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Tissue gold levels after chrysotherapy*

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Although the use of gold salts in the treatment of rheumatoid arthritis is well established, the mode of action is still not known. The finding that gold is taken up by synovial tissue macrophages and accumulates in the lysosomes (Persellin and Ziff, 1966) has led to speculation that perhaps it acts either by lysosome stabilization, as does hydrocortisone (Weissmann and Thomas, 1963), or by the inhibition of the lysosomal enzymes, acid phosphatase, β-glucuronidase, and cathepsin, as is known to occur *in vitro* (Ennis, Granda, and Posner, 1968). These mechanisms would presuppose a site of action of gold within the synovial membrane and cavity. Yet information on the quantitative aspects of gold deposition in the body during chrysotherapy is scanty, and such data as there are suggest that the bulk of the gold both in man (Gottlieb, Smith, and Smith, 1972) and in animals (Betrand, Waine, and Tobias, 1948) is selectively concentrated in the lymph nodes, liver, and bone marrow, with relatively small concentrations in articular structures.

This report concerns a study of tissue gold concentrations in synovium, striated muscle, bone, and fat in patients who have received chrysotherapy, and is part of a larger study set up to attempt to define those factors which might improve the success rate of this form of therapy.

Methods and materials

Small specimens of synovial membrane, striated muscle, bone, and fat were removed from sixteen patients who had previously received gold injections and were undergoing surgery as part of their planned programme of combined medicosurgical management. For obvious reasons it was not possible to examine specimens of all four tissues in *all* patients. However, it was possible to compare the gold content in synovium with that in one of the other tissues (muscle, bone, or fat) on 28 occasions and relate these findings to the individual patient's total gold dosage and the interval since the last injection.

DETERMINATION OF TISSUE GOLD LEVELS

Tissue samples (300–500 mg) were weighed into tared porcelain crucibles and dry-ashed overnight at 450°C. The crucibles were re-weighed after cooling, and the residues were dissolved in 1·0 ml of 0·1 N nitric acid solution.

Gold levels in tissue digests were measured by comparison with gold chloride standard solution (0–500 μg/100 ml in 0·1 N HNO_3), using a Perkin-Elmer Model 303 Atomic absorption spectrophotometer. Results were expressed as μg gold/g wet weight tissue.

Results (Tables)

In each of the three comparisons (synovium/muscle, synovium/bone, and synovium/fat) the patients were divided into two groups. Group I consisted of patients who were currently receiving gold injections, the mean interval since last injection was measured in weeks. Group II consisted of patients who had not received gold injections for some years. Fortunately, the mean total dose of gold administered to the two groups was similar in each of the three comparisons.

Table I shows a comparison of synovial gold levels with those in striated muscle. In group I, comprising five patients, the ratio of the mean of the synovial

Table I *Comparison of gold levels in synovium and striated muscle*

Group	*No.*	*Mean total gold given (g) (range)*	*Mean interval since last injection (range)*	*Mean tissue gold level (μg/g)*	
				Synovium (range)	*Muscle (range)*
I	5	1·46 (0·28–4·42)	4·2 wks (1–8)	23·82 (0·26–76)	2·96 (0·39–6)
II	6	1·38 (0·34–3·2)	4·1 yrs (1–9)	0·45 (0–1·2)	1·00 (0–1·7)

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Table II *Comparison of gold levels in synovium and bone*

Group	*No.*	*Mean total gold given (g) (range)*	*Mean interval since last injection (range)*	*Mean tissue gold level (μg/g)*	
				Synovium (range)	*Bone (range)*
I	5	2·13 (0·28–4·42)	3·6 wks (1·5–8)	19·26 (0·19–76)	2·20 (0·19–4·4)
II	4	2·19 (1·2–4·0)	10·3 yrs (1–28)	0·80 (0–1·3)	0·87 (0–2·6)

