BED REST, SALICYLATES, AND STEROID IN RHEUMATIC FEVER

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Bed rest has been an essential part of the treatment of rheumatic fever since 1877, when Sibson showed that there were fewer residual valve lesions in patients who had been so treated. Salicylates were introduced by MacLagan in 1876, and since then and until the advent of steroids have been accepted, together with bed rest, as routine in the treatment of the disease. Few would deny that bed rest is likely to be of benefit, on the basis of resting the body and thereby the heart and thus sparing a damaged or potentially damaged organ; and Taussig and Goldenberg (1941) showed that there was a higher incidence of valvular disease in patients who had refused it. The position regarding salicylates is less clear. All agree that the drugs are effective in controlling temperature and arthritis, but there is less agreement about their effect on the heart. Thus Coburn (1943) claimed that in high dosage they reduced the incidence of carditis, but this has been denied by others (Warren *et al.*, 1946). When steroids were introduced by Hench *et al.* (1949) it was hoped that they would minimize or prevent heart damage, but again there have been conflicting reports on their efficacy, and a detailed study of several hundred patients, some treated with salicylates and others with steroid, showed no significant difference between them (Co-operative Clinical Trial, 1955).

In the years 1948–50 we treated most of our patients with bed rest alone, for we were not convinced that salicylates were of value except for their effect on symptoms. In 1950–1 we took part in the Co-operative Clinical Trial above in which we used cortisone, salicylate, and A.C.T.H.; later, in 1951–2, we used salicylates and hormone in larger doses and for longer periods. The purpose of this study is to describe the course of the disease in patients treated by bed rest alone and to relate the degree of rheumatic activity to heart damage, to compare cases treated by bed rest with others given salicylates or steroid, and to assess the role of each of these three treatments—bed rest, salicylate, and steroid—in the management of the disease.

Bed-rest Series (1948–50)

During this period we treated 125 patients with bed rest and analgesics such as codeine or phenadoxone hydrochloride ("heptalgin") to control joint pain but without salicylate or steroid. Another 14 had courses of these drugs for 7 to 14 days with no demonstrable effect, and these 139 patients are discussed together. All were under 17 years of age and fulfilled the criteria for diagnosis of rheumatic fever as defined by Duckett Jones (1944); 80 were boys and 59 were girls; 69 were aged between 3 and 10 years and 70 between 11 and 16.

On admission to the unit all patients were put first into side wards, where they remained until they were well enough to be transferred to the main ward and their nose and throat swabs were known to be negative for

β -haemolytic streptococci; any found to have positive swabs were given intramuscular penicillin. Prophylaxis with penicillin or sulphonamides was not used at the time. For the first few days, and if the temperature was raised or there was acute arthritis, pericarditis, or any other evidence of active carditis, they were kept at complete rest, being washed and fed (stage 1); later they were allowed to feed themselves (stage 2) and then to wash (stage 3). In most cases stage 3 was reached by the end of the first week of admission, and patients were then kept at this stage until there had been no signs of rheumatic activity for at least two weeks.

Patients were examined daily with special reference to carditis, arthritis, skin rashes (erythema marginatum), and nodules. Chest skiagrams for heart size were taken within the first few days if patients were well enough to be taken to the x-ray department; these were repeated every two months, or more often if changes in size were suspected. Many patients were also screened. A full electrocardiogram was taken on the day of admission. If any abnormality was detected the graph was repeated, sometimes daily, and standard leads were repeated as a routine every three weeks. The temperature (oral) and pulse were recorded four-hourly, and the sleeping pulse each night at about 2 a.m. The weight was measured weekly, using a weighing-chair. Blood samples were taken each week for sedimentation rate (E.S.R.) (Westergren); the haemoglobin was estimated on admission and once every three weeks thereafter; the white-cell and differential counts on admission and later as necessary. The antistreptolysin O titre (A.S.T.) was estimated on admission and then every three weeks.

Arthritis.—Most of the 139 patients presented with acute arthritis, often after infection of the upper respiratory tract; a few had only vague limb pains but nevertheless fulfilled the Duckett Jones's criteria for diagnosis. The total duration of arthritis in 52 patients admitted within 14 days of onset—who, if they had received salicylates before admission, had them for a maximum period of 13 days—is shown in Table I. In nearly half (44%) it was for seven days or less; in less than a quarter it persisted for more than a fortnight. Most patients with such persistent arthritis were over 10 years of age, showing the tendency for arthritis to last longer in the older age-groups.

Erythema marginatum occurred in 10% of all cases. In some it persisted for only a few days and in others it recurred off and on throughout the illness, even up to the time of discharge from hospital, long after the E.S.R. had returned to normal.

