COMPARISON OF CORTISONE AND ASPIRIN IN TREATMENT OF JUVENILE RHEUMATOID ARTHRITIS

BY

B. M. ANSELL, M.R.C.P.

E. G. L. BYWATERS, F.R.C.P.

AND

I. C. ISDALE, M.R.C.P.

Special Unit for Juvenile Rheumatism, Canadian Red Cross Memorial Hospital, Taplow, Maidenhead, Berks

In 1954 and 1955 reports were published on "a comparison of cortisone and aspirin in the treatment of early cases of rheumatoid arthritis," by a Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, A.C.T.H., and other Therapeutic Measures in Chronic Rheumatic Diseases (*British Medical Journal*, 1954, **1**, 1223 ; 1955, **2**, 695). These concerned 61 adult patients aged between 17 and 59 years admitted to six centres in England and Scotland. At the same time the committee started a similar trial in juvenile rheumatoid arthritis (Still's disease), which was defined for this purpose as beginning before the age of 16.

Of the 25 patients taken into this trial, 22 came from this centre and 1 each from Edinburgh (Dr. Duthie), Sheffield (Dr. West), and Manchester (Professor Kellgren). They have been treated and followed along the same lines to one year from the start of treatment, at first in hospital and then as out-patients with cortisone (13 patients) or with aspirin (12 patients), their allocation to one or other treatment being determined by a random order list held centrally. The criteria for admission were slightly less exclusive than for the adult trial ; the disease had to be present for a period up to nine months, and three cases of less than three months' duration were included when the diagnosis was otherwise clear (one in the cortisone group and two in the aspirin group). The polyarthritis had to be of the rheumatoid type involving two or more joints (compared with four or more joints in the adult group). There was bilateral involvement of hands, knees, ankles, or wrists in all but two patients, one in each group. A sheep-cell agglutination was performed in all but one during the first year of observation, and, as is usual in this age group, gave a positive result in only two cases (one in each group). Joint biopsies confirmed the diagnosis in seven patients.

The two groups of patients were almost identical at the commencement of treatment (Table I).

TABLE I.—*Still's Disease: Comparability of Group Means at Start*

	Cortisone (13 Cases)	Aspirin (12 Cases)
Age (years)	9·3	9·4
Males	4	4
Duration (months)	4·7	5·5
Functional capacity (I–V)	3·4	3·1
Disease activity (0–2)	1·4	1·3
Joint tenderness (0–3)	1·3	1·3
Range joints (degrees)	98	104
Left grip (mm. Hg)	143 (12)	154
Walking time (seconds)	21 (7)	29 (7)
Peg time (seconds)	43 (7)	46 (5)
B.S.R. (mm./hour)	38	38
Haemoglobin (g.%)	11·8	11·4

Treatment

Therapy was given initially in 12-week courses separated by one week without treatment. It started in all but one of the cortisone group with a standard dosage for the first week (300, 200, 100, 100, 100, 100, and 100 mg. a day), following which the dosage was adjusted to the individual patient's requirements—between 25 and 200 mg. of cortisone a day. Only one of the 13 children started on a reduced dose ; he was an extremely wasted boy aged 2 years who was given 50 mg. a day during the first week, increased by the eighth week to 75 mg. a day.

The dosage of aspirin adopted was for the older children the same as in the adult trial, starting at 6 g. a day for the first week, 2 g. a day for the second week, and being individually adjusted thereafter at between 3 and 6 g. a day. Smaller children were given proportionately less, down to an initial starting dose of 1.3 g. at the age of 2. In both groups treatment was gradually withdrawn during

TABLE II

	Cortisone (13 Cases)						Aspirin (12 Cases)					
Weeks from start	0	1	8	12	13	1 yr.	0	1	8	12	13	1 yr.
Mean functional capacity	3·4	3·1	2·7	2·8	3·1	1·9	3·1	2·7	2·9	2·2	2·1	1·5
No. in grade I and II (the two highest grades)	1	2	5	4	4	11	2	6	8	8	8	11
Mean dis. activity	1·4	1·2	0·7	1·0	1·2	0·7	1·3	1·2	1·0	0·9	0·9	0·4
No. inactive	0	1	5	3	3	4	1	1	1	3	3	7
Joint tenderness	1·3	0·73	0·30	0·37	0·96	0·26 (12)	1·3	0·76 (11)	0·37	0·43	0·60	0·14
Tenderness in affected wrist	1·3 (10)	0·7 (10)	0·3 (10)	0·3 (10)	1·2 (10)	0·3 (10)	1·2 (5)	0·8 (4)	0 (5)	0·4 (5)	0·4 (5)	0·4 (5)
Range of joint movement	98	106	114	116	104	122 (12)	104	106	117	118	112	127
Left grip (mm. Hg)	143 (12)	164 (12)	192 (12)	167 (12)	146 (12)	205 (12)	154	183 (10)	166	189 (11)	176	227 (11)
Right grip (mm. Hg)	155 (12)	179 (12)	194 (12)	177 (12)	151 (12)	205 (12)	168	196 (10)	168	173 (11)	167	231 (11)
Walking time (seconds)	7 improved between 0 and 1 year. 3 not recorded				3 did not improve.		8 improved between 0 and 1 year. 1 not recorded				3 did not improve.	
B.S.R. (mm./hr.)	38	21	18	27	37	25	38	38	28	23	25	18 (11)
Haemoglobin (g.%)	11·8	12·1	12·7	12·9 (12)	11·6	13·2	11·4	10·9 (11)	12·2	12·1 (11)	11·9	12·5 (11)

