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GOLD THERAPY IN RHEUMATOID ARTHRITIS

REPORT OF A MULTI-CENTRE CONTROLLED TRIAL

ARRANGED BY

THE RESEARCH SUB-COMMITTEE OF THE EMPIRE RHEUMATISM COUNCIL*

(1) Introduction

In 1938 Sir Stanley Davidson, then the Chairman of the Scientific Advisory Committee of the Empire Rheumatism Council (E.R.C.), made plans for a "double-blind" controlled trial of gold salts in the treatment of rheumatoid arthritis. The outbreak of World War II prevented this multi-centre trial being put into execution, but Fraser (1945) carried out in one centre, Glasgow, the trial which should have been conducted in many centres throughout Great Britain. Some 3 years ago Sir Stanley again observed that the only thing we really knew about gold therapy after 30 years of using it was that it produced several toxic effects. He suggested that the multi-centre "double-blind" controlled trial previously contemplated and planned should be put into execution by the Research Sub-Committee of the E.R.C. This was done; the present report gives the results of that trial.

Gold salts, employed widely in the treatment of tuberculous disease after World War I (Møllgaard and others, 1924), were first given by Landé (1927) to fourteen arthritic patients and by Pick (1927) to two, the former reporting benefit, the latter none. It was, however, the papers published by Forestier (1929, 1932, 1934), in which he claimed beneficial results in a large series of cases of rheumatoid arthritis, that brought chrysotherapy to the attention of the medical profession in many parts of the world, including Great Britain. As a result, many reports on therapeutic trials with gold were published, including papers by Slot and Deville (1934), Buckley (1934), Hartfall and Garland (1935, 1936), Pemberton (1935), Bach (1936), Hartfall, Garland, and Goldie (1937), Copeman and Tegner (1937), and others following soon after. These workers claimed that considerable benefit resulted but that the incidence of toxic side-effects was higher than that reported by Forestier; thus Hartfall and others (1937) recorded 40 per cent. of treated cases as suffering from toxic reactions. These included rashes, stomatitis, intestinal colic, diarrhoea, vomiting, icterus, purpura, and one case of agranulocytosis. Renal damage, varying from albuminuria to severe toxic nephritis, and hypoplasia or complete aplasia of the bone marrow were found to be additional serious complications which might occur. Hartfall and others (1937) also noted that gold salts were of doubtful value when used in forms of arthritis other than rheumatoid arthritis.

Although these extensive trials had been carefully carried out, the failure to include a control series of

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* The following have served as Members of the Research Sub-Committee at some time during the period covered by this trial:

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The report was prepared jointly by Dr. F. Dudley Hart (Chairman at the initiation of the trial) and Dr. E. Lewis-Faning (Hon. Med. Statistician to the Empire Rheumatism Council), with the assistance of all members of the Research Sub-Committee. The *x*-ray films were assessed by Dr. Ifor Pennant Williams.

patients treated with placebos given by injection makes it difficult to assess the value of the conclusions reached. Between 1940 and 1958, the results of trials incorporating a control series of patients not treated with gold, were reported by Ellman, Lawrence, and Thorold (1940), Fraser (1945), Waine, Baker, and Mettier (1947), Adams and Cecil (1950), and Lockie, Norcross, and Riordan (1958). Of these studies the only one which conformed to modern control requirements, *i.e.* a "double-blind" trial in which neither the patient nor the physician knows which subjects receive gold and which placebos, was the trial reported by Fraser (1945), which had been carried out as part of a multicentre investigation planned in 1939 by the E.R.C.

Ellman and others (1940) divided their patients into three groups of thirty. The first group received 0·2 g. Solganol B weekly, the second group received 0·1 g. weekly, and the control group received sterile almond oil, all administered by intramuscular injection. Treatment was continued for 9 months in each case, with a rest period of 6 weeks half way through the course. In all three groups there were several patients whose illness had lasted only a few months. The method of allocating cases is not recorded and the physicians knew to which group each patient belonged, *i.e.* it was not a "double-blind" trial. When a patient was free of joint pain, with painless movements and a normal erythrocyte sedimentation rate, the disease was considered inactive. At the end of the 9-month period of therapy the disease was considered to be inactive in fourteen (47 per cent.) of the first group, in eight (27 per cent.) of the second group, and in one (3 per cent.) of the control group. Toxic effects occurred more commonly in the first (large dose) group (eight stomatitis, eight dermatitis, one agranulocytosis, and one jaundice), as compared with one stomatitis and five dermatitis in the second (small dose) group. Of 25 complications, 24 occurred when the erythrocyte sedimentation rate had become normal.

Fraser (1945) reported 110 cases with active disease of 2 to 5 years' duration. Patients were observed for only one year. Of 57 patients given a total of 1·0 g. Myocrisin by weekly intramuscular injections of 0·1 g., 24 were found to be "greatly improved" and twelve "moderately improved", compared with four and six respectively in the control group of 46 patients. "Great improvement", as assessed by the physician, occurred, therefore, in 42 per cent. of the treated as compared with 8 per cent. of the controls, though the patients' own assessments of their condition gave a figure of 56 per cent. greatly improved in the treated group as compared with 33 per cent. in the control group. Of nineteen "incapacitated" patients, seventeen were able to resume employment in the treated group, as compared with four of fourteen in the control group. Treatment was stopped because of toxic reactions in four of the treated patients and three of the controls.

Waine and others (1947) studied 58 patients with active rheumatoid arthritis treated with gold. All received a total dose of at least 0·5 g. gold (as sodium aurothiomalate or aurothiosulphate), the average dose being 1·6 g. of the metal. Injections were given at weekly, bi-weekly, or monthly intervals. A series of 62 consecutive patients with rheumatoid arthritis treated only by "supportive" therapy was used as a control group. Since they received no injection of a placebo the trial cannot be considered satisfactory by modern standards. The authors state that the rate of significant improvement was twice as high in the gold-treated cases as in the controls (57 per cent. as compared with 29 per cent.).

Adams and Cecil (1950) reported a series of 106 patients with rheumatoid arthritis treated by chrysotherapy during the first year of their illness, and compared it with a series of 83 cases given conventional therapy without injections. There was thus no satisfactory control series. Two preparations of gold were used—Solganol B oleosum (aurothioglucose) and Myocrisin (sodium aurothiomalate). The initial dose was 10 mg., rising to 50 mg. in the majority of cases, although some received 100 mg. at weekly intervals. The total amount of gold in a course was 1·0-1·5 g. "Remission" occurred in 66 per cent. of gold-treated cases one year after the institution of therapy, but only in 24·1 per cent. of the control group. When a remission occurred it did so on an average some 10 months later in the control group than in the gold-treated group (17·1 months and 7·1 months respectively). The average time from remission to later relapse, when it occurred, was the same in both groups—27 months. Their conclusions were that chrysotherapy increases the incidence and accelerates the appearance of remissions if administered during the first year of the disease.

Lockie and others (1958) compared 507 patients who received gold salts with 566 "control" patients who had never had chrysotherapy. The control group received no injections of a placebo. No details are given of the comparability of the two groups as regards age or duration of disease. The majority of patients received sodium aurothiomalate, but a few were given aurothioglucose. The gold salt was administered intramuscularly at weekly intervals, beginning with a dose of 10 mg.,

then 20 mg., then 40 mg., until a total of 500 mg. had been given. Thereafter the dose was determined by the clinical condition of the patient. The authors state that a minimal amount of 300 mg. of the gold preparation was required before the course of the disease was favourably influenced. The authors concluded that the use of gold salts affords patients a 20 per cent. better chance of complete recovery or of major improvement.

In all the reports discussed above, the authors claimed that the patients treated with gold received some benefit and that when a control series was incorporated in the trial, the treated cases showed greater improvement than the controls. In contrast, two other reports claim no difference between the treated and the control groups. Thus, Merliss, Axelrod, Finebury, and Melnik (1951) compared a control series of 44 subjects with rheumatoid arthritis, who received saline or serum injections, with 27 subjects who received a slow-acting gold preparation, aurothioglycolanilide (Lauron). No case was treated for less than 6 months. Dosage, duration of therapy, and frequency of injections varied in different cases. The degree of subjective improvement and the fall in the erythrocyte sedimentation rate was stated to be similar in the treated and control series.

Brown and Currie (1953) gave injections of gold, copper, saline, and arsenic at weekly intervals to 38, 60, 60, and 21 patients with rheumatoid arthritis, physiotherapy to 22, and aspirin by mouth to 19. The total dose of gold was 0·8-1·0 g. sodium aurothiomalate, divided over thirteen injections. Assessed at the end of the course of injections and at 3 and 12 months later, chrysotherapy did not emerge, by any mode of assessment, as a superior form of therapy.

Assessment of the duration of beneficial results after the completion of treatment with gold has been made by two groups of workers. Snorrason (1952) compared 295 gold-treated cases with 169 patients who had never received chrysotherapy. The preparation used was Sanocrysin, given intravenously in doses of 25 to 100 cg. at 5- to 7-day intervals. The number of injections varied from two to seven, depending on the reactions and general condition of the patients. The author claimed that after 4 years 72 per cent. of the gold-treated patients were "arrested" as compared with 23 per cent. of the control series, but relapses set in subsequently, so that after 10 years both groups showed an equal return of progressive disease. Ragan (1951) studied the same problem and came to a similar conclusion, namely, that gold salts did not permanently alter the natural course of the disease.

The editors of the comprehensive Rheumatism Review in the *Annals of Internal Medicine* (1959) state: "The value of gold therapy continues to have solid support from those clinicians most experienced in its use, but statistical proof of its efficacy is still lacking."

In view of the criticisms made of most of the trials discussed above, and because of the conflicting results obtained in those trials which were best controlled, the E.R.C. felt that there was a real need for making a carefully controlled investigation into the value of gold in rheumatoid arthritis.

(2) General Design of the Trial

For this "double blindfold" trial, 200 patients with rheumatoid arthritis were divided equally into two groups, balanced for sex, age, and duration of disease.

Patients in the Treated Group (alternatively termed the "gold" group) were given a total of 1 g. sodium aurothiomalate over a period of 20 weeks by intramuscular injection of 50 mg. at weekly intervals.

Patients in the Control Group were given a total dose of 0·01 mg. (1/100 mg.) sodium aurothiomalate over 20 weeks by injection of 0·5 μg. at weekly intervals. The controls therefore received 1/100,000 the quantity of gold that the treated group received.

Both groups were given simple supportive measures—namely, rest, splints, aspirin, and physiotherapy. All injections were given in the participating units.