Nodules.—These were noted in 34%. They usually appeared after six to eight weeks of rheumatic activity, rarely before that time. They were found earliest and most often over the olecranon processes, where they might be preceded by thickening of the subcutaneous tissue ("prenodular thickening"). Other sites were the patellae, the malleoli, the scapulae, the tendons of the wrists, hands, and feet, the spine, and the scalp. Their duration varied greatly; they might disappear within a few weeks or persist long after all other signs of activity had subsided and be present at the time of discharge from hospital.

Other criteria of rheumatic activity—temperature, sleeping pulse, sedimentation rate, weight, and anaemia—are best considered in relation to the duration of the disease before admission. 65 had been seen within 14 days of onset and the other 74 after 14 days (Table I).

Temperature.—About half (52%) of the cases admitted within 14 days of onset had, as would be expected, raised temperature, but this persisted for only one week in the majority. Nevertheless a few had continuous fever for three weeks.

Sleeping Pulse.—The total number of weeks the sleeping pulse was raised on two or more occasions in any one week above 80, 90, 100, and 110 a minute was noted. Very few patients had a rate above 110, and in many of the younger ones it was persistently between 80 and 90. The figure of above 100 was therefore chosen as a convenient dividing-line. The sleeping pulse was above 100 twice or more in any one week in 36 of the 139 (25%), and in most of them for a total of three weeks or less (22 out of 36). Another and better way of expressing the sleeping pulse was the total number of weeks during which it was above the discharge level (assumed normal) after the temperature had returned to normal. On this basis, 53 (38%) had raised rates, and these persisted for more than three weeks in 35. Tachycardia occurred more often in the recent cases, but the difference was not marked (Table I). Though the group as a whole showed this low incidence of raised sleeping pulse there was always tachycardia in the most severe cases. Thus in four patients who died the sleeping pulse was persistently above 120 for at least two months before death (Fig. 1). No other cases in the series had quite such persistent tachycardia, though in two with severe attacks the sleeping pulse was above 110 for four and six consecutive weeks; both had recurring fever and high sedimentation rates during this time and pericardial effusions. Fig. 2 illustrates the course of the disease in one of these cases and shows how such activity can subside with bed rest alone. In a few the sleeping pulse was slow, below 60, even when there was some carditis. Such bradycardia was noted in 15% of all cases.

E.S.R.—An E.S.R. of 20 mm./hr. or more (Westergren) was taken as abnormal. The total number of weeks for which the E.S.R. was abnormal was counted for each case. Twenty-six cases did not have raised rates at any time, though four of them had been admitted within 14 days of onset. Of the remainder, the E.S.R. was raised for totals of 1–3, 4–9, and 10 or more weeks in similar numbers of cases (Table I).

Anaemia.—Anaemia that could be attributed to rheumatic activity and not to iron deficiency was uncommon. In some severe cases, however, the haemoglobin fell from normal to below 70% in a few weeks, to rise again as activity subsided.

Weight.—Marked loss of weight was observed in only the worst cases. Often, however, there was a failure to gain weight at a normal rate when rheumatic activity was present; later, as it subsided, normal weight increment occurred (Fig. 2). This rise in weight

(provided heart failure could be excluded) was a very useful sign that activity was coming to an end.

A.S.T.—The antistreptolysin O titre was 200 or more in 85% of all patients and in 90% of those admitted within 14 days.

Carditis.—Two grades of carditis were distinguished, A and B. Twenty-five out of 139 patients had no abnormal clinical signs in the heart at any time, though in five of them the P–R interval was 0.18 second or more.

FIG. 1.—Persistent tachycardia above 120 in a child aged 7 who died after eight weeks in hospital.

FIG. 2.—Treatment by bed rest. Sleeping pulse persistently above 110, raised temperature and E.S.R. for four weeks, and then subsiding activity with gain in weight (4 kg.).

TABLE I.—Bed-rest Series (139 Patients). Duration of Rheumatic Activity

Admission	No.	Arthritis (Days); Duration in 52 Cases Admitted Within 14 Days of Onset			Temperature			Sleeping Pulse						E.S.R. 20 mm. hr. or More (Westergren) for Total of				
					Above 99° F. on Admis- sion	Days Remained Elevated			Above 100 in Any One Week			Raised Above Discharge Level						
						1-7	8-14	15+	1-7	8-21	22+	Total	1-3 Wks.	4+ Wks.	Total	1-3 Wks.	4+ Wks.	
		Weeks																
Total	139				59 (41%)	31 (22%)	8 (5%)	20 (14%)	36 (25%)	22 (15%)	14 (10%)	53 (38%)	18 (13%)	35 (25%)	26	38	37	38
Within 14 days	65	23 (44%)	18 (35%)	11 (21%)	34 (52%)	21 (32%)	3 (5%)	10 (15%)	18 (27%)	10 (15%)	8 (12%)	28 (43%)	12 (18%)	16 (25%)	4	25	16	20
After 14 days	74	—	—	—	25 (34%)	10 (15%)	5 (6%)	10 (13%)	18 (24%)	12 (16%)	6 (8%)	25 (33%)	6 (9%)	19 (24%)	22	13	21	18

