INVITED ARTICLE

GOLD THERAPY
II HISTORICAL, CHEMICAL, PHARMACOLOGICAL AND BIOLOGICAL PROFILE OF ANTI-ARTHRITIC GOLD COMPOUNDS

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Indications for Gold Therapy (Injectable)

Gold therapy is indicated in the treatment of rheumatoid arthritis, Felty's syndrome, polyarticular juvenile rheumatism, psoriatic arthritis and palindromic rheumatism. There are very few contraindications to the administration of gold drugs, but patients who have had a serious adverse reaction to gold, particularly a haematological side effect, should not be given the drugs (1). Serious hepatic disease and serious renal disease are usually considered as contraindications to gold therapy, and patients with serious haematological disease in general are not given gold therapy. Most rheumatologist would agree that gold therapy should be avoided during pregnancy, although there are numerous instances of the drug being administered during pregnancy without any serious adverse reactions being recorded (2). The drug administration schedule for injectable gold was derived empirically from Forestier's original use of these compounds (3). Gold compound injections are started in those patients who have failed to respond to an unhurried trial of non-steroidal anti-inflammatory drugs (1). An initial test dose of 10 mg is given on the first week, followed by 25 mg intramuscularly in the second week. In subsequent weeks 50 mg intramuscularly is given for 20 weeks, followed by maintenance therapy every 2-4 weeks. Maintenance therapy is given for an indefinite period of time if there are no instances of any serious side effect related to the duration of gold. Consideration for discontinuing gold is usually on the basis of either no response, toxicity or the development of a complete remission. It is generally held that those patients who have not responded to the drug by at least twenty months of therapy probably will not gain sufficient benefit. If a patient develops remission it is recommended that the non-steroidal drug be slowly discontinued initially, then the interval between injections of the gold compound be increased gradually prior to completely stopping the gold drug. Should relapse of clinical symptoms occur, the nonsteroidal drug therapy should be reviewed and restarted at maximum tolerable anti-inflammatory dose and the injectable gold therapy should be restarted or increased to weekly injections until the previously achieved clinical response is obtained (1). When patients are being treated with injectable gold therapy it is recommended that a clinic monitoring form be used to record the efficacy, toxicity and haematological and urinary test results. The general response to injectable gold therapy is that 65-70% improve clinically. The majority of these patients have that is known as a partial remission, although complete remission with no evidence of disease activity occurs in approximately 10% of all patients treated with the drug (1). The response to therapy usually occurs after a period of 10-12 weeks. Approximately 20-30% of patients have to discontinue therapy because of no response. In the studies that have been done there is no clinical evidence to suggest that the drug should be withheld from the elderly rheumatoid patient. In this age group the injectable compound has been shown to be as effective as for young people at any time period examined after three months of therapy (4).

INDICATION FOR AURANOFIN$_{TM}$

The oral compound, Auranofin$_{TM}$ is available in 3mg compressed tablets. The usual initiating dose is 3mgs b.i.d. and this can be increased to 3mgs t.i.d. In clinical studies of rheumatoid arthritis it has been shown that the oral gold compound is better than placebo but it is somewhat inferior in efficacy to the injectable gold compounds (5). The time of onset of benefit with the oral gold compound is again in the order of 5-10 weeks but claims of complete disease suppression have not been reported. As described in the section on chemistry and pharmacology, the oral compound is not equivalent to the injectable compounds and has probably more properties akin to the immunosuppressive drugs such as Azathioprine, Methotrexate and Cyclophosphamide. At present it is common practise for rheumatologists to use injectable gold compounds, D-pencillamine or Chloroquine before considering the use of Auranofin$_{TM}$.

ADVERSE EFFECTS OF INJECTABLE GOLD COMPOUNDS

The major limiting factor to the use of injectable gold compounds is toxicity. Approimately 30-50% of patients who receive the injectable gold compound will develop some form of toxicity (1).

