GOLD THERAPY IN RHEUMATOID ARTHRITIS

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Although much has been written on the treatment of chronic arthritis of the rheumatoid type by injections of gold compounds no statistical study that shows the difference between the results in treated and untreated cases seems to have been published as yet.

History

Hartfall, Garland, and Goldie (1937) found a statistically significant difference in the recovery rate of cases of rheumatoid arthritis treated with different gold compounds. The nearest approaches to our present study, however, are the animal experiments carried out on the "infectious arthritis of mice and rats." This is a naturally occurring epidemic disease of rodents, and sometimes arises spontaneously in laboratory animals. It can be transmitted from one animal to another artificially by injecting fluid from the joints or internal organs of infected animals into the joints of the healthy animals. Collier (1939) found that injection of such gold compounds as aurodetoxin and solganal B into rats protects them against experimental infection. Findlay, Mackenzie, and MacCallum (1940) have shown that infectious arthritis of rodents is due to a pleuropneumonia type of organism. Like Collier, they were able to show that gold compounds would protect against the inoculated disease, solganal B being the most efficacious. Arsenical compounds also had a prophylactic action, but not so great as that of gold. No effect was produced by any of the sulphonamide derivatives. These results are the most suggestive, as Swift and Brown (1939) claim to have isolated a pleuropneumonia-like organism from human cases of acute rheumatism.

Mode of Investigation

Solganal B was the gold compound used for this particular investigation. From the cases of rheumatoid arthritis coming under our care only typical cases were chosen. These were divided into three groups of thirty cases. One group was injected with solganal B in doses of 0.2 gramme weekly, having first been tested for sensitivity by means of three initial weekly injections of 0.01, 0.05, and 0.1 gramme respectively. Doses of 0.3 gramme were sometimes used in resistant cases in this group, which will subsequently be referred to as Group I or "the large-dose group." Group II, or the "small-dose group," was treated by means of weekly doses of 0.1 gramme of solganal B, this dose never being exceeded. These patients were tested initially for sensitivity by two injections of 0.01 and 0.05 gramme respectively. Group III, or the "control group," was given weekly injections of sterile almond oil. (This is an innocuous oil often used for suspending gold compounds.) All injections were made into the gluteal muscles. Treatment was continued for periods of nine months in each case. It was divided into two courses by an interval of six weeks. Progress was assessed by monthly recordings of the blood sedimentation rate (Westergren) and of the circumference of any swollen joints. Radiography and clinical examination of affected joints were carried out before and after treatment. The urine was tested for albumin weekly. All results are those found at the end of nine months' treatment.

In an attempt to ascertain that the three groups were similar the ages at the onset of the disease were averaged for each group, also the duration of the disease and the initial blood sedimentation rate. They are shown in Table I.

TABLE I.—Age at Onset of the Disease, Duration of the Disease, and Initial Sedimentation Rate in Each Group of Patients

	Group I Gold (Large Doses)	Group II Gold (Small Doses)	Group III Controls
Age at onset in years :			
Minimum	18	17	15
Maximum	56	68	70
Average	40	39	39
Duration in years :			
Minimum	0.2	0.2	0.2
Maximum	37	26	25
Average	7	8	7
Initial sedimentation rate in mm. :			
Minimum	8	7	2
Maximum	60	69	55
Average	25	33	24

The average age of the patients and the duration of the disease in the three groups, as can be seen, are almost identical. The average initial sedimentation rate in Group II is slightly higher (8 to 9 mm.) than in the other two groups, but the difference is not considered sufficient to be of prognostic significance.

Results

In assessing the results it was decided to take count not of the cures but of the cases in which the disease has been rendered inactive. A patient who has had the complaint for several years can never be cured, as destruction of cartilage and bone causes permanent impairment of the function of the joint. What chemotherapy can hope to do is to render the disease inactive so that no further damage will be done, and it is usually found that when this happens the patient is able to return to a full, useful, and above all comfortable existence despite extensive damage to joint structures. We have used the following criteria of inactivity of the disease: (a) the patient must be completely free of subjective joint pain; (b) if there is limitation of movement in any joints this must be painless; (c) the sedimentation rate must be normal. Though many of the patients were able to get about and carry on their normal duties, their cases have not been classed as inactive on account of some degree of pain on prolonged use of the joints or on attempting movement of the joints through their maximum possible range. Owing to the difficulty of finding accurate standards for grades of improvement we have not attempted to split up the group of patients improved by the treatment but not rendered inactive. Table II shows these results in tabular form.