Another 50 had soft (grade 1-2) diastolic murmurs at the mitral or aortic areas or both, transitory in 38 and constant in 12; the P-R interval was 0.18 second or more in a third. None of these 75 cases with minimal or no carditis had enlargement on x-ray examination. They were designated as cardiac group A. The other 64 (group B) had loud (grade 3 or more) murmurs on admission or developing shortly afterwards and persisting; some also had enlargement. Thirty-five were seen in first attacks of rheumatic fever; the other 29 had had previous rheumatic fever or chorea. The P-R interval was 0.18 second or more in 33%.

Pericarditis occurred in 15 cases—friction in 2 and effusion in 13. Four of the 13 with effusions developed heart failure and died, and were the only cases of failure and death in the series.

Relationship Between the Degree of Carditis and Other Features of the Attack

The sex distribution was similar in the two cardiac groups (A, nil or slight; and B, more marked)—rather more boys than girls in both. The age distribution, however, was different; most of the patients in A were aged 10 or less (62%), whereas in B most were over 10 (Table II). There was more often a family history of

TABLE II.—*Bed-rest Series. Sex and Age Distribution, and Incidence of Positive Family History*

Cardiac Group	No. of Cases	Sex		Age in Years on Admission		Positive Family History*
		M	F	1-10	11-16	
A	75	60%	40%	62%	38%	18%
B	64	54%	46%	36%	64%	30%

* History of rheumatic fever, chorea, or rheumatic heart disease in parents or siblings.

rheumatic fever, rheumatic heart disease, or chorea in parents or siblings in group B than in A—30% compared with 18% (Table II).

The duration of arthritis was analysed only in cases admitted within 14 days, and most of those in group B were admitted after 14 days (45 out of 64). There were therefore too few cases in group B with arthritis to make any comparison between the two cardiac groups possible.

The incidence of erythema marginatum was similar in the two groups—8% of A and 12% of B.

Nodules were much more frequent in B than in A—53% compared with 17%. In group A only 1 out of 25 with no carditis had nodules, as compared with 18% of those with transitory diastolic murmurs and 41% with constant diastolic murmurs. In B the incidence was similar in those with or without known previous attacks—54% and 52% (Table III).

TABLE III.—*Bed-rest Series: Incidence of Nodules*

	Total No. of Cases	No. with Nodules	% with Nodules
Cardiac group A	75	13	17%
No carditis	25	1	4%
Transitory grade 1-2 murmurs	38	7	18%
Constant	12	5	41%
Cardiac group B	64	34	53%
First attacks	35	19	54%
Second	29	15	52%

The incidence of pyrexia, raised sleeping pulse, and raised E.S.R. in the two cardiac groups as a whole and in those cases admitted within 14 days is shown in Table IV. The incidence of all three was higher in

TABLE IV.—*Bed-rest Series: Percentage of Cases with Raised Temperature, Sleeping Pulse, and E.S.R.*

Cardiac Group	No. of Cases	Temperature Above 99° F.		Sleeping Pulse			E.S.R. 20 or More (Westergren) for Total of		
		On Admission	For 3+ Weeks	Above 100	Raised after Temperature Normal	Raised for 3+ Weeks	0-3	4-9	10+
Total	139	41%	14%	25%	38%	25%	46%	27%	27%
A	75	33%	2.7%	14.8%	28.5%	12%	55%	29%	16%
B	64	53%	28%	39%	48%	39%	35%	23%	41%
65 Cases Admitted within 14 Days									
A	46	43%	2%	15%	35%	13%	54%	28%	17%
B	19	74%	47%	58%	63%	52%	21%	16%	63%

group B than in A, particularly in the 65 cases admitted within 14 days (46/75 of A and 19/64 of B). Thus in these recent cases there was continuous fever for more than three weeks in 47% of B and 2% of A; tachycardia, evidenced (a) by a raised sleeping pulse above 100 at any time in 58% of B and 15% of A, and (b) by sleeping pulse raised above discharge level for more than three weeks after the temperature was normal in 52% of B and 13% of A. Most cases in A had E.S.R.s raised for a total of three weeks or less (54%), whereas in 63% of B the E.S.R. was raised for 10 weeks or more.