The trial was designed to permit comparison of the two groups as regards:

(1) Clinical and functional assessments at 1, 3, 6, 12, 18, and 30 months after treatment was started.

(2) Radiological change over 18 and 30 months.

(3) The number of patients who had to be withdrawn from the trial, or for whom a change of treatment became essential.

(4) The incidence of complications.

This report presents the results during the 18 months after the start of the trial, *i.e.* to approximately 1 year after each patient had completed the course of treatment.

(3) Criteria for Admission to the Trial

Patients were eligible for admission if they:

(*a*) Were attending for out-patient treatment.

(*b*) Had had active rheumatoid arthritis for not less than 1 year and not more than 5 years.

(*c*) Were aged 20 to 64 years.

(*d*) Had bilateral involvement of hands and/or wrists (*i.e.* one hand and opposite wrist, both hands, and/or both wrists) in addition to the involvement of at least one other joint.

(*e*) Had an erythrocyte sedimentation rate (Westergren) of 20 mm. or more in 1 hour.

(*f*) Had not previously received gold therapy.

(*g*) Had not received chloroquine, phenylbutazone,* or systemic steroid therapy (corticotrophin, cortisone, prednisone, or prednisolone) in the 3 months preceding admission to the trial.

(4) Allocation of Patients to Treatment

Gold was supplied† for the treated group in 1-ml. ampoules containing 50 mg. sodium aurothiomalate, and for the control group in 1-ml. ampoules identical in appearance containing 0·5 μg. sodium aurothiomalate.

Stocks of the ampoules were held centrally by the statistician.

24 centres participated in the trial (see Appendix II), but, because of the stringent criteria for admission to the trial, the selection of eight to ten patients at any one centre was not easy and in the event the assembling of 200 patients occupied 18 months—from January, 1957, to May, 1958. To ensure that males and females should be represented in the same proportions in the gold and control groups, each centre was asked to submit the names of "even" numbers of each sex (2 males and 6 females; 4 males and 4 females, etc.).

When a suitable patient presented, particulars of the name, sex, age, and duration of disease were sent to the statistician, who then allocated the patient to one of the two groups according to a pre-arranged randomized system—ensuring that in the aggregate the treated and the control groups would be balanced in regard to sex, age, and duration of disease. He then despatched sufficient supplies for the total course of injections, labelled only with the patient's name. This system ensured that neither the patient nor the assessor knew to which of the two groups the patient had been allocated. That this ignorance was maintained is supported by the fact that it had been agreed that after the 18th-month assessment a second course of injections could be given at the discretion of the physician in charge; slightly more requests for a second course were made on behalf of the controls.

A proforma for recording the assessments (Appendix I) accompanied the drug, as well as a post-card for notifying the statistician of the exact dates on which treatment was started and the initial *x*-ray film was taken.

Because of one late cancellation, the treated group comprised only 99 instead of 100 patients.

In the event (see Appendix II) it proved impossible for every centre to obtain even numbers of each sex but, in the aggregate, the treated and control groups as initially comprised were similar as regards the three factors (sex, age, and duration of disease). Males comprised 29 per cent. of each group. The mean age of all 99 patients in the gold group was 48·7 years, and that of the 100 controls was 48·6 years. The disease was of short duration (1-3 years) in 66 and 68 per cent. respectively, and of longer duration (3-5 years) in 33 and 32 per cent. respectively.

(5) Withdrawals and Changes of Treatment

The criteria were regulated by the following instructions:

(*a*) The course of injections was to be continued for the whole period of 20 weeks, whether a remission occurred or not.

(*b*) The course should be discontinued only for serious toxic effects. Milder side-effects should be met by a reduction of the weekly dose and corresponding extension of the treatment period to not more than 25 weeks.

(*c*) Each patient's medical practitioner should be informed that the patient was being put on a course of gold and that a controlled investigation was being carried out. He was asked not to prescribe any other form of therapy coincidentally and was specifically requested to withhold corticosteroids and phenylbutazone.

(*d*) If deterioration occurred to such an extent as to necessitate other treatment—in particular with corticosteroids or phenylbutazone—assessments should be continued but the new treatment should be noted on the record form. Admissions to hospital and the reason for such should also be recorded.

* In order to speed up the selection of the last forty patients, the requirement that phenylbutazone should not have been previously received, was relaxed.

† Messrs. May and Baker Ltd.

(*e*) In emergencies, the physician in charge could be informed whether the patient was in the gold or the control group, and this was in fact done in three instances: because of dermatitis in one case, thrombocytopenic purpura in the second, and haematemesis attributed to thrombocytopenic purpura in the third. All these three patients were receiving gold salts.

(*f*) During the first 18 months of the trial, *i.e.* until one year after the end of completing the course of injections, no treatment other than as stated in Section 2, should be given.

(6) Assessment

Indices for comparing the progress of the two groups were derived from data recorded on the standard proforma (Appendix I) at each examination. For the initial assessment, two examinations were made on consecutive weeks: Week −1 and Week 0 (the latter being the date of the first injection).

Data recorded at the first assessment and at every subsequent examination comprised:

1. Functional capacity (physician's estimate) in five grades.
2. Subjective estimate of fitness by the patient in five grades.
3. Assessment of joints involved (42 joints were listed).
4. Strength of grip in each hand (mm. Hg).
5. Haemoglobin concentration (g. per cent.).
6. Erythrocyte sedimentation rate (mm./hr, Westergren).
7. W.B.C. (total and differential counts) per cu. mm.
8. Sheep cell agglutination test (S.C.A.T.) initially and at 18 and 30 months.
9. Complications present at, or occurring between, each assessment.
10. Number and nature of analgesic tablets taken daily (assessed retrospectively at each attendance).
11. Radiological examination of hands and wrists initially and at 18 and 30 months.

Details of the conventions laid down to secure uniformity of assessment are given in their respective sections.

(7) Withdrawals (Table I)

Strictly speaking, all patients who, for any reason, failed to complete the course of twenty weekly injections, or who could not be examined at the required 12- and 18-month points, or had to be given other forms of therapy, were withdrawals. These numbered 35, of whom 24 were on gold. As will appear later, it was not necessary to discard entirely the records of all of these patients from the analysis.

The reasons for withdrawal, in four broad groups, are shown in Table I.

Toxicity.—Toxic reactions in the *gold* group, involving fourteen withdrawals, included ten cases of dermatitis, four of which were severe enough to need admission to hospital.

One of these patients died from pneumonia complicating bronchitis in the fifteenth month. He was a 58-year-old male with rheumatoid disease of one year's duration, who developed a slight generalized pruritus in the third month. Gold therapy was discontinued after eleven injections, but the rash persisted and he was admitted to hospital for treatment of it 4 months later. Seven months later, that is, 11 months after discontinuing gold therapy, he developed pneumonia on pre-existing chronic bronchitis and died. Gold therapy undoubtedly caused his dermatitis, but in the opinion of his physician it was in no way responsible for his death.

TABLE I

REASONS FOR WITHDRAWAL IN THE TWO GROUPS

Group		Gold	Control
Toxicity (mainly rash)	Less than ten injections	3	2
	Ten to twenty injections	11*	2*
Deterioration needing Change of Treatment	Put on steroids at 9 months (gold)	1	—
	Put on steroids at 3 months (control)	—	1
	Changed at 14 to 16 months	2*	2*
Death at 13th Month: Carcinoma of Uterus		1*	0
Failure to Attend		6 (1*)	4 (2*)
	Total	24	11

* Included in the analysis at least to the 12th month (see text p. 100).

Of the other three patients with gold dermatitis of sufficient severity to warrant admission to hospital, one male aged 57 was detained for 17 days with a generalized eruption, which developed in the third month of treatment; one female aged 48 developed a rash in the eighth week, which cleared on dimercaprol after a 15-day stay in hospital; and one male aged 40 developed a gold dermatitis after thirteen injections. The erythrocyte sedimentation rates of these three cases at the time of the development of the rash were 50, 8, and 56.

Even in these "severe" cases the patient's condition was never critical, and in seventeen less severe cases of dermatitis the systemic effects were of minor importance.

The remaining four withdrawals because of toxic reactions were due respectively to oedema and malaise in the first month; stomatitis in the third month; corneal ulcer in the third month; and thrombocytopenic purpura, hepatitis, and pulmonary embolism just after the twelfth month.

All but three of the fourteen withdrawals received more than half of the total injections and are included in either the 18-month assessment (ten cases) or the 12-month assessment (eleven cases). The case of purpura and hepatitis noted above suffered a severe relapse of his rheumatoid arthritis, was admitted to hospital for a period of 5 months, and was finally withdrawn from the trial and given steroid therapy.

In the *control* group, two out of four cases of "toxicity" are included in the analysis: one with stomatitis and the other with a rash treated at 12 months with chloroquin and at 15 months with corticotrophin. The other two patients, who developed rashes and/or albuminuria, are excluded since they received only five injections.

Deterioration.—Of the three cases deteriorating on gold, one was given steroids at the ninth month and is excluded, while the other two were given phenylbutazone at the fourteenth month and triamcinolone at the sixteenth month respectively and are included.

In the *control* group, one case given steroids after ten injections is excluded, and two given steroids at 14 and 16 months respectively are included.

In brief, the withdrawals comprise two groups:

Patients	Gold-Treated	Controls
Group 1 (Complete withdrawals)	9	5
Group 2 (Partial withdrawals)	15	6
Total	24	11

Only those in Group 1 (the fourteen complete withdrawals) were entirely excluded from the analysis. Their exclusion reduced the number in the trial to 90 treated patients and 95 controls.

The statistical analysis which follows was carried out both including and excluding the withdrawals in Group 2. Every tabulation was done both ways—but for reasons of space only those in which these 21 withdrawals were included are published here. In no instance did the results differ materially when Group 2 withdrawals were excluded.

(8) Complications

Table II shows the incidence of complications in each group. These occurred in 21 patients in the gold group and twelve in the control group; if the cases withdrawn from the series are added, the figures are 35 : 16. A few patients had more than one complication. Most of these side-effects were skin reactions, 22 in the gold group and seven in the controls, all the latter being relatively mild.