TABLE II.—Results at the End of Nine Months' Treatment or Observation

	Rendered Inactive	Improved	Unaltered	Worse	Totals
Gold (large doses)	14	14	2	0	30
Gold (small doses)	8	20	1	1	30
Controls	1	22	6	1	30

From this it will be seen that of those treated with large doses of gold 14 (47 per cent.) became inactive within nine months of starting treatment. Of those treated with small doses of gold 8 (27 per cent.) and of the controls 1 (3 per cent.) have become inactive. Reference to a statistical table (Loewenthal and Wilson, 1939) shows that the probability of these results not being due to chance would be expressed as within the limit of $P = 0.005$ in the large-dose group and $P = 0.05$ in the small-dose group. The former, which means that it is 199 to 1 against the results being due to chance, is considered very convincing evidence by statisticians; and the latter, which indicates 19 chances to 1, is thought to be satisfactory evidence of the value of a method of treatment.

TABLE III.—*Alteration in Sedimentation Rate at the End of Nine Months' Treatment*

	Sedimentation Rate Raised	Sedimentation Rate Lowered	Sedimentation Rate Reduced to less than 10 mm.
Gold, large doses ..	2	28	23
Gold, small doses ..	1	29	11
Controls ..	17	13	4

In Table III the final changes in the blood sedimentation rate are summarized. From this it can be seen that in the control cases there is, on the average, no marked change in the sedimentation rate at the end of nine months. The rate has been increased in 17 (57 per cent.) and reduced in 13 (43 per cent.). In cases treated with small doses of gold, on the other hand, the sedimentation rate has become lowered in 29 (97 per cent.), and in cases treated with large doses of gold it has become lowered in 28 (93 per cent.). On examining the results in the last column of Table III—that is, the number of cases in which the sedimentation rate is normal at the completion of nine months' treatment—one finds that in the large-dose group 23 (77 per cent.) have become normal, whereas in the small-dose group 11 (37 per cent.) and in the control group only 4 (13 per cent.) have become so. These results are of statistical significance both as regards the comparison between gold and control cases and between cases receiving large and small doses of gold.

TABLE IV.—*Effect of Gold Treatment on Swelling of Joints in Rheumatoid Arthritis*

	Increased	Unaltered	Diminished	Total
Gold, large doses ..	3 (8%)	10 (26%)	26 (66%)	39
Gold, small doses ..	10 (14%)	19 (27%)	42 (59%)	71
Controls ..	8 (18%)	22 (50%)	14 (32%)	44

Table IV shows the effect of the treatment on joint swelling. The swelling is diminished in 66 per cent. of swollen joints when the larger doses of gold are used, in 59 per cent. of joints treated with the smaller doses, and in 32 per cent. of the control cases.

Table V shows the alterations in the radiographic appearances during treatment. Unfortunately radiographs before and after treatment are not available in a number of the cases. The following points have been studied: destruction of cartilage, decalcification of bone, and swelling of soft tissues.

TABLE V.—*Effect of Gold Therapy on the Radiographic Appearances of Joints in Rheumatoid Arthritis*

	Number of Cases			Totals
	Improved	Unaltered	Aggravated	
Decalcification of bone :				
Gold (large doses) ..	2 (29%)	3	2	7
Gold (small doses) ..	2 (22%)	7	0	9
Controls ..	0 (0%)	8	4	12
Erosion of cartilage :				
Gold (large doses) ..	1 (14%)	4	2	7
Gold (small doses) ..	0 (0%)	8	1	9
Controls ..	1 (8%)	9	2	12
Periarticular swelling :				
Gold (large doses) ..	6 (86%)	1	0	7
Gold (small doses) ..	7 (78%)	2	0	9
Controls ..	0 (0%)	9	3	12

As can be seen from the table there is a tendency towards improvement in bone decalcification, no definite change in the amount of cartilage destruction, and a marked improvement in the periarticular swelling in treated cases. It seems probable that the amount of bone decalcification denotes the extent to which a joint, or possibly the limb as a whole, is used, so that its improvement may simply be a measure of greater mobility of the joint following freedom from pain. As is well known, repair of cartilage, if it takes place at all, is a very slow process, so that probably a nine-months period of observation would be inadequate to show marked changes. Nevertheless in two cases there did appear to be a definite increase in joint space not attributable to altered position at the time of the radiograph. As one of these was a control case the result cannot be attributed to treatment.

