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GOLD THERAPY IN RHEUMATOID ARTHRITIS

FINAL REPORT OF A MULTICENTRE CONTROLLED TRIAL*

ARRANGED BY

THE RESEARCH SUB-COMMITTEE OF THE EMPIRE RHEUMATISM COUNCIL†

Introduction

In the earlier report of the first 18 months of this trial (Empire Rheumatism Council, 1960), it was shown that, by all criteria except radiological, patients with active rheumatoid arthritis treated over a period of 5 months with a total dose of 1 g. sodium aurothiomalate (Myocrysin) fared better than those treated with a total dose of 0·01 mg. of the same substance given in a "double blindfold" trial over the same period. These patients have now been followed for a further year, *i.e.* for 2 full years since the last injection was given and for 30 months since the start of the trial. What follows is the final report on this multicentre double-blind controlled trial of the effects of gold in rheumatoid arthritis.

* Presented at a meeting of the Heberden Society on December 2, 1961.

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

Ex Officio

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Dr. O. Savage (*Hon. Med. Secretary*)
Dr. R. M. Mason (*Deputy Hon. Med. Secretary*)
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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.

Losses to the Trial (Table I, overleaf)

In the previous report—based on the findings during the first 18 months—nine out of 99 patients treated with gold and five out of 100 controls‡ were excluded because they had received less than half the injections, or had changed treatment because of deterioration, or had failed to attend for assessment (Table I). The analysis at Month 18 was therefore based on ninety patients in the gold-treated series and 95 controls. No interim assessments were made between the 18th and 30th months, and at the latter assessment a further thirteen from each series had been lost to the trial. The reasons for the losses in both periods are shown in Table I.

Since the purpose of this report is to compare the gold and control series 30 months from entry to the trial, *i.e.* 2 years after *completing* the course of treatment, this analysis is based on a follow-up of 77 patients in the gold series and 82 controls.

Second Courses of Therapy

Initially it was agreed that after Month 18 assessment a second course of injections of the same type could be given at the discretion of the physician in charge. Such second courses were requested for sixteen of the gold series and twenty of the controls.

Two of the controls given second courses were subsequently withdrawn: one developed cancer of the cervix; and the other developed albuminuria after six injections of the second course, deteriorated rapidly, and becoming progressively crippled was started on prednisolone.

A comparison of the subsequent progress of those who did and did not receive a second course is made in a later section of this report.

‡ Although the term "controls" is used for the series of patients receiving the smaller dose of gold, this does not imply that the changes and complications occurring therein can with certainty be considered simply as part of the natural history of rheumatoid arthritis.

TABLE I

LOSSES FROM THE FOLLOW-UP OF PATIENTS IN THE TRIAL

Exclusions		Series	
		Gold	Control
(1) From 18-month Analysis	Toxicity and less than half the injections	3	2
	Deterioration involving change of treatment	1	1
	Failed to attend for assessment at Months 12 and 18	5	2
	Total	9	5
(2) Additional from 30-month Analysis	Deaths (Gold at 12* and 15* mths; Control at 29 mths)	2	1
	Concurrent disease (cancer of cervix)	—	1
	Deterioration involving change of treatment	10	6
	Failed to attend for assessment at Month 30	1	5
	Total	13	13
Total Losses up to Month 30		22	18
No. available for analysis at Month 30		77	82

* Included to 12 months in the previous (18-month) report; in neither case was gold therapy considered responsible for death.

TOXICITY (Table II)

The incidence of toxic effects can be measured as:

(*i*) The number of persons who experienced at least one toxic reaction, expressed as a percentage of the number at risk,

or

(*ii*) The number of toxic reactions recorded per patient at risk.

(*i*) *Persons Experiencing at least One Toxic Reaction.*—Arising out of the first course of therapy, toxic reactions were recorded in 35 per cent. of the 99 patients on gold and in 16 per cent. of the 100 controls.

From the second course of therapy given after 18 months in the trial, three (19 per cent.) of the sixteen receiving gold and one (5 per cent.) of the twenty controls had side-effects (Table II). Two of those on gold had also experienced toxicity in the first course. (Further details of these are given on p. 317, para. 1.)

All these reactions occurred during the period of injections, with the one exception of a patient on gold who developed purpura and hepatitis 6 months after completing the first course, suffered a severe relapse of the rheumatoid arthritis, and was admitted to hospital for a period of 5 months.

Because of these reactions, fourteen of the 35 gold-treated reactors and four of the sixteen control reactors failed to complete the first course of injections. Only one patient failed to complete the second course—a

TABLE II

INCIDENCE OF TOXIC REACTIONS

Course		First		Second	
Series		Gold	Control	Gold	Control
Total Entrants		99	100	16	20
(*i*) Toxic Reactions	At least one toxic reaction	35(35%)	16(16%)	3(19%)	1(5%)
	No reaction	64	84	13	19
(*ii*) Complications Recorded	Dermatitis (hospitalized)	4	—	—	—
	Dermatitis (less severe)	17	7	1	—
	Purpura (hepatitis in one patient)	2	1	—	—
	Albuminuria	4	3	1	—
	Amyloidosis	—	—	—	1
	Stomatitis or gingivitis	3	2	1	—
	Oedema and malaise	1	3	—	—
	Corneal ulcer or keratitis	2	—	—	—
	Fever	1	—	—	—
	Flare of arthritis	1	1	—	—
	Ulcer or haematemesis	2	—	—	—
	Dyspepsia	3	—	—	—
	Total Complications	40	17	3	1
Complications per Patient		0·40	0·17	0·19	0·05

control patient who developed signs of amyloidosis after six injections.

(*ii*) *Mean Number of Toxic Reactions per Patient.*—During the initial course of injections, five patients on gold and one of the controls each reported two complications, so that there were forty complications in all for the gold series and seventeen for the control series, *i.e.* the mean number of complications per patient was 0·40 and 0·17 for the gold and control series respectively. Comparable rates for the second course were 0·19 and 0·05, the lower levels for the second course being due, at least in part, to the fact that only six of the 35 on gold and only three of the sixteen controls who had reactions on the first course of therapy were amongst those for whom a second course was requested.

Types of Reaction

The toxic reactions recorded on the first course (gold 40, control 17) are listed in Table II. Dermatitis was the most frequent type of reaction (gold 21, control 7) and in four of those on gold was severe enough to require admission to hospital.*

Apart from these skin reactions, toxic effects were infrequent (gold 19, control 10). They included four cases of albuminuria in the gold series as compared with three in the control series.* The fact that more cases of oedema were reported in the controls than in the gold series (gold 1, control 3) accords with the results in another trial (Meanock and Lewis-Faning, 1961) and reminds us again that this condition is frequently a feature of the disease rather than a side-effect of the treatment.

There were fourteen in the gold series and four controls in whom injections were stopped because of toxic reactions. The former comprised ten cases of dermatitis (including the four admitted to hospital) and one case each of stomatitis, oedema, corneal ulcer, and buccal ulcer. Three of the four control reactors who did not complete the injections had dermatitis, and one had albuminuria.

Three patients developed toxic reactions during or after the second course of gold. One, who was free from reaction in the first course, developed dermatitis 2 weeks after the final injection of the second course. The second, who had had albuminuria in the first course, experienced stomatitis in the second, and injections were stopped for 3 weeks. The third had albuminuria during both courses—after the seventeenth injection in the first and after the fourteenth in the second.

In the control series only one reaction in the second course was reported—this was the patient referred to above (p. 317) who developed signs of amyloidosis after six injections.

Sensory peripheral neuropathy confined to the lower extremities was reported in only two patients, both at Month 30 (gold 1, control 1).

In this study, therefore, 35 per cent. of the gold-treated cases and 16 per cent. of the controls developed toxic side-effects during the first course of therapy. These led to withdrawal from therapy in fourteen of the gold-treated cases, four of whom needed admission to hospital, and in four of the controls. During the second course, 19 per cent. of those receiving gold (3 of 16) and 5 per cent. of the controls (1 of 20) suffered toxic effects, injections being stopped only in the one control case. Side-effects were clearly more frequent in the gold series, but were seldom serious or severe.

The relation between toxicity and therapeutic effect is examined in a subsequent report (p. 335).

Comparison of Gold and Control Series at the Start of the Trial

Tables III and IV (overleaf) show that the two series were similar at the start of the trial in respect of all factors examined. This was true for all entrants (gold 99, control 100), for those followed to 18 months (gold 90, control 95), and for the somewhat smaller group followed to 30 months (gold 77, control 82). The mean levels for both groups were little affected by the interim losses.