Of the 65 patients admitted within 14 days of onset 56 were seen in their first attack of rheumatic fever, and any carditis was assumed to be new and recent: 46 were in cardiac group A (16 with no carditis and 30 with soft diastolic murmurs) and 10 in B (Table V). Per-

TABLE V.—*Bed-rest Series: 56 Patients Seen Within 14 Days of First Attacks: Numbers and Percentage with Raised Temperature, Sleeping Pulse, and E.S.R.*

Cardiac Status	No. of Cases	Temperature Raised for More than 3 Weeks	S.P. Raised for More than 3 Weeks after Temperature Normal	E.S.R. Raised for 10+ Weeks
Group A	46	1 (2%)	6 (13%)	8 (17%)
No carditis	16	0 (0%)	3 (19%)	0 (0%)
Grade 1-2 murmurs	30	1 (3%)	3 (10%)	8 (27%)
Group B	10	6 (60%)	7 (70%)	5 (50%)
Total	56	7 (12.5%)	13 (23%)	13 (23%)

sistent fever for more than three weeks was unusual in cases in group A and never occurred without clinical evidence of carditis, but was present in 6 out of 10 in group B. The E.S.R. was never raised for 10 weeks or more in patients without carditis, but was so raised in 27% of those with soft diastolic murmurs and in 50% of those in group B. Sleeping pulse raised above discharge level for more than three weeks after the temperature had returned to normal, though more common in B than in A, occurred as or more often in cases in group A with no carditis as in those with soft diastolic murmurs, and did not occur in 3 out of 10 with marked carditis in B.

Loss of weight and anaemia were uncommon and were seen only in group B cases. The incidence of raised A.S.T. was similar in the two groups—87% of A and 80% of B. In A there was no difference in incidence of raised A.S.T. in cases with no abnormal clinical signs (87%), with transitory diastolic murmurs (89%), or with constant diastolic murmurs (84%).

Thus the incidence of erythema marginatum and raised A.S.T. was similar in the two cardiac groups.

That of nodules was much higher in B than in A, and loss of weight and anaemia, both of which were uncommon, occurred only in the most severe cases of group B. Of the other criteria of activity, temperature, sleeping pulse, and E.S.R., all were more often abnormal in B than in A. Generally, E.S.R. and temperature were more closely related to carditis than sleeping pulse rates, but, as pointed out earlier, a prolonged raised sleeping pulse rate was invariable in the most severe cases and carried a bad prognosis. The four patients who died showed the following characteristics: loud murmurs and cardiac enlargement on admission in first attacks of rheumatic fever; nodules; pericarditis; and severe continued activity as judged by recurring temperature, E.S.R. between 40 and 100, and sleeping pulse rate above 110 for at least two months before death.

A striking feature of this study of the course of rheumatic fever in hospital in patients treated by bed rest alone was the short duration of activity in many cases. Thus arthritis persisted for a total of seven days or less in half the cases; only half had raised temperatures on admission which lasted for a week or less in the majority; only a third had sleeping pulse rates raised above discharge level after the temperature returned to normal; and in nearly half the cases the E.S.R. was raised above 20 mm./hour Westergren for a total of three weeks or less.

When the degree of carditis was related to rheumatic activity there was close correlation between carditis and nodules, prolonged raised temperature and E.S.R., but not with erythema marginatum or raised A.S.T. The sleeping pulse rate, though always raised to high levels in the worst cases, was as often raised in patients with no heart disease as in those with soft diastolic murmurs, and was sometimes normal in patients with recent carditis and loud murmurs. It is concluded, therefore, that nodules, prolonged raised temperature, and E.S.R. are usually better guides to prognosis than sleeping pulse rate, though in a few a persistently high sleeping pulse rate may portend a bad outcome. The outlook is worst, and death may occur, in patients with loud murmurs and cardiac enlargement in whom activity continues for two months or more, with recurring fever, high E.S.R., sleeping pulse rates above 110, nodules, and pericarditis.

Results of Treatment by Bed Rest Alone Compared with Treatment by Salicylate and Steroid

In 1950-1 we took part in the joint U.S.-U.K. trial (Co-operative Clinical Trial, 1955) and treated 86 patients with six-week courses of A.C.T.H., cortisone, or salicylate. All these patients were on prophylactic sulphonamide 1 g. daily. Of our bed-rest cases 89 would have qualified for treatment in the trial, as they were comparable in all respects; the other 50 included in the foregoing analysis fulfilled criteria for diagnosis but not for treatment, as they had only one minor criterion of activity (raised E.S.R.), whereas to qualify for treatment one major or two minor criteria were necessary.

We are grateful to Professor J. Knowelden, of the London School of Hygiene and Tropical Medicine, for part of the following analysis of the 86 trial cases and the 89 comparable ones treated by bed rest. The method of analysis is different from the one we used in the total bed-rest series of 139 patients but the same as in the report published by the Joint Committee (Co-operative Clinical Trial, 1955).