Numbers in parentheses denote number of observations if less than total number of cases observed.

the 12th week. If symptoms recurred during the 13th week of observation the 12-week course was repeated. These 12-week courses were later replaced by continuous treatment, the aim being to employ the minimum dosage that would produce maximal functional efficiency and relief of symptoms without producing serious side-effects.

Assessments included the patient's functional capacity in five grades; the activity of the disease process (none, mild, or severe); the strength of grip (in mm. Hg); a timing test, using either pegs or walking; joint tenderness in four grades and range of movement. Sedimentation rates and haemoglobin levels were also measured. *X*-ray films were taken of the affected joints in all patients before treatment and at one year.

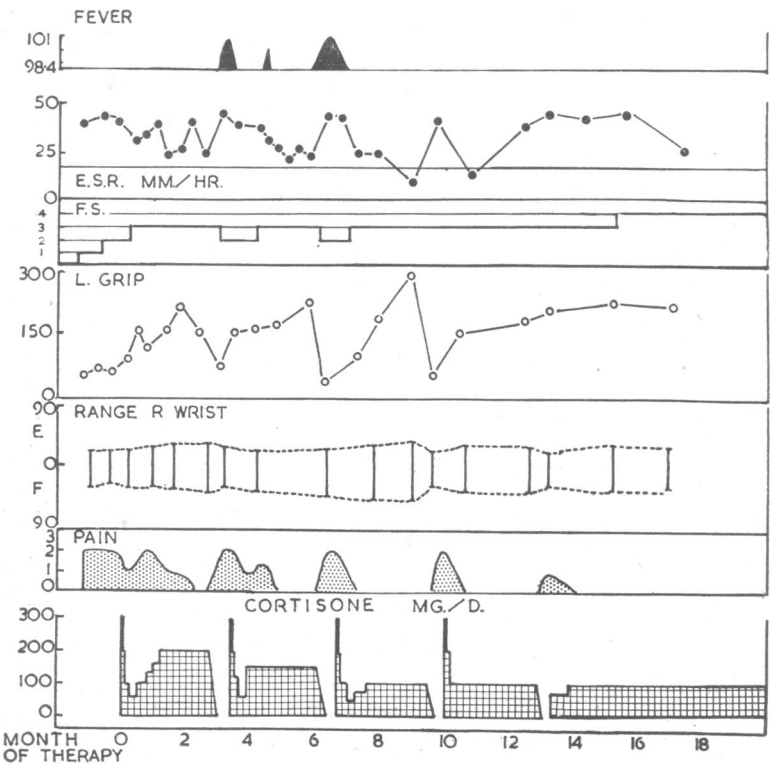

FIG. 1.—Data in case of a girl aged 14 with Still's disease treated with cortisone.

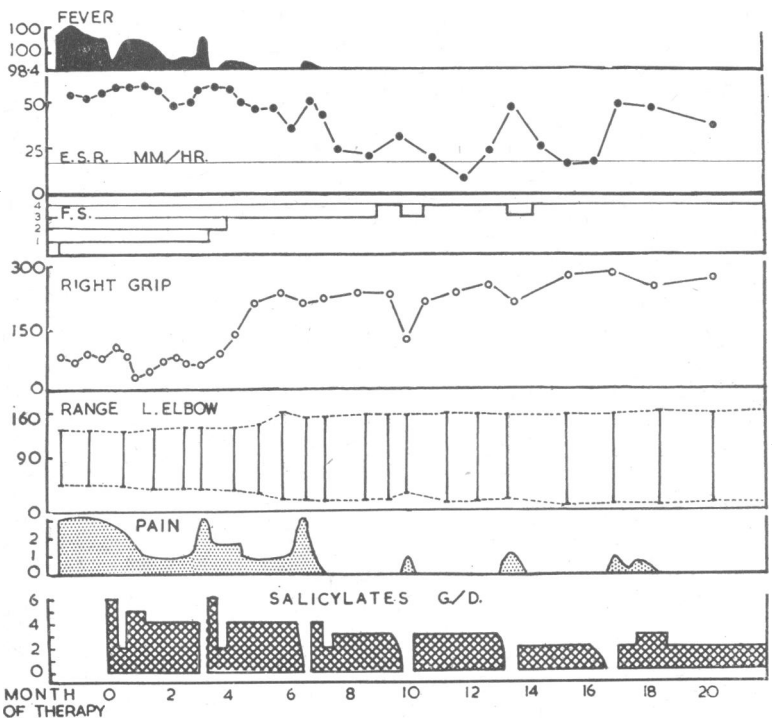

FIG. 2.—Data in case of a girl aged 15 with Still's disease treated with aspirin.