A comprehensive series of statistical tests demonstrated that neither the losses from the trial up to 18 months, nor subsequent losses up to 30 months prejudiced the *initial* similarity of the two series. The omission of eleven patients on gold and seven controls whose treatment was changed because of deterioration may, however, have introduced some bias in the subsequent results of the follow-up, though any such bias was present about equally in both series. In the earlier analysis (to 18 months) group assessments, both including and excluding cases in which treatment was changed, did not differ materially.

Differences referred to throughout the report are considered to be statistically significant only if they attain the 0·05 probability level. No such differences could be demonstrated from the data in Tables III and IV.

* See previous report for details.

TABLE III

SIMILARITY OF THE GOLD-TREATED AND CONTROL SERIES AT START OF TRIAL

Factors Compared		Excluding Withdrawals up to 18 Months		Excluding all Withdrawals up to 30 Months	
		Gold	Control	Gold	Control
No. of Patients		90	95	77	82
No. of Males		26(29%)	27(28%)	22(29%)	23(28%)
Age (yrs) (Mean ± S.E.)		48·7±0·98	48·6±0·98	48·5±1·08	48·4±1·07
Duration of Symptoms (yrs)	1 to 3	59(66%)	65(68%)	49(64%)	56(68%)
	3 to 5	31(34%)	30(32%)	28(36%)	26(32%)
Type of Onset	Acute	29(32%)	25(26%)	27(35%)	20(24%)
	Non-Acute	59	70	49	62
	Not Known	2	—	1	—
Number of Joints Involved (Mean ± S.E.)		17·3±0·92	19·2±0·95	17·6±1·00	18·2±0·98
Functional Capacity ("Mean")*—Physician's Assessment (Grade)		2·3	2·2	2·3	2·2
Fitness ("Mean")—Estimated by Patient (per cent.)		59·5	60·2	60·1	60·7
Strength of Grip (Mean ± S.E.)	Right	144·5	144·8	148·1	146·0
	Left	148·9	144·8	149·7	145·3
Haemoglobin Concentration (g. per cent.) (Mean ± S.E.)		12·4±0·17	12·3±0·15	12·3±0·19	12·3±0·17
Erythrocyte Sedimentation Rate (mm./hr Westergren) (Mean ± S.E.)		41·6±2·07	37·9±1·96	42·3±2·35	38·8±2·32
S.C.A.T.† (per cent.)	Negative −5 to −3	2	7	3	7
	Negative −2 to −1	21	14	23	15
	Positive 0 to +1	22	26	19	23
	Positive +2 to +3	24	23	25	24
	Positive +4 to +7	17	17	16	20
	Not Known	13	13	14	11

* 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 under Results—S.C.A.T.).

TABLE IV

SIMILARITY OF THE TWO SERIES AT START OF TRIAL

(A) Functional Capacity (Physician's Estimate),† showing percentage in each grade

Series		Grade					
		1 (Best)	2	3	4	5	Mean*
(*a*) Gold 90; Controls 95 (*i.e.* excluding withdrawals up to 18 months)	Gold	9	53	34	3	—	2·3
	Control	12	57	32	—	—	2·2
(*b*) Gold 77; Controls 82 (*i.e.* excluding withdrawals up to 30 months)	Gold	10	52	34	4	—	2·3
	Control	11	60	29	—	—	2·2

† For definition of grades see previous report.
* See footnote to Table III for use of term "Mean".

(B) Percentage Fitness (Patient's own Estimate)

Series		Fitness (per cent.)					
		100	75	50	25	1	Mean
(*a*) Gold 90; Controls 95 (*i.e.* excluding withdrawals up to 18 months)	Gold	3	42	44	10	—	59·5
	Control	5	40	46	8	—	60·2
(*b*) Gold 77; Controls 82 (*i.e.* excluding withdrawals up to 30 months)	Gold	4	42	45	9	—	60·1
	Control	6	40	44	10	—	60·7

Results

Comparison of Progress in the Two Treatment Series

In the previous report the progress of the two treatment series at Months 0, 1, 3, 6, 12, and 18 was tabulated, analysed, and compared. In the present report the data presented will be those relating to Months 0, 18, and 30 only.

Functional Capacity (Table V)

This was estimated by the physician in five grades.* Table V shows the percentage with given grades of severity at Months 0, 18, and 30 in each series. The "mean"† grades (last column) indicate that both groups were improved in function at 18 months, but that subsequently there was no change.

Detailed examination shows that, at the start, 10 per cent. of both series were in Grade 1, *i.e.* the highest functional grade—fully employed or employable in normal work and able to undertake normal physical recreation. At Month 6 (end of the injection period) 41 per cent. of the gold series as compared with 23 per cent. of the control were in this top grade, and the distributions by grade were significantly different. At Month 12 the position was much the same, and by Month 18 (see Table) 48 per cent. of the gold series had attained this grade as compared with only 27 per cent. of the controls. 12 months later, this advantage to the gold-treated series still persisted, 51 per cent. being in Grade 1 compared with 29 per cent. of the controls.

Re-grading by Functional Capacity.—By the 18th month of the trial, the percentage of patients in each series who were upgraded or downgraded were as follows:

Gold: Upgraded 58, downgraded 8, no change 34.
Control: Upgraded 27, downgraded 7, no change 66.

Between 18 and 30 months, the percentages were:

Gold: Upgraded 14, downgraded 14, no change 72.
Control: Upgraded 7, downgraded 7, no change 86.

Comparing Month 30 with the initial assessment —33 per cent. of the controls, but 60 per cent. of the gold series—nearly double the proportion—finished in a higher grade than that in which they started:

Gold: Upgraded 60, downgraded 12, no change 28.
Control: Upgraded 33, downgraded 11, no change 56.

In consequence, the distributions of the two groups by grade, were significantly different at Month 30. These proportions, however, relate only to those followed for the complete 30 months, and if it is held that the patients excluded because treatment was changed owing to deterioration (gold 11, control 7) should be added to the number downgraded, then the revised percentages become:

Gold: Upgraded 52, downgraded 23, no change 25.
Control: Upgraded 30, downgraded 18, no change 52.

The distributions were still significantly different at Month 30, the advantage lying with the gold series.

In the event, not all of the patients excluded fell into a lower grading subsequent to their exclusion, probably because of a spontaneous remission or a response to the new treatment rather than because of a response to the gold therapy of the trial.

* For definitions of these grades see previous report.
† Adopted as a convenient summarization of the distributions, although statistically unjustifiable because the grades are not quantitative, but qualitative.

TABLE V

GRADE OF FUNCTIONAL CAPACITY (PHYSICIAN'S ESTIMATE) AT PERIODICAL ASSESSMENTS, SHOWING PERCENTAGE IN EACH GRADE AT EACH ASSESSMENT

(GOLD 77; CONTROL 82)

Month of Assessment	Series	Grade					
		1 = Best	2	3	4	5	"Mean"*
0	Gold	10	52	34	4	—	2·3
	Control	11	60	29	—	—	2·2
18	Gold S	48	38	12	2	—	1·7
	Control S	27	52	21	—	—	1·9
30	Gold S	51	32	13	2	1	1·7
	Control S	29	50	20	1	—	1·9

* See footnote to Table III for use of term "Mean".
S = Significant difference between the distributions of the two groups.

In order to allow for differences between the two groups as regards the *amount* of upgrading and downgrading which was possible, the actual score was expressed as a percentage of the possible score* over the whole 30 months of the trial. The results (below) confirmed the significant advantage to the gold series as regards functional improvement.

Actual as Percentage of Possible Score

Series	Upgrading	Downgrading
Gold	56 S	5
Control ..	30	4

S = Significant difference.

Patient's Own Estimate of Fitness (Table VI)

At each assessment, the patient himself graded his condition as 100, 75, 50, 25, or 1 per cent. fit. During the course of injections the mean grade rose from an initial level of 60 per cent. for both series, to 79 per cent. for the gold series, but to only 72 per cent. for the controls (see previous report). At Month 6 the distributions of the two series by grade showed a significant difference. Thereafter little change in the mean occurred in the gold series, but the controls continued to improve (last column, Table VI) so that at Month 18,† and also at Month 30, there was little difference between the means of the two series, and the distributions were not significantly different.

Regrading by Patient's Estimate.—By Month 18 the percentages of patients who felt better or worse in each series were as follows:

Gold: felt better 62; felt worse 5; no change 33.
Control: felt better 51; felt worse 9; no change 40.

Between Month 18 and Month 30 the proportions were:

Gold: felt better 19; felt worse 23; no change 58.
Control: felt better 11; felt worse 11; no change 78.

Comparing Month 30 with the initial assessment, the results were:

Gold: felt better 64; felt worse 13; no change 23.
Control: felt better 51; felt worse 9; no change 40.