Arthritis.—29 of the joint trial cases and 40 of the bed-rest cases had arthritis on admission. The duration in the two groups is shown in Table VI. At the end of

TABLE VI.—*Joint Involvement at Start of Therapy at Specified Times*

Time from Start of Therapy in Days	U.S.-U.K. Trial (86 Cases)		Bed Rest (89 Cases)	
	No.	%	No.	%
1	29	100.0	40	100.0
2	18	62.1	34	85.0
3	14	48.3	33	82.5
4	14	48.3	24	60.0
5	11	37.9	23	57.5
6	10	34.5	21	52.5
7	6	20.7	15	37.5
8	4	13.8	15	37.5
15	3	10.3	9	22.5
22	2	6.9	8	20.0
29	2	6.9	6	15.0
36	1	3.4	4	10.0
43	3	10.3	4	10.0
50	6	20.7	2	5.0
57	4	13.8	1	2.5
63	1	3.4	—	—
13th week	1	3.4	—	—

one week (day 8) 13.8% of the joint trial cases and 37.5% of the bed-rest series still had arthritis; two weeks later (day 22) these figures were 6.9% and 20%. After six weeks (day 43) 10% of both series had arthritis. There was then an increase in the proportion of cases with arthritis in the treated series, due to withdrawal relapse, but the proportion in the bed-rest series continued to fall.

Temperature.—57% of the bed-rest and 43% of the U.S.-U.K. trial cases had fever on admission, and this higher incidence of temperature in the bed-rest series continued until day 23 (Fig. 3). It was then similar in

Fig. 3.—Percentage of 89 patients treated by bed rest and 86 treated in the U.S.-U.K. trial with raised temperature.

both until day 42, when there was an increase in the number of cases with fever in the treated series. At the end of nine weeks the incidence of raised temperature was again similar in the two.

E.S.R.—In both series, nearly 90% of cases had rates of 20 or more on admission. Fig. 4 shows the percentage with raised E.S.R. in all the joint trial cases, in those of the joint trial treated by salicylates, and in the bed-rest series. The E.S.R. returned to normal more slowly in the bed-rest cases, but the level at 13 weeks was similar in all three groups.

Thus arthritis, raised temperature, and E.S.R. all tended to persist longer in the bed-rest than in the treated cases. Nevertheless the incidence of arthritis

was similar in the two by the sixth week, the temperature by the fourth week, and the E.S.R. by the eighth week.

FIG. 4.—Percentage of 89 patients treated by bed rest and 86 treated in the U.S.-U.K. trial with raised E.S.R.

Carditis

Of the 175 cases, 42 had no carditis on admission (29 of the 89 in the bed-rest series and 13 of 86 in the U.S.-U.K. trial). Murmurs developed in hospital in 18 out of the 29 in the bed-rest series (Grade 1-2 in 16 and grade 3 in 2) and in only 2 out of the 13 in the trial (grade 1-2 in both) (Table VII). The remaining 133

TABLE VII.—42 Cases with No Carditis on Admission

	Total No. of Cases	U.S.-U.K. Trial (86 Cases)	Bed-rest Series (89 Cases)
No carditis on admission ..	42	13	29
Murmurs developed in hospital in ..	20	2	18
Grade 1-2	18	2	16
„ 3	2	0	2

TABLE VIII.—84 Cases with Carditis on Admission in First Attacks: Number of Cases Reverting to Normal

	Total No. of Cases	U.S.-U.K. Trial (86 Cases)	Bed-rest Series (89 Cases)
Carditis on admission ..	84	47	37
Reverted to normal in hospital ..	21	18	3
Grade of murmur that disappeared:			
Grade 1-2	20	17	3
„ 3	1	1	0

had carditis on admission; 49 of them had had previous attacks of rheumatic fever and carditis that could have been “old”—26 in the U.S.-U.K. trial and 23 in the bed-rest series; there was no difference in changes in cardiac status in hospital between the two groups. The other 84 had been admitted in first attacks with carditis that was assumed to be recent, 47 in the trial and 37 in the bed-rest series (Table VIII). Murmurs disappeared in hospital in 21 cases—in 18 out of the 47 in the U.S.-U.K. trial and in only 3 out of 37 in the bed-rest series. Of these 21 cases 20 had only minimal carditis evidenced by soft diastolic murmurs, but in one case in the U.S.-U.K. trial grade 3 murmurs disappeared. Five of the 84 with recent carditis died in hospital—4 of the 37 in the bed-rest series and only 1 of the 47 in the U.S.-U.K. trial. In none of the four in the bed-rest series that died had there been further demonstrable streptococcal infection to cause fresh rheumatic activity.