Table III *Comparison of gold levels in synovium and fat*

Group	*No.*	*Mean total gold given (g) (range)*	*Mean interval since last injection (range)*	*Mean tissue gold level (μg/g)*	
				Synovium (range)	*Fat (range)*
I	4	1·97 (0·28–4·42)	5·4 wks (1·5–8)	20·14 (0·25–76)	1·27 (0·07–3·2)
II	4	1·19 (0·34–2·22)	3·17 yrs (0·7–9)	1·76 (0–5·94)	1·22 (0–4·3)

levels to the mean of the muscle levels was 8·05:1, whereas in group II, comprising six patients, the corresponding ratio was 0·45:1. Using Wilcoxon's nonparametric ranking test on the synovial:muscle ratios for individual patients in the two groups, the difference between the two groups was significant at the 1% level. Tables II and III show the results of the synovium/bone and synovium/fat content, respectively. The ratio of the mean synovium gold ratio to that of bone and fat in group I was 8·75 and 15·8, whereas in group II the corresponding ratios were 0·92 and 1·4, respectively.

However, using the same statistical technique as with the synovial/muscle comparison, the difference between groups I and II was not statistically significant in either case.

Discussion

Recent years have seen a number of attempts to place chrysotherapy on a more rational basis in order to improve efficacy and minimize side effects. Most workers have concentrated on measuring serum gold levels, but despite two reports to the contrary (Krusius, Markkanen, and Peltola, 1970; Lorber, Atkins, Chang, Lee, Starrs, and Bovy, 1973), the overwhelming weight of opinion (Gerber, Paulus, Bluestone, and Pearson, 1972; Jessop and Johns, 1973; Lidsky, Sharp, Duffy, Masri, and Seibert, 1973; Yamanaka, Miyagi, Mita, and Yamasaki, 1973), including our own (Billings, Grahame, Marks, Wood, and Taylor, 1974), is that clinical response does not relate to circulating blood gold levels. As yet little attention has been paid to tissue levels. Clearly tissue gold levels are unlikely to prove a practicable procedure in monitoring gold therapy in individual patients, but their study could help to elucidate some of the mystery that enshrouds gold therapy at the present time. Of factors likely to influence gold deposition in synovial membrane, both the total dose of gold salt injected and the interval since the last injection are likely to be important. In the present study, by taking groups whose mean total dose of gold injected was almost identical, it was possible to 'neutralize' the effect of total dose and thereby show the substantial fall that occurs in synovial tissue concentration of gold when injections are discontinued. This may explain the well known observation that relapse sometimes occurs when chrysotherapy is discontinued and may be obviated by continuous 'maintenance' therapy (Ziff and Baum, 1972). Furthermore, by the concurrent analysis of specimens of a nonarticular tissue, i.e. striated muscle, bone, or fat, it has been possible to show seeming selective deposition of gold in synovial tissue during 'active' chrysotherapy. It has yet to be determined whether there is selective retention of gold in muscle, bone, and fat, or preferential loss of gold from the synovium, after chrysotherapy has been discontinued.

Summary

Tissue gold concentrations were measured in specimens of synovium, striated muscle, bone, and fat obtained at operation from groups of patients suffering from rheumatoid arthritis who had received a similar mean total dose of gold by intramuscular injection. In the groups of patients who were currently

receiving injections the mean synovial gold level exceeded the muscle, bone, and fat gold levels by ratios of 8·05, 8·75, and 15·80, respectively, whereas in the groups of patients whose chrysotherapy had been discontinued some years earlier the corresponding ratios were 0·45, 0·92, and 1·4, respectively.

These results may provide a rational basis for adequate long-term maintenance chrysotherapy in the management of rheumatoid arthritis.

