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STUDIES WITH RADIOACTIVE GOLD*

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Although steroids, because of their more rapid action and ease of administration, have to some extent replaced gold compounds in the treatment of rheumatoid arthritis, there is evidence that, as regards both resistance to treatment and incidence of serious complications, gold compounds have the advantage (Kammerer and Cecil, 1958). The value of gold therapy has recently been confirmed by a double-blind trial (Empire Rheumatism Council, 1960). Minor complications are, however, frequent in patients treated with gold and may often necessitate interruptions in the course of treatment.

It would, therefore, appear advantageous to obtain more information on the pharmacology and mode of action of these compounds and particularly on the mechanism by which patients become either resistant or hypersensitive to them. Except that patients receiving small doses are more likely to be resistant and that the frequency of sensitivity reactions is independent of total dosage, little is known of the factors involved (Ellman, Lawrence, and Thorold, 1940).

Although chemical methods for the estimation of gold in blood and urine are available, these are technically difficult, and are of a degree of sensitivity which render the accurate assessment of the minute amounts occurring in the body fluids of patients under treatment with gold a matter of some uncertainty. Radioactive gold, on the other hand, can be estimated in amounts far below those found during therapy, and can, moreover, be detected in the tissues by scanning methods which enable the distribution throughout the body to be determined at frequent intervals after administration.

Distribution and Concentration in Body Fluids

The distribution of administered gold in the tissues has been studied both in experimental animals and in man. In guinea-pigs, De Witt (1918) studied the concentration of gold after the administration of four organic gold compounds. The highest concentration was found in the spleen with three of the four derivatives and in the lymph glands in the last. Lesser amounts were found in the liver, kidneys, and skin, and little elsewhere. In dogs, Eichelberger and McCluskey (1926) and Bertrand, Waine, and Tobias (1948) found that aurothiosulphate reached its greatest concentration in the kidneys with smaller amounts in the liver and spleen. Aurothioglucose was found by Swartz, Christian, and Andrews (1960) to concentrate most in the kidneys, but almost as much in the suprarenals after an interval of 30 minutes; lesser amounts were found in the spleen, liver, muscle and blood. Koppenhöfer (1936) found deposits chiefly in the liver, spleen, kidneys, and bone marrow. In healthy animals the gold was found chiefly in the parenchymal cells, in tuberculous animals in the reticulo-endothelial cells. Deposits have also been found in the suprarenal cortex and in the pituitary body. According to Michelazzi (1934), gold also enters the reticulo-endothelial cells of the synovial membrane. The quantity is small in healthy membrane, but much larger deposits are found in inflamed membrane with cellular proliferation. Bertrand and others (1948) similarly found a relatively high concentration in the synovial membrane, tendon, muscle, and bone in chemically-induced arthritis in rabbits. In a biopsy of synovial membrane from a patient with rheumatoid arthritis taken 24 hours after the injection of ^{198}gold sodium thiosulphate, they found much higher concentrations in the synovial membrane and fluid than in muscle, fascia, or skin. When sulphur is labelled in the thioglucose compound instead of gold, there is greater retention in all tissues except the liver, spleen, and kidneys, indicating that it is the gold itself which accumulates in the latter tissues (Swartz and others, 1960). The pharmacology of gold compounds has been studied in patients with rheumatoid arthritis by Freyberg, Block, and Levey (1941), Freyberg (1942), and Freyberg, Block, and Wells (1942), using a colorimetric method of assessment. In the blood, gold was found mainly in the plasma. Only insignificant traces were found in the cells. In the plasma, gold was found almost exclusively in the protein fraction. The plasma concentration of

* The cost of radioactive gold compounds for this investigation was covered by a grant from the Medical Research Council.

gold was found to vary in proportion to the weekly dose, remaining fairly constant when the weekly dosage was kept constant with no tendency to accumulate in the blood. Plasma concentrations following intramuscular injection were of the order of 0·5-1 mg./100 ml. for every 50 mg. gold administered in the weekly dose, whether this was in the form of aurothiomalate (Myocrisin), gold sodium thiosulphate, or aurothioglucose (Solganal B). If the drug was suspended in oil, the plasma concentration was rather lower (0·3-0·7 mg./100 ml.). Gold was excreted chiefly in the urine; faecal excretion was small and irregular though related roughly to the amount injected. In the urine, larger amounts were excreted on the day of injection, and tailed off rapidly thereafter, so that in a patient on weekly injections only some 15 per cent. of the administered dose actually appeared in the urine. Gold was found in the blood and urine after administration ceased, but in gradually decreasing amounts, for several months to a year. When a total of less than 500 mg. gold (1 g. Myocrisin) had been given, the excretion ceased earlier.

Calcium aurothiomalate in oil injected intramuscularly did not appear in the blood or urine at all during the first day, and even after this high values were seldom encountered. These, however, persisted much longer after administration ceased. In the skin, gold was found in concentrations of nil (in severe dermatitis) to 0·4 mg. per g. There was no relationship between gold content and skin reactions. Smith, Peak, Kron, Hermann, Del Toro, and Goldman (1958) compared the excretion of gold in four groups of rheumatoid patients: (1) responding to gold therapy, (2) relapsed during maintenance therapy, (3) with a low tolerance for gold, (4) showing little or no response. They found hyper-excretion in Groups 2 and 4 and hypo-excretion in Group 3.

Verhaeghe and Lebeurre (1954) used radioactive colloidal gold in human arthritis investigated by a scanning technique. Injected intramuscularly, gold appeared to pass selectively into one pathological joint, but another joint, apparently equally affected, showed little evidence of radioactivity. If injected into an arthritic knee joint, the gold could be detected over the liver, the bladder, and the other knee joint. Clemmeser (personal communication) found that gold combined chiefly with the $alpha_1$ globulin fraction in the plasma.