These figures exclude, however, the patients whose treatment was changed because of deterioration (gold 11, control 7) and, if these are added to those who "felt worse", the revised percentages—based on 88 gold and 89 controls—become:

Gold: felt better 56; felt worse 24; no change 20.
Control: felt better 47; felt worse 16; no change 37.

The distributions in these categories are significantly different, but it should be noted that the chief constituent of the difference is the "no change" category—more of the gold series than the controls felt better, but also more of them felt worse.

Expressing the actual score for re-grading as a percentage of the possible score, the only significant differences between the gold and control patients occurred at Month 3 and Month 6 (previous report) and between Months 18 and 30, showing advantage to the gold series at each stage.

Actual as Percentage of Possible Score for Upgrading

Series	Months			
	0-3	3-6	18-30	0-30
Gold	30	37	24	53
Control ..	19	20	11	43

* The method of computation was explained in the previous report.
† *Erratum:* In the previous report the footnote to Table VII (p. 104) should have read "S = Significant difference between the proportions 100 per cent. fit", and *not* "S = Significant difference between the distributions".
In that Table the distributions were significantly different at 6 and 12 months, but not at 18 months.

TABLE VI

PERCENTAGE FITNESS (PATIENT'S OWN ESTIMATE), IN EACH GRADE AT EACH ASSESSMENT
(GOLD 77; CONTROL 82)

Month of Assessment	Series	Fitness (per cent.)					
		100	75	50	25	1	Mean
0	Gold	4	42	45	9	—	60·1
	Control	6	40	44	10	—	60·7
18	Gold	40	39	17	3	1	78·6
	Control	26	49	24	1	—	74·7
30	Gold	40	35	19	4	1	77·3
	Control	28	49	18	5	—	75·0

It will be seen that over the whole period the actual upgrading score attained was 53 per cent. of the possible score in the gold series, and 43 per cent. in the controls, not a significant difference.

Whilst, therefore, the patient's subjective estimates of improvement supported, to some extent, the results of the physicians' objective assessments, they were less conclusive as to the advantage to the gold series after a 30-month follow-up.

Joints Involved, Clinical Assessment

A joint was considered affected if two of three features—swelling, tenderness, and limitation of movement—were present. The 42 joints examined at each assessment comprised proximal, interphalangeal, and metacarpophalangeal joints (20), metatarsophalangeal (10), wrists, elbows, shoulders, hips, knees, and ankles (12).

The record form indicated which of the 42 joints examined were active at each assessment and it was possible, adopting the conventional definitions below, to calculate for each patient, at each successive assessment, the number of joints which became newly affected, quiescent, or re-activated.

A newly affected joint was one recorded at the current assessment as active for the first time during the survey period.

A joint becoming quiescent was one recorded as active at the previous but not at the current assessment.

A re-activated joint was one which was recorded at some earlier assessment (during the trial) as becoming quiescent, but which at the current assessment had again become active.

Mean Number of Joints Active (Tables VII and VIII).—At the outset the mean number of joints affected per patient was nearly the same for both series (gold 17·6, control 18·2). At Month 18 both series showed a reduction, greater in the gold series, so that the means were significantly different (gold 7·7, control 11·9). This difference of 4·2 joints per patient contracted by Month 30 to 1·9 (not significant) because the mean number of affected joints rose slightly in the gold series, and declined in the controls (gold 8·8, control 10·7).

Alternatively (last column of Table VII), it can be said that at Month 18 the average number of joints affected per patient in the gold series fell to 44 per cent. of the initial number and that at Month 30 it rose again to 50 per cent. In the controls it declined to 66 per cent. at Month 18 and declined further to 59 per cent. at Month 30.

TABLE VII

MEAN NUMBER OF JOINTS AFFECTED PER PATIENT

(GOLD 77; CONTROL 82)

Month of Assessment	Mean Number of Joints Affected		Trend (Month 0 = 100 per cent.)	
	Gold	Control	Gold	Control
0	17·6±1·00	18·2±0·98	100	100
18	7·7±0·83 S	11·9±0·99	44	66
30	8·8±0·92	10·7±1·07	50	59

S = Significant difference between the two series.

The extent to which these changes in the mean number of joints affected arose from newly affected joints, those which became quiescent, and those which re-activated is analysed in Table VIII. In the construction of this Table, all the information available from intermediate assessments (Months 3, 6, and 12) was utilized in counting the numbers of new, quiescent, and re-activating joints within the period 0 to 18 months. For example, a joint inactive at Month 0, active at Month 3, inactive at Month 12, and active again at Month 18 was included under all three counts—new, quiescent, and re-activating. Table VIII is to be read as follows:

In the gold series 17·6 joints per patient were active at the outset. Over the first 18 months, the mean number of newly affected joints per patient was 4·3, the mean number which became quiescent was 20·6, and the mean number re-activating was 6·4. As a result the mean number active at Month 18 was 7·7 (*i.e.* 17·6 + 4·3N − 20·6Q + 6·4R). Between Month 18 and Month 30 a mean number of 1·7 new, 2·7 quiescent, and 2·1 re-activating joints was recorded, so that at Month 30 8·8 joints were active per patient (7·7 + 1·7N − 2·7Q + 2·1R).

TABLE VIII

MEAN NUMBER OF JOINTS PER PATIENT BECOMING NEWLY AFFECTED, QUIESCENT, OR RE-ACTIVATED BETWEEN ASSESSMENTS

(GOLD 77; CONTROL 82)

State of Joints	0 to 18 Months		18 to 30 Months	
	Gold	Control	Gold	Control
Active at Start of Period ..	17·6	18·2	7·7 S	11·9
Became Newly Affected ..	+ 4·3	+ 5·6	+1·7	+ 0·8
Became Quiescent	−20·6	−18·9	−2·7 S	− 4·2
Became Re-activated	+ 6·4	+ 7·0	+2·1	+ 2·2
Active at End of Period ..	7·7 S	11·9	8·8	10·7

S = Significant difference between the two series.

It will be noted that, in the first period, fewer joints became newly affected and re-activated, and more became quiescent in the gold series than in the controls, but that in the final period more joints became newly affected and fewer became quiescent in the gold series.

Actual as a Percentage of the Possible Number of Joints Affected (Table IX).—A refinement—allowing for differences between the two treatment series as regards the number of joints which *could* become newly affected, or quiescent, or re-activating—expresses the actual numbers in these categories as percentages of the possible numbers. The formulae used in calculating these indexes are given in the Appendix.

NEWLY AFFECTED JOINTS.—Over the whole 30 months, the percentage of *possible* new joints, *i.e.* those not initially active, which became affected, was similar for the two groups (gold 24·6 per cent., control 27·1 per cent.).

In the two periods, however, the results were different. In the first 18 months the percentage becoming newly affected was significantly lower in the gold series—17·8 per cent. as against 23·6 per cent. in the controls. From the 18th to the 30th month (the possible numbers were here reduced by the number which had already become active in the first period) the proportion was significantly higher in the gold series (8·4 per cent.) than in the controls (4·5 per cent.). The gold-treated series did better in respect of the extension of the arthritis to new joints up to 18 months, but worse thereafter.

QUIESCENT JOINTS.—Joints recorded as inactive at any assessment (Months 1, 3, 6, 12, 18, and 30), but which had been active at the preceding assessment, were counted as quiescent. Some became quiescent more than once during the trial. Over the whole 30 months, in the gold series 83 per cent. of a possible 2,179 became quiescent, as against 75 per cent. of a possible 2,531 in the control series.

This advantage to the gold-treated patients over the whole period, although statistically significant, was not large, and was limited to the first 18 months, in which period 81 per cent. of the possible number became quiescent compared with only 68 per cent. in the control series. In the final period (18 to 30 months), an equal proportion of the "possible" joints became quiescent in both series (35 per cent.) and this contrasts with the previous result (Table VIII), which shows that the mean number of joints becoming quiescent was significantly higher in the control series. This emphasizes the necessity of taking into account the number of joints that *could* become quiescent.

JOINTS WHICH RE-ACTIVATED.—A count of these at each assessment comprised joints which had been recorded as quiescent at an ealier assessment, but which were recorded as becoming active again at the current assessment.

Over the whole 30 months, 41 per cent. of the possible number (see Appendix) became re-activated in the gold series as compared with 49 per cent. in the control series. This statistically significant advantage to the gold group was a feature both of the first 18 months (gold 34 per cent.; control 44 per cent.) and in diminished degree of the second period—18 to 30 months—also (gold 15 per cent., control 18 per cent.).

