COMBINED ASPIRIN AND CORTISONE TREATMENT OF ACUTE RHEUMATIC FEVER A CONTROLLED TRIAL IN YOUNG MEN

BY

J. D. H. SLATER

London

For many years large doses of salicylate have been used in the treatment of acute rheumatic fever (Coburn, 1936, 1943; Manchester, 1946). Although the acute manifestations of the disease are partially suppressed (Illingworth, Burke, Doxiadis, Lorber, Philpott, and Stone, 1954), there is no convincing evidence that chronic damage to the heart is prevented (Bywaters, 1950).

However, the introduction of the adrenocortical hormones in 1948 brought hope of a more radical form of treatment (Hench, Kendall, Slocumb, and Polley, 1949). Anecdotal studies have emphasized the value of steroid therapy in acute rheumatic fever (Massell, 1954; Debré, Mozziconacci, and Caramanian, 1955), and there is evidence that carditis is less likely to develop if large doses of cortisone are given at an early enough stage in the disease (Roy and Massell, 1956). Nevertheless, two well-controlled therapeutic trials comparing the effects of aspirin, cortisone, and adreno-cortico-trophic hormone in children (M.R.C. and A.H.A., 1955) and in American airmen (Houser, Clark, and Stolzer, 1954) have shown that *when used singly* each of these drugs has a similar effect on the course of the acute disease. These trials have not, however, assessed the effect of cortisone, because there were no untreated controls and no patients treated with both aspirin and steroids.

The present paper describes a controlled therapeutic trial in 28 young men designed to assess the response to cortisone. The course of acute rheumatic fever was followed when using high doses of salicylate, either alone or combined with cortisone.

Methods

In the British Army many patients with doubtful or mild rheumatic fever are admitted to hospital so that the diagnostic criteria laid down by Duckett Jones (1944) have been modified and made more rigid. These are described in detail elsewhere

(Slater and Rosenbaum, 1959), but are similar to the criteria used by Houser and others (1954) and in the M.R.C. and A.H.A. Trial (1955). All soldiers with suspected acute rheumatic fever in the Aldershot area between June, 1955, and June, 1956, were seen personally and assessed for entry to the trial. No case which satisfied the diagnostic criteria was excluded. The treatment to be given was determined at random by the toss of a coin.

Aspirin.—This was given in five separate doses totalling 1 to 1½ gr. per lb. body weight per day. The exact amount was governed by the development of tinnitus and slight deafness. Blood salicylate levels were estimated 2 hours after the morning dose once weekly and with few exceptions were always above 30 mg. per 100 ml.

Cortisone.—This was given by mouth in the following doses: 300 mg. per day on the first day; 200 mg. per day on the second, third, and fourth days; 100 mg. per day for the remainder of the first 3 weeks; 50 mg. per day thereafter, unless treatment had already been stopped.

Except for the addition of cortisone to the members of one group, the therapy in each case was identical. Salt intake was restricted to less than 1 g. NaCl per day and extra potassium (76 mEq/day) was given as the citrate. Intramuscular penicillin was given for 10 days from the day of entry to the trial and thereafter oral sulphadimidine 1 g. daily. A strict and standard regime for mobilizing the patient was used. Usually this took about 4 weeks. Drug treatment was continued until full clinical recovery *and* until three consecutive erythrocyte sedimentation rate estimations (Westergren) were below 10 mm./hr. These were performed at 4-day intervals after the first normal reading. The patient was not allowed to begin getting up unless the erythrocyte sedimentation rate was normal on the fourth and eighth days after stopping drug treatment.

Assessment of progress was made at standard times on specially-prepared charts. Entries were made at least every morning until the patient began to get up, and at weekly intervals thereafter. Apical systolic murmurs were recorded by a modified version of Levine's grading (Levine and Harvey, 1949), the length of the murmur also being noted. Apical and basal diastolic murmurs were listened for in the appropriate positions with the bell and diaphragm of the stethoscope respectively. The pulse rate and oral temperature were recorded 4-hrly when the patient was febrile and otherwise 12-hrly. The pulse rate during sleep was taken nightly at 2 a.m. An erythrocyte sedimentation rate, chest radiograph (by a standard technique), and total white blood cell count were recorded weekly unless otherwise stated. After admission to the trial, 12-lead electrocardiographic tracings

were taken on alternate days for 8 days and then at weekly intervals until two consecutive tracings were normal.

Results

Table I shows that the main clinical features of the disease at the time of entry to the trial were comparable. On the day that therapy was begun, an equal proportion of patients in each group had evidence of cardiac involvement, the extracardiac manifestations of the disease were similar in degree, in all patients treatment was begun less than 10 days from the onset of symptoms, and equal numbers had had a previous attack. The patients receiving aspirin and cortisone were on the whole slightly younger than those given aspirin alone.