Material and Methods

The distribution of gold in the body was investigated in ten patients (Table I) by two techniques after the injection of radioactive gold:

(1) Zonal distribution throughout the body, using a scintillation counter;
(2) Concentration in blood, synovial fluid, and urine, using a wet counter.

In addition, biopsy specimens of skin, subcutaneous tissue, synovial membrane, and articular cartilage from a patient undergoing excision of an inflamed popliteal bursa were subjected after solution in aqua regia to gold assay in the wet counter.

Samples of blood (10 ml. from each patient) were collected in tubes containing Heller and Paul's potassium ammonium oxalate.

The gold was administered intramuscularly in the form of sodium aurothiomalate containing ^{198}Au.* The solution was supplied in two batches each containing 50 mg. sodium aurothiomalate in 5 ml., and having a total activity of 5 and 12 mc. respectively at the time of despatch. Approximately 1 ml. of this solution was

* Supplied by the Radiochemical Centre, Amersham, Bucks. Sodium aurothiomalate contains 50 per cent. gold.

TABLE I

PATIENTS STUDIED WITH RADIOACTIVE GOLD

Case No.	Criteria	Sex	Age (yrs)	Duration of Symptoms (yrs)	Number of Joints Affected	Sheep Cell Agglutination Test	Erythrocyte Sedimentation Rate at Time of Study (mm./hr)	Plasma Fibrinogen at Time of Study (mg. per cent.)
1	Responsive to Gold	M	71	2	7	1 : 128	32	670
2		M	61	15	4	1 : 64	10	330
3		M	52	7	13	1 : 4	7	350
4		M	45	7	8	1 : 128	5	330
5	Resistant to Gold	F	50	15	15	1 : 4	70	1,250
6		F	63	13	19	1 : 128	30	560
7		F	43	9	21	1 : 128	19	540
8	Hypersensitive to Gold	M	57	13	25	1 : 64	93	900
9		M	45	7	6	0	7	330
10	No Previous Gold	M	27	1	4	1 : 4	7	610

injected into each of ten patients suffering from rheumatoid arthritis, the site being the gluteal muscle in all except one, whose age made this site undesirable from the point of view of gonadal radiation. In eight of the patients the radioactive gold compound was injected alone. In Cases 2 and 3 it was mixed with the normal dose of natural gold. Seven patients were under treatment with gold at the time. All but one (Case 10) had had treatment with gold at some time previously. The patients were chosen to clarify various aspects of gold therapy, as shown in Table I. Of those described as resistant to gold, two (Cases 6 and 7) had made a satisfactory response initially, but had relapsed when the dosage was reduced or the treatment temporarily discontinued because of complications and had subsequently been resistant to further treatment. The third (Case 7) had shown no objective improvement throughout, despite continued high dosage. Of those hypersensitive to gold, one had a fixed skin eruption and was unable to receive even the smallest dose without suffering severe irritation with spread of the eruption. The other developed an eruption only when the disease became quiescent and could tolerate a sufficient dose to control the arthritis as soon as the disease became active again. Of the ten patients studied, six had a positive sheep cell agglutination test and seven had evidence, either from the erythrocyte sedimentation rate or from the plasma fibrinogen, of active disease at the time of the investigation.

Results

Blood Concentration of Gold.—The gold level in the plasma (Table II) varied from 0·11 to 0·17 mg./100 ml. (mean 0·15) on the first day after the injection. Thereafter it fell gradually, reaching a mean value of 0·02 mg./100 ml. by the end of the second week. The average value during the first week was 0·11, and for the second week 0·04 mg./100 ml.

The values in Cases 2 and 3, in which the radioactive gold was mixed with 25 mg. natural gold (Solganal B and Myocrisin respectively), do not differ substantially from the mean, indicating that the plasma level is directly proportional to the dose used. The lowest plasma levels were encountered in Cases 8 and 9, those who were hypersensitive to gold. In Case 9, a slightly lower dose of gold had been administered, but Case 8 had received the full amount. In Cases 5 and 6, who had received large amounts of gold in the past and who had become resistant, the plasma concentration fell more slowly and had reached about one-third of the initial value by the 16th day, whereas the mean had already fallen to one-seventh of the initial value by the 14th day. There was no obvious relationship between the plasma level and the activity of the disease.

Three samples of plasma taken on the 14th day were dialysed for 24 hours against tap-water. There was no reduction of the gold concentration, indicating that all the gold was combined with protein. In a sample of 5 ml. plasma, which was clotted by the addition of 0·03 ml. calcium chloride 40 per cent., the gold content of the serum was retested, and this was found to have one-third of the plasma concentration, indicating that much of the gold had attached itself to fibrin.

TABLE II

PLASMA CONCENTRATION OF GOLD AFTER INTRAMUSCULAR INJECTION

(mg./100 ml.)

Case No.	Dose of Sodium Aurothiomalate (mg.)	Day After Injection										
		1st	3rd	4th	5th	6th	9th	10th	11th	13th	14th	16th
1	10		0·10		0·10		0·05			0·03		
2	11	0·16	0·08			0·09			0·06		0·01	
3	11	0·17	0·09			0·09		0·06			0·009	
4	11	0·11		0·08		0·07			0·04		0·005	
5	11		0·12		0·11		0·07					0·05
6	12		0·11		0·14		0·08					0·04
7	11	0·15		0·13		0·11			0·06		0·01	
8	10		0·07		0·05		0·03					0·02
9	7		0·08		0·05		0·04					0·01
10	11	0·17		0·12		0·11			0·08			
Mean ..	10·4	0·15	0·13	0·11	0·09	0·09	0·05	0·06	0·06	0·03	0·02	

The red cell concentration of gold (Table III) was on an average about one-quarter of the plasma level on the first day after administration. Thereafter it fell, but less rapidly than the plasma level, so that by the end of the second week it approached and in some instances exceeded the latter.