TABLE IX

NEWLY AFFECTED, QUIESCENT, AND RE-ACTIVATING JOINTS, ACTUAL AS PERCENTAGE OF POSSIBLE NUMBER

(GOLD 77; CONTROL 82)

State of Joints	Series	Period of Assessment (mths)		
		0–18	18–30	Total (0–30)
Newly Affected	Gold	17·8 (1,879) S	8·4 (1,545) S	24·6 (1,879)
	Control	23·6 (1,948)	4·5 (1,488)	27·1 (1,948)
Quiescent	Gold	81·3 (1,963) S	35·6 (592)	82·9 (2,179) S
	Control	68·0 (2,284)	35·4 (979)	75·0 (2,531)
Re-activating	Gold	34·1 (1,436) S	14·9 (1,106) S	41·0 (1,596) S
	Control	43·6 (1,318)	18·3 (977)	48·6 (1,552)

* Significant difference between the two treatment series.

Figures in brackets indicate the "possible" number of joints on which the percentages are based (see Appendix, p. 333).

The possible numbers are calculated as follows:

Newly Affected = (0–18) Inactive at start;
(18–30) Inactive at start, less joints newly affected up to Month 18;
(0–30) Inactive at start.

Quiescent = (0–18) Active at start, plus newly affected and re-activating up to Month 12;
(18–30) Active at Month 18;
(0–30) Active at start, plus newly affected and re-activating up to Month 18.

Re-activating = (0–18) Quiescent up to Month 12;
(18–30) Quiescent up to Month 18, less those which re-activated;
(0–30) Quiescent up to Month 18.

Summary of Joints Affected.—In summary, the gold series fared better as regards new joints, quiescent joints, and re-activating joints in the first 18 months. Subsequently, however, the gold patients did no better than the control patients as regards quiescent joints, fared worse as regards newly affected joints, and showed an advantage over the controls only in regard to the re-activated joints.

It is these contrasts that account for the mean number of joints affected per patient being significantly lower in the gold series than in the controls at Month 18, but not at Month 30.

Strength of Grip (Table X)

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 seconds, the hand being held away from the body. The mean of two grips with each hand was recorded.

In the previous report it was shown that for each hand the mean values of the gold and control series were significantly different by Month 6, with advantage to the gold series. This advantage was maintained to the 18th month (Table X), but by the 30th month the mean grip of those treated with gold had fallen considerably, whilst that of the controls was unchanged, so that the small residual advantage to the gold series was no longer statistically significant at Month 30.

TABLE X

MEAN STRENGTH OF GRIP (mm. Hg)
(GOLD 77; CONTROL 82)

Hand	Series	Month of Assessment		
		0	18	30
Right ..	Gold	148±7	180±7S	168±7
	Control	146±7	157±7S	159±7
Left ..	Gold	150±7	180±7S	167±7
	Control	145±7	155±7S	156±7

S = Significant difference between the two series.

Laboratory Investigations

Haemoglobin Concentration (Table XI).—During the first 18 months, the mean haemoglobin level in the gold series increased from 12·3 to 13·0 g. per cent., but in the control group from 12·3 to only 12·5 g. per cent. At Month 18, therefore, the levels of the two series were just significantly different. The earlier analysis indicated that this advantage to the gold-treated series was present as early as the 6th month. By Month 30, however, the haemoglobin concentration had fallen in the gold series, and had risen slightly in the controls, so that at the end of the trial the mean levels were again almost identical.

TABLE XI

MEAN HAEMOGLOBIN CONCENTRATION
(g. per cent. ±S.E.)
(GOLD 77; CONTROL 82)

Series	Month of Assessment		
	0	18	30
Gold	12·3±0·19	13·0±0·17S	12·8±0·17
Control	12·3±0·17	12·5±0·18S	12·7±0·18

S = Significant difference between the two series.

Erythrocyte Sedimentation Rate (Table XII).—The results were similar to those for grip and haemoglobin levels. The mean E.S.R. fell in the gold series to a level significantly below that in the control series by Month 6. The advantage was maintained to Month 18, when the mean rates were 27 for the gold series and 33 for the controls, but by Month 30 the mean rate for the gold series had risen again to 32—precisely the same level as that for the controls—and the advantage present in the former from Month 6 to Month 18 had disappeared.

TABLE XII

MEAN ERYTHROCYTE SEDIMENTATION RATE
(mm./hr Westergren)
(GOLD 77; CONTROL 82)

Series	Month of Assessment		
	0	18	30
Gold	42±2·4	27±2·3	32±3·0
Control	39±2·3	33±2·3	32±2·4

White Cell Count.—This investigation was not done consistently for every patient at each assessment, and the results are based on the "total" counts of 74 patients in the gold series and 75 controls, and on "polymorph" counts of 61 in each group—not always the same patients at each assessment.

No differences in the mean total or polymorph counts were found at the start, at 18 months, or at 30 months. The total count of the gold series had been significantly lower than that of the controls at Months 1, 3, and 6 (see previous report).

Sheep Cell Agglutination Test (Table XIII).—In order to aggregate the records from the different centres, the titre which each 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 as −1, −2, −3, etc.

Table XIII shows the percentages in the dilution categories for Months 0, 18, and 30, but because the test was not done regularly on many of the patients, particularly at the 18th month, the interpretation of the results is largely speculative.

66 of the 77 gold-treated patients and 73 of the 82 controls were tested at the outset, and the distributions (by dilution groups) were very similar. 70 per cent. of the gold series and 75 per cent. of the controls were positive. By Month 18 the proportion positive in both groups had fallen to 61 per cent., and at Month 30 this proportion was hardly changed (gold 63 per cent., control 65 per cent.).

This apparent similarity, however, of the gold and control series as regards the proportion with positive tests, masks important differences in the *distribution* of the positive results by titre. In the gold series there was a *decrease* in the proportion of high positive titres (titres 4 and over) at Month 18—from 18 to 7 per cent.—and an *increase* in the proportion of low positives. But in the controls there was a *slight increase* in the proportion of high positives and a *decrease* in the proportion of low positives. As a result, the distributions of the gold and control series were almost significantly different at Month 18. Subsequently, the proportion of high positives increased again in the gold series, so that at Month 30 the distributions were again very similar.

It seemed possible that the feature of few high positives in the gold series at Month 18 might be due to the relatively small number tested at this point and to the consequent fortuitous omission of tests in high positive patients. To examine this, the analysis was repeated, using only the 36 patients on gold and the 45 controls for whom there were assessments at all three points (Months 0, 18, and 30). The feature persisted: the proportion of high positives in the gold series fell from 22 per cent. (at Month 0) to 6 per cent. (at Month 18), and then increased to 31 per cent. (at Month 30). In the controls the proportion of high positives increased from 20 per cent. (at Month 0) to 31 per cent. (at Month 18) and to 33 per cent. (at Month 30). As a result there was a significant advantage to those on gold at Month 18 even in this small group who were tested at all three assessments.

CHANGE IN S.C.A.T. TITRES (Tables XIV and XV, opposite).—For the patients (gold 36, control 45) in whom this test was performed at all three assessments (Months 0, 18, and 30) the change in S.C.A.T. titres is analysed in Table XIV, which is to be read as follows:

Taking the patients who were *Highly Positive Initially* (+4 to +8 dilutions above minimal positive value), there were eight on gold, and nine controls in this high-titre group at the start. At Month 18, the titres of six of the eight on gold had decreased (one became negative), but only one of the nine controls showed a lower titre. At Month 30 all but two (on gold) had reverted to the initial high titre.

The figures for other dilution groups can be interpreted similarly.

Summarizing these changes, the evidence is that in the gold series up to 18 months, the agglutination titres shifted to lower dilutions to a greater extent than in the controls (Table XV, top section).

TABLE XIII

SHEEP-CELL AGGLUTINATION TEST
Percentage Distributions*

Month of Assessment	Series	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	27	30	23	29	18	70	66	11
	Control	8	17	25	26	27	22	75	73	9
18	Gold	6	33	39	26	28	7	61	46	31
	Control	13	26	39	19	17	25	61	54	28
30	Gold	11	26	37	19	19	25	63	53	24
	Control	8	27	35	18	18	29	65	62	20

* The titre regarded as minimal positive at each Centre = 0.

† Numbers on which percentages are based.