Table VI gives a rough indication of the alterations in physical signs during treatment. Unfortunately a detailed study has not been carried out on the small-dose cases.

TABLE VI.—*Effect of Gold Therapy on the Physical Signs in Rheumatoid Arthritis*

	Number of Joints			Totals
	Improved	Unaltered	Increased	
Gold (large doses) ..	49 (54%)	39 (43%)	2 (2%)	90
Controls ..	39 (35%)	59 (55%)	10 (10%)	108

These results only take into consideration gross changes in physical signs such as the return to full movement in a joint which was previously limited or the disappearance of periarticular swelling in a joint in which this was previously marked. As can be seen the physical signs show improvement in a higher proportion of the treated cases and aggravation in a higher proportion of the controls. Our clinical impression was that the difference between the two groups of cases was greater than is indicated in the table. Possibly this was due to changes of amelioration being greater in degree than in number in the treated group.

While these results provide evidence that aurothioglucose (solganal B) does have an antagonistic effect on the disease process in rheumatoid arthritis and that this effect is more marked when 0.2 gramme is the weekly dose than when it is only 0.1 gramme, they do not take into consideration the toxic effects of gold on the patient.

Toxic Effects

Ever since gold therapy was introduced the toxic effects occurring in this form of treatment have figured prominently. Some workers have limited their use of gold compounds considerably on this account, and it is agreed that these effects are a deterrent to the more general use of the method. In recent papers (Ellman, 1938; Ellman and Lawrence, 1938) it was suggested that the more serious toxic effects occurred only after the sedimentation rate of the blood had become normal, and this was actually found to be the case in all such instances up to that time. Since then we have noted one exception to this rule. Out of a total of twenty-five cases of gold intoxication which we have encountered 96 per cent. have occurred in the presence of a normal sedimentation rate. It is remarkable how often dermatitis and stomatitis appear if the injections are continued after the sedimentation rate has become normal. This is particularly the case when the larger doses are used. We therefore stop the course of gold injections if the sedimentation rate falls below 12 mm. After three to four weeks' rest the injections are resumed, but a smaller dose—about 0.02 gramme weekly—is given.

The most important of the toxic effects are stomatitis, exfoliative dermatitis, toxic jaundice, and the blood dyscrasias (purpura, agranulocytosis, and aplastic anaemia). Table VII shows the incidence of these in the two groups of cases treated with gold. Cases of small ulcers on the gum due to artificial dentures are not included in this table as they are common to gold and control groups alike. The term "dermatitis" has been applied only to the itchy scaly eruption typical of gold intoxication. Urticaria and mild erythema are often met with in rheumatoid arthritis even when not treated with gold, and have therefore been omitted from this table.

TABLE VII.—*Incidence of Toxic Effects in Cases treated with Large and Small Doses of Gold*

	Gold (Large Doses)	Gold (Small Doses)
Stomatitis ..	8	1
Dermatitis ..	8	5
Agranulocytosis ..	1	0
Jaundice ..	1	0

As can be seen from the table stomatitis and dermatitis are common complications and are more frequent when large doses of gold are used. The case of jaundice was mild and evanescent. We have not met with the severe fatal form

recorded by Hartfall, Garland, and Goldie (1937). Our case of agranulocytosis (Ellman and Lawrence, 1935) was unfortunately fatal: purpura haemorrhagica was also present. We have not had any further case of this type since adopting the above-mentioned principle of using great caution when the blood sedimentation rate has become normal. Albuminuria was often met with when the larger doses were employed. It proved transient, and was not associated with other evidence of kidney damage. It was not considered an indication for stopping the treatment.

Discussion

The results provide definite evidence of the ability of aurothioglucose to alter favourably the course of the disease in cases of rheumatoid arthritis. Our observations of course refer to results at the end of nine months' observation. We have so far no evidence as to the relapse rate, as cases have not been followed up for more than a year or two after completion of treatment. Recurrence has, however, not been encountered among patients in whom the disease has been rendered completely inactive. We have had several relapses in patients who abandoned treatment while the disease still showed signs of activity.