TABLE III

RED BLOOD CELL CONCENTRATION OF GOLD
(mg./100 ml.)

Case No.	Day After Injection							
	1st	3rd	4th	6th	7th	10th	11th	14th
1					0·02			
2	0·03	0·01		0·02			0·01	0·006
3	0·03	0·02		0·03		0·02		0·01
4	0·02		0·01	0·01			0·01	0·01
7	0·06		0·02	0·03			0·01	0·01
9		0·02						
10	0·05		0·02	0·01			0·006	
Mean ..	0·04	0·02	0·02	0·02	0·02	0·02	0·01	0·008

Synovial Fluid.—Of the ten patients studied, seven had substantial effusions into one or both knee joints. Samples of synovial fluid were aspirated in the first instance on the 5th or 6th day after administering the gold, and again in five of the patients at the end of the 2nd week (Table IV). The gold levels in the synovial fluid were all slightly lower than those in the plasma on the 5th and 6th day, the mean value in the synovial fluid being 0·07 mg./100 ml. as against 0·09 mg. in the plasma. At the end of the second week, the mean values in synovial fluid and plasma were identical (0·02 mg./100 ml.), but in one sample the synovial fluid level was then four times the plasma level.

TABLE IV

SYNOVIAL FLUID CONCENTRATION OF GOLD
(mg./100 ml.)

Case No.	Day After Injection			
	5th	6th	14th	15th
2		0·06	0·003	
4		0·05	0·02	
5	0·08			0·04
6	0·07			0·02
7		0·10		
8	0·04			0·01
10		0·10		
Mean ..	0·07		0·02	

Tissue Concentrations.—In Case 7, a popliteal bursa had for some time been causing much discomfort. It was therefore decided to excise it, and this was done by Mr. F. R. Zadik on the 15th day after the administration of radioactive gold. The bursa, which weighed 30 g. and contained 15 ml. fluid with fibrin clot, was found to communicate with the knee joint, the aperture being obstructed by a plug of fibrin. Samples were taken of articular cartilage, skin, and subcutaneous fat. Each tissue was dissolved in 10 ml. aqua regia, and the concentration of radioactive gold was estimated. The fibrin clot from the bursa was similarly treated. The concentrations of gold were as follows:

Tissue	Concentration of Radioactive Gold (mg./100 g.)
Skin	0·05
Subcutaneous Fat	0·12
Synovial Membrane	0·02
Cartilage	0·64
Fibrin Clot (from Bursa)	0·67

There was thus a very high concentration in both the fibrin clot and the articular cartilage. The latter must be accepted with caution as only a very small sample (0·03 g.) was available.

Urinary Excretion of Gold.—As the patients taking part in this study were all out-patients, the collection of 24-hr specimens of urine was of necessity somewhat patchy and complete information is thus not available (Table V, opposite). As in Freyberg's series, maximal excretion occurred on the first day, when some 5 per cent. of the administered gold was excreted. By the end of the first week an average of 1·68 mg. (*i.e.* some 15 per cent. of the dose) had been passed in the urine, and by the end of the second week 1·94 mg. (*i.e.* some 20 per cent. of the dose) had appeared. Excretion by this time was slight and further measurements were impossible. There was no obvious relationship between excretion and disease activity. Cases 5 and 6, who were resistant to gold, did not excrete it more rapidly; indeed, their excretion was on most days below the average.

Zonal Distribution of Gold.—Five patients (Cases 1, 5, 6, 8, 9) were investigated with the aid of the scintillation counter.

TABLE V

DAILY EXCRETION OF GOLD IN URINE

(mg./24 hrs)

Case No.	Day After Injection														
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th
1		0·15	0·21	0·14	0·16	0·10	0·10	0·15	0·11	0·12	0·12	0·14	0·003	0·008	0·005
2	←———	1·35	———→	0·23	0·20	0·13	0·11			0·07					
3		0·11	0·11		0·10		0·07			0·008					
4	0·82	0·13	0·14	0·23	0·24	0·13	0·11	0·09		0·01	0·03	0·01			
5			0·12	0·06	0·05	0·05	0·02	0·002	0·002	0·002					
6		0·17	0·08	0·11	0·07	0·1	0·09	0·07	0·01						
7	0·33	0·16	0·14	0·104	0·16	0·12	0·3								
8		0·3		0·10	0·10	0·10		0·01		0·01					
9			0·17	0·18	0·16	0·10	0·12	0·08	0·12		0·006	0·002	0·006		
10	0·24	0·36	0·1	0·1	←———		0·45		———→						
Average ..	0·46	0·20	0·13	0·13	0·14	0·10	0·12	0·07	0·05	0·03	0·05	0·05	0·005	0·008	0·005

Absorption of gold began almost immediately after injection and within 5 minutes it could be detected in all parts of the trunk and in the proximal parts of the limbs. Within 15 minutes counts were obtainable over the hands and feet.

The highest counts were made during the first 2 weeks over the site of injection and the lowest over the fingers and feet, with intermediate values over the remainder of the trunk, diminishing towards the periphery. The values were in general proportional to the mass of tissue in the vicinity of the counter. Radioactivity continued to be distributed in this way up to the 20th day, when the site of injection ceased to give the highest values, which were then encountered over the liver, spleen, or kidneys. After the 21st day, owing to reduction of radioactivity, the values even at these sites came so close to the background level that the results were extremely variable and ceased to be reproducible.

As an illustrative example, average values of all readings taken between the 2nd and 16th days after injection are shown for Patients 1, 5, and 6 in Figs 1, 2, and 3 (overleaf), together with the mean concentrations in the plasma and where available the synovial fluid concentration of gold. All the counts were corrected after deduction of the background count for deterioration of radioactivity to the theoretical count on the day of administration of the gold. The higher of the two gluteal counts indicates the side which was injected and this is associated with a higher count in the iliac fossa on the same side. Counts in the loins and midthighs and at other sites, on the other hand, show no relationship to the side injected.