The most common side effect is skin rash which occurs in approximately 30% of patients. Skin rash is usually represented by a dry itchy area, approximately 1-10 cm in diameter. Most lesions are slightly erythematous with scaly patches resembling a seborrheic rash. The most common distribution is the hands, forearm, trunk and shins, and occasionally face. The drug should be discontinued following the development of skin rash and should not be reintroduced until the rash has completely resolved. The drug should then be administered in low doses of 10 or 25 mg intramuscularly. Severe skin rash problems in the form of nummular eczema, total exfoliation and intense pruritis have been known to develop. Though the development of such a problem constitutes a medical emergency appropriate support measures such as observation of electrolytes should be undertaken. In our experience these problems are less common when a strict monitoring system is in force.

Mouth ulcer occurs in approximately 20% of patients who receive injectable gold therapy. They may or may not be painful and in appearance resemble the aphthous ulcer. The most common site of occurrence of these ulcers is in the mucous membrane in the vestibule of the mouth. Occasionally the lesion is present on the tongue or the hard palate. The development of a mouth ulcer is a definite contraindication to gold therapy until the mouth ulcer has resolved. On occasion mouth ulcer has preceded the development of pemphigoid-like bullous skin lesions.

There is a wide variation in the freqency of proteinuria from 0-40% depending on the study (1,4,5,6,7). One reason for this discrepancy in the literature has been the wide variation in the definition of what constitutes proteinuria (1). Most authors agree that persistent spillage of urine in amounts of 1+ by dip stick over two to three weeks warrants a 24 hour urine protein examination. If proteinuria is less than 500 mg for 24 hours the drug should be continued. Between 500 and 3,000 mg for 24 hours, gold therapy should be withheld until it is established that renal function is normal. Patients whose proteinuria is greater than 3,000 mg for 24 hours should have the gold therapy stopped until the proteinuria resolves. There are no well documented cases of any long term serious or permanent damage due to gold therapy. The most common histological lesion is that of a membranous glomerular nephritis (8), although heavy metal tubular damage does occur during injectable gold therapy (9). Proteinuria secondary to oral gold is extremely uncommon (5). When microscopic haematuria develops gold therapy should be stopped immediately and a cause for the haematuria sought. Once the proteinuria has reduced in quantity or the haematuria has resolved gold therapy may be reinstituted at a reduced dosage.

Most laboratories now specify a value of 150,000/mm^3 as a lower level of normal for a platelet count. Physicians monitoring gold therapy, however, should observe a platelet count of less than 200,000/mm^3 as an indication to withhold gold therapy. A falling platelet count even within the normal range may be equally ominous. A sudden change in a weekly platelet count which has been steady at 400,000/mm^3 to 210,000/mm^3 behoves a physician to withhold the gold therapy until a repeat platelet count confirms a stable value above 200,000/mm^3 on at least two occasions one week apart. When a fall in platelet count results in a value which is persistently less than 200,000/mm^3 extreme caution is advised and whenever facilities are available, blood should be tested for the presence of platelet surface associated IgG auto-antibodies (10). Kelton and co-workers at McMaster University have shown a strong correlation between the presence of IgG antibodies in the surface of platelets and thrombocytopenia secondary to injectable gold sodium thiomalate (10). These platelet antibodies do not appear to be present with the much rarer gold induced thrombocytopenia secondary to bone marrow suppression. Although it has been stated that thrombocytopenia secondary to injectable gold therapy may occur precipitously, we believe that close observation of changes in platelet count even within the normal range will result in earlier identification of some patients who may potentially develop a sudden thrombocytopenia. The development of thrombocytopenia secondary to injectable gold therapy is an absolute contraindication to the further use of the gold compound. There have been many studies over the past five years which now indicate that the presence of HLA DR3 may be indicative of an increased risk of a patient developing thrombocytopenia associated with platelet surface antibodies. This work has recently been reviewed by Dr. Peter Ford (11).

