis includes pericarditis and/or endocarditis.

Most patients were seen for follow-up purposes at intervals of three months, six months, and one year according to our usual practice; the assessment of cardiac status in all cases in the trial is based on that observed during their in-patient admission and that observed at the first annual follow-up visit.

The number of cases is small owing to the decrease in incidence of rheumatic fever; the 51 patients were referred here from a fairly wide area over a period of approximately two years. None was excluded.

Of the 51 patients, 27 were males and 24 females; 19 were aged 10 and under and 32 were 11 and over (Table I). There were 26 patients in the test group and 25 in the control group; a slightly higher proportion of penicillin-treated cases were admitted earlier in the disease, but most patients were admitted less than one month from the onset.

TABLE I.—Series Divided into Test and Control: Sex, Age, Duration Onset to Admission

Group	No. of Cases			Age in Years		Duration from Onset Before Admitted (Days)		
	M	F	Total	10 and Under	11 and Over	14	15-28	29-56
Test	13	13	26	11	15	19	5	2
Control	14	11	25	8	17	13	9	3
Total	27	24	51	19	32	32	14	5

Results

The incidence of carditis during the acute phase and at one year is shown in Table II. Of the 19 penicillin-treated patients with carditis, four had pericarditis only and one had both pericarditis and endocarditis. Of the 19 controls with carditis, two had pericarditis only and two had both pericarditis and endocarditis. One child in the control group, with pericarditis only during the first attack, had a recurrence of rheumatic fever while

TABLE II.—Incidence of Carditis During Admission and at One Year

Group	No. with Carditis during Admission	No. with Pericarditis Only	No. with Pericarditis and Valvulitis	Cardiac State at One-year Follow-up			No. with no Organic Murmurs at One Year	No. with Diminished Murmurs at One Year
				Improved	Worse	Same		
Test	19 (73%)	4	1	18	0	1	10 (53%)	4
Control	19 (76%)	2	2	15	1	3	7 (37%)	6
Total	38	6	3	33	1	4	17	10

*N.S. ($\chi^2=1.02$)

taking prophylactic penicillin, but suffered no further heart disease. Two other children had recurrences, but without cardiac deterioration at the end of the second attack.

All the seven test and six control patients who had no carditis during the acute stage of illness had normal hearts at one-year follow-up, and this is consistent with the findings on those of our bed-rest series of 125 patients who had no carditis (Thomas, 1961).

Of the 19 test patients with carditis at onset, 18 improved, none deteriorated, and one remained the same. Of the 19 control patients, 15 improved, one deteriorated very slightly, and three remained the same. The patient who deteriorated had a grade 2 basal diastolic murmur on admission and at one year, but his mitral diastolic murmur, which was graded 1 in hospital, was more clearly audible (grade 2) at follow-up.

Ten of the 15 test patients who had endocarditis while in hospital had normal hearts at the annual follow-up visits, and 7 of the 17 control cases who had endocarditis were similarly without any detectable cardiac damage at one year. Four of the improved test patients and six of the improved control patients had diminished murmurs. All six patients in the two groups who had pericarditis alone improved and were left with normal hearts clinically, radiologically, and electrocardiographically, including one patient who had pericarditis and atrial gallop rhythm during the acute attack. She lost both abnormalities rapidly and her heart has remained normal since.

In Table III an attempt is made to detail the degrees of cardiac involvement more precisely, both initially and at one year.

Of the 15 penicillin-treated patients with endocarditis, 12 had grade 1-2 murmurs and three had at least one grade 3 murmur. At one year 14 of these patients were improved—10 completely and 4 with diminution of murmurs. Of the 12 with grade 1-2 murmurs, 11 improved and 1 remained the same, and all three of those with grade 3 murmurs improved, two of them having no organic heart disease and one having diminished murmurs.

Of the 17 control patients with endocarditis, 15 had grade 1-2 murmurs and 2 had grade 3. Of the 17 patients, 13 were improved at one-year follow-up—seven completely and six showing diminution of murmurs.

Of the 15 with grade 1-2 murmurs, 11 improved, one deteriorated slightly, and three remained the same. The two patients with grade 3 murmurs improved with diminution of murmurs.