In all patients so examined, higher counts were obtained over the right than over the left hypochondrium and the former in general gave, apart from the injection site, the highest count of any part of the body. The pectoral regions and loins gave, on the whole, somewhat similar values to those of the left hypochondrium and to the iliac fossa on the opposite side of the body from the injection site. In scanning the limbs, the hips were excluded because of their proximity to the site of the injection. All joints of the fingers were grouped together and also all joints of the feet. Thus, in each patient, fourteen joints or groups of joints were scanned. Of the seventy "joints" scanned in this group of five patients, forty were in sequence with the non-articular zones, six gave values which were too low, and 24 gave values which were too high to be in sequence. 35 of the seventy joints scanned were giving rise to symptoms at the time of examination; of these, seventeen gave too high a count compared with seven of the 35 painless joints. This difference is significant ($P = 0{\cdot}04$). The high counts found over painful joints were not limited to the early stages of the investigation when the gold was mainly in the blood stream, but persisted throughout the 19 days of the study.

The two patients resistant to gold who were

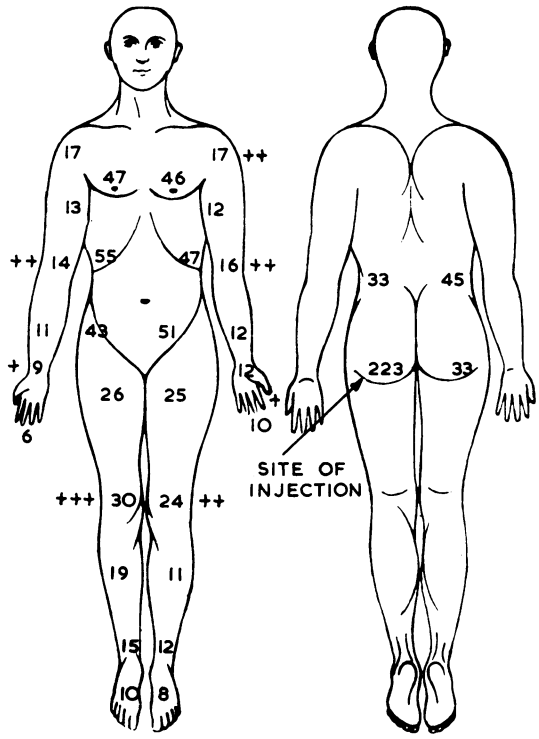

Fig. 1.—*Patient* 1, average counts per second of all readings from the 2nd to 16th day inclusive.

Dose: 1 mc. in 10 mg. sodium aurothiomalate.
Average plasma gold: 0·07 mg./100 ml.

In this and subsequent figures, the plus signs indicate presence and severity of pain and tenderness.

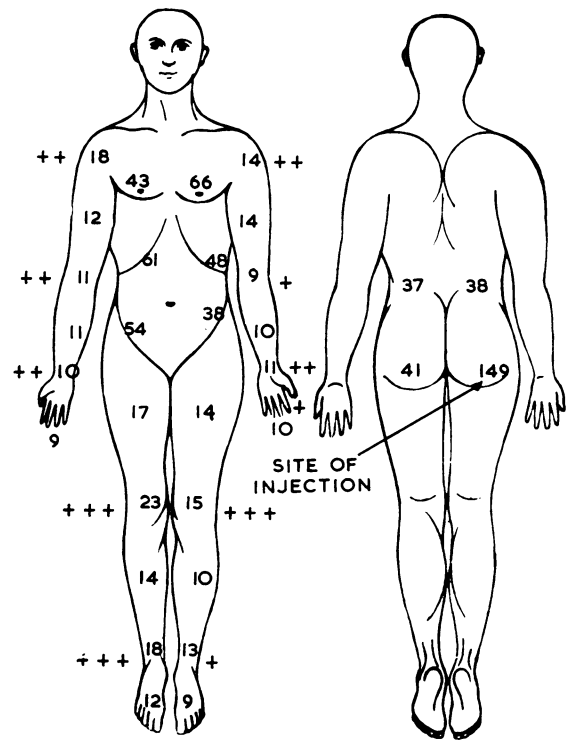

Fig. 2.—*Patient* 5, average counts per second of all readings from the 2nd to 16th day inclusive.

Dose: 1 mc. in 10 mg. sodium aurothiomalate.
Average plasma gold: 0·08 mg./100 ml.
Average synovial fluid gold: 0·06 mg./100 ml.

Fig. 3.—*Patient* 6, average counts per second of all readings from the 2nd to 16th day inclusive.

Dose: 1·2 mc. in 12 mg. sodium aurothiomalate.
Average plasma gold: 0·09 mg./100 ml.
Average synovial fluid gold: 0·05 mg./100 ml.

Fig. 4.—*Patient* 6, average counts per second during the first and second day.

Dose: 1·2 mc. in 12 mg. sodium aurothiomalate.
Plasma gold: 0·11 mg./100 ml.

Fig. 5.—*Patient* 6, average counts per second during 3rd to 7th day.

Dose: 1·2 mc. in 12 mg. sodium aurothiomalate.
Average plasma gold: 0·14 mg./100 ml.
Average synovial fluid gold: 0·07 mg./100 ml.

Fig. 6.—*Patient* 6, average counts per second during the 8th to 16th day.

Dose: 1·2 mc. in 12 mg. sodium aurothiomalate.
Average plasma gold: 0·06 mg./100 ml.
Average synovial fluid gold: 0·02 mg./100 ml.

examined with the scintillation counter (Cases 5 and 6, Figs 2 and 3) showed no evidence of hold-up at the site of injection, and had an adequate concentration in the plasma and synovial fluid and in the region of the affected joints.