TABLE XIV

CHANGE IN S.C.A.T. TITRES FOR PATIENTS TESTED AT MONTHS 0, 18, AND 30
(GOLD 36; CONTROL 45)

S.C.A.T. Dilution Groups* at Start	Series	Total at Start	Dilutions at Month 18					Dilutions at Month 30				
			+4 to +8	+2 to +3	0 to +1	−1 to −2	−3 to −5	+4 to +8	+2 to +3	0 to +1	−1 to −2	−3 to −5
+4 to +8	Gold	8	2	3	2	1	—	6	—	1	—	1
	Control	9	8	1	—	—	—	9	—	—	—	—
+2 to +3	Gold	12	—	5	4	3	—	3	5	1	3	—
	Control	13	5	4	1	2	1	6	2	1	3	1
0 to +1	Gold	8	—	2	1	5	—	1	2	2	2	1
	Control	12	1	2	1	6	2	—	2	4	5	1
−1 to −2	Gold	8	—	—	2	3	3	1	—	1	4	2
	Control	6	—	—	2	2	2	—	1	—	4	1
−3 to −5	Gold	—	—	—	—	—	—	—	—	—	—	—
	Control	5	—	—	3	—	2	—	—	3	—	2
Distribution at End of Each Period	Gold	36	2	10	9	12	3	11	7	5	9	4
	Control	45	14	7	7	10	7	15	5	8	12	5

* 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 XV

SUMMARY OF THE CHANGE IN THE S.C.A.T. TITRES OF PATIENTS TESTED AT MONTHS 0, 18, AND 30
(GOLD 36; CONTROL 45)

Time of Test	Series	Agglutination Titre			No. of Patients
		Higher	Same	Lower	
Month 18	Gold	4	11	21	36
	Control	13	17	15	45
Between Months 18 and 30	Gold	14	18	4	36
	Control	10	26	9	45
Between Months 0 and 30	Gold	8	17	11	36
	Control	12	21	12	45
Between Months 0 and 30, including Patients not Tested at Month 18	Gold	12	24	11	47
	Control	15	29	13	57

Between 18 and 30 months, a reverse trend was present—more shifted to higher dilutions in the gold than in the control series (Table XV, second section).

When the titres at Month 30 were compared with the initial levels, it was found that about as many patients had changed to higher titres as had changed to lower titres, and this was true of both the gold and control series. It also held when the numbers were increased—as they could be for this last comparison—by the patients tested at Months 0 and 30, but not at Month 18 (Table XV, Sections 3 and 4).

Analgesic Tablets Taken (Table XVI)

At each attendance the number and type of analgesic tablets taken per day were recorded retrospectively. In the few patients taking tablets other than aspirin, the dose was estimated in terms of the aspirin equivalent.*

* See previous report for details.

At the start, both series were taking an average of eight tablets per day. At Month 18 the gold-treated patients had reduced this to five per day, but the controls were practically unchanged. At Month 30, both series were taking an average of six tablets per day.

TABLE XVI

MEAN NUMBER OF ANALGESIC TABLETS TAKEN PER PATIENT

(GOLD 77; CONTROL 82)

Series	Month of Assessment		
	0	18	30
Gold	8·0±0·49	5·2±0·49S	6·0±0·55
Control	7·7±0·49	7·4±0·55S	6·2±0·53

S = Significant difference between the two series.

Radiological Findings

X-ray films of the hands were available at entry to the trial, and also at Months 18 and 30 for all but two of the gold-treated patients (whose 30-month films were unsatisfactory) and one of the controls (who refused *X*-ray examination at the final assessment). *X*-ray films of the wrists were unassessable in two other patients on gold and one other control. Assessment of radiological progress was therefore restricted to 75 gold-treated patients and 81 controls for hands and to 73 on gold and 80 controls for wrists. The films were read by one observer (Dr. Ifor Pennant Williams), who was unaware to which treatment series each patient belonged.

Comparison at the Start of the Trial (Table XVII). —The metaphalangeal joints, the proximal interphalangeal joints of the fingers, and the interphalangeal joints of the thumbs were examined—a total of twenty joints for each patient. In the gold series, four joints were unassessable (two patients with one joint each, and one with two). In the control group five joints were unassessable (two patients with two each, and one with one).

Table XVII, Section A, shows that the average number of joints per patient initially affected in any way, the average number of joints per patient which were narrowed, and the average number of erosions present for each patient, were similar in the two treatment series at the start of the trial.

The two series differed, however, in regard to the wrists (Table XVII, Section B)—a point noted also in our previous report. A higher proportion of the control patients than those on gold (73 as against 45 per cent.) were graded for the right wrist as "nil or only slightly affected". For the left wrist the comparable proportions were 65 and 49 per cent.—a similar type of difference, but not significant. Taking both wrists together, the higher proportion of controls with neither wrist more than slightly affected still persisted (control 58 per cent., gold 38 per cent.), and there were fewer controls with advanced signs in at least one wrist (control 10 per cent., gold 24 per cent.). This was the only factor examined in the whole survey for which the two groups were not similar initially.

Change in Radiological Signs (Tables XVIII and XIX, opposite).—Progression was assessed by comparing the Month 18 film with the initial film; and the Month 30 film with both the Month 18 film and the initial film. In each of these three comparisons the following particulars were recorded for each patient as regards joints of the hands:

(*a*) The number of joints which had narrowed,
(*b*) The number of new erosions,

TABLE XVII

RADIOLOGICAL COMPARISON OF THE TWO GROUPS AT START OF TRIAL

(A) Initial Radiological Signs in the Joints of the Hands (mean per person)
(GOLD 75; CONTROL 81)

Series	Gold	Control
Joints Affected in Any Way	6·3±0·51	5·9±0·52
Narrowed Joints	2·8±0·39	2·4±0·37
Erosions Present	7·1±0·75	6·8±0·77

(B) Initial Radiological Assessment (per cent.) of Wrists (in four grades)
(GOLD 73; CONTROL 80)

Grade	Left Wrist		Right Wrist		Both Wrists		
	Gold	Control	Gold	Control	Grade*	Gold	Control
Nil or Slight (0)	49	65	45 S	73	0, 0	38 S	58
Moderate (1)	33	26	36	20	0, 1 (or 1, 0)	18	23
Marked (2)	18	9	19	7	1, 1	19	10
					0, 2 (or 2, 0) 1, 2 (or 2, 1)	12	4
					2, 2	12	6

*0, 0 = Nil or slight in both hands; 0, 1 = Nil or slight in one hand, moderate in the other, etc.
S = Significant difference between the two series.

TABLE XVIII

RADIOLOGICAL ASSESSMENT OF PROGRESSION OF RHEUMATOID ARTHRITIS IN HANDS

(GOLD 75; CONTROL 81)

Months			0–18		18–30		0–30	
Series			Gold	Control	Gold	Control	Gold	Control
(1) Assessable Joints		Left	749	806	749	802	749	806
		Right	747	809	746	797	747	809
		Both	1,496	1,615	1,495	1,599	1,496	1,615
Narrowed Joints	(2) Assessable Joints which could Narrow (not initially narrowed)	Left	644	708	600	654	644	708
		Right	642	715	595	662	642	715
		Both	1,286	1,423	1,195	1,316	1,286	1,423
	(3) Joints which did Narrow	Left	44	54	63	81	105	123
		Right	47	53	67	82	120	132
		Both	91	107	130	163	225	255
	(4) Actual Joints which Narrowed as Percentage of Possible Number ((3) as percentage of (2))	Left	6·8	7·6	10·5	12·4	16·3	17·4
		Right	7·3	7·4	11·3	12·4	18·7	18·5
		Both	7·1	7·5	10·9	12·4	17·5	17·9
Erosions	(5) New Erosions which Developed	Left	115	179	97	110	184	273
		Right	135	157	86	114	206	277
		Both	250	336	183	224	390	550
	(6) New Erosions per Assessable Joint ((5) ÷ (1))	Left	0·15±0·02	0·22±0·03	0·13±0·03	0·14±0·02	0·25±0·04	0·34±0·04
		Right	0·18±0·03	0·19±0·03	0·12±0·02	0·14±0·02	0·27±0·04	0·34±0·04
		Both	0·17±0·02	0·21±0·02	0·12±0·02	0·14±0·02	0·26±0·04	0·34±0·04
	(7) Extension of Old Erosions	Left	47	49	49	69	50	56
		Right	69	75	73	91	81	99
		Both	116	124	122	160	131	155
	(8) Extensions per Assessable Joint ((7) ÷ (1))	Left	0·06±0·01	0·06±0·01	0·07±0·01	0·09±0·02	0·07±0·01	0·07±0·01
		Right	0·09±0·02	0·09±0·01	0·10±0·02	0·11±0·02	0·11±0·02	0·12±0·01
		Both	0·08±0·01	0·08±0·01	0·08±0·02	0·10±0·01	0·09±0·02	0·09±0·01

Note: Items (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 XIX

PERCENTAGE RADIOLOGICAL ASSESSMENT OF "PROGRESSION" IN THE WRISTS

(GOLD 73; CONTROL 80)

Months	Wrist		Left		Right		Both		
	Series		Gold	Control	Gold	Control	Grade*	Gold	Control
0–30	Progression Grade	Nil or Slight 0	36	34	32	34	0, 0	22	23
		Moderate 1	25	29	37	33	0, 1	15	16
		Marked 2	23	23	16	23	1, 1	15	16
		Very marked 3	16	15	15	11	0, 2+	8	6
							1, 2+	16	13
							2+, 2+	23	26
		Total	100	101	100	101	—	99	100
0–18		2 and 3 Combined	10	21	11	16	2+ in one or both hands	14	28
18–30		2 and 3 Combined	11	14	15	12	2+ in one or both hands	17	18

* 0, 0 = Nil or slight in both hands; 0, 1 = Nil or slight in one hand, moderate in the other, etc.