TABLE II

COMPLICATIONS RECORDED IN THE TWO GROUPS

Group		Gold	Control
No. of Patients with Complications	(*a*) Not necessitating withdrawal	21	12
	(*b*) Necessitating withdrawal (see Table I—"Toxicity") ..	14	4
	Total	35	16
Complications	Dermatitis (severe)	4	0
	Dermatitis (less severe)	17	7
	Pneumonia, rash, death	1	0
	Purpura (hepatitis in one)	2	1
	Albuminuria	4	3
	Stomatitis or gingivitis	3	2
	Oedema and malaise	1	3
	Corneal ulcer or keratitis	2	0
	Fever	1	0
	Flare of arthritis	1	1
	Ulcer or haematemesis	2	0
	Dyspepsia	3	0

Apart from these skin reactions, toxic effects were infrequent in either group, though there were four cases of albuminuria in the gold group as compared with three in the control group. In the four patients on gold the albuminuria disappeared spontaneously within a month of its appearance; in one patient it appeared with two separate courses of gold, after the seventeenth injection in the first course, and after the fourteenth in the second. Renal function tests were normal.

In this study, therefore, complications were noted in about one-fifth of the gold-treated cases and one-eighth of the control series; if withdrawals are added, 35 per cent. of the gold-treated cases as compared with 16 per cent. of the controls suffered toxic side-effects. The only troublesome side-effects were present in the gold-treated cases. It is clear that such side-effects were significantly more frequent in the gold group, but they were seldom serious or severe.

(9) Comparison of Gold and Control Groups at Beginning of Trial (Tables III and IV)

Table III and Table IV (overleaf) show that the two groups were similar at the start of the trial in respect of all the factors examined. In the detailed analyses these tabulations were made in three sections (A, B, and C) in which the comparison between the treatment and control groups was based respectively on:

(A) All entrants (Gold 99, Controls 100).

(B) All entrants less Group 1 (complete) withdrawals (Gold 90, Controls 95)—see Section 7.

(C) Excluding both Group 1 and Group 2 withdrawals (Gold 75, Controls 89)—see Section 7.

The differences referred to throughout the report are considered to be statistically significant only if they attain the 0·05 probability level. (Any exceptions to this rule are specifically stated.) No

TABLE III

SIMILARITY OF THE GOLD-TREATED AND CONTROL GROUPS AT START OF TRIAL AFTER EXCLUDING GROUP 1 WITHDRAWALS‡

Factors Compared		Group	
		Gold	Control
No. of Patients		90	95
No of Males		26 (29%)	27 (28%)
Mean Age (yrs)		48·7±0·98	48·6±0·98
Duration of Symptoms (yrs)	1 to 3	59 (66%)	65 (68%)
	3 to 5	31 (34%)	30 (32%)
Type of Onset	Acute	29 (32%)	25 (26%)
	Non-acute	59	70
	Not known	2	—
Mean Number of Joints Involved	Total	17·3±0·92	19·2±0·95
	Girdle	0·9	0·8
	Intermediate	1·5	1·6
	Peripheral	14·8	16·8
Functional Capacity ("Mean")* (Physician's Assessment)		2·3	2·2
Fitness (Mean)—"Estimated by Patient" (per cent.)		59·5	60·2
Mean Strength of Grip	Right	144·5	144·8
	Left	148·9	144·8
Mean Haemoglobin Concentration (g. per cent.)		12·4±0·17	12·3±0·15
Mean Erythrocyte Sedimentation Rate (mm./hr, Westergren)		41·6±2·07	37·9±1·96
S.C.A.T.†	Negative −5 to −3	2	7
	Negative −2 to −1	19	13
	Positive 0 to +1	20	25
	Positive +2 to +3	22	22
	Positive +4 to +7	15	16
	Not known	12	12

* The use of the term "Mean" here and in Tables IV and V is unjustifiable statistically, but convenient as an index to summarize the distributions.

† Minimal positive titre at each centre = 0 (see also Results—S.C.A.T.).

‡ See Section 7.

TABLE IV

SIMILARITY OF THE TWO GROUPS AT START OF TRIAL

(GOLD 90; CONTROLS 95.—INITIAL FUNCTIONAL CAPACITY)

(*i*) Functional Capacity (Physician's estimate),† showing percentage in each grade

Group	Grade					Mean Grade*
	1 (best)	2	3	4	5	
Gold	9	53	34	3	—	2·3
Control	12	57	32	—	—	2·2

(*ii*) Functional Capacity (Patient's own estimate of fitness), showing percentage in each grade

Group	Grade (per cent. fit)					Mean Grade
	100	75	50	25	1	
Gold	3	42	44	10	—	59·5
Control	5	40	46	8	—	60·2

* See footnote to Table III.

† For definition of grades, see Section 11.

such differences could be demonstrated from the data in Tables III and IV.

Note on Grip Values

Because three types of sphygmomanometer—on which the possible *maximum* readings varied from 250 to 450—were distributed between the centres, the index "mean grip value" (Table III) is of doubtful validity. But when the distributions of grip value in broad categories in the two groups were compared and tested by χ^2 (all values of 250 and over forming a single category) again no real difference was apparent.

(10) Effect of Withdrawals on the Composition of the Groups

After a series of statistical tests it was not possible to deduce that the omission of Group 1 withdrawals alone, or Groups 1 and 2 withdrawals together, prejudiced the comparison of the two groups. The initial similarity of the groups when based on all the 199 entrants (A) still held good when Group 1 withdrawals were omitted (B), and also when both groups of withdrawals were omitted (C). Indeed, the values of each index were throughout so similar for A, B, and C that only the results of B are actually presented.

(11) Results

Comparison of Progress in the Two Treatment Groups

Functional Capacity (Table V)

(*i*) *Physician's Assessment.*—This was estimated objectively on the basis of examination and interrogation in five grades:

(1) Fully employed or employable in normal work and able to undertake normal physical recreations.

(2) Fully employed in special work after vocational training, or doing light or part-time work in normal occupation. Limitation in the amount of physical recreation that could be taken. Housewives able to do all but the heaviest housework.

(3) Not employed or unemployable. Very limited physical activity and little or no capacity for physical recreation. Housewives able to do light housework and/or limited shopping only. In-patients in hospital for treatment but up and about in the ward.

(4) Confined to hospital, house, or wheel-chair, but able to look after themselves in the essentials of life. In-patients in hospital for treatment sitting up but not getting about.

(5) Confined to bed and unable to look after themselves. In-patients on complete rest in bed.

Table V (opposite) shows the percentage with given grades of severity at each assessment in each group. The "mean"* grades (last column) indicate that both groups improved in function during the trial—the gold group perhaps more than the controls —a possibility now to be examined further.

At the start, about 10 per cent. of both groups were in Grade 1, *i.e.* the highest functional grade. Little change was apparent during the first month, but after 3 months, 22 per cent. of the gold group as against only 15 per cent. of the controls were in this top grade. By the end of the injection period

* Adopted as a convenient summarization of the distributions although statistically unjustifiable because the grades are not quantitative but qualitative.

TABLE V

FUNCTIONAL CAPACITY (PHYSICIAN'S ESTIMATE) AT PERIODICAL ASSESSMENTS
(GOLD 90; CONTROLS 95)
PERCENTAGE IN EACH GRADE AT EACH ASSESSMENT

Month of Assessment	Group	Grade					"Mean" Grade*
		1 = best	2	3	4	5	
0	Gold	9	53	34	3	—	2·3
	Control	12	57	32	—	—	2·2
1	Gold	9	62	26	3	—	2·2
	Control	14	54	33	—	—	2·2
3	Gold	22	57	20	1	—	2·0
	Control	15	64	20	1	—	2·1
6	Gold S	41	47	11	1	—	1·7
	Control	23	60	16	1	—	2·0
12	Gold S	40	44	12	1	2	1·8
	Control	23	55	22	—	—	2·0
18	Gold S	43	42	13	2	—	1·7
	Control	25	49	25	—	—	2·0

* See footnote to Table III.
S = Significant difference between the distribution of the two groups.

this advantage was increased, the proportions in Grade 1 being 41 per cent. of the gold group as compared with 23 per cent. of the controls, and the distributions were significantly different ($\chi^2 = 6{\cdot}2$, $P < {\cdot}05$). At the 12th month the position was the same, and at the 18th month there were 43 per cent. of the gold group in Grade 1 as compared with only 25 per cent. of the controls.

An almost identical picture was produced when Group 2 withdrawals (see Section 7) were omitted.

Re-grading.—Table VI shows that a larger percentage of patients on gold than controls were upgraded at every assessment. At the 12th and 18th month more controls were downgraded than upgraded, but this was true of the gold group only at the 12th month.

Comparing the 18th month with the initial assessments (last line of Table), 26 per cent. of the controls, but 56 per cent. on gold—more than double the proportion—finished in a better grade than they started. 9 per cent. of both groups finished in a lower grade, and 65 per cent. of the controls but only 35 per cent. on gold finished in the same grade.

The last two columns of Table VI take into account

TABLE VI

RE-GRADING OF FUNCTIONAL CAPACITY (PHYSICIAN'S ESTIMATE), SHOWING PERCENTAGE OF TOTAL RE-GRADED AT EACH ASSESSMENT
(GOLD 90; CONTROLS 95)

Month of Assessment	Group	Upgrading	Downgrading	No Change	Actual as Percentage of Possible Scores	
					Upgrading	Downgrading
1	Gold	12	3	84	9	1
	Control	4	3	93	4	1
3	Gold	24	1	74	20	0·4
	Control	14	2	84	12	0·7
6	Gold	28	1	71	29	0·4
	Control	15	1	84	14	0·7
12	Gold	11	15	74	15	6
	Control	6	12	82	8	4
18	Gold	9	6	84	13	2
	Control	6	9	85	7	3
Complete 18 months	Gold	56 S	9	35	51 S	4
	Control	26	9	65	25	4

S = Significant difference.

the *amount* of upgrading and downgrading which was *possible* for each group of patients—*i.e.* the amount of change which actually occurred is expressed as a percentage of that which was possible. To illustrate the method, consider the initial grading of the ninety patients on gold: eight were in Grade 1 and could not therefore be upgraded at all; 48 were in Grade 2 and could each have moved up one grade (48); 31 were in Grade 3 and could each have moved up two grades (62); three were in Grade 4 and could each have moved up three grades (9). Thus the total possible score for upgrading in the first month (or for the whole period) in the gold group was 48 + 62 + 9 = 119. The actual score at the end of the first month was 11, *i.e.* 9 per cent. of the possible score. Over the whole 18 months the actual score was 51 per cent. of the possible score; for the controls it was only 25 per cent.

The figures were not affected when the Group 2 withdrawals were omitted, the actual figures as a percentage of the possible scores for the whole period still being gold 51 per cent. and controls 25 per cent.

(*ii*) *Patient's Own Estimate of Fitness* (Table VII).—For the subjective estimate of function, the patient graded his own condition at each assessment as 100, 75, 50, 25, or 1 per cent. fit. The analysis of these results supports the objective assessments of the previous section. The mean grade rose in both groups during the period of injections and with advantage to the gold group. During the follow-up period there was some slight retrogression.