The progress of events during the first 16 days after administration is illustrated in Patient 6 (Figs 4 to 6). There was a progressive fall in the count over the site of injection. Over the trunk in general, the count did not change though there was a slight rise over the liver and spleen. Over the limbs on the other hand, the count tended to rise progressively. This increase did not occur more in the joints than over the inter-articular zones and was not particularly related to the sites of pain. It was, however, somewhat patchy in distribution. These changes occurred despite a falling plasma and synovial fluid level and continued excretion of gold in the urine.

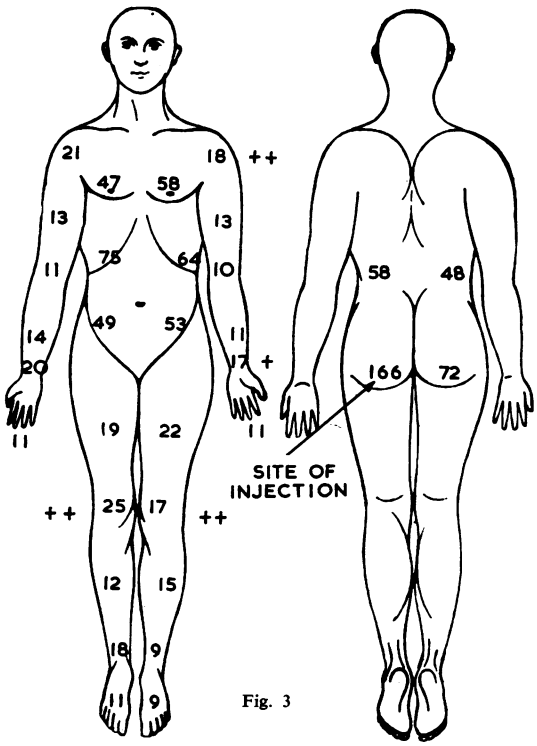

Fig. 3

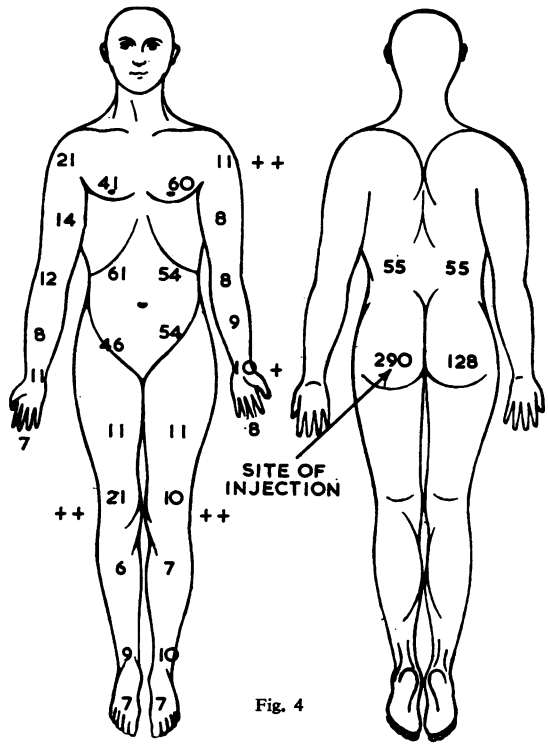

Fig. 4

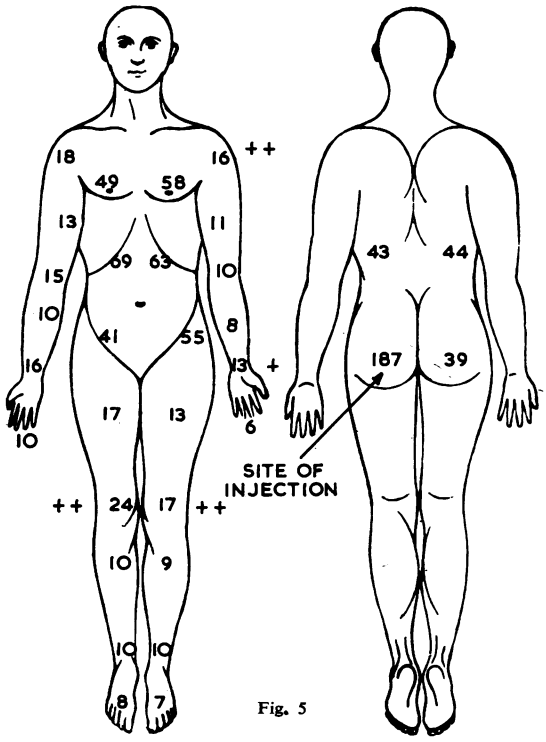

Fig. 5

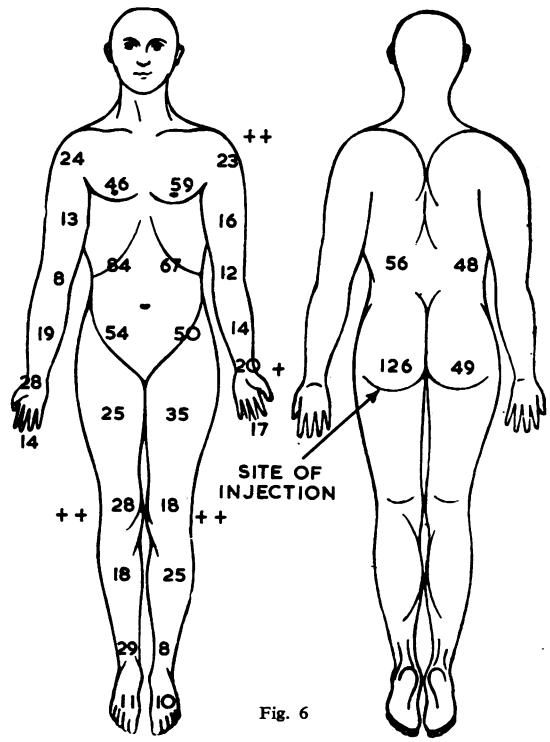

Fig. 6

Changes in counts in the remaining four patients were similar. In some, however, there was a progressive increase in counts in both trunk and limbs. In one (Case 1), the corrected count at the site of injection also showed a progressive increase, reaching a maximum on the 11th day and thereafter subsiding. This may have been due to diffusion towards the skin, possibly from lymphatic spread.