In the absence of similar proof for other methods we therefore recommend the adoption of this treatment as a routine for all cases in which the disease shows evidence of a progressive course. Prolonged observation of these cases before instituting gold therapy, in the hope that spontaneous remission may occur, is not considered advisable, as permanent destruction of cartilage may result and complete restoration to normal will then be impossible. General constitutional, physical, and orthopaedic treatment, together with specific occupational therapy where possible, should of course be combined with the gold treatment in order to restore the maximal functional efficiency to the joints.

With regard to dosage, this is a difficult point to decide. The weekly dose of 0.1 gramme used by most workers nowadays has the advantage of causing fewer toxic effects. On the other hand, a dose of 0.2 gramme weekly will cure a larger proportion of cases, but produces toxic effects more readily. We consider that the most suitable dosage is still undecided.

Summary

A series of ninety typical cases of rheumatoid arthritis were divided into three equal groups. One group was used as a control, while the other two were treated with large and small doses of gold respectively.

Pain, limitation of movement, periarticular swelling, blood sedimentation rate, and radiographic signs have been studied in each group.

From the data obtained from these three groups at the end of nine months' treatment statistical evidence of the value of aurothioglucose (solganal B) in the treatment of rheumatoid arthritis is produced.

Suggestions are brought forward as to a method of reducing the frequency of toxic effects resulting from the gold compound.

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WARTIME PRECAUTIONS FOR DIABETICS

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In a country where air raids are daily events and invasion a possibility diabetics are liable to special dangers, against which they should be warned and forearmed. Mild cases not on insulin are in no real danger, as neither starvation nor departure from proper diet for a day or two is of grave consequence. But it must be clearly understood that most insulin cases owe their health entirely to regular daily injections and that it is not safe to stop them. True, some diabetics who need only small doses (under 20 units a day) can miss insulin for a few days without danger, although of course sugar would almost certainly recur. But more severe cases depending on larger doses—30 to 60 or more units a day—may get into serious trouble from missing even one dose, and to miss two or three doses would certainly be dangerous. Sugar returns as soon as the insulin action is exhausted, even if no food is eaten; acetone bodies rapidly follow, and coma from ketosis may result within a day or two. A second danger is that hypoglycaemia may occur if adequate carbohydrate is not available or is not eaten to balance the insulin, and it might come on with protamine-insulin the following night if supper was omitted. The following advice and precautions on various difficulties are therefore given.

Routine Precautions

Diabetics can rest assured about the stocks of insulin in this country; these are enough for two years, and fresh supplies are being made, as before the war, by British manufacturers. But circumstances might arise in which its local distribution would be temporarily upset, and I should advise insulin patients to have a month's supply in hand. Most diabetics who buy their own insulin have already seen to this, and I hope doctors will arrange that insured cases have a reserve. Many doctors have been in the habit of prescribing a month's supply for their panel patients, and the prescription of a small reserve is quite in order and should be done.

It is wise for all diabetics to carry insulin and a syringe with them whenever there is the slightest possibility that they may not get back home at the time planned for the next injection. Every diabetic who travels or works away from home should certainly do this. Diabetics should also carry a small supply of carbohydrate, such as sugar, chocolate, biscuits, in their pockets, so that if the regular timing of meals is upset enough carbohydrate can be eaten to balance the insulin and prevent hypoglycaemia.

It is essential also that every insulin patient should carry on his person the information that he is a diabetic taking insulin. This has always been advised in peacetime, but is much more important now. Imagine what would happen after an air raid injury to any severe insulin patient with no such information on his person. A suitable card is provided by the Diabetic Association, 124, Baker Street, London, W.1, and this or something similar should be carried inside the national identity card. It should state the kind and dose of insulin in units and the amount of carbohydrate per day, and the patient's usual doctor or hospital he attends. Any diabetic who neglects this runs the gravest risk.

Enforced Omission of Insulin or Food

If a diabetic cannot get his usual insulin, it is best for him, as a general rule, to continue to eat his usual carbohydrate but no fat and only a little protein. This proce-