At the end of the injection period of 6 months, the percentage of patients describing themselves as 100 per cent. fit were 41 and 22 per cent. for the gold and control groups respectively, compared with 3 and 5 per cent. at the start of the trial. At the eighteenth month, 37 per cent. of the treated group and 23 per cent. of the controls described themselves as completely fit.

The omission of the withdrawals did not affect these results.

Re-grading.—Table VIII (opposite) shows that the percentage of patients who felt improved (upgraded) at each successive assessment after 1, 3, and 6 months was substantial in both groups, but after the injections ended the proportions upgraded were smaller and similar in both groups.

Expressing the actual score as a percentage of the possible score for upgrading, significant differences between the two groups occur at the third and sixth months, and over the 18 months as a whole.

63 per cent. of the gold group, but only 48 per cent. of the controls, assessed themselves as more fit at the end of the trial than at the start (last line of Table). The actual/possible score during the 18 months was 50 per cent. for the gold group and 38 per cent. for the controls.

Similar results were obtained when the withdrawals were omitted.

Joints Involved, Clinical Assessment

A joint was considered affected if two out of three features—swelling, tenderness, limitation of movement—were present. The 42 joints examined at each clinical assessment comprised proximal interphalangeal and metacarpophalangeal joints (20),

TABLE VII

SUBJECTIVE WELL-BEING (PATIENT'S OWN ESTIMATE), SHOWING PERCENTAGE IN EACH GRADE AT EACH ASSESSMENT
(GOLD 90; CONTROLS 95)

Month of Assessment	Group	Functional Capacity (per cent. "fit")					Mean Grade
		100	75	50	25	1	
0	Gold	3	42	44	10	—	59·5
	Control	5	40	46	8	—	60·2
1	Gold	8	40	41	9	2	60·2
	Control	5	44	42	8	—	61·2
3	Gold	20	51	26	3	—	70·6
	Control	11	54	33	2	1	67·0
6	Gold S	41	46	12	1	—	78·8
	Control	22	53	22	2	1	71·7
12	Gold S	35	47	11	4	2	74·7
	Control	18	56	24	2	—	71·1
18	Gold S	37	41	19	2	1	75·1
	Control	23	47	27	2	—	71·2

S = Significant difference between the distributions of the two groups.

TABLE VIII

RE-GRADING OF FUNCTIONAL CAPACITY (PATIENT'S OWN ESTIMATE), SHOWING PERCENTAGE OF TOTAL RE-GRADED AT EACH ASSESSMENT
(GOLD 90; CONTROLS 95)

Month of Assessment	Group	Upgrading	Downgrading	No Change	Actual as Percentage of Possible Scores	
					Upgrading	Downgrading
1	Gold Control	17 12	11 7	72 81	10 7	6 3
3	Gold Control	43 29	1 5	56 65	30 S 19	0·5 2
6	Gold Control	38 25	2 3	60 72	37 S 20	0·8 1
12	Gold Control	10 13	20 17	70 71	14 13	9 6
18	Gold Control	14 13	12 12	73 75	16 12	4 5
Complete 18 months	Gold S Control	63 48	6 10	31 42	50 S 38	3 4

S = Significant difference between the two groups.

metatarsophalangeal (10), wrists, elbows, shoulders, hips, knees, and ankles (12).

At the start of the trial the mean number of joints affected per patient was not significantly different in the two groups—17·3 per patient in the gold group and 19·2 per patient in the control group (Table IX). At the assessment after 18 months the mean for the gold group had been reduced by more than one half (to 8·0 joints), but that for the control group by only one third (to 12·5). The differences between the means of the two groups were significant at the 3rd month and at subsequent assessments.

The 42 joints were also considered in three groups:

(1) Peripheral—hands, wrists, feet, and ankles (34).
(2) Girdle—shoulders and hips (4).
(3) Intermediate—elbows and knees (4).

The mean number of peripheral and intermediate joints affected became significantly less in the gold group from the third month onwards; for the girdle joints the trends followed the same pattern but the differences did not reach significance level.

Newly Affected, Quiescent, and Re-activating Joints.—At each assessment, the number of active joints for any patient, and therefore the mean for a group of patients can also be calculated by adding to the number of joints active at the previous assessment, the number of newly affected and the number of re-activating joints, and deducting the number becoming quiescent.

The following conventional definitions were adopted:

A *newly affected* joint is one recorded as active for the first time during the survey period.
A joint becoming *quiescent* is one recorded as active at the previous but not at the current assessment.
A *re-activating* joint is one which was recorded at any previous assessment (during the trial) as becoming quiescent, but which at the current assessment was again active.
(There could be no re-activating joints at Month 1 because there was no earlier assessment at which they could be recorded as quiescent.)

These definitions of necessity ignore any compensatory changes occurring between assessments—

TABLE IX

MEAN NUMBER OF JOINTS INVOLVED PER PATIENT AT EACH ASSESSMENT
(GOLD 90; CONTROLS 95)

Group	Month of Assessment					
	0	1	3	6	12	18
	Mean ± S.E.	Mean ± S.E.	Mean ± S.E.	Mean ± S.E.	Mean ± S.E.	Mean ± S.E.
Gold Control	17·3 ± ·92 19·2 ± ·95	14·3 ± ·86 15·6 ± ·79	10·5 ± ·73 S 14·0 ± ·87	7·8 ± ·67 S 12·6 ± ·95	7·5 ± ·76 S 12·7 ± ·91	8·0 ± ·81 S 12·5 ± ·95

S = Significant difference between the two groups.

such as a joint recorded active at both the sixth and twelfth months which may have become quiescent and re-activated again in the interim.

Table X shows the sequence of events and is to be read as follows:

The mean number of joints affected per patient in the gold group at the start of the trial was 17·3. After one month, the mean number of newly affected joints recorded per patient was 2·0, whilst the mean number recorded as quiescent was 5·0 (17·3 + 2·0— 5·0 = 14·3, the mean number active at month 1). Similar calculations have been made for subsequent assessments.

At every assessment after the first month, the mean numbers of newly affected and reactivating joints were higher in the control group. The mean number of quiescent joints was less in the control group at 3 and 6 months.

The resulting trend in the average number of joints affected per patient is best appreciated by expressing the successive values as percentages of the initial value (last line of Table). In the gold group there was a steady decline from 100 per cent. (Month 0) to 43 per cent. (Month 12) and then a slight increase at Month 18 to 46 per cent. The greatest decline was between the 3rd and 6th month —the latter half of the period of injections. The

TABLE X

MEAN NUMBER OF NEWLY AFFECTED, QUIESCENT, AND REACTIVATING JOINTS PER PATIENT AT EACH ASSESSMENT

(GOLD 90; CONTROLS 95)

State of Joints		Month of Assessment											
		0		1		3		6		12		18	
		Gold	Control	Gold	Control	Gold	Control	Gold	Control	Gold	Control	Gold	Control
Newly Affected		—	—	2·0	1·5	0·9	1·1	0·5	0·8	0·9	1·3	0·7	0·8
Quiescent		—	—	5·0	5·1	5·8	3·9	4·4	3·9	3·1	3·5	2·4	2·9
Reactivating		—	—	—	—	1·1	1·2	1·2	1·7	1·9	2·3	2·2	2·4
*Joints Involved	Mean No. per Patient	17·3	19·2	14·3	15·6	10·5	14·0	7·8	12·6	7·5	12·7	8·0	12·5
	Percentage of Initial Number	100	100	83	81	61	75	44	66	43	66	46	65

* The mean values for "joints affected" which were computed independently for Table IX, can also be computed in this Table by successively adding to the value for any specific month, the mean of the newly affected and reactivating joints and deducting the quiescent joints: *e.g.* 14·3 (Month 1) + 0·9 + 1·1 − 5·8 = 10·5 at Month 3.

TABLE XI

NEWLY AFFECTED, QUIESCENT AND REACTIVATING JOINTS

(GOLD 90; CONTROLS 95)

ACTUAL AS PERCENTAGE OF POSSIBLE NUMBER

Joints Involved	Group	Month of Assessment					Total
		1	3	6	12	18	
Newly Affected	Gold	8·2 (2,224) S	3·9 (2,041) S	2·2 (1,962) S	4·1 (1,919) S	3·2 (1,764)	20·8 (2,113) S
	Control	6·4 (2,162)	5·2 (2,023)	4·2 (1,917)	6·6 (1,837)	4·4 (1,672)	24·8 (2,093)
Quiescent	Gold	28·2 (1,556)	39·6 (1,288) S	40·8 (947) S	39·7 (706) S	30·4 (672) S	
	Control	26·4 (1,828)	25·1 (1,483)	28·1 (1,329)	27·4 (1,198)	22·0 (1,204)	
Reactivating	Gold		23·0 (439)	12·9 (859) S	15·0 (1,143) S	15·4 (1,255) S	
	Control		23·2 (482)	22·4 (742)	22·7 (953)	20·8 (1,068)	
Became Quiescent and did not again Reactivate by 18th month	Gold	17·1 (1,556) S	24·1 (1,288) S	26·7 (947) S	27·9 (706) S		
	Control	12·6 (1,828)	11·1 (1,483)	16·0 (1,329)	18·9 (1,198)		

S = Significant difference between the two groups.

Figures in brackets indicate the "possible" numbers of joints on which the percentages are based. Thus, the possible number of:

Newly affected = Those not affected initially, less those which had become newly affected at earlier assessments.

Quiescent = Those active at the previous assessment.

Reactivating = Those which had become quiescent at earlier assessments.

decline in the controls was only to 66 per cent. (at Month 6) of the initial value and this level persisted until the end of the trial period.

Newly Affected Joints (Table XI).—A more refined index is obtained by expressing the actual number of newly affected joints as a percentage of the possible number—the possible number *at any assessment* being the summation (for all patients in the group) of the number of joints NOT initially affected, less the total which had become newly affected at earlier assessments.

Over the whole 18-month period (last column of Table) in the gold group 20·8 per cent. of joints not initially affected became active (440 out of a possible 2,113). In the control group 24·8 per cent. did so (519 out of a possible 2,093).

The difference between the groups varied at each assessment. At the end of the first month the index was 28 per cent. *higher* in the gold group than in the controls, but it was 25 per cent. lower at the third month. The gold group showed most advantage as regards newly involved joints at the sixth month—the end of the injection period—when the index was at a level only 52 per cent. of the control group.

After the first month the differences between the two groups were significant at every assessment except the last.