(*c*) The number of extensions of erosions which were visible in the earlier of the two films.

The summation of these for all patients in each treatment series is shown in Table XVIII (Rows 3, 5, and 7). Discrepancies between the counts for the whole 30-month period and the summation of the 0 to 18- and the 18 to 30-month periods arise from "observer error", whereby a joint thought to be narrowed at Month 18 might look "normal" at Month 30, or an erosion extended at Month 18 might not be visible at Month 30, either because it had become unrecognizable or because of a slight rotation of the finger. Also, three erosions at Month 18 may coalesce to give one large one at

Month 30. It is therefore better to regard the three readings (periods) as separate experiments.

Three indices of progression of the disease in the patients were derived from these counts—Rows 4, 6, and 8 of Table XVIII. They show that, measured radiologically, there were no statistically significant differences between the gold series and the controls as regards joint narrowing, the development of new erosions, or the extension of old erosions throughout the whole trial or in the earlier or later part of it. Nevertheless, the *consistency* of the slightly higher mean values in the control group as regards joint narrowing and new erosions in either hand is perhaps more important than any numerical test of significance.

Progression in the wrist in each period was assessed radiologically in four grades (Table XIX), with the following rough guides:

0	*Nil or Slight:*	No change, or small erosion and/or small area of cartilage loss, *i.e.* joint narrowing.
1	*Moderate:*	Two to five erosions and/or narrowing involving two or three carpal joints.
2	*Marked:*	Four to eight erosions. Narrowing very obvious.
3	*Very marked:*	Virtually every joint in the wrist showing narrowing and erosions.

Here again no differences between the two treatment groups were manifested in either period of the trial as regards the percentages in the four progression categories.

In view of this, for economy in space, only the percentages showing marked and very marked progression (Grades 2 and 3 combined) are tabulated for the first and second periods of the trial.

There is a suggestion in these figures that in the first 18 months, a higher percentage of the control group showed moderate or marked progression (gold 14 per cent., control 28 per cent.), but the difference is not statistically significant.

To obtain some general measure of the progression in the hands a scoring system was used by which a joint which narrowed scored one point, a new erosion scored two points, and an extension of an old erosion scored one point. The actual scores were then expressed as percentages of the possible scores* (Table XX). No significant differences were seen, but again the consistency with which the index was slightly in favour of the gold-treated series is very suggestive. The actual score as a percentage of the possible score for radiological progression in both hands together over the complete 30 months of the trial was 8·6 per cent. for the gold series as compared with 10·5 per cent. for the controls, and the advantage to the gold-treated patients was of this order in each hand and for each period of the trial.

Patients Given a Second Course

As explained earlier (see p. 315), sixteen of the gold-treated patients and eighteen controls received a second course of injections after the 18-month assessment. For brevity, the one-course group will be referred to as Group A, and the two-course group as Group B.

A review of the requests for second courses revealed that where a reason was stated, the most

* A detailed explanation of the computation of these possible scores was given in the previous report and was adopted unchanged for all three periods examined in Table XX.

TABLE XX

RADIOLOGICAL ASSESSMENT OF "PROGRESSION" IN HANDS ALONE (TOTAL FOR ALL PATIENTS)
(GOLD 75; CONTROL 81)

Months	Series		Gold			Control		
	Hand		Left	Right	Both	Left	Right	Both
0–18	Score	Actual	321	386	707	461	442	903
		Possible	6,636	6,618	13,254	7,156	7,187	14,343
		Actual as Percentage of Possible	4·84	5·83	5·33	6·44	6·15	6·30
18–30	Score	Actual	306	312	618	370	401	771
		Possible	6,592	6,563	13,155	7,070	7,038	14,108
		Actual as Percentage of Possible	4·64	4·75	4·70	5·23	5·70	5·46
0–30	Score	Actual	523	613	1,136	725	785	1,510
		Possible	6,636	6,618	13,254	7,156	7,187	14,343
		Actual as Percentage of Possible	7·88	9·26	8·57	10·13	10·92	10·53

* 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 this Table.

usual one was deterioration in the patient's condition. There were, therefore, three main points for study: to determine whether the two-course patients were a select group in that their progress had been unsatisfactory; to note how their progress between the 18th and 30th months compared with that of those who did not receive a second course; and to decide whether, if the two-course patients *were* select sub-groups, their exclusion would have modified the conclusions reached from the earlier analysis.

Both in the gold-treated and in the control series, Groups A and B were similar at the start of the trial as regards sex, age, duration of symptoms, and type of onset. Group B in each series contained fewer males but, on the small numbers involved, the sex proportions were not significantly different. Also, as regards most of the factors used in assessing progress, these sub-groups were not significantly different at the outset except, possibly, in respect of grip.

Functional Capacity (Physician's Estimate) (Table XXI)

The distributions by functional grade of patients in Groups A and B were not dissimilar at the start of the trial. By Month 18, however, there was a smaller percentage of Group B (6 as against 59 per cent.) in the best grade, and higher percentages of Group B in the other grades. This was true of both series, and implies that, by this index, patients subsequently given a second course were those who had fared relatively badly up to Month 18. (This does not mean, of course, that *all* who did badly received a second course, nor that *all* who received a second course *had* done badly.)

That the Group B patients were a select group who did not do so well up to Month 18, was confirmed by the percentages upgraded and downgraded between Months 0 and 18:

Gold:

A—upgraded 64; downgraded 5; no change 31

B—upgraded 38; downgraded 19; no change 43

Control:

A—upgraded 34; downgraded 5; no change 61

B—upgraded nil; downgraded 17; no change 83

Between Month 18 and Month 30 (there were no interim assessments) no group showed much change in the percentage distribution by functional grading (Table XXI), but the actual score for *downgrading* as a percentage of the possible score was significantly higher for Group B than for Group A in the gold series (12 as against 4 per cent. of the possible score), indicating that, despite their additional course of gold, their condition deteriorated. No corresponding significant difference was found in the control series.

Comparing the gold and control patients who had only one course (Group A), the advantage to the gold group at Month 18 was maintained at Month 30: 61 per cent. of the gold series, but only 36 per cent. of the controls, were in the highest grade (Table XXI), and this is in accordance with the conclusion reached earlier, based on Groups

TABLE XXI

GRADE OF FUNCTIONAL CAPACITY (PHYSICIAN'S ESTIMATE) OF GROUPS A AND B, PERCENTAGE IN EACH GRADE AT EACH ASSESSMENT

Series	Month of Assessment	Group	Grade											
			1 = Best		2		3		4		5		"Mean"*	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Gold	0	A	7	11	34	56	19	31	1	2		—	61	2·2
		B	1	6	6	38	7	44	2	12		—	16	2·6
	18	A	36	59	20	33	5	8		—		—	61	1·5
		B	1	6	9	56	4	25	2	12		—	16	2·4
	30	A	37	61	17	28	7	11		—		—	61	1·5
		B	2	12	8	50	3	19	2	12	1	6	16	2·5
Control	0	A	8	12	37	58	19	30		—		—	64	2·2
		B	1	6	12	67	5	28		—		—	18	2·2
	18	A	21	33	33	51	10	16		—		—	64	1·8
		B	1	6	10	56	7	39		—		—	18	2·3
	30	A	23	36	31	48	10	16		—		—	64	1·8
		B	1	6	10	56	6	33	1	6		—	18	2·4

* See footnote to Table III for use of the term "Mean".
A = One course.
B = Two courses.

A and B combined. In other words, the exclusion of the B Groups from the earlier analysis would not have modified the conclusions regarding the advantage of those treated by gold.

Furthermore, the fact that those who had second courses of gold did no better subsequently than those who had second courses of the control injections suggests that the former were resistant to gold therapy.

Patient's Estimate of Fitness (Table XXII)

A very similar picture is given by the patients' subjective estimates of fitness. In Group A of the gold series, the percentage feeling 100 per cent. fit increased from 5 to 49 per cent. between Months 0 and 18, but in Group B of the gold series it rose from nil to only 6 per cent. (one out of the sixteen patients). At Month 18 the distributions were significantly different. The controls gave a similar picture.

Further analysis showed that the percentages grading themselves at Month 18 as "more fit" or "less fit" than at the start of the trial were as follows:

Gold:

A—more fit 69; less fit 3; no change 28
B—more fit 38; less fit 12; no change 50

Controls:

A—more fit 56; less fit 8; no change 36
B—more fit 33; less fit 11; no change 56

By this index also, therefore, Group B had improved less than Group A up to the time of receiving the second course.