Comparison of the course in the two series shows that rheumatic activity subsided more slowly on all criteria in the bed-rest series, but the temperature was similar in both series by the fourth week, arthritis by the sixth week, and the E.S.R. by the eighth week. Fewer of the drug-treated cases developed murmurs in hospital and in more of them they disappeared. But this applied mainly to soft (grade 1-2) murmurs and may have little effect on prognosis, for in our experience few such cases subsequently develop serious heart disease. Nevertheless, four patients in the bed-rest series died and only one in the treated.

Thus by these various criteria the bed-rest series did worse, but no prophylaxis was used in this group and the two studies were not run concurrently. Further, we may have been dealing with a more severe form of the disease in the earlier series, since there was a higher proportion of cases with significant heart disease on admission: 59% with carditis had grade 3 murmurs as compared with 38% in the U.S.-U.K. trial.

A Third Series, Treated with Larger Doses of Cortisone and Salicylate

An analysis of cardiac status in the U.S.-U.K. trial cases 13 weeks after starting treatment and one year later showed no significant difference between those treated with cortisone, A.C.T.H., or salicylate (Co-operative Clinical Trial, 1955). A criticism of this trial has been that the dosage was too low and the duration of treatment too short, and that, if longer courses had been given, steroids might have proved more effective than salicylate. With this in mind, we treated a third series with 12-week courses of cortisone or salicylate in alternate cases.

Just as there had been less carditis on admission in the U.S.-U.K. trial cases than the bed-rest series, so in this third series there was less than in the U.K.-U.S. trial, again showing a tendency for the disease to become less severe over the years: this coincided with a fall in the overall incidence of notifiable rheumatic fever. Thus only 2 out of 26 patients with carditis on admission, all of whom had been admitted in first attacks within 14 days of onset, had grade 3 murmurs, as compared with 3 out of 13 in the U.S.-U.K. trial and 6 out of 15 in the bed-rest series admitted within a similar period. The patients in the new trial received 300 mg. of cortisone daily for two days, 200 mg. for five days, 100 mg. for six weeks, and then by weekly reductions to 25 mg. in the last and twelfth week, and salicylates on a body-weight basis in the form of calcium aspirin. During the stay in hospital no significant change occurred in the two cases with grade 3 murmurs. Of the other 24 with carditis on admission evidenced by grade 1-2 murmurs, similar numbers lost murmurs as in the U.S.-U.K. trial (16 out of 24—9 on salicylates and 7 on cortisone—as compared with 17 out of 29 in the U.S.-U.K. trial); and of the remaining 21 with no carditis on admission, 8 developed murmurs (5 on salicylate and 3 on cortisone) as compared with 2 out of 13.

We concluded, therefore, that longer courses of cortisone or salicylate have no advantage over the shorter ones used in the U.S.-U.K. trial, and that cortisone has none over salicylate in preventing or minimizing carditis, as evidenced by the development or disappearance of murmurs. The latter conclusion has been supported by the findings of the Combined Rheumatic Fever Study Group (1960) in America. Whether salicylate or cortisone therapy is more bene-

ficial during treatment in hospital than bed rest alone is difficult to assess, for the bed-rest and drug-treated series were not run concurrently, there was no prophylaxis in the bed-rest series, and more had serious heart disease on admission. Certainly the duration of rheumatic activity as judged by fever and E.S.R. was shorter in the drug-treated cases, and fewer developed murmurs and more lost them. This change applied, however, only to those with soft murmurs: there was no difference between the treatment groups in patients with grade 3 murmurs. Thus if steroid or salicylate influenced carditis in the development or disappearance of murmurs during hospitalization, it was only so far as grade 1-2 murmurs were concerned; and this, as has been pointed out, may have little effect on prognosis.

Four patients in the bed-rest series died in hospital, only one in the U.S.-U.K. trial, and none in the recent series treated with 12-week courses of salicylate and cortisone. Was this due to some beneficial effect of the drugs or to there being more severe cases in the earlier bed-rest series? The following features characterized the four fatal cases in this group: all were seen in first attacks with grade 3 murmurs and cardiac enlargement, and had rheumatic activity for minimum periods of eight weeks before death, with recurring fever, high sleeping pulse and sedimentation rates, nodules, and pericarditis. Signs of heart failure ultimately developed that did not respond to digitalis, mersalyl, and other measures. Two other cases in the bed-rest series had a similar degree of activity, but this subsided after five and six weeks' bed rest; both had pericardial effusions but not severe valve lesions. There were thus six patients with severe continued activity for five to six weeks, four of whom died in heart failure.