The figures for the three types of joints (Peripheral, Girdle and Intermediate) showed only slight deviations from the overall trend. For all three types, there was an excess of newly involved joints in the gold group at the end of the first month and this tendency was reversed in the third month; the main advantage to the gold group was at the 12th month for peripheral joints, and at the 18th month for girdle joints, but at the sixth month for the intermediate joints. The non-significant difference in the overall figures at the eighteenth month can be attributed to an excess of newly affected intermediate joints in the gold group at that assessment.

Joints which became Quiescent (Table XI).—Joints which were recorded as inactive at any specified assessment, but which were active at the preceding assessment, have been counted as becoming quiescent. Some became quiescent more than once during the trial. The average number per patient in the two treatment groups was shown in Table X.

To make allowance for possible differences in the number of joints which *could* become quiescent, the actual numbers were expressed as percentages of the possible numbers, *i.e.* the numbers active at the previous examination (Table XI).

The outstanding feature is the remarkable increase in this index at the third month when 39·6 per cent. of the possible number in the gold group compared with only 25·1 per cent. in the control group became quiescent. Furthermore, these levels were maintained at the sixth and twelfth months, but at the eighteenth month—one year after completion of therapy—a smaller percentage of the possible number became quiescent, particularly in the gold group (30·4 per cent.).

Similar trends and differences were apparent for each group of joints—peripheral, girdle, and intermediate—but for the last two types fewer significant differences could be demonstrated, probably because of the smaller number of joints involved.

Re-activating Joints (Table XI).—These comprise all joints which, having once been recorded during the trial as active, became quiescent and subsequently again active. Some joints became reactive more than once during the 18 months.

The average number per patient recorded as reactivating at each assessment was shown in Table X, but to allow for differences in the number of joints which *could* reactivate, the actual numbers were expressed as percentages of the possible numbers—*i.e.* the number of joints which were quiescent (as earlier defined) at the preceding assessment (Table XI).

At the end of the first month no joint *could* be recorded as reactivating. At the third month the percentage which did so was similar in each group (23 per cent. of those recorded as quiescent at the first month). But at the sixth month, only 12·9 per cent. in the gold group compared with 22·4 per cent. in the control group became reactivated, and this significant difference was materially unchanged at the twelfth and eighteenth months.

Peripheral joints showed a similar picture, but girdle joints showed no advantage to the gold group. Intermediate joints gave a statistically significant advantage at the sixth month, no difference at all at the twelfth month, and a non-significant advantage at the eighteenth month.

Quiescent Joints which did not Reactivate (Table XI).—The two groups have already been compared as regards the joints which became quiescent and those which again became active. In the final section of Table XI they are compared as regards the percentage of joints which became *and remained* quiescent, at least as far as the eighteenth month.

Although there was a small but significant advantage to the gold group in this respect even as early as the first month of therapy, the outstanding feature is the much higher proportion of joints in the

gold group which became inactive at the third, sixth, and twelfth months, and had not become active again by the eighteenth month (gold group 24 to 28 per cent. of the possible number, compared with 11 to 19 per cent. in the control group). Peripheral, girdle, and intermediate joints showed similar features.

Summary of Joints Affected.—The analysis of joints affected showed an advantage to the gold as compared with the control group, in that fewer joints became newly affected or reactivated, whilst more became quiescent and more stayed quiescent. These features were exhibited as early as the third month of the trial, and the number of active joints at the eighteenth month was reduced to 46 per cent. of the initial number in the gold group but to only 65 per cent. in the control group.

Throughout this section, the figures (of Tables IX to XI) were almost unchanged when the Group 2 withdrawals were omitted.

Strength of Grip (Table XII)

The strength of the grip of each hand was measured at each assessment in mm. Hg, with an initial bag pressure of 30 mm. maintained for 3 sec., the hand being held away from the body. The mean of two grips with each hand was recorded.

Special standard grip meters were supplied to each centre but (as noted in Section 9) three types of sphygmomanometer were used on which the maximum grip which could be recorded varied considerably. In the analysis, therefore, 250 mm. Hg was perforce taken as the maximum, although values above this (even up to 440) were actually recorded. As a result, the mean grip values in Table XII are minimal, but on the assumption that the three types of sphygmomanometer were similarly distributed between the gold and control groups, the means may be compared.

The Table shows that for each hand, the mean values (which were very similar for the gold and control groups up to the end of the first month of therapy) started to diverge at the third month, the gold group then showing a greater, but not a significantly greater, improvement. At the sixth and later assessments this difference became more pronounced, being outside the likelihood of a chance result. The mean grips of the two hands were very similar throughout, and when the withdrawal groups were omitted, they were materially unaltered.

From more detailed analysis (not shown in the Table) it was noted that the percentage of patients in the highest group (225+) increased over the 18 months in the gold group from 12 to 34 per cent. for the right hand and from 17 to 33 per cent. for the left hand, whereas the increases in the control group were only from 15 to 23 per cent. and from 13 to 22 per cent. for the right and left hands respectively.

Haemoglobin Concentration (Table XIII)

Both groups had approximately the same average concentration at the start of the trial (12·4 and 12·3 g. per cent. respectively). By the end of the course

TABLE XII

MEAN STRENGTH OF GRIP (mm. Hg)
(GOLD 90; CONTROLS 95)

Hand	Group	Month of Assessment					
		0	1	3	6	12	18
Right	Gold	144 ± 6	151 ± 6	167 ± 7	184 ± 6 S	177 ± 7	180 ± 7 S
	Control	145 ± 6	151 ± 7	155 ± 6	159 ± 6	162 ± 6	159 ± 7
Left	Gold	149 ± 6	147 ± 6	172 ± 6	183 ± 6 S	181 ± 6 S	180 ± 6 S
	Control	145 ± 6	147 ± 6	155 ± 6	157 ± 6	155 ± 7	155 ± 7

S = Significant difference between the two groups.

TABLE XIII

MEAN HAEMOGLOBIN CONCENTRATION (g. per cent. ± S.E.)
(GOLD 90; CONTROLS 95)

Group	Month of Assessment					
	0	1	3	6	12	18
Gold	12·4 ± 0·17	12·3 ± 0·14	12·5 ± 0·15	13·0 ± 0·13 S	13·1 ± 0·21 S	13·0 ± 0·11 S
Control	12·3 ± 0·15	12·4 ± 0·14	12·5 ± 0·14	12·6 ± 0·11	12·6 ± 0·19	12·4 ± 0·20

S = Significant difference between the two groups.

of injections these averages had been increased to 13 g. per cent. in the gold group and to 12·6 g. per cent. in the controls—a significant difference. By the end of the trial the control group level had fallen to 12·4 g. per cent., significantly lower than that in the gold group which remained at 13 g. per cent.

The same deductions could be drawn when the withdrawals were omitted.

Erythrocyte Sedimentation Rate (Table XIV)

At the beginning of the trial the mean erythrocyte sedimentation rate was slightly but not significantly higher in the gold group (42 as against 38 mm./hr). In both groups the level remained practically unchanged one month after the start of the trial, and at the third and sixth months it fell considerably in the gold group (to 21 mm./hr), but only slightly in the control group (to 33 mm./hr). At the eighteenth month it increased a little in the gold group (to 27 mm./hr); so that, whereas the third, sixth, and twelfth months showed real differences between the groups, at the eighteenth month the differences failed to reach significance (Table XIV). When the withdrawals were omitted, the results were barely altered.

White Cell Count (Table XV)

This investigation was not done consistently for every patient at each assessment, particularly as regards the differential count. The following comments were derived from the "total" counts of about 84 patients in the gold group, and 87 in the control group, and from polymorph counts in 66 and 70 patients respectively—not always the same patients at each assessment (Table XV).

The mean total W.B.C. in the gold group fell during the period of injections from an initial 8,200 to 7,000; rose at the twelfth month to 7,600, and fell again at the eighteenth month to 7,300. In the control group it fluctuated between 7,800 and 8,000 during the first 12 months but fell to 7,250 at the eighteenth month (Table XV).

Polymorphs varied between only 66 and 68 per cent. of the total count in both groups throughout the trial.

The evidence suggests that during the administration of gold the number of white cells was slightly reduced, and that this was equally true of polymorphs and lymphocytes.

It may be of interest to quote the number of patients in each group showing a total W.B.C. count

TABLE XIV

MEAN ERYTHROCYTE SEDIMENTATION RATE (mm./hr, Westergren)
(GOLD 90; CONTROLS 95)

Group	Month of Assessment					
	0	1	3	6	12	18
Gold	42 ± 2	43 ± 2	28 ± 2	21 ± 2 S	23 ± 2 S	27 ± 2
Control	38 ± 2	37 ± 2	36 ± 3 S	33 ± 2 S	34 ± 2 S	32 ± 2

S = Significant difference between the two groups.

TABLE XV

MEAN WHITE CELL COUNTS—TOTAL AND POLYMORPHS

White Cell Count	Group	Month of Assessment					
		0	1	3	6	12	18
Total	Gold	8,219 ± 409 (90)	7,352 ± 238 (82)	7,020 ± 243 (85)	7,006 ± 195 (81) S	7,575 ± 274 (80)	7,292 ± 241 (84)
	Control	7,812 ± 202 (95)	8,099 ± 280 S (89)	7,818 ± 266 S (88)	7,764 ± 234 S (87)	7,767 ± 239 (90)	7,247 ± 227 (91)
Polymorphs (per cent.)	Gold	67 ± 1 (77)	67 ± 1 (66)	67 ± 1 (68)	66 ± 1 (66)	68 ± 1 (65)	66 ± 1 (68)
	Control	67 ± 1 (81)	65 ± 1 (75)	66 ± 1 (70)	68 ± 1 (69)	66 ± 1 (72)	66 ± 1 (76)

Figures in brackets indicate the numbers of patients for whom W.B.C. readings were recorded, and on which the mean values are based.

S = Significant difference between the two groups.

below 5,000 in comparison with the number tested on each occasion:

Group	Month					
	0	1	3	6	12	18
Gold	3 (90)	7 (82)	13 (85)	10 (81)	8 (80)	9 (84)
Controls	2 (95)	4 (89)	5 (88)	6 (87)	5 (90)	8 (91)

Sheep-Cell Agglutination Test (S.C.A.T.)

This test is not standardized, and there were differences in technique at the various participating centres. As a result, what Centre X would record as 1/16, Centre Y might record as 1/32, and Centre Z as 1/128, etc. In order to aggregate the records of all Centres, the titre which each Centre regarded as the *minimal positive* was taken as 0, successive doubling dilutions above this as +1, +2, +3, etc., and titres below the minimum positive were recorded as −1, −2, −3, etc.