The response to treatment of specified features of the disease is shown in Table II, and the Figure (opposite).

TABLE I
SPECIFIC CLINICAL FEATURES AT THE BEGINNING OF TREATMENT

Clinical Features		Group			
		Aspirin Alone (15 Cases)		Cortisone and Aspirin (13 Cases)	
		Range	Mean	Range	Mean
Age (yrs)		18-24	20·3	17-21	18·8
Duration of Symptoms (days)		1-7	3·8	1-8	4·3
Temperature (° F.)		99·8-101·8	100·6	99·4-103·0	100·9
Erythrocyte Sedimentation Rate (mm./hr)		34-110	64·2	20-115	64·0
Pulse Rate during Sleep		60-98	75·3	68-96	79·5
Number of Inflamed Joints		1-8	2·8	1-5	2·4
Number of Patients with	Abnormal Heart Murmurs	1		1	
	Past Rheumatic Fever	4		4	
	Preceding Sore Throat	11		7	
	Prolonged P-R Interval	4		4	
	Leucocytosis	4		4	

TABLE II
RESPONSE TO TREATMENT

Duration of Symptoms and Therapy		Group			
		Aspirin Alone (15 Cases)		Cortisone and Aspirin (13 Cases)	
		Mean	Range	Mean	Range
Fever (hrs)		35·7	12-88	9·3	4-12
Inflamed Joints (days)		3·67	2-6	1·8	1-3
Raised Erythrocyte Sedimentation Rate (days to first normal reading)		22·1	15-43	17·5	7-29
Drug Therapy (days)		33·8	22-52	37·6	24-44
Complete Rest in Bed (days)		47·8	23-87	46·5	34-91

Figure.—Response to treatment of fever and joint inflammation in 6 days, and of raised erythrocyte sedimentation rate in 60 days.

The duration of fever and painful joints was shortened by giving cortisone as well as aspirin. No patient receiving cortisone had fever for longer than 12 hours from the time that therapy was started compared with nine out of twelve patients on aspirin alone. Conversely, six out of eleven patients on the combined therapy had lost their fever in less than 12 hours whereas none of the patients on aspirin alone did so. Ten out of thirteen patients receiving cortisone had painless joints within 72 hours of starting treatment, but only one of those on aspirin alone was free of joint symptoms within this time; in contrast it took 4 to 6 days for

joint symptoms to subside in seven out of the fifteen patients on aspirin alone, whereas all the patients on the combined therapy were symptom-free in 3 days or less. Despite the small numbers, these differences are considerable, consistent, and highly significant statistically.

In addition, the duration of a raised erythrocyte sedimentation rate (time to first normal reading) was shortened by giving cortisone; three patients had normal values at 8 days compared with none in the aspirin group. The erythrocyte sedimentation rate also fell more rapidly in the patients on the combined therapy (Table III). Taking mean

TABLE III
ERYTHROCYTE SEDIMENTATION RATE (mm./hr) AT SPECIFIED TIMES

Erythrocyte Sedimentation Rate		Aspirin Alone (15 Cases)		Cortisone and Aspirin (12 Cases)†	
		Mean	Range	Mean	Range
During Treatment	Initial reading ..	64.0 (100%)	34-110	64.2 (100%)	20-115
	Fall 1st to 8th day ..	27.3 (58%)	0-70	38.2 (40%)	0-82
	Fall 1st to 15th day ..	32.0 (50%)	0-102	58.0 (9.7%)	16-95
After Stopping Treatment	1st day	5.0	2-9	4.1	2-6
	4th day	4.8	2-12	10.2	2-26
	8th day	5.1	2-18	11.0	3-20
	15th day	4.0	1-14	9.7	2-25
	22nd day	3.9	1-10	7.2	2-30
	29th day	4.5	2-9	5.7	2-12

* Number of patients with an abnormal erythrocyte sedimentation rate.
† Excluding one patient whose sedimentation rate remained elevated until a septic tooth was extracted.

values, the sedimentation rate at 15 days had fallen to 50 per cent. of the initial reading in patients given aspirin alone compared with 10 per cent. in patients on the combined treatment.

Two patients in each treatment group developed new abnormal murmurs in the heart. The duration of a prolonged P-R interval on the electrocardiogram was 6, 10, and 40 days for three patients treated with aspirin alone, and 11, 13, 15, and 143 days in four patients receiving the combined therapy. Changes in pulse rate were not analysed because, after the temperature became normal, the pulse rate was below 90 per min. in every case. Two patients on the combined treatment developed bradycardia with ventricular rates of below 50 per minute.