Results

Two patients in the cortisone group were withdrawn from treatment at the 14th and 22nd weeks respectively: in the first because there was a complete lack of response, and it was thought that aspirin should be used; and in the second because of dislocation of the hip and osteoporosis treated in an orthopaedic hospital. Both of these patients subsequently did well and the condition became inactive. After detailed consideration it was thought best to include the one-year observations (which were all available) on both these patients, although their exclusion would make little difference to the results.

Table II shows the mean results for each group. Each assessment is based on the full number of patients, except where indicated in parentheses. The time taken to insert pegs proved to be of no value, and the walking time (time for 22 yards) was measured only in those with lower-limb disability. Eight of these patients, however, were unable to walk at the beginning of their treatment. The times recorded, however, show the same pattern as the other criteria and the same lack of difference between the two treatment groups. The number improved as regards walking between 0 and 1 year is therefore given instead of actual times, and is seen to be similar in the two groups.

The results in general are very similar to those in the adult trial, except that in both treatment groups rather more children improved than adults. While the groups are small for any extensive statistical analysis, the tabulated means for the two groups show that there was little essential difference between the two groups over the course of the year in any of the assessments. In the cortisone group there was some slight worsening in most criteria at the 12th and more at the 13th week, when therapy had been tapered off or stopped, which was seen in only a few criteria in the aspirin group. In general, however, by one year both groups had improved equally in every respect. Two illustrative cases are depicted in Figs. 1 and 2.

The mean figure at one year is very slightly better in most respects in the aspirin group, with the exception of the haemoglobin, which is slightly higher in the cortisone group—a finding similar to that in the adult group trial. There is no significant difference, however, between these when tested.

X-ray films were inspected for each patient without knowledge of the treatment group assigned. Erosions were seen in 3 out of 13 on cortisone and in 2 out of 12 on aspirin before treatment was started (Table III). At one year the number with erosions had increased to 6 and 5 respectively. There is thus little difference in the *x*-ray progression between the two groups. In three cases there was an apparent healing of what had originally been interpreted as an erosion; this is illustrated in Fig. 3.

Complications in the cortisone group during the first year were few, apart from "mooning." One patient showed a blood pressure of 150/100 on one occasion at the 11th month, normal before and after. One

TABLE III.—*Juvenile Suppressive Trial: X-ray Analysis*

	No. with Erosions	
	Cortisone	Aspirin
Before treatment	3/13	2/12
Grades	3 Grade I	1 Grade I
		1 ,, II
One year	6/13	5/12
Grades	2 Grade I	2 Grade I
	2 ,, II	1 ,, II
	2 ,, III	2 ,, III
Two years	7/11*	5/11
Grades	3 Grade I	1 Grade I
	4 ,, III	4 ,, III

* 1 dead. 1 not yet reached 2-year mark.

patient from another centre was found to have a dislocated left hip at the fifth month and later fractured the right femur on falling out of bed at the 11th month. Another patient from a different centre had some inconstant glycosuria and derived no benefit from cortisone, being changed therefore by her physician to aspirin after the 13th week. There were three intercurrent infections—none serious (sinusitis, pharyngitis, and cystitis). However, after the end of the first year one patient was found to have a collapsed dorsal vertebra, and one month after this developed jaundice. This was due to severe haemolytic anaemia and agranulocytosis, from which the patient died three weeks later. The cause of this was not ascertained, despite full necropsy investigations.

Complications in this aspirin group were few—mainly intercurrent infections such as chicken-pox, appendicitis, influenza, and left upper lobe pneumonia, none of which could be imputed to the drug.

Cortisone dosage at the end of the first year before tapering off was maintained at between 50 and 100 mg. a day (mean 68.8 mg.) in the six patients on treatment. Of the remaining seven, one had been changed to aspirin at the 13th week, one had been taken off treatment because of dislocation of the hip at six months, and the rest did not need medication. Regular aspirin therapy was maintained also on only 6 of the 12 patients, at a dosage of 1.3–4 g. a day (mean 3.2 g.). The other six needed no regular medication.