A positive reaction was not made a condition of entry to the trial, but the test was asked for at entry and "annually thereafter". It was hardly to be expected therefore that comprehensive data at every assessment would be available for analysis and, whilst the percentages in the various "dilution groups" are given in Table XVI, the large numbers *not* tested even at the twelfth and eighteenth months preclude any firm deductions from a comparison of these distributions.

78 of the 90 cases on gold and 83 of the 95 controls were tested at the outset, and the distributions were very similar (first line of Table XVI).

The proportions of positive to negative were 73 to 27 per cent. in the gold group, and 76 to 24 per cent. in the controls. At the eighteenth month the proportion positive had fallen in both groups to 64 and 60 per cent. respectively. But this apparent similarity masks an important change in the make-up of the positives of the two groups. In the gold group there was a decline in the proportion at high positive titres—from 19 per cent. initially, to nil (0 per cent.) at the twelfth month, with a slight rise to 6 per cent. at the eighteenth month, and an increase in the proportion with low positive titres. In the control group, on the other hand, there was a decrease in the proportion with low and moderate positive titres and an increase in the proportion with high positive titres from 19 to 26 per cent. As a result the distributions of the gold and control groups were significantly different at the eighteenth month.

These results must be accepted with some reserve because they are based at the eighteenth month on the results of tests on only 57 per cent. of the gold group and 65 per cent. of the controls.

Change in S.C.A.T. Titres.—Only 26 of the gold group and 36 of the controls had complete records at every assessment from which the time of change from positive to negative or *vice versa* could be established, and these were too few for useful examination.

But 56 patients on gold and 58 controls were tested initially and again at *either* the twelfth or the eighteenth month (or both). For these, the change

TABLE XVI

SHEEP-CELL AGGLUTINATION TEST

PERCENTAGE DISTRIBUTIONS*

Month of Assessment	Group	S.C.A.T.							No. of Patients Tested†	No. of Patients Not Tested
		Negative			Positive					
		−5 to −3	−2 to −1	Total	0 to +1	+2 to +3	+4 to +8	Total		
0	Gold	3	24	27	26	28	19	73	78	12
	Control	8	16	24	30	27	19	76	83	12
1	Gold	10	17	27	23	40	10	73	30	60
	Control	11	25	36	25	22	17	64	36	59
3	Gold	7	33	40	40	17	3	60	30	60
	Control	24	16	40	14	32	14	60	37	58
6	Gold	16	22	38	50	9	4	63	45	45
	Control	14	22	36	28	20	16	64	50	45
12	Gold	16	22	38	35	28	—	63	51	39
	Control	12	23	35	29	25	11	66	52	43
18	Gold	6	30	36	30	28	6	64	50	40
	Control	13	27	40	19	15	26	60	62	33

* The titre regarded as minimal positive at each centre = 0 (see also Section 11 Results: S.C.A.T.).
† Numbers on which the percentages are based.

in S.C.A.T. titres is analysed in Table XVII and can be summarized as follows:

Very Positive Initially (+4 to +8 dilutions above minimal positive value).

There were thirteen on gold and ten controls in this group. Titres in eleven of the thirteen on gold decreased, two of them sufficiently so as to become negative, but only two of the ten controls showed a decrease in titre and in neither did the test become negative.

Moderately Positive Initially (+2 to +3 dilutions above minimal positive value).

This group comprised eighteen on gold and sixteen controls. Titres of eleven of the former decreased, including three who became negative, but in only five of the controls did the titre decrease, and in five the titre rose.

Slightly Positive Initially (0 to +1 dilutions).

Five of eleven on gold became negative; three moved to a higher positive titre.

Seven of seventeen controls became negative; five moved to a higher positive titre.

Negative Initially

Of fourteen on gold, five changed to positive.
Of fifteen controls, six changed to positive.

Thus the evidence is that in the gold group the agglutination titres became less positive to a greater extent than in the control group. It is perhaps worth remarking that this contrasts with the results reported in rheumatoid arthritic patients treated with prednisolone, where there was "a general rise in agglutinating titres amongst those with positive tests" (Joint Committee M.R.C. and Nuffield Foundation, 1959).

Analgesic Tablets Taken (Table XVIII)

At each attendance the numbers of analgesic tablets taken per day together with the type of tablet was assessed retrospectively.

Aspirin or soluble aspirin, taken by the majority of patients, were considered as equivalent.

TABLE XVII

CHANGE IN S.C.A.T. TITRES
(GOLD 56; CONTROLS 58)

S.C.A.T. Dilution Groups* at Start	Group	12th or 18th Month Dilutions*					
		+4 to +8 (very positive)	+2 to +3 (moderately positive)	0 to +1 (slightly positive)	−1 to −2 (slightly negative)	−3 to −5 (moderately negative)	Total
+4 to +8	Gold	2	4	5	1	1	13
	Control	8	2	—	—	—	10
+2 to +3	Gold	—	7	8	3	—	18
	Control	5	6	2	2	1	16
0 to +1	Gold	—	3	3	5	—	11
	Control	2	3	5	6	1	17
−1 to −2	Gold	1	1	2	4	4	12
	Control	—	—	3	3	2	8
−3 to −5	Gold	—	—	1	—	1	2
	Control	—	—	3	1	3	7

* Minimal positive at each centre = 0.
Figures in boxes = No change
Figures to right of boxes = Change to lower dilutions
Figures to left of boxes = Change to higher dilutions

TABLE XVIII

MEAN NUMBER OF ANALGESIC TABLETS TAKEN (PER PATIENT)
(GOLD 90; CONTROLS 95)

Group	Month of Assessment					
	0	1	3	6	12	18
Gold	8·0 ± ·46	7·4 ± ·48	6·5 ± ·46	5·6 ± ·49	4·6 ± ·48 S	5·0 ± ·46 S
Control	7·7 ± ·46	7·5 ± ·44	7·3 ± ·44	7·0 ± ·48	7·1 ± ·49	7·4 ± ·53

S = Significant difference between the two groups.

Other types (below) were used very infrequently and for counting purposes were converted by the following convenient working rules:

Drug	Tablets of Aspirin
Bufferin, Antoin, Berex, Ce-K-sal ..	1
Co. Codeine, Codis, Veganin	1½
Paynocil	2
Paracetamol, Enseals of Sodium Salicylate	½

Table XVIII shows the mean number of tablets taken per patient at each assessment. Even by such an insensitive index as this, the gold group appeared to fare better. At the start both groups were taking an average of eight tablets per day. Whilst this level remained practically unchanged in the controls, it steadily declined in the gold group to five per day at the eighteenth month and was significantly lower than the level for the controls at the twelfth and eighteenth months.

Radiological Findings

X-ray films of the hands and wrists were available for all patients at entry to the trial, and again at the eighteenth month, except for a proportion of the withdrawals. For those who died or who were not assessed beyond 12 months, only initial films were available. The films were read by a single observer (Dr. Ifor Pennant Williams), who was unaware to which of the groups each patient belonged.

Comparison at the Start of the Trial (Table XIX).—From the initial films the following records were made for each person:

HANDS

(*i*) The number of joints initially affected in any way (20 joints examined per person).

(*ii*) The number of joints unassessable (because of advanced progression, films technically unsatisfactory, or amputation).

(*iii*) The number of joints which had already narrowed.

(*iv*) The number of erosions of any type.

WRISTS

(*v*) An assessment was made of the initial state of each wrist in four grades according to the following rules:

0 *Nil or Slight:* No definite cartilage loss, *i.e.* joint narrowing. Not more than two small erosions.

1 *Moderate:* Definite narrowing and/or a few (2-5) erosions.

2 *Marked:* Extensive narrowing and many erosions.

3 *Unassessable:* Progression too advanced; films technically unsatisfactory, etc.

From these data the indices given below were constructed and compared for the two groups:

TABLE XIX

RADIOLOGICAL COMPARISON OF THE TWO GROUPS AT START OF TRIAL

(*a*) Radiological signs (initially) in joints of the hands

Group	Gold	Control
No. of Patients	90	95
Joints Initially Affected in Any Way (Means—per person)	6·2 ± ·47	5·9 ± ·46
Narrowed Joints (Means—per person)	2·9 ± ·39	2·3 ± ·33
Erosions Present (Means—per person)	7·0 ± ·70	7·0 ± ·69

(*b*) Radiological assessment (initially) of wrists (in four grades)

Wrist	Left		Right		Both		
Grade	Gold (per cent.)	Control (per cent.)	Gold (per cent.)	Control (per cent.)	Grades	Gold (per cent.)	Control (per cent.)
Nil or Slight 0	47 S	62	44 S	68	0, 0	36 S	54
Moderate 1	31	28	34	23	0, 1 (or 1, 0)	19	21
Marked 2	19	9	18	9	1, 1	17	14
Unassessable 3	3	—	3	—	0, 2 (or 2, 0) 1, 2 (or 2, 1)	12	3
					0, 3; 1, 3; 2, 2; 3, 3	17	8

S = Significant difference between the distributions of the two groups.

(1) The mean number of joints of the hands affected in any way (per person).
(2) The number of joints unassessable.
(3) The mean number of joints of the hands which showed narrowing (per person).
(4) The mean number of erosions present (per person).
(5) A distribution of the wrists by severity grades.

In the gold group only six joints of the hands were unassessable initially (four patients with one joint each, and one with two). In the control group only three joints were unassessable (three patients with one each).

Judged by the number of joints affected in any way, or by the number of joints which were narrowed or by the number of erosions present, the two groups as initially constituted were similar at the start of the trial, although there was a slight but not significant excess of narrowed joints in the patients on gold (Table XIX).

These three indices were hardly affected by the exclusion of the withdrawals.

The two groups differed, however, with regard to radiological assessment of the wrists. This arose because a higher proportion of the control patients than of those on gold (68 as against 44 per cent.) were graded for the right wrist as "nil or only slightly affected". For the left wrist the comparable proportions were 62 and 47 per cent. In the gold group 21 per cent. of right wrists and 22 per cent. of left wrists showed marked changes or were so advanced as to be unassessable as compared with only 9 per cent. in the controls.

Taking both wrists together, the higher proportion of the controls with neither wrist more than slightly affected still persisted (controls 54 per cent., gold 36 per cent.). At the same time there were fewer controls with advanced signs in at least one wrist (controls 11 per cent., gold 29 per cent.).

These differences were still apparent when the withdrawals were omitted.

This difference in the radiological severity of rheumatoid arthritis in the wrists is the only factor in which the two groups were found to differ initially. This is not perhaps very important, but illustrates the difficulty of assembling two groups of patients which will not differ in any particular.