If the grades of all murmurs in each patient are added—for example, basal diastolic murmur (grade 2), mitral systolic murmur (grade 1), and mitral diastolic murmur

TABLE III.—Comparison of Cardiac State at Onset and at One Year

Group	No. with Carditis	No. with Endocarditis	No. with Murmurs Initially Graded		All Cases			Grade 1-2			Grade 3		
			1-2	3	Im- proved	Deteriorated	Same	Im- proved	Deteriorated	Same	Im- proved	Deteriorated	Same
Test	19	15	12	3	14	0	1	11*	0	1	3†	0	0
Control	19	17	15	2	13	1	3	11‡	1	3	2§	0	0
Total	38	32	27	5	27	1	4	22	1	4	5	0	0

* 8 improved completely; 3 had diminished murmurs.
 † 2 " " " " " " " " " " " "
 ‡ 7 " " " " " " " " " " " "
 § Murmurs diminished.

(grade 1) making four—the average grading during the acute stage of illness for those with endocarditis is 3.3 for the test group and 2.7 for the controls (Table IV). The degree of improvement in the penicillin-treated group is greater than in the control group, although the final state of the two groups is similar, as seen in Table III, the treated group having slightly more widespread carditis initially.

The effect of penicillin on the duration of a raised antistreptolysin-O (A.S.O.) before return to normal is shown in Table V. Of the 26 test cases, 24 had complained of sore throats before the onset of rheumatic fever and all 25 controls had sore throats. In 19 test cases and 23 controls an A.S.O. titre of 200 or more was found at the first test. This total of 42 (82%) is in accord with the usual proportion of cases with raised A.S.O. titres in acute rheumatic fever.

TABLE IV.—Comparison of Mean Murmur Grading at Onset and at One Year

Group	No. with Endocarditis Only	Mean Murmur Grading		Degree of Improvement at One Year
		On Admission	At One Year	
Test	15	3.3	0.64	2.66
Control	17	2.7	1.3	1.4

TABLE V.—Incidence of Sore Throat, Recovery of Causative Organism: Mean Duration Onset to First A.S.O. and to First Normal A.S.O.

Group	No. with Sore Throat Preceding Illness	No. with A.S.O. 200 or More on Admission	No. with Positive Nose or Throat Swabs for Group A Haem. Strep.	Mean Duration Onset to Time 1st A.S.O. Taken (Weeks)	Mean Duration Onset to 1st Normal A.S.O. (Weeks)
Test	24	19	3	3.3	23.7
Control	25	23	2*	3.9	17.9
Total	49	42 (82%)	5		

N.S. (t=1.45, P=0.2-0.1)

* Both of these were treated with 1.2 megaunits of benzathine penicillin. They were added to the test group to see if this would influence the difference in cardiac state at one year between the test and control groups, but there was no significant difference.

Group A β-haemolytic streptococci were grown from throat and nose swabs of five patients (three test, two control). (It is realized that a single negative culture does not exclude infection; in fact, significantly more organisms were found on quadruple swabbing (Saslaw *et al.*, 1959).) The two control cases were each treated with one injection of benzathine penicillin 1.2 megaunits, which was agreed at the start of the trial, and the organisms had been eliminated on further culture. The mean duration from onset to the time the first A.S.O. was taken was similar in both groups—3.3 weeks in the test cases and 3.9 weeks in the control cases.

The mean duration before the A.S.O. titres reached normal levels was 23.7 weeks in the test group and 17.9 weeks in the control group. (This average was taken, of course, on those 42 out of the total of 51 cases which had a raised A.S.O. in the first instance.) The duration of in-patient stay varied considerably and therefore the frequency of A.S.O. determinations was greater in some, and the interval before out-patient visits was also slightly variable, so that comparison of time intervals is not always accurate.

Discussion

This small scheme was devised to see if we could repeat the results shown by Mortimer *et al.* (1959). These authors also reported a trial involving 173 adult

patients who were treated with cortisone or aspirin: 102 of these patients were treated additionally with 600,000 units of penicillin in oil containing aluminium stearate upon admission to the study and at three-day intervals for four injections. The 71 remaining patients received the first injection of penicillin after a delay of five or six days. The incidence of valvular heart disease eight months after onset was 30% in the group who received penicillin immediately and 54% in those in whom there was a delay in starting.