Thus these results, although based on a small number of patients, give no reason to think that the effects of cortisone relative to those of aspirin in childhood are different from those reported in the adult group of rheumatoid arthritis patients.

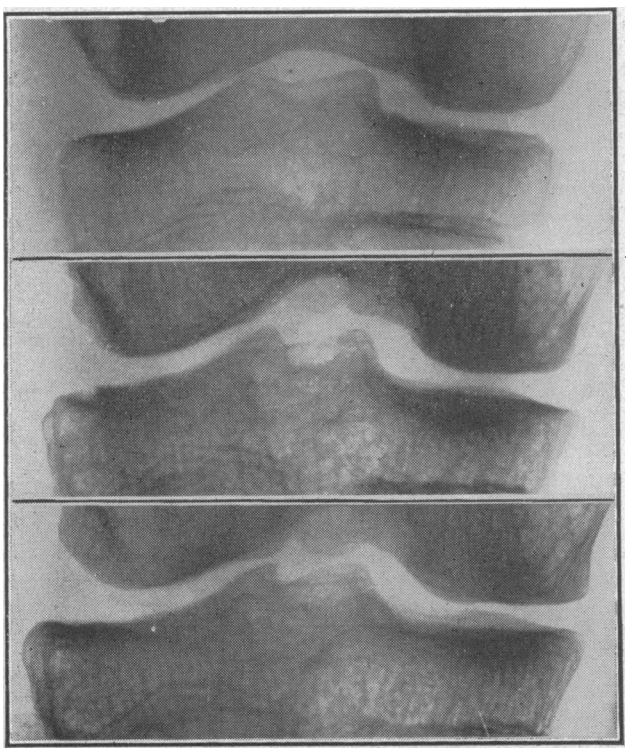

FIG. 3.—*X*-ray films showing healing of what had been thought to be an erosion. Top film was taken on January 13, 1953; the middle one on November 20, 1953; and the bottom one on December 29, 1954.

Summary

Twenty-five children with juvenile rheumatoid arthritis (Still's disease) defined as starting before the age of 16 years have been treated with cortisone (13 patients) and with aspirin (12 patients) in a controlled therapeutic trial similar to that started in adults by the Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials.

The polyarthritis in this juvenile group had to be of the rheumatoid type involving two or more joints and present for a period up to nine months. These patients were assessed at intervals up to the period of one year from the start of treatment, maintenance dosage at the end of the year being between 50 and 100 mg. cortisone (mean 69 mg.) in the six patients on treatment.

Assessment showed that results during the first 13 weeks and at one year were similar to those in the adult trial except that in both groups rather more children improved than did adults. Both treatment groups improved clinically and functionally to a similar extent. *X*-ray films showed an increase in the number with erosions—from three to six in the cortisone group and from two to five in the aspirin group. Complications which could be ascribed to the drugs were few.

The effects of cortisone relative to those of aspirin in childhood were no different from those reported in the adult group of rheumatoid arthritis patients.

The members of the Joint Committee are: Sir Henry Cohen (chairman), Dr. E. G. L. Bywaters, Dr. W. S. C. Copeman, Sir Charles Dodds, Dr. J. J. R. Duthie, Professor A. Bradford Hill, Mr. H. Osmond-Clarke, Professor F. T. G. Prunty, Dr. J. Reid, Dr. H. F. West, Professor J. H. Kellgren, and Mr. W. A. Sanderson (joint secretaries).

The subcommittee which made the original plans on which this trial is based consisted of: Professor J. H. Kellgren (chairman), Dr. E. G. L. Bywaters, Dr. W. S. C. Copeman, Dr. J. J. R. Duthie, Dr. H. F. West, Professor A. Bradford Hill, and Professor F. T. G. Prunty.

Thanks are due to Professor J. H. Kellgren, Dr. H. F. West, and Dr. J. J. R. Duthie, who permitted us to include their three patients, and to Dr. J. T. Boyd, who provided helpful guidance.

It is just a hundred years since William Henry Perkin (1838–1907) discovered mauve, an event which proved the starting-point of the synthetic dyestuffs industry. While still a student at the London University Chemical School Perkin fitted up a makeshift laboratory at his home in London, and in 1854 discovered amino-azonaphthalene, the first azo dye. During the Easter vacation of 1856, while attempting the synthesis of quinine, he made the experiment of oxidizing aniline with potassium dichromate and obtained a precipitate which proved to have ".fast" dyeing properties and which he named aniline purple. The name "mauve" was given to it in France. Its discovery led to a search for other synthetic dyes; more important for medicine, it rationalized the study of the action of chemical agents on living cells, and was later to influence the trend of Ehrlich's work. Salicylic acid, methylene blue, congo red, the sulphonamides and sulphones, antrycide, and proguanil are examples of substances of value to medicine which stem from Perkin's original discovery of mauve.