Table III shows that after the withdrawal of drug treatment there was a transient rise in the erythrocyte sedimentation rate in the patients receiving the combined treatment. This happened without clinical evidence of renewed rheumatic activity or change in the heart rate, except that one man had a mild recurrence of joint symptoms with fever on the fourth day after treatment was discontinued. Another patient treated with aspirin alone experienced a similar mild relapse on the 24th day after drug treatment was discontinued. Although not satisfying the requisite diagnostic criteria, both these events were regarded as mild recurrences of rheumatic activity and treatment was restarted. Chiefly because of this rebound rise in erythrocyte sedimentation rate, the mean length of drug therapy and of complete rest in bed was similar in both groups.

Both aspirin and cortisone were well tolerated, except by one man who developed vomiting, over-breathing, and mental disorientation after one week's treatment with aspirin alone. Cortisone did not cause any definite toxic effects but produced a more rapid gain in weight. After 2 weeks' treatment patients receiving cortisone had gained a mean of 5 kg. compared with 0.5 kg. in the aspirin group. Whatever the treatment, most patients developed mild mooning of the face and acne became worse. No specific record of these changes was kept because they were so slight and could hardly be measured.

Discussion

The results of this controlled study show that the fever and joint inflammation of acute rheumatic fever in young men can be alleviated more rapidly by giving cortisone together with large doses of aspirin than by giving aspirin alone. Also the

erythrocyte sedimentation rate fell to normal more rapidly but there was a transient rise when treatment was stopped. Owing to the design of the trial this meant that the length of drug treatment and the time spent in bed were similar in each group. There were probably too few cardiac manifestations to justify comment, but the addition of cortisone did not seem to influence the duration of a prolonged P-R interval.

Although the numbers are small these results would appear valid because the patients formed an unusually homogeneous group and were observed personally under uniform conditions. Unlike other larger trials, there was no loss of information from grouping together dissimilar cases or from the use of case notes instead of seeing the patients personally.

Because cortisone shortens the duration of the extracardiac manifestations of acute rheumatic fever, it does not follow that subsequent chronic heart disease will be lessened. This is a difficult question which will take decades to answer. But, assuming that there is some parallel between joint inflammation and cardiac inflammation, it seems unlikely that the more rapid relief of one will not be accompanied by some amelioration in the other. The careful and fully-controlled studies of Illingworth, Lorber, Holt, and Rendle-Short (1957) have shown that, in children with acute rheumatic fever, cortisone gives better results than aspirin, and that cortisone with combined aspirin is better than cortisone alone. Not only were the acute manifestations reduced more rapidly, but fewer heart murmurs were present one year later in the cortisone-treated patients. Superficially, the disappointing results of the Anglo-American trial (1955) and the trial by Houser and others (1954) appear to differ from the findings of Illingworth and his co-workers. Both studies compared the relative effects of orally administered aspirin with intramuscular injections of cortisone. For the first 7 days of therapy more patients receiving cortisone had fever and joint involvement, but this is probably explained by the slow absorption of intramuscular cortisone which may also cause local inflammation. Thereafter these manifestations were less frequent in the hormone-treated cases, but there was a greater tendency for them to reappear at the end of treatment. The signs of carditis were also little influenced by the form of treatment although soft apical systolic murmurs and nodules disappeared more rapidly in the group receiving cortisone.

In diseases which cause long-term disability, therapeutic trials which show equal effects with different drugs during the acute phase are difficult

to interpret. Assuming that drug treatment is better than no treatment, useful conclusions depend largely on how the drugs produce their beneficial effects. Although aspirin may have some specific anti-inflammatory effect in rheumatic fever, it also has a powerful non-specific analgesic and antipyrexial action. Refined techniques (Peterson, Black, and Bunim, 1958) have shown that salicylate does not stimulate adrenocortical function. Cortisone, however, is a well-known anti-inflammatory agent and it is unlikely that it would relieve the acute manifestations of rheumatic fever other than by suppressing the inflammatory process. Therefore, apart from the question of toxicity, to show that cortisone is as effective as aspirin in relieving the acute manifestations of rheumatic fever could reasonably be interpreted as indicating that cortisone is the better form of treatment.

Both the present study and the two trials described above show that the erythrocyte sedimentation rate falls to normal more rapidly when rheumatic fever is treated with cortisone. In the other trials treatment was stopped after 6 weeks irrespective of the progress of the patient, following which there was a recrudescence of rheumatic activity and a "rebound" rise in the erythrocyte sedimentation rate in a greater proportion of hormone-treated subjects. In the present study, treatment was continued until, by pre-arranged criteria, the disease was judged to be quiescent. Nevertheless, a small transient rise in the erythrocyte sedimentation rate was seen in the patients who had been given cortisone. In the absence of other signs of continuing rheumatic activity, this may be a non-specific response to a sharp fall in the steroid dose. For example, Robinson, Wolfson, and Duff (1951) found that, in patients with eye disease who were treated with corticotrophin, an initially normal erythrocyte sedimentation rate rose to high levels when the steroid dose was suddenly reduced. However, since our ability to detect continuing mild rheumatic activity is clearly limited, a definite rise in the erythrocyte sedimentation rate to abnormal levels after stopping steroid therapy (especially if the dose has been reduced gradually) should be viewed with concern even in the absence of other signs of the disease.