Mortimer *et al.* found the degree of reduction of valvular disease significant in patients with moderate or no signs of valvulitis at the time penicillin therapy was instituted. Of those patients without advanced valvular disease, 52% of the control group exhibited valvular disease one year later compared with only 21% of the penicillin group, which on the chi-square test is significant at the 1% to 5% level.

From the results of the study by Mortimer *et al.* the favourable action of penicillin was presumed to have been due to the elimination of streptococci either from the oropharynx or from the valves. Group A streptococci were isolated from the oropharynx in only 15% of their cases, but 79% had a positive A.S.O.

A possible explanation for the difference in the results might be in the estimation of the cardiac state initially and also in the severity of cardiac involvement. Rheumatic fever now generally takes a much milder form in this country, whereas in Chile it still appears in severer forms. Only five of our patients had grade 3 murmurs, all of whom improved, and many of the rest had trivial murmurs. Seven out of 15 test patients and 7 out of 17 control patients with endocarditis lost all their murmurs before they were discharged from hospital, and three additional patients in each group lost some but not all their murmurs before discharge.

The murmurs heard in our patients seem to differ in behaviour from those reported by Mortimer *et al.* They claimed that if a murmur was heard on three occasions in the first 48 hours after admission it was to be regarded as "fixed" or non-reversible, and, with the exception of three control patients, all those 27 cases with "fixed" murmurs had organic murmurs at one year. This is not our experience. Seventeen of our patients had murmurs on admission (nine test, eight control), many of which lasted for approximately six weeks, but 11 of them had no organic murmurs at follow-up.

The significant findings in Mortimer's group related to those patients who had what those authors called "non-fixed" reversible murmurs—that is, where there was no organic murmur, or inconstantly heard murmurs, during the first 48 hours. However, in our series, 13 patients were heard to develop murmurs after admission to hospital—six in the test group and seven in the control group. The six in the test group were already on or had completed the course of bactericidal doses of penicillin when the murmurs were first heard. (This does not confirm the advantage of early penicillin suggested by Mortimer *et al.*) Two of each group had organic murmurs left at one year, and one other control patient had lost one of his murmurs while still retaining the other.

Conclusions and Summary

The results of our series of cases of rheumatic fever treated with penicillin do not show any significant difference in cardiac state at one year between the

penicillin-treated and control groups. The numbers are small, 51 patients in all, but the improvement rate in both groups is high—93% in the treated group and 76% in the controls. The same proportion of both groups had carditis initially, 84% of the murmurs being fairly trivial, grade 1-2, and only 16% having grade 3 murmurs. All those with grade 3 murmurs improved, two having no organic murmurs and three diminished murmurs.

Half of the test group with endocarditis had involvement of only one valve, whereas two-thirds of the control group had only one valve affected.

A raised A.S.O. titre on admission was found in 82% of the patients, though only 10% had positive oropharyngeal cultures. The mean duration from onset of illness to the first A.S.O. estimation was similar in the two groups, but the A.S.O. titre was unexpectedly slower to return to normal in the group who received penicillin. However, the two means are not significantly different ($t=1.45$; $P=0.2-0.1$).

We have therefore been unable to repeat the results obtained by Mortimer *et al.*, and have discontinued treatment with bactericidal penicillin, except where positive throat or nose cultures are obtained.

REFERENCES

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PREGNANCY AND ADRENOCORTICAL HORMONES

SOME ASPECTS OF THEIR INTERACTION IN RHEUMATIC DISEASES*

BY

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Although various disturbances of reproduction have been induced in experimental animals by the use of very large doses of adrenocortical hormones, there is little information on whether the administration of therapeutic doses carries any hazard in human reproduction; it is also not known whether the tendency to improvement usually seen in the serious rheumatic diseases during pregnancy may be modified by such therapy.

In this paper the results of pregnancies in women who were receiving adrenocortical hormones are described, and attention is drawn to the need for further investigation of this problem.

Material.—Ten patients with rheumatic diseases who between them have had 20 pregnancies, of which the details are set out in Table I, have been studied; treatment with corticosteroids or with corticotropin was given during 13 pregnancies. Five of the patients were under the care of Dr. W. S. C. Copeman at the West London Hospital, and the remainder were under the care of Professor J. H. Kellgren at the Manchester Royal Infirmary.

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