In those joints over which the counts were relatively high and out of sequence, it may be said that the difference was greater at first when the blood level was high and became less in the later stages as the blood and synovial fluid levels fell.

Discussion

The plasma levels assessed by using radioactive gold are higher than those of Freyberg and others (1941, 1942) using a colorimetric method. In general it may be said that their plasma level is in the region of 0·5 to 1 mg./100 ml. for every 50 mg. administered. In Cases 2 and 3, in which a combined dose of radioactive and inactive gold totalling 30 mg. each had been given, the total gold level may be calculated from the figures for radioactive gold as 0·5 to 1·0 mg./100 ml. in the first week.

The high proportion of gold which is combined with protein in the plasma is confirmed by the dialysis experiments carried out in this study. According to Libenson (1945), the gold-protein complex *in vitro* does not release gold ions in solution, but in view of the presence of gold in the urine, and as this was found in the absence of proteinuria, it is evident that some uncombined gold is present *in vivo*. According to Simon (1954), gold in plasma is combined with the β and α_2 fractions. It would appear, however, from the plasma-serum difference encountered in this study, that a proportion of the gold is combined with fibrinogen.

The distribution of gold in the body as measured by scanning confirms the experimental findings. However, the interpretation of tissue concentrations, whether determined by scanning or by direct estimation on tissue samples, must be accepted with caution. As the gold is probably at first confined to the blood stream by reason of its protein binding, tissue levels of gold will at first be a measure of vascularity and thus, indirectly, of the presence of inflamed tissue. Only when the blood level has become very low will a true measure of tissue concentration be obtained. This may explain the difference between the low concentration in synovial membrane in my own patient on the 15th day and the high values encountered by Bertrand and others (1948) on the first and fifth day after injection. The fact that high scanning counts over certain joints persisted into the third week may depend on the deposition of gold in other joint tissues (*e.g.*, the articular cartilage) or on the presence of gold combined with the fibrin deposits which abound in rheumatoid joints. The relatively high value in subcutaneous fat in Case 7 suggests that gold may to some extent combine with the fat. It was not found in the fatty layer, which separated from the extracting fluid, but this would not be expected, since any gold compound would be broken down in the presence of aqua regia.

Previous workers do not seem to have made any estimate of gold concentrations in articular cartilage, whether normal or diseased, and the values obtained on a single small sample cannot be taken as indicative of those encountered in diseased cartilage as a whole. Dunstone (1959) found that, whereas normal cartilage shows equal binding capacities for sodium, potassium, magnesium, calcium, strontium, and barium ions and these correlate equally with the sulphate content, copper and beryllium were bound to a greater extent. This he attributed to the greater binding by chondroitin sulphate of multinuclear ions. It is possible that a similar affinity exists for gold.

If, however, a concentration of the order of 0·6 mg./100 g. is commonly encountered after a dose of 10 mg. of a gold compound, and if with higher dosage there is a proportionate increase, doses up to 200 mg. should result in values of the order of 12 mg./100 g., possibly with further increases on repeated administration. Since a therapeutic effect is seldom apparent before the fifth injection, it would seem likely that the concentration resulting from a single dose is inadequate. In searching for a possible mode of action of gold, we must, therefore, consider pharmacological effects occurring with concentrations possibly of the order of 20 mg./100 g.

No satisfactory explanation of the mechanism by which gold produces its effect has been forthcoming. Chrysotherapy was first introduced by Forestier (1929) on the assumption that tuberculosis has an aetiological relationship to the disease, but of this there has been no satisfactory proof. Other workers have suggested an effect on tissue uptake of oxygen or on glutathione metabolism. Clinical experience with gold treatment would suggest that gold may have a general anti-inflammatory effect,

since it has a pronounced effect, when given in high dosage, on both the erythrocyte sedimentation rate and the degree of joint swelling (Ellman and Lawrence, 1938). Moreover, it is common experience that ulcers on the gums due to badly fitting dentures do not heal so rapidly in patients receiving gold. Skin infections such as boils also tend to be refractory. Perforation or haemorrhage from peptic ulceration of the stomach or duodenum also appear more frequently, in the author's experience, in persons receiving high dosages of gold.

It is known that heavy metals are powerful enzyme inhibitors and that this inhibition tends to be specific and may occur at a high dilution, apparently by blocking those groups in the enzyme which are responsible for its specificity. In the living cell the effect is enhanced by the fact that, even though the metal is in low dilution in the surrounding medium, a considerable quantity may be fixed by the cell (Dreschel, 1921). Enzymes are thought to play a part in the process of inflammation at several stages and it seems likely that enzyme responses are similar to those encountered in non-rheumatoid subjects.

According to Ungar (1952), when a cell is damaged, an enzyme cytofibrokinase is released. This in turn releases the proteolytic enzyme fibrinolysin from a precursor profibrinolysin, which is present in plasma in association with the euglobulin fraction and is thought also to exist in the tissues. Fibrinolysin, like trypsin, is capable of breaking down a wide variety of protein substances. According to Ungar, by breaking down cell protein, it releases histamine, heparin, and certain polypeptides. The polypeptides have the property, not only of producing pain, but also of increasing capillary permeability, and would thus be capable of causing the changes found in inflammation.

A natural proteolytic inhibitor is found in normal serum (Landsteiner, 1900) and several drugs have been shown also to act as anti-fibrinolysins. These include salicylic acid, antipyrine, amino-pyrine, 3-hydroxy 2-phenylcinchoninic acid, and p-aminophenol. The administration of cortisone or ACTH also results in an increased anti-fibrinolytic activity of the serum (Ungar, 1953).