This small study gives support from a different age-group to the conclusions reached by Illingworth and others (1957) on the benefits of adrenocortical steroid therapy in acute rheumatic fever as seen in children.

Until evidence on the state of the heart in later life becomes available, it would seem rational to recommend cortisone or an appropriate analogue

in the treatment of acute rheumatic fever in patients of all ages.

Summary

A controlled therapeutic trial of the value of cortisone in the treatment of acute rheumatic fever in young adults is described.

28 patients were randomly divided into two treatment groups. High doses of aspirin were used and therapy was identical except for the addition of cortisone to one group.

The duration of fever, joint involvement, and raised erythrocyte sedimentation rate was considerably reduced by giving cortisone in addition to aspirin.

I am grateful to Dr. J. H. Edwards for much constructive criticism, and to Drs. G. S. Wakefield and D. Beavan for their co-operation with some of the cases. I am also indebted to the Army Medical Authorities, whose interest made this work possible.

REFERENCES

- Bywaters, E. G. L. (1950). *Proc. roy. Soc. Med.*, **43**, 199.
- Coburn, A. F. (1943a). *U.S. Nav. med. Bull.*, **41**, 1324.
- (1943b). *Bull. Johns Hopk. Hosp.*, **73**, 435.
- Debré, R., Mozziconacci, P., and Caramanian, M. K. (1955). "La maladie de Bouillaud", ed. R. Debré and P. Soulié. Expansion Scientifique Française.
- Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Ann. rheum. Dis.*, **8**, 97.
- Houser, H. B., Clark, E. J., and Stolzer, B. L. (1954). *Amer. J. Med.*, **16**, 168.
- Illingworth, R. S., Burke, J., Doxiadis, S. A., Lorber, J., Philpott, M. G., and Stone, D. G. H. (1954). *Quart. J. Med.*, **23**, 177.
- , Lorber, J., Holt, K. S., and Rendle-Short, J. (1957). *Lancet*, **2**, 653.
- Jones, T. Duckett (1944). *J. Amer. med. Ass.*, **126**, 481.
- Levine, S. A., and Harvey, W. P. (1949). "Clinical Auscultation of the Heart." Saunders, Philadelphia and London.
- Manchester, R. C. (1946). *Arch. intern. Med.*, **78**, 170.
- Massell, B. F. (1954). *New Engl. J. Med.*, **251**, 183, 221, 263.
- Medical Research Council and American Heart Association (1955). *Brit. med. J.*, **1**, 555.
- Peterson, R. E., Black, R. L., and Bunim, J. J. (1958). *Arthr. and Rheum.*, **1**, 29.
- Robinson, W. D., Wolfson, W. Q., and Duff, I. F. (1951). "Proc. 2nd Clinical ACTH Conference, 1950", ed. J. R. Mote, vol. 2, p. 549.
- Roy, S. B., and Massell, B. F. (1956). *Circulation*, **14**, 44.
- Slater, J. D. H., and Rosenbaum, S. (1959). *Ann. rheum. Dis.*, **18**, 285.

Traitement combiné du rhumatisme articulaire aigu par l'aspirine et la cortisone**RÉSUMÉ**

On décrit un essai contrôlé de la cortisone dans le traitement du rhumatisme articulaire aigu chez les jeunes adultes.

Vingt-huit malades furent répartis au hasard entre deux groupes de traitement. On employa des doses fortes d'aspirine, les mêmes pour les deux groupes, mais un de ces groupes reçut de la cortisone en plus.

La durée de la fièvre, la sévérité de l'atteinte articulaire et la vitesse de sédimentation globulaire accusèrent une diminution considérable chez ceux qui reçurent de la cortisone en plus de l'aspirine.

Tratamiento combinado del reumatismo poliarticular agudo con aspirina y cortisona**SUMARIO**

Se describe una prueba controlada del valor de la cortisona en el tratamiento de la poliartritis articular aguda en adultos jóvenes.

28 enfermos fueron divididos al azar en dos grupos de tratamiento. Se emplearon altas dosis de aspirina, iguales en ambos grupos, pero uno de tales grupos recibió cortisona además de la aspirina.

La duración de la fiebre, afectación articular y velocidad de sedimentación eritrocitaria se redujeron considerablemente cuando se administró cortisona además de aspirina.