Subsequently, little difference in the progress of Groups A and B on gold could be distinguished. Certainly the mean grade of the former was slightly reduced (83 to 80 per cent. fit), whilst the mean grade of the latter went up (63 to 67 per cent. fit), but on the small numbers involved the change in the distributions was not greater than could arise by chance. Similar remarks apply to the A and B sub-groups in the control series.

Taking Group A only, over the whole 30 months of the trial, the actual score for upgrading as a percentage of the possible score was 58 per cent. in the gold series as against 49 per cent. in the control series—a non-significant difference similar to that found in the general analyses based on Groups A and B combined. Nor could any real difference be found between the progress of those who had two courses of gold and those who had two courses of control treatment.

Other Criteria

The results of comparing Groups A and B with regard to other criteria (joints affected; new, quiescent, and re-activated joints; grip; haemoglobin concentration; erythrocyte sedimentation rate; sheep cell agglutination titres; and analgesic tablets) were all in conformity with those given by Functional Capacity and Patient's Estimate of Fitness (above).

Space does not permit the presentation of these tabulations;* it will suffice to conclude with those relating to the radiological assessment.

* The tabulations are available if required.

TABLE XXII

PERCENTAGE FITNESS (PATIENT'S OWN ESTIMATE) OF GROUPS A AND B IN EACH GRADE AT EACH ASSESSMENT

Series	Month of Assessment	Group	Fitness (per cent.)											
			100		75		50		25		1		"Mean"*	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Gold	0	A	3	5	26	43	27	44	5	8	—		61	61·1
		B	—		6	38	8	50	2	12	—		16	56·3
	18	A_S	30	49	22	36	7	11	2	3	—		61	82·8
		B^S	1	6	8	50	6	38	—		1	6	16	62·6
	30	A	28	46	19	31	12	20	2	3	—		61	79·9
		B	3	19	8	50	3	19	1	6	1	6	16	67·3
Control	0	A	4	6	25	39	28	44	7	11	—		64	60·2
		B	1	6	8	44	8	44	1	6	—		18	62·5
	18	A	20	31	29	45	14	22	1	2	—		64	76·6
		B	1	6	11	61	6	33	—		—		18	68·1
	30	A_S	22	34	31	48	7	11	4	6	—		64	77·7
		B^S	1	6	9	50	8	44	—		—		18	65·3

* See footnote to Table III for use of the term "Mean".
S = Significant difference between the distributions of A and B.
A = One course.
B = Two courses.

Radiological Progression (Tables XXIII and XXIV)

When assessed radiologically, Groups A and B were generally similar at the start of the trial as regards the mean number of joints per person affected, the mean number of narrowed joints per person, and the number of erosions present (Table XXIII). In the control series Group B had significantly *fewer* erosions present initially than Group A. Grading of the wrists (not shown in the Tables) was similar for Groups A and B in each series.

TABLE XXIII

RADIOLOGICAL COMPARISON OF GROUPS A AND B AT START OF TRIAL
(mean number of joints affected per person)

Initial Radiological Signs in Joints of the Hands	Group	Series	
		Gold	Control
Affected in Any Way ..	A	6·1±0·58	6·5±0·62
	B	7·2±1·03	4·1±0·72
Narrowed	A	2·8±0·40	2·6±0·45
	B	3·0±1·14	1·7±0·51
Erosions Present	A	7·1±0·89	7·5±0·94S
	B	7·1±1·14	4·3±0·84S

S = Significant difference between the groups.
A = One course.
B = Two courses.

During the first 18 months, the number of joints which narrowed (as a percentage of the number which could narrow) was significantly higher in Group B than in Group A in the gold series, but this did not apply in the control series. The same was true for the 18 to 30-month period, so that over the whole trial 24 per cent. of hand joints of the two-course gold patients narrowed, as against only 16 per cent. of the one-course gold patients (Table XXIV(*i*)). No difference was found between Groups A and B in the control series.

No significant differences appeared between Groups A and B at either Month 18 or Month 30 as regards the number of new erosions or extensions of old erosions. The separate data for each hand have therefore been omitted (Table XXIV(*ii*) and (*iii*)).

Although at Month 18 a higher proportion of the wrists in Group B showed marked or very marked progression than those in Group A, the differences were not significant on the small numbers involved and had disappeared entirely at Month 30.*

Thus the radiological evidence based on joint narrowing in the hands and on the progression of the disease in the wrists supports the conclusion reached from the clinical assessments that Group B fared relatively poorly up to receiving their second course, and that they did no better after their second course than Group A. Furthermore, a radiological comparison of the gold and control series based on Group A patients only in no way modifies the conclusions drawn from the comparison of Groups A and B combined (p. 327 and Table XVIII), nor was there any evidence that those who had second courses of gold therapy showed more or less radiological progression than those who received a second course of control therapy.

Summary of Second Courses

The comparison of those who had a second course of treatment (Group B) with those who did not (Group A) showed that up to the time of receiving a second course, Group B had improved to a lesser

* The tabulations are available if required.

TABLE XXIV

RADIOLOGICAL PROGRESSION IN JOINTS OF THE HANDS IN GROUPS A AND B

Progression Assessed	Months	Gold						Control					
		Left		Right		Both		Left		Right		Both	
		A	B	A	B	A	B	A	B	A	B	A	B
(*i*) Joints which Narrowed (Percentage of those which could Narrow	0–18	6 S	9	6 S	13	6 S	11	9	5	8	6	8	5
	18–30	9 S	18	11	14	10 S	16	12	15	11	16	11	16
	0–30	15	22	17 S	26	16 S	24	17	18	18	20	18	19
(*ii*) Mean Number of New Erosions (per Assessable Joint)	0–18					0·17±0·03	0·16±0·04					0·20±0·02	0·24±0·07
	18–30					0·11±0·03	0·19±0·05					0·13±0·02	0·17±0·03
	0–30					0·24±0·04	0·35±0·08					0·33±0·04	0·39±0·07
(*iii*) Mean Number of Extensions of Old Erosions (per Assessable Joint)	0–18					0·07±0·01	0·10±0·03					0·08±0·01	0·06±0·02
	18–30					0·08±0·02	0·07±0·02					0·10±0·02	0·11±0·03
	0–30					0·09±0·02	0·07±0·02					0·10±0·02	0·08±0·02

S = Significant difference between the groups.
A = One course.
B = Two courses.

degree. Despite the very small numbers in Group B, significant differences were found in the patient's own estimate of physical well-being, the number of joints newly affected and becoming quiescent, and changes in strength of grip and in erythrocyte sedimentation rate, and frequency of joint narrowing measured radiologically. In most of the other assessments, differences not large enough to reach statistical significance, but all tending the same way, were apparent—showing Group B at a relative disadvantage at the time of receiving the second course.

After receiving the second course Group B remained at a disadvantage: the mean grade of functional capacity fell, whilst that of Group A remained stationary; more joints became newly affected; strength of grip declined more; and a larger proportion of joints narrowed.

Thus the patients given a second course comprised a select sub-group which fared relatively badly during the first 18 months, and did no better after receiving a repeat course.

Furthermore, those who had a second course of gold subsequently did no better than those who had a second course of control therapy, whereas those who did well on a single course of gold had a distinct advantage over the control group.

Discussion

Initially 99 patients were given a 5-month course of twenty weekly gold injections and 100 subjects received control injections; 77 of the former and 82 of the latter were followed for 30 months, 2 full years from the end of the 5-month period of therapy. At the start of the trial the only difference noted between the two series was in regard to radiological assessment of the wrists, which were affected to a lesser degree in the control series. According to the physician's estimate of functional capacity, and analysed in various ways, the results clearly demonstrate an advantage to the gold-treated patients from Month 6 right through to the end of the trial at Month 30. The patient's own estimate of fitness supported the physician's estimate, but was less conclusive, little advantage showing to the gold-treated patients by Month 30. In the first 18 months the gold-treated patients showed fewer newly affected joints than the controls, fewer joints re-activating, and a larger number becoming quiescent; after Month 18 some of this advantage disappeared as more joints were newly affected in the gold series than in the control series from Month 18 to Month 30. Similarly, the haemoglobin concentration, erythrocyte sedimentation rate, and daily consumption of analgesic tablets, were significantly better in the gold series from Month 6 to Month 18 and thereafter deteriorated, so that by Month 30 little, if any, advantage remained. The sheep cell agglutination titres up to Month 18 shifted in the gold-treated series to lower dilutions than in the control series, but from Month 18 to Month 30 a reverse trend was apparent, so that over the whole trial as many titres rose as fell in both gold and control series. As regards radiological findings, no significant differences were seen between the gold and control series in joint narrowing, development of new erosions, or extension of previous erosions, in either period of the trial. Where small differences occurred, although statistically not significant, they were consistently in favour of the gold series.