Change in Radiological Signs over 18 *Months.*—Progression was assessed by comparing the eighteenth month film with the initial film, and there was recorded on a standardized proforma for each joint of the hands (Table XX):

(*a*) if narrowing had occurred,
(*b*) the number of new erosions,
(*c*) the number of extensions of erosions seen in the initial film.

TABLE XX
RADIOLOGICAL ASSESSMENT OF PROGRESSION OF RHEUMATOID ARTHRITIS IN HANDS

Group			Gold (87)	Control (93)
(1) No. of Assessable Joints		Right	867	929
		Left	869	926
		Both	1,736	1,855
Narrowed Joints	(2) No. of assessable joints not initially narrowed	Right	745	827
		Left	738	816
		Both	1,483	1,643
	(3) No. of joints which subsequently narrowed	Right	61	65
		Left	58	65
		Both	119	130
	(4) Actual joints which narrowed as per cent. of possible number. (3) as per cent. of (2)	Right	8·2	7·9
		Left	7·9	8·0
		Both	8·0	7·9
New Erosions	(5) No. of new erosions which developed	Right	174	198
		Left	155	216
		Both	329	414
	(6) New erosions per assessable joint. (5) ÷ (1)	Right	0·20 ± ·03	0·21 ± ·03
		Left	0·18 ± ·03	0·23 ± ·03
		Both	0·19 ± ·03	0·22 ± ·03
Extensions of Old Erosions	(7) No. of extensions	Right	77	79
		Left	62	55
		Both	139	134
	(8) Extensions per assessable joint. (7) ÷ (1)	Right	·09 ± ·02	·09 ± ·01
		Left	·07 ± ·01	·06 ± ·01
		Both	·08 ± ·01	·07 ± ·01

Note Items 4, 6 and 8 were computed in two ways:
(*a*) by relating, *e.g.* the total new erosions for all patients to the total assessable joints;
(*b*) individually for each patient; and calculating the mean ± S.E. of the resulting series.
The two methods gave almost identical means.

TABLE XXI

RADIOLOGICAL ASSESSMENT OF "PROGRESSION" IN THE WRISTS

Wrist			Right		Left		Both		
Group			Gold (per cent.)	Control (per cent.)	Gold (per cent.)	Control (per cent.)	Grades*	Gold (per cent.)	Control (per cent.)
Progression Grade	Nil	0	29	32	31	25	0, 0	19	14
	Slight	1	40	36	38	35	0, 1	16	20
	Moderate	2	17	17	17	18	1, 1	23	18
	Marked	3	7	9	7	16	0, 2+	4	9
	Very Marked	4	7	7	7	5	1, 2+	18	14
							2+, 2+	20	25
	Total		100	101	100	99		100	100
No. of Wrists			84	92	84	92		83	92

* 0, 0 = Nil in both hands; 0, 1 = Nil in one, Slight in the other, etc.

Progression in each wrist was assessed in five grades (Table XXI) according to the following rules:

0 *Nil:* No change.

1 *Slight:* Small erosion and/or small area of cartilage loss, *i.e.* joint narrowing.

2 *Moderate:* 2-5 erosions and/or narrowing involving 2-3 carpal joints.

3 *Marked:* 4-8 erosions. Narrowing very obvious.

4 *Very marked:* Virtually every joint in the wrist showing narrowing and erosions.

Measurements of progression derived from this information were for each group:

(1) Number of joints narrowed as a percentage of the number which could narrow (Item 4 of Table XX).

(2) Mean number of new erosions per assessable joint (Item 6 of Table XX).

(3) Mean number of extensions of old erosions per assessable joint (Item 8 of Table XX).

(4) Percentage distribution of wrists in the five grades of progression (Table XXI).

Not one of these four indices indicated any difference between the treated and control groups as regards the extent of progression of the disease measured radiologically.

Some consideration was given to the view that the separate comparison of these four radiological signs did not give an adequate picture of the amount of progression in the two treatment groups, since combinations of the four assessments could vary greatly between patients. One patient might for example have three joints narrowed and one wrist showing marked progression. Another might have three joints with extensions of old erosions and one new erosion. Was the overall amount of progression equal in the two cases?

Somewhat diffidently, therefore, an arbitrary method of scoring was devised to combine these indices. The actual and possible scores for each sign are shown below:

Radiological Sign		Score (units per joint)	
		Actual	Possible
(*a*) Joints of Hands	Narrowing	1	1 (but nil if initially narrowed)
	New erosion	2	8 (based on a maximum of four new erosions actually recorded in any joint)
	Extension of old erosion	1	0*
	Total		9 = possible score per joint 90 = possible score for ten joints of each hand
(*b*) Wrists	Slight progression	2	
	Moderate progression	4	
	Marked progression	7	
	Very marked progression	9	9 = possible score for each wrist
	Total		198 = possible score for both hands and both wrists combined

* The possible score for extensions of old erosions ought to depend on the number of erosions initially present in each joint. In the absence of this information no possible score could be determined for extensions.

The overall actual and possible scores for each treatment group are shown in Table XXII, and also the actual score expressed as a percentage of the possible score. This index also showed no real difference between the gold and control groups as regards either hand or both hands combined, nor was there any difference when the wrist assessments were added to those of the hands.

The radiological comparison of the two groups diverges from the clinical assessments: first in that, at the outset, the two groups were similar clinically, but that the wrists of the gold group were more severely affected radiologically; secondly, in that the gold group showed advantage over the controls by every clinical index used, yet there was no difference radiologically.

It is perfectly reasonable to expect such divergences because the clinical and radiological assessments are measuring different aspects of the disease. At the start of the trial the clinical assessment of a specified joint indicated if it was the site of active arthritis at that point of time, whereas the radiological assessment was a measure of the progress of the disease from its onset to the start of the trial (a period varying from 1 to 5 years). It is worth noting that, although (radiologically) the patients in the gold group were the more severely affected as regards the wrists at the start of the trial, yet clinically they showed a greater degree of improvement.

Furthermore, progression of joint changes as judged radiologically does not parallel the clinical progress of arthritis in a joint. A comparison of the clinical and radiological assessments of just one joint (metacarpophalangeal 2) may be cited as evidence. In thirty patients (Gold 18, Controls 12), the features of active arthritis in this joint as assessed clinically disappeared by the sixth month and did not appear again, but the radiological assessment showed no change.

The radiological assessment of healing is difficult, but nevertheless two observers agreed that ten patients showed partial or general healing. Six of these were in the gold group and four were controls.

(12) Discussion

The initial assessment showed the two groups to be comparable and that withdrawals and changes of treatment failed to alter this comparability. The fact that more second courses of control injections were requested than of gold indicates that patient and physician remained genuinely ignorant of the material being used, *i.e.* that the trial remained truly "blind". On comparing the gold-treated and control groups, it is apparent that by all criteria, except radiological progression, the gold-treated group showed a definite and greater degree of improvement than the control group from the third month onwards, and this was maintained until the eighteenth month, that is, over one year after completion of the course of injections, although slightly reduced in degree after the twelfth month. A later assessment will be made after a further one year's follow-up, but to date the advantage clearly lies with the gold-treated group. Although part or all of this improvement may disappear within the next few years, one cannot ignore any form of therapy which gives temporary amelioration of symptoms in a progressive and painful disease, unless the hazards of therapy outweigh the advantages: such hardly seems to have been the case in this trial, though skin reactions were troublesome in a significant number of gold-treated patients and albuminuria was noted on four occasions. Steroid therapy and dimercaprol (B.A.L.), not available to the earlier workers with gold salts, can today effectively reduce the severity of such side-effects and lessen the dangers of this form of therapy.

TABLE XXII

RADIOLOGICAL ASSESSMENT OF "PROGRESSION"
(GOLD 87; CONTROLS 93)

ACTUAL AS PERCENTAGE OF POSSIBLE SCORES

Group		Gold			Control		
Hand		Right	Left	Both	Right	Left	Both
Hands Alone	Actual Score (total for all patients)	486	429	915	540	552	1,092
	Possible Score (total for all patients)	7,688	7,690	15,378	8,265	8,224	16,489
	Actual as per cent. of Possible Score*	6·32	5·58	5·95	6·53	6·71	6·62
Hands and Wrists Combined	Actual Score (total for all patients)	708	647	1,355	783	835	1,618
	Possible Score (total for all patients)	8,444	8,446	16,890	9,008	8,970	17,978
	Actual as per cent. of Possible Score*	8·38	7·66	8·02	8·69	9·31	9·00

* For tests of significance, this index was calculated for each patient and the means and standard errors computed from the resulting series. The means thus obtained differed only slightly from the overall values shown in the Table.

The results of this trial have confirmed the widely-held view that gold salts are of some value in the treatment of early, active cases of rheumatoid arthritis. Radiological improvement could hardly have been expected for, as related previously, radiological examination measures essentially the end result of pre-existing rheumatoid disease up to that point in time. On the other hand the extent of progression during the period of observation was the same in both groups. This suggests that the natural course of the disease had not been altered. If radiological examination 2 years after the end of treatment confirms this observation, it would appear that only symptomatic improvement may have been achieved at the expense of some toxic effects. The fact that the advantage to the treated group as regards subjective well-being had diminished slightly at the twelfth and eighteenth month suggests that the improvement achieved may be of a temporary nature. A similar trend evident in respect of other factors, particularly the erythrocyte sedimentation rate, would lend support to this view. The assessment at the thirtieth month may clarify this point. Until this information becomes available, it would be unwise to assume that the value of chrysotherapy has been established. It remains a fact, however, that 18 months after the start of the trial the group given gold has emerged superior to the control group in all respects except radiological progression. It remains to be seen how long this advantage lasts and whether it can be maintained by further courses of gold or by the prolonged use of small doses of gold at longer intervals.

(13) Summary and Conclusions

(1) 200 out-patients, aged 20 to 64, with active rheumatoid arthritis of 1 to 5 years' duration and previously untreated with gold salts, were divided into two groups. Both were given simple supportive measures, but no corticosteroids, phenylbutazone, or antimalarial drugs were allowed. The treatment group received twenty weekly injections of 50 mg. sodium aurothiomalate (Myocrisin), making a total dosage of 1 g.; the controls received twenty weekly injections of 0·5 μg. of the same substance, a total dose of 0·01 mg.

(2) Assessments were made at the start and at 1, 3, 6, 12, and 18 months in 24 centres in Great Britain. Cases were allocated centrally by a pre-arranged randomized system, the two groups being balanced for age, sex, and duration of disease. Patients and physicians remained ignorant of the material injected, ampoules being identified by the patient's name only.