Were there any comparable cases in the drug-treated series? In the U.S.-U.K. trial there were four with this degree and duration of activity before the start of therapy; three were then given hormone (two A.C.T.H. and one cortisone) and the other salicylate. The three that were treated with hormone developed failure from sodium retention, but this responded to digitalis and mersalyl as activity was suppressed by the drug, and continued to subside after treatment had been stopped. All three made a good recovery and remained well over the next seven to eight years. The one that was given salicylates showed little response and the activity continued for many weeks, though the patient ultimately made a good recovery. Two other patients in the U.S.-U.K. trial and one in the third series were treated with salicylates within two weeks of admission, but then had recurring activity, for which they were given further courses of salicylate with little or no effect. One died in hospital; the other two were left with serious heart disease and died three and five years later.

Thus, of 13 patients in all three groups with continued or recurring activity and serious heart disease, three who were treated in the U.S.-U.K. trial with steroid made a good recovery; of four given salicylate (three in the U.S.-U.K. trial and one in the third series) one recovered, one died in hospital, and the other two were left with gross heart disease and died three and five years later; and of the six treated by bed rest, four died in hospital and two recovered. Treatment with hormone therefore appeared to be more effective than salicylate or bed rest alone.

Not only was salicylate ineffective in controlling activity in these cases, but there was reason to believe that it may have been harmful in three of them.

Thus in the one patient who died in hospital in the U.S.-U.K. trial, severe failure developed soon after the start of a fifth course of aspirin therapy. Treatment was changed 10 days later from aspirin to cortisone, but failure persisted and death occurred after another five weeks.

Another patient in this trial was treated with two courses of aspirin because of recurring activity. Failure developed shortly after the start of both of them and subsided on their withdrawal (Fig. 5). In the first course, 3 g. of acetylsalicylic acid was given daily. Two days later there

FIG. 5.—Two episodes of heart failure after administration of aspirin. (Pul. oed.=pulmonary oedema. Hil. cong.=hilar congestion.)

was dyspnoea, the venous pressure was raised, and a chest skiagram showed pulmonary oedema. The drug was stopped and the patient put on a low-sodium diet (0.6 g./day) but no other treatment. The respiration rate and venous pressure returned to normal during the ensuing week and the skiagram then showed some congestion but no oedema. The second course of aspirin (3.7 g. daily) was given four months later, when the patient was on digitalis and low-salt diet. After two days there was some dyspnoea, with a rise in venous pressure; the dose was reduced to 2.3 g. daily. During the next six days dyspnoea persisted and the venous pressure continued to rise. The drug was then discontinued and mersalyl given, with clinical improvement. A chest skiagram still showed pulmonary oedema five days afterwards, but this cleared in another four days. In both episodes, therefore, failure developed within a few days of starting salicylate therapy and receded shortly after its withdrawal.

The third patient treated in the most recent trial developed pulmonary oedema soon after the start of two courses of "disprin," but this was controlled by salt restriction, digitalis, and mersalyl, and salicylate therapy was continued.

In two of the four patients in the bed-rest series who died there was also a suspicion that short courses of salicylate given towards the end of the illness might have been harmful.

In one there were signs of heart failure eight days before death that responded to digitalis. As failure improved there was a rise in temperature and E.S.R., and because of this salicylate 4 g. daily was given. After two days failure returned (salicylate level, 11 mg./100 ml.) and the patient died two days later.

The other was started on enteric-coated salicylate 4 g. daily because of continued activity. Three days later there

was sudden acute dyspnoea, with signs of consolidation of the right lung and death within eight hours, despite treatment with oxygen, morphine, digitalis, aminophylline, and penicillin. At necropsy there was typical rubbery consolidation of the whole of the right lung from rheumatic pneumonia.

All these patients who appeared to deteriorate on salicylate had had cardiac enlargement and active disease, and the drug had been given in the hope of controlling the activity. In those who survived it was ineffective in controlling activity but caused heart failure. In the others, death from heart failure, in one case with rheumatic pneumonia, followed shortly after starting treatment. The mechanism by which salicylates precipitate failure is not fully understood. Phear (1955) suggested it was due to the sodium content of salicylate and bicarbonate mixtures, but it has also been recorded with other forms of salicylate—that is, aspirin (Granville-Grossman and Sergeant, 1960). Other factors suggested have been increased plasma volume (Reid *et al.*, 1950) and increased plasma volume with pulmonary capillary damage (Sutcliffe, 1955); and Hetzel *et al.* (1959) have shown that salicylates can cause sodium and fluid retention. Raised cardiac output from the increased metabolism that salicylate induces (Cochran, 1954) is another possibility which should receive serious attention.

Before the introduction of hormone we found that persistent severe activity often precipitated heart failure in patients with cardiac enlargement, that this failure did not respond to digitalis, mersalyl, and other measures so long as activity persisted, and that sometimes death resulted. Salicylates were ineffective in controlling activity and sometimes appeared to do harm. Steroid, on the other hand, suppressed activity in similar cases treated in the U.S.-U.K. trial. Though the preparations used at that time (A.C.T.H. and cortisone) caused temporary failure from sodium retention, this responded to digitalis and mersalyl as the activity subsided, and the patients made a good recovery. Now we have drugs, such as prednisone, which cause little or no retention. Since they have been available we have used them in all patients with enlargement and marked activity; the activity has been controlled and failure has not developed. We have also used them in patients with failure and activity, again with control of the activity, the failure then responding to digitalis and mersalyl.