The natural proteolytic inhibitor is increased in diseases associated with increased tissue destruction, and in general parallels the erythrocyte sedimentation rate and the fibrinogen plasma level (Shulman, 1952). In rheumatoid arthritis, for example, serum anti-fibrinolytic activity is related to the activity of the disease process. Fibrinolysin on the other hand, is reduced in rheumatoid arthritis, particularly in the less active forms, rising to a normal level when the disease becomes very active (Thomas and Dingle, 1955).

With a view to elucidating the possible inhibitory effects of gold on inflammatory enzymes, a number of experiments have been made by the author. Although these have appeared to indicate an inhibitory effect on clot lysis by streptokinase from aurothioglucose in concentrations as low as 2 mg./100 ml. in some experiments, the effect has not been consistent and aurothiomalate has not been found to have a similar action. This could be interpreted as indicating that aurothiomalate is converted into another compound in the body, but it is not proposed to lay claim to the correctness of these views till further work has been done.

The information on the causes of gold resistance and gold hypersensitivity which has been derived from this study is mainly of a negative character. Indeed, the absence of any relationship between excretion of and tolerance to gold would appear at first sight to contradict the findings, already referred to, of Smith and others (1958). In their two patients with toxic reactions, excretion of gold was diminished, whereas in the present study it was, if anything, increased. In their study, however, excretion was measured just before the onset of dermatitis, whereas in the present cases skin reactions had been present for several months or years. A possible explanation is that a rapid passage of gold into the tissues is associated with the onset of sensitivity and that this results in a transient decrease of the excretion in the urine. With regard to gold resistance, Smith and others (1958) found that 17 to 28 per cent. of the administered dose was excreted in one week after the injection of gold in resistant patients receiving 12 to 50 mg. weekly compared with an average excretion of 14 per cent. of the dose in responding patients. In the present study, only 13 per cent. of the administered dose was excreted by resistant patients, the same amount being the average for the whole series. When the dose was increased to 100 mg. weekly, the patients in Smith's series went into remission, but in the present study the resistant patients received 200 mg. weekly for prolonged periods without benefit. It is thus apparent that, though drug resistance may, in patients receiving relatively small doses, be due to high excretion, other factors (possibly the presence of extensive fibrin deposits capable of binding the gold ions and rendering them biochemically inactive) may be responsible for the more extreme examples of drug resistance.

Summary

The distribution of gold in the body was investigated in ten patients with rheumatoid arthritis. These included four who were responsive to gold, three who were resistant, two who had developed hypersensitivity reactions, and one who had not previously received gold. Aurothiomalate, containing ^{198}Au, was injected intramuscularly as a single dose of 10 mg., and its subsequent distribution was followed by means of a scintillation counter. The concentration in blood, synovial fluid, and urine was also determined.

The plasma level varied from 0·11 to 0·17 mg./100 ml. on the first day and thereafter fell gradually to a mean value of 0·02 mg./100 ml. by the end of the second week. Where radioactive gold was mixed with inactive gold, the plasma levels of the radioactive variety were in the same range, indicating that the blood level was directly proportional to the dosage used.

The lowest plasma levels were encountered in two patients who were hypersensitive to gold. The slowest fall in the plasma level occurred in two patients who had become resistant to gold therapy. There was no relationship between the plasma level and the activity of the disease process.

The gold in the plasma appeared to be completely bound to protein mostly to fibrinogen. The red cell concentration of gold varied from one-quarter of the plasma level on the first day to a value equal to or greater than the plasma level by the end of the second week. The concentration in the synovial fluid was slightly less than that in the plasma at the end of the first week, but became equal to or greater than the plasma level by the end of the second week. Fluid and fibrin clot from a popliteal bursa removed at operation showed a gold concentration of 0·67 mg./100 ml. (plasma level 0·01 mg./100 ml.). A similar high concentration was found in a biopsy sample of articular cartilage from the same patient.

The injected gold was excreted slowly in the urine, 15 per cent. in the first week, and 20 per cent. by the end of the second week, by which time very small quantities were being passed. Excretion was unrelated to disease activity or response to therapy, but was more rapid in patients with sensitivity reactions.

Apart from the site of injection, the highest scanning counts were obtained over the right hypochondrium, but high values were also noted over the left hypochondrium, pectoral regions, and loins. In the limbs, the counts were greatest proximally and diminished as the scanner was moved peripherally. Of the seventy joints scanned, forty gave counts in sequence with the non-articular zones, six gave counts which were lower and 24 counts which were higher than those expected from their position in the limb. Painful joints gave high counts 2·5 times more often than symptomless joints. This phenomenon was not limited to the period of time immediately following the injection but persisted when the level in the blood had become negligible.

It is suggested that gold compounds may have a local action on inflamed tissues by inhibition of the enzymes concerned in the inflammatory process.

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Études avec l'or radioactif

RÉSUMÉ

La distribution d'or dans l'organisme fut étudiée chez dix malades atteints d'arthrite rhumatismale. Sur ces dix cas, quatre étaient réceptifs à l'or, trois y étaient résistants, deux avaient manifesté des réactions d'hypersensibilité et un recevait de l'or pour la première fois. On injectait par voie intramusculaire une seule dose de 10 mg. d'aurothiomalate contenant la forme radioactive ^{198}Au et on déterminait sa distribution dans l'organisme au moyen d'un scintilloscope. Le taux d'or dans le sang, le liquide synovial et l'urine était aussi déterminé.

Le taux sanguin oscillait entre 0,11 et 0,17 mg. par 100 c.c. le premier jour, baissant progressivement pour atteindre une moyenne de 0,02 mg. par 100 c.c. à la fin de la deuxième semaine. Quand on mélangeait l'or radioactif avec de l'or inactif, les taux sanguins de la forme radioactive étaient au même niveau, indiquant que le taux sanguin était directement proportionnel au dosage employé.