To sum up, in general the evidence is that, by most of the indices used, the gold-treated patients fared better than the controls from the 3rd to the 6th month up to Month 12, and that this advantage was on the whole maintained up to Month 18, *i.e.* one full year after the completion of the 5-months' course of treatment; after this period the gold-treated patients deteriorated to an appreciable extent, though they retained some small advantage over the controls in regard to some criteria at Month 30.

When the trial was first organized it was left to the individual physician to give a second course of injections if he considered such a course to be indicated, both physician and patient remaining unaware which treatment was being given. Sixteen gold-treated patients and eighteen controls received second (repeat) courses. The analysis has shown that these patients, both gold-treated and controls, comprised a select sub-group who did badly on both courses in both groups. This appears to confirm the impression long held by many clinicians that, if one full course of gold gives little or no benefit, a second course is unlikely to give better results. Additional weight is given to this when it is noted that those who received a second course of gold did no better subsequently than those who received a second course of control injections, whereas those who had only one course of gold still showed some advantage at Month 30 over the controls who had received only one course.

Summary and Conclusions

(1) 159 out-patients aged 20 to 64 years, with active rheumatoid arthritis of 1 to 5 years' duration, who had received gold salts in a 5-month course of

twenty weekly injections, were followed for a total of 30 months from the start of treatment. 77 received weekly injections of 50 mg. sodium aurothiomalate (Myocrysin) to a total dosage of 1 g. (gold series), and 82 received 0·5 μg. weekly of the same substance to a total dosage of 0·01 mg. (control series).

(2) Considerable improvement by all criteria except radiological examination was seen from Month 3 (halfway through the course of injections) to Month 18 (one year after completion of the course). Thereafter, a reverse trend was noted, so that by Month 30 most of the advantage seen in the gold-treated series at Month 18 had disappeared, though by some criteria the gold-treated series still remained significantly better than the control series, albeit by only a slender margin.

(3) Second courses of injections were given to sixteen gold-treated patients and eighteen controls. The main reason for giving a second course was failure to respond satisfactorily to the first. Analysis of the assessments of these patients confirmed that they formed relatively "bad" groups up to the time of receiving the second course, and that subsequently they did no better. In addition, the sixteen who received two courses of gold did no better than the eighteen who received two courses of control injections.

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

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APPENDIX

Newly Affected, Quiescent, and Re-activating Joints

Let i = Months of assessment 0, 1, 3, 6, 12, 18, 30, and for any group of patients;
T_i = Total number of joints examined (generally 42);
A_i = Joints active at assessment i
I_i = Joints inactive at assessment i $\}$ $(A+I=T)$
N_i = Joints becoming active for the first time in the trial at assessment i
Q_i = Joints becoming quiescent at assessment i
R_i = Joints becoming reactive at assessment i
Σ = Summation for all patients in a treatment group.

e.g. $\Sigma\overset{18}{\underset{1}{N}}$ = Total number of newly affected joints recorded by all patients at Months 1, 3, 6, 12, and 18, whilst

ΣI_0 = Number of joints recorded as inactive at Month 0 (start of trial) by all patients.

Then the following formulae give actual numbers as a percentage of the possible numbers:

Newly Affected Joints as Percentage of Possible Number

$$0 - 18 \text{ months} = 100\ \Sigma\overset{18}{\underset{1}{N}} \Big/ \Sigma I_0$$

$$18 - 30 \text{ months} = 100\ \Sigma N_{30} \Big/ \left(\Sigma I_0 - \Sigma\overset{18}{\underset{1}{N}}\right)$$

$$0 - 30 \text{ months} = 100\ \Sigma\overset{30}{\underset{1}{N}} \Big/ \Sigma I_0$$

Joints becoming Quiescent as Percentage of Possible Number

$$0 - 18 \text{ months} = \frac{100\left(\Sigma\overset{18}{\underset{1}{Q}}\right)}{\Sigma A_0 + \Sigma\overset{12}{\underset{1}{N}} + \Sigma\overset{12}{\underset{3}{R}}}$$

$$18 - 30 \text{ months} = 100\ \Sigma Q_{30} \,/\, \Sigma A_{18}$$

$$0 - 30 \text{ months} = \frac{100\ \Sigma\overset{30}{\underset{1}{Q}}}{\Sigma A_0 + \Sigma\overset{18}{\underset{1}{N}} + \Sigma\overset{18}{\underset{3}{R}}}$$

Re-activating Joints as Percentage of Possible Number

$$0 - 18 \text{ months} = 100\ \Sigma\overset{18}{\underset{3}{R}} \Big/ \Sigma\overset{12}{\underset{1}{Q}}$$

$$18 - 30 \text{ months} = 100\ \Sigma R_{30} \Big/ \Sigma\overset{18}{\underset{1}{Q}} - \Sigma\overset{18}{\underset{3}{R}}$$

$$0 - 30 \text{ months} = 100\ \Sigma\overset{30}{\underset{3}{R}} \Big/ \Sigma\overset{18}{\underset{1}{Q}}$$

Chrysothérapie de l'arthrite rhumatismale. Rapport final d'un essai contrôlé, multicentral

Résumé et Conclusions

(1) Des malades externes, au nombre de 159, âgés de 20 à 64 ans, atteints d'arthrite rhumatismale évolutive pendant 1 à 5 ans, qui avaient reçu une série d'injections hebdomadaires de sels d'or pendant 5 mois, furent surveillés pendant 30 mois dès le commencement du traitement. Parmi eux, 77 reçurent des injections hebdomadaires de 50 mg. d'aurothiomalate de soude (Myocrisin) atteignant une dose totale de 1 gramme (série traitée) et 82 malades reçurent 0,005 mg. hebdomadaires de la même substance, atteignant une dose totale de 0,01 mg. (série témoin).

(2) Une amélioration considérable selon tous les critères, sauf un examen radiologique, fut observée dès le troisième mois (après la moitié des injections) jusq'au 18-ème mois (un an après la fin des injections). Après cela on nota une tendance opposée, de manière que vers le 30-ème mois, la plupart des avantages observés dans la sèrie traitée à l'or s'était évanouie. Selon certains critères, toutefois, la série traitée se portait significativement mieux que la série témoin, quoique la marge entre les deux était très petite.

(3) Une deuxième série d'injections fut administrée à 16 malades ayant été traités par des sels d'or et à 18 témoins. La raison principale de la deuxième série fut la réponse peu satisfaisante à la première. L'analyse des évaluations de ces malades confirme qu'ils formaient des groupes relativement "mauvais" justqu'au moment de recevoir la deuxième série et qu'après cela ils ne se sont pas améliorés. De plus, les 16 qui avaient reçu deux séries d'injections d'or n'en ont pas profité plus que les 18 qui avaient reçu deux séries d'injections témoins.

Crisoterapia en la artritis reumatoide. Informe final sobre una investigación controlada multicentral

Sumario y Conclusiones

(1) Ciento cincuenta y nueve enfermos externos, de edad de 20 a 64 años, con artritis reumatoide evolutiva de 1 a 5 años de duración, recibieron una serie de inyecciones semanales de sales de oro durante 5 meses y fueron seguidos durante 30 meses desde el comienzo del tratamiento. Entre estos, 77 recibieron inyecciones semanales de 50 mg. de aurotiomalato de sodio (Myocrisin) con una dosis total de 1 gramo (serie tratada) y 82 enfermos recibieron 0,005 mg. semanales del mismo producto con una dosis total de 0,01 mg. (serie de control).

(2) Una mejoría considerable según todos los criterios, salvo un examen radiológico, fué observada desde el tercer mes (en medio de las inyecciones) hasta el diecioctavo mes (un año después del fin de las inyecciones). A continuación se notó una tendencia opuesta, de modo que hacia el treinteno mes la mayoría de las ventajas observadas en la serie tratada con oro desapareció. Según ciertos criterios, sin embargo, la serie tratada con oro andó significativamente mejor que la serie testiga, aunque el margen entre los grupos fué muy pequeño.

(3) Una segunda serie de inyecciones fué administrada a 16 enfermos tratados con oro anteriormente y a 18 testigos. La razón principal de la segunda serie fué la respuesta terapéutica poco satisfactoria a la primera. Un análisis de valoraciones de estos enfermos confirma el hecho de que se trata aquí de grupos que fueron relativamente "malos" antes de recibir la segunda serie y que cambiaron poco después. Además, los 16 que recibieron dos series de inyecciones de oro no se hallaron mejor que los 18 que recibieron dos series de inyecciones testigas.