DISCUSSION

DR. B. VERNON-ROBERTS (*London*) In your first group it was only a matter of weeks since the last dose of gold had been given and since one knows that, in patients who have had the total dose of gold that you had given, the serum gold would be high at that time, it is not surprising that the wet synovial tissue would have a high total gold level. I think also that your conclusions may be a bit awry in relation to the loss of gold from the tissue. John Jessop and I have been carrying out a study of gold distribution throughout the body in twenty cases at autopsy and in another twenty cases after synovectomy, using a photochemical technique. In synovial tissue from a patient receiving gold, who has had 3½ g already, the surface layer has black deposits which indicate the presence of gold. However, in a patient who has been on gold, the last time 3 years previously, the deposits of gold are in the deeper tissues, and in a patient who had 3½ g of gold but has not had gold for 5 years there are heavy deposits in the deeper tissues in the synovium. We have confirmed with neutron activation analysis studies that, in some cases, up to 20 years after gold therapy heavy amounts persist in the synovium. We must not ingore that gold spreads throughout the body. After long periods of treatment and a long interval since treatment, heavy deposits of gold may be present in the kidney, seminiferous tubules, adrenal cortex, spleen, liver, and bone marrow.

DR. BILLINGS This is the sort of work we would have liked to have done. I would agree that it appears that when gold is given initially the synovial fluid and serum gold levels equilibrate soon after injection and one can detect high concentrations of gold in synovial fluid shortly afterwards, so that would perhaps explain why you are getting surface gold deposition initially and concentration of gold in the deeper structures of the synovium later. I agree also that gold is deposited throughout the body, and we have found high concentrations of gold in many other tissues, even after periods of 10–20 years. I am not sure how you can correlate a slide of a tissue with gold in it with the actual gold concentration as measured by our method. We found that we had three patients who had had no gold in any of their tissues detectable by our method. You might be interested to know of these patients, one had gone 2 years since the last injection and had only been given 340 mg; the second patient had not had gold for 13 years and had had 1 g, and the third patient had had his last injection 28 years before and had had 4 g. So there is a suggestion that the less you are given the quicker it is gone.

PROF. E. G. L. BYWATERS (*Taplow*) I gather your analysis was not on fat-free synovium. It seems possible that fat, with a low content of gold, might affect your results.

DR. BILLINGS It is extremely hard to separate the two, and perhaps it does alter the figures.

DR. A. G. S. HILL (*Stoke Mandeville*) To pursue Dr. Vernon-Roberts's theme, a short paper was presented by Nunn and Tribe (1963) to this Society many years ago dealing with two patients in whom the gold was not only demonstrable in lymphatic channels in muscle by photohistochemical methods, but was visible in plain radiographs of the upper arm muscles taken many years after the last injection of gold, thus providing another instance of its persistence in large quantities.

DR. BILLINGS I think this is one of the points of the paper. Muscle does seem to be more selective in its concentration of gold than other tissues.

DR. A. G. S. HILL (*Stoke Mandeville*) In our cases the muscle was taken from near the site of injections.

DR. J. H. GLYN (*London*) If, as it seems, the implications of your remarks are that the response of the synovial membrane depends to some extent on the concentration of the gold in the membrane, it gives some justification to the treatment when you have monoarticular or periarticular arthritis of introducing the gold directly into the cavity. This does not seem to have caught on. I have occasionally used it with, I think, success. I would like to know what your views would be on propagating this as a method of treatment.

DR. BILLINGS I would think that one of the dangers of putting gold straight into the synovial fluid is that it may not be the same form of gold as that injected into muscle and then transported to the joint. I think that it is the nature of the transported gold which is little understood, and we are following this up with the University of Surrey in order to see whether we can finally identify the nature of sodium aurothiomalate (Myocrisin) after injection and its arrival at tissue sites. So I think it would be wrong to assume that you were doing the same intra-articularly as intramuscularly.

DR. M. MCMAHON (*Cork*) In relation to Dr. Glyn's remark, I have used it on ten cases intra-articularly in knee joints. The most recent case had trouble with one knee and I gave him 10 mg on one occasion to the knee joint. He has been symptom free now for 6 months. I have done this on at least seven or eight occasions and each time the knee joint seemed to be the most successful. I tried it on shoulder and wrist joints, but the knee joint seems to respond the best.

DR. BILLINGS I think this is a very interesting comment and obviously something one should follow up.

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