Les taux sanguins les plus bas furent trouvés chez les deux malades hypersensibles à l'or. La baisse la plus lente du taux sanguin se produisit chez deux malades devenus résistants à l'aurothérapie. Il n'y eut pas de rapport entre le taux sanguin et l'activité de la maladie.

L'or sanguin semblait être complètement lié à la protéine, surtout au fibrinogène. Le premier jour, le taux d'or érythrocytaire était quatre fois moindre que le taux plasmatique, mais vers la fin de la deuxième semaine il lui devenait égal et même supérieur. Dans le liquide synovial il y avait un petit peu moins d'or que dans le plasma pendant la première semaine, mais il y en avait autant ou plus vers la fin de la deuxième semaine. Le liquide et un caillot fibrineux d'une bourse poplitée enlevée à l'opération ont montré un taux d'or de 0,67 mg./100 c.c. (taux plasmatique 0,01 mg./100 c.c.). Des taux aussi élevés ont été trouvés dans un échantillon biopsique d'un cartilage articulaire du même malade.

L'or injecté était excrété lentement dans l'urine: 15% pendant la première semaine et 20% au bout de la seconde, après quoi l'élimination se faisait en très petites quantités. L'excrétion procédait indépendamment de l'activité morbide ou de la réponse thérapeutique, mais elle était plus rapide chez des malades accusant des réactions de sensibilité.

En dehors de l'endroit de l'injection, le scintilloscope donnait les plus grands chiffres à l'hypocondre droit, mais le chiffre était aussi élevé à l'hypocondre gauche, dans la région pectorale et lombaire. Dans les membres, le maximum des scintillations était dans la partie proximale, diminuant à mesure qu'on passait l'appareil vers l'extrémité. Sur 70 articulations examinées au scintilloscope, 40 ont donné des chiffres en concordance avec les zones non-articulaires, dans 6 ces chiffres ont été inférieurs et dans 24 supérieurs à ceux calculés pour la position respective dans le membre. Les articulations douloureuses donnaient des chiffres élevés 2,5 fois plus souvent que les articulations asymptomatiques. Ce phénomène n'était pas limité à la période immédiatement après l'injection, mais persistait quand le taux sanguin devenait negligeable.

On suggère que les sels d'or peuvent exercer une action locale sur des tissus inflammés par l'inhibition des enzymes impliqués dans le processus inflammatoire.

Estudios con el oro radioactivo

SUMARIO

La distribución de oro en el cuerpo fué estudiada en diez enfermos con artritis reumatoide. Entre ellos hubo cuatro casos con buena respuesta terapéutica al oro, tres casos resistantes, dos con manifestaciones de hipersensibilidad y uno que no había recibio auroterapia anterior. Se inyectaba por vía intramuscular una sola dosis de 10 mg. de aurotiomalato conteniendo la forma radioactiva ^{198}Au y se estudiaba su distribución en el cuerpo por medio de un "centellometro" (*scintillation counter*). Se determinó también la concentración de oro en la sangre, el líquido sinovial y la orina.

Las cifras plasmáticas variaban entre 0,11 y 0,17 mg. por 100 c.c. durante el primer día, bajando poco a poco y alcanzando una media de 0,02 por 100 c.c. al cabo de la segunda semana. Cuando se mezclaba el oro radioactivo con el inactivo, las cifras de la forma radioactiva quedaban al mismo nivel, indicando así que la concentración sanguínea es directamente proporcional a la dosis empleada.

Las más bajas concentraciones sanguíneas fueron encontradas en los dos enfermos hipersensibles al oro. La más despacia baja de la concentración sanguínea ocurrió en dos enfermos que adquirieron resistencia a la auroterapia. No hubo relación entre la tasa plasmática y la actividad de la enfermedad.

El oro sanguíneo parecía estar completamente ligado a proteinas, particularmente al fibrinógeno. El primer día la cifra del oro eritrocitario fué cuatro veces menor que la del oro plasmático, pero hacia el fin de la segunda semana fué igual o mayor. En el líquido sinovial hubo algo menos de oro que en el plasma durante la primera semana, pero al cabo de la segunda semana el oro sinovial alcanzaba o rebasaba la tasa plasmática. El líquido y un coágulo fibrinoso de una bolsa poplitea extirpada en una operación dieron una concentración de oro de 0,67 mg. por 100 c.c. (en el plasma 0,01 mg. por 100 c.c.). Similares concentraciones altas fueron encontradas en un espécimen de biopsia del cartílago articular del mismo enfermo.

El oro inyectado fué eliminado lentamente en la orina: el 15% durante la primera semana, el 20% durante la segunda y luego muy pequeñas cantidades fueron excretadas. La excreción fué independiente de la actividad mórbida o de la respuesta terapéutica pero fué más rápida en enfermos con reacciones de sensibilidad.

Fuera del sitio de la inyección, el centellómetro dió los mayores resultados en el hipocondrio derecho, pero altas cifras fueron también obtenidas en el hipocondrio izquierdo, las regiones pectorales y lumbares. En los miembros, las cifras fueron mayores proximalmente. disminuyendo al pasar el aparato hacia la extremidad, Sobre 70 articulaciones examinadas, 40 dieron cifras en conformidad con las zonas no-articulares, en 6 estas cifras fueron inferiores y en 24 superiores a las anticipadas según la posición en el miembro. Articulaciones

doloridas dieron cifras altas 2,5 veces más frecuentemente que articulaciones asintomáticas. Este fenómeno no se limitaba al período inmediatamente después de la inyección, sino persistía cuando la concentración sanguínea era mínima.

Se sugiere que los compuestos de oro pueden ejercer una acción local sobre tejidos inflamados por inhibición de enzimas implicadas en el proceso inflamatorio.