(3) As assessed by functional capacity (judged by the physician), subjective fitness (judged by the patient), joint involvement, grip strength, number of analgesic tablets taken daily, sheep cell agglutination titre, haemoglobin and sedimentation rate, the gold-treated patients improved to a greater degree than the controls from the third month onwards, and this improvement was still apparent 12 months after the last injection was given, although it was reduced in degree. No such advantage was demonstrated by radiological examination.

(4) Toxic effects, mainly dermatitis, were more than twice as common in the gold-treated group as in the controls and they were also more severe. Dangerous toxic reactions were uncommon.

(5) Gold therapy undoubtedly improved the average clinical condition of the majority of patients in the gold-treated group over a period of 18 months. A further assessment in one year's time will show if this improvement is being maintained.

Our thanks are due to all participants in the various centres for their close co-operation, to the staff of the Department of Medical Statistics in the Welsh National School of Medicine for their invaluable assistance, particularly Miss Kathleen Davies for organizing the routine follow-up of the patients, and also to Messrs. May and Baker for generous supplies of Myocrisin (sodium aurothiomalate) used in both groups of cases throughout the trial.

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Crysothérapie de l'arthrite rhumatismale

Rapport sur des recherches contrôlées et effectuées dans de divers centres arrangées par le Sous-Comité des Recherches du *Empire Rheumatism Council*

RÉSUMÉ ET CONCLUSIONS

(1) Deux cents malades, d'un âge entre 20 et 64 ans, atteints d'arthrite rhumatismale évolutive, présente depuis 1 à 5 ans, non hospitalisés, sans traitement antérieur par des sels d'or, furent divisés en deux groupes. Les deux groupes reçurent un traitement symptomatique, mais on ne leur permit pas de corticostéroïdes, de phénylbutazone ni d'antipaludiques. Le groupe traité reçut des injections hebdomadaires, 20 en tout, de 50 mg. d'aurothiomalate de soude (Myocrisin), c'est-à-dire une quantité totale de 1 gramme; le groupe témoin reçut 20 injections hebdomadaires de 0,5 microgramme de la même substance, faisant une quantité totale de 0,01 mg.

(2) L'évaluation des résultats s'effectua au début du traitement et 1, 3, 6, 12 et 18 mois après, dans 24 centres médicaux de Grande Bretagne. Les malades furent assignés à leurs groupes respectifs par tirage au sort, après un ajustement pour faire les deux groupes correspondre en ce qui concerne l'âge, le sexe et la durée de la maladie. Autant les médecins que les malades ignoraient le moyen employé et les ampoules du médicament ne se distinguaient que par le nom du malade auquel elle étaient destinées.

(3) Selon l'évaluation de la capacité fonctionnelle (jugée par le médecin) de l'état subjectif (jugé par le malade), de l'implication articulaire, de la force de la poigne, du nombre des comprimés analgésiques pris par jour, du titre d'agglutination des globules de mouton, de l'hémoglobine et de la vitesse de sédimentation, l'amélioration des malades traités par des sels d'or fut plus prononcée que celle des témoins à partir du troisième mois, et cette amélioration fut encore apparente, bien que réduite, 12 mois après la dernière injection. Cet effet favorable ne se manifesta pas radiologiquement.

(4) Les manifestations toxiques, surtout la dermatite médicamenteuse, fut plus sevère et plus de deux fois plus fréquente chez le groupe traité par des sels d'or. Des réactions toxiques graves furent peu communes.

(5) Il n'est pas douteux que le traitement par des sels d'or produisit une amélioration de l'état clinique moyen pendant plus de 18 mois. On effectuera une autre évaluation un an plus tard pour voir si l'amélioration se maintient.

Crisoterapia en la artritis reumatoide

Informe sobre una investigación controlada en diversos centros y conducida por el Subcomité de Investigaciones del *Empire Rheumatism Council*

SUMARIO Y CONCLUSIONES

(1) Dos cientos enfermos con artritis reumatoide evolutiva presente durante uno a cinco años, no hospitalizados, de una edad comprendida entre 20 y 64 años, no tratados anteriormente con sales de oro, fueron divididos en dos grupos. Ambos grupos recibieron terapéutica sintomática, pero no se les permitieron ni los corticosteroides, ni la fenilbutazona ni los antipalúdicos. El grupo en él que se llevó a cabo el experimento recibió inyecciones semanales, en número de 20, de 50 mg. de aurotiomalato sódico (Myocrisin) con una dosis total de 1 g.; el grupo testigo recibió otras 20 inyecciones semanales de 0,5 microgramos de la misma substancia, con una dosis total de 0,01 mg.

(2) La valoración de los resultados se realizó a comenzar el tratamiento y a los 1, 3, 6, 12 y 18 meses en 24 centros médicos de Gran Bretaña. Los enfermos fueron asignados a sus grupos respectivos por sorteo, equilibrándose estos grupos en cuanto a edad, sexo y duración de la enfermedad. Tanto los médicos como los enfermos desconocian el fármaco usado y las ampollas administradas no presentaban otra indicación que el nombre del paciente a que iban destinadas.

(3) Evaluada la capacidad funcional (a través del juicio del médico), la sensación subjetiva respecto al estado general (juzgada por el enfermo), la afectación articular, la fuerza para asir, el número de comprimidos analgésicos tomados diariamente, el título de la aglutinación de los eritrocitos de carnero, la hemoglobina y la velocidad de sedimentación, los enfermos tratados con oro mejoraron más que los testigos, majoría que se hacia aparente del tercer mes en adelante y que todavía se apreciaba, aunque disminuida, 12 meses después de la última inyección. Este efecto beneficioso no se manifestó radiológicamente.

(4) Las manifestaciones tóxicas, sobre todo dermatitis, fueron más severas y más de dos veces más numerosas entre el grupo que recibió crisoterapia. Fueron poco corrientes las reacciones tóxicas graves.

(5) Indudablemente la crisoterapia produjo una media mejoría clínica que perduró por un período superior a 18 meses. Posteriores valoraciones que llevaremos a cabo en el plazo de un año nos mostrarán si esta mejoría se mantiene todavía.

See also Appendices I and II (overleaf)

APPENDIX I

STANDARD ASSESSMENT FORM

TREATMENT A or B (leave blank)				DATE OF ENTRY TO TRIAL		
Name of Patient	*Sex* M F	*Age*	*Duration of R.A.* .... mths	*Type of Onset* Acute Non-acute	*Centre*	*Responsible Investigator*

Time of Assessment				Weeks before Start of Trial		Months after Start of Trial											
				—1	0	1		3		6		12		18		30	
Date of Assessment																	
Functional Capacity (1-5) (See p. 102)																	
Patient's Own Estimation of Fitness (1, 25, 50, 75, 100 per cent. well) ..																	
Joints Involved (see note on p. 104)	Side		Right	Left	R. L.	R. L.	R. L.	R. L.	R. L.	R. L.	R. L.	R. L.	R. L.	R. L.	R. L.	R. L.	R. L.
	Hands	Proximal interphalangeal	1	1													
			2	2													
			3	3													
			4	4													
			5	5													
		Metacarpophalangeal	1	1													
			2	2													
			3	3													
			4	4													
			5	5													
	Wrists																
	Elbows																
	Shoulders																
	Hips																
	Knees																
	Ankles																
	Feet	Metatarsophalangeal	1	1													
			2	2													
			3	3													
			4	4													
			5	5													
	Total Joints Affected																

Appendix I (cont.)

Strength of Grip (See note on p. 108) ..														
Haemoglobin Concentration (g. %)														
Erythrocyte Sedimentation Rate (Westergren) (mm./hr)														
White Blood Count Total and Differential (per cu. mm.)														
S.C.A.T. (Give titre if positive) ..														
Complications in Period														
Analgesic Tablets (Total number and usual type taken per diem assessed retrospectively)														
Admission to Hospital (Reason and dates of admission and discharge)														
Withdrawal (Give reason and date) ..														

N.B.—Please make sure that X-ray films of hands and wrists are done at entry to trial and 18 and 30 months later.

APPENDIX II

Persons and Centres participating in the Trial

CENTRE	PHYSICIAN-IN-CHARGE AND OTHER ASSESSORS	PATIENTS
Aberdeen	Dr. Logie Bain, Dr. F. W. Wigzell	8
Bath	Dr. G. D. Kersley	7
Cardiff	Dr. Kenneth Lloyd	8
Droitwich	Dr. J. W. T. Patterson	1
Edinburgh	Dr. J. J. R. Duthie, Dr. J. Knox, Dr. J. M. Bremner	9
Glasgow	Dr. T. N. Fraser, Dr. S. W. Grant	12
Gloucester	Dr. G. R. Fearnley, Dr. W. R. Blatchley	8
Leeds	Prof. S. J. Hartfall, Dr. V. Wright, Dr. R. A. H. Morison, Dr. C. N. Watson	5
London		
Arthur Stanley Institute, Middlesex Hospital	Dr. O. Savage, Dr. J. H. Glyn, Dr. N. Cardoe, Dr. J. J. P. Lomas	12
Chase Farm Hospital, Enfield	Dr. R. M. Mason	7
Postgraduate Medical School, Hammersmith	Prof. E. G. L. Bywaters, Dr. B. Ansell, Dr. J. T. Scott	4
London Hospital	Dr. W. Tegner, Dr. R. M. Mason, Dr. R. R. P. Hayter, Dr. W. G. Wenley	12
Middlesex Hospital	Dr. A. C. Boyle, Dr. D. C. Beatty	4
Prince of Wales' General Hospital, Tottenham	Dr. J. H. Glyn	2
Royal Free Hospital	Dr. A. T. Richardson, Dr. E. A. Kaufmann, Dr. E. D. R. Campbell	9
West London Hospital Medical School	Dr. O. Savage, Dr. M. Joule	6
Westminster Hospital	Dr. F. Dudley Hart, Dr. D. M. Burley	11
Manchester		
Royal Infirmary	Prof. J. H. Kellgren, Dr. A. S. Dixon, Dr. A. J. Popert	10
Withington Hospital	Dr. H. Stuart Barber	9
Newcastle	Dr. Malcolm Thompson, Dr. R. K. McCuish	16
Reading	Dr. R. I. Meanock	15
Sheffield	Dr. G. R. Newns	6
Stoke Mandeville	Dr. A. G. S. Hill, Dr. R. E. H. Partridge, Dr. J. N. McCormick	8
Sunderland	Dr. I. C. Cowan	10
Total No. of Patients		199