Conclusions

Our present views of the treatment of rheumatic carditis, based on experience of bed rest alone and short and longer courses of salicylate and hormone, are therefore as follows. The majority of cases with rheumatic fever to-day are mild and respond to bed rest alone; though salicylates may be helpful in relieving joint pains and other symptoms they do not significantly alter the course of the disease or the cardiac status. Steroids are not of proved value in these cases, for, though they may shorten the duration of rheumatic activity, there is no evidence that they benefit the heart, except possibly in the development or disappearance of soft diastolic murmurs in hospital; and a separate study has shown that this may have little effect on the prognosis five years later (unpublished data).

Steroids without a salt-retaining action are indicated, however, in all patients with cardiac enlargement and marked activity, for by suppressing the activity they lessen the risk of failure developing, or, if failure is

already present, allow a satisfactory response to digitalis and mersalyl which otherwise might not occur. Salicylates do not adequately control activity and are potentially dangerous in such cases, since they may precipitate lung oedema or rheumatic pneumonia. Continuous prophylaxis is an essential background measure.

Summary

The course of rheumatic fever in hospital in patients treated by bed rest alone and not given prophylaxis has been studied, and the degree of carditis related to other features of the attack. Prolonged raised temperature and sedimentation rate were more closely related to carditis than the sleeping pulse, but in severe attacks persistent tachycardia was a constant feature and carried a poor prognosis. Anaemia and loss of weight were uncommon and occurred only in the worst cases. Nodules were rare without heart disease, but were present in a quarter of those with slight carditis and in half of those with severe carditis.

The course in hospital in some patients treated by bed rest has been compared with that in others who were given six-week courses of A.C.T.H., cortisone, or aspirin, together with prophylactic sulphonamide. The two groups were comparable in most respects, although (a) they were not run concurrently; (b) only the drug-treated series was given prophylaxis; and (c) the latter had less heart disease at the start. Arthritis, temperature, and sedimentation rate subsided more slowly in the bed-rest series, but the temperature was similar in the two by the fourth week, arthritis by the sixth week, and the sedimentation rate by the eighth week; the rapid subsidence of activity in some of the bed-rest cases was striking. There was little difference in changes in cardiac status in the two groups, except in the development or disappearance of soft (grade 1-2) murmurs, and this may have no important effect on the residual heart state five years later.

A third group of 47 cases was treated with 12-week courses of either cortisone or salicylate and did no better than those who had salicylate, cortisone, or A.C.T.H. for only six weeks.

Conclusions are drawn on the role of bed rest, salicylate, and steroid in the management of the disease. In many cases bed rest with salicylate to control fever and joint pain suffices, but in a few with severe attacks and cardiac enlargement delta-steroids are indicated and salicylates are potentially dangerous since they predispose to pulmonary complications.

REFERENCES

- Coburn, A. F. (1943). *Bull. Johns Hopk. Hosp.*, **73**, 435.
- Cochran, J. B. (1954). *Brit. med. J.*, **1**, 733.
- Combined Rheumatic Fever Study Group (1960). *New Engl. J. Med.*, **262**, 895.
- Co-operative Clinical Trial of A.C.T.H., Cortisone, and Aspirin (1955). *Brit. med. J.*, **1**, 555.
- Granville-Grossman, K. L., and Sergeant, H. G. S. (1960). *Lancet*, **1**, 575.
- French, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, **24**, 181.
- Hetzel, B. S., Charnock, J. S., and Lander, H. (1959). *Metabolism*, **8**, 205.
- Jones, T. D. (1944). *J. Amer. med. Ass.*, **126**, 481.
- MacLagan, T. (1876). *Lancet*, **1**, 342.
- Phear, D. N. (1955). *Arch. Midx. Hosp.*, **5**, 172.
- Reid, J., Watson, R. D., and Sproull, D. H. (1950). *Quart. J. Med.*, **19**, 1.
- Sibson, F. (1877). *System of Medicine*, edited by J. R. Reynolds, **4**, 526. Macmillan, London.
- Sutcliffe, J. (1955). *Brit. J. Radiol.*, **28**, 314.
- Taussig, H. B., and Goldenberg, M. (1941). *Amer. Heart J.*, **21**, 440.
- Warren, H. A., Higley, C. S., and Coombs, F. S., jun. (1946). *J. Lab. clin. Med.*, **31**, 485.