Bone marrow suppression secondary to either injectable gold therapy or oral gold therapy apears to be due to a direct action of the drug on the marrow cells (12). Bone marrow suppresion secondary to the gold compounds is rare but is a sufficiently serious complication to warrant strict monitoring on a weekly basis (1). We recommend that a fall in either platelet count as recorded above, or a fall in haemaglobin below 10 gram per cent, and/or a fall in total white count below 4,000/mm^3 requires immediate discontinuation of therapy until cause and effect have been established. A reversal of the white cell differential ratio and/or a rise in monocyte count above 10% are also indications for immediate discontinuation of the gold drug until at least two normal values one week apart have been recorded. If any of the above indicators of haemopoiesis remain abnormal a bone marrow examination and investigation for auto-antibodies to white cells, red cells and platelets is essential before gold therapy can be reintroduced. Bonemarrow suppression secondary to gold compounds is an absolute contraindication to further continuation of therapy.

Despite this potential for the rare side effect of bone marrow suppression it should be noted that return to normal of the haemaglobin is one of the first indices to become normal during clinical improvement. Recent

work in our laboratory by Dr. Andrew Harvey has shown that some forms of rheumatoid anaemia have a humoral basis and it can be postulated that the modulation of the humoral mechanisms by the injectable gold compounds may result in improvement of the rheumatoid anaemia (13). In spite of the potential for gold compounds to induce marrow suppression, injectable gold compounds are now recognised as being the treatment of choice for Felty's syndrome (14). The drug should be administered in exactly the same manner as described for rheumatoid disease. The majority of physicians will start with lower doses such as 10 mg or 25 mg weekly until an observed rise in the absolute white count takes place. Those physicians who have no accessibility to the assessment of bone marrow tissue should be advised to avoid using gold compounds in the treatment of Felty's syndrome.

The immediate allergic reaction or nitritoid reaction appears to be unique to the gold sodium thiomalate. This reaction is manifest by flushing, sweating, headache, joint pain, hypertension, hypotension, and on occasion chest pain which has led to myocardial infarction (15). It is our opinion that some aspect of the variable structure of the gold sodium thiomalate may be related to precipitating this toxic reaction. The nitritoid reaction is not seen with any other gold compound, is usually mild and self limiting. Patients need only be switched to either gold thioglucose or the oral gold compound if they find the nitritoid reaction intolerable.

Pulmonary injury associated with gold therapy has been reported in the form of a diffuse interstitial lung disease, usually with radiologically visible infiltrates (16,17,18). Fortunately pulmonary toxicity is rare and usually responds to the withdrawal of the injectable gold compound. Idiopathic toxicity in the form of cholestatic jaundice (19) and also acute enteral colitis (20) has also been reported secondary to the injectable gold compounds, particularly gold sodium thiomalate. Hepatic toxicity is rare but appears to be predominantly of the cholestatic type either with frank jaundice or with elevated bilirubin, alkaline phosphatase, SGOT and SGPT. The drug should be stopped immediately. The condition may appear early or late in the treatment regime. No specific mechanism of action has been determined. In general the condition is self limiting but in 1937 Hartfall and colleagues in a review of 900 patients treated with injectable gold compounds recorded 85 cases of toxic jaundice, two of which resulted in death from sub-acute necrosis of the liver (21). This incidence is not observed in any modern study and it is not possible to determine from Hartfall's paper what co-intervening factors may have been present. In view of the rare association of hepatic toxicity with the injectable gold compounds all other causes of jaundice should be excluded before assuming a cause and effect relationship to the gold compound.

Rarely the deposition of gold in the lens of the eye (22) and the cornea has been reported (23), but this does not seem to result in any specific damage to visual acuity.

There is no apparent increase in the incidence of toxicity in elderly patients receiving gold compounds (4), although specific caution should be taken with regard to haematological toxicities, since bone marrow aplasia secondary to any drug is more commonly recorded in the elderly than in the young. In a study from our own unit in 1983 it was shown that the elderly responded to gold sodium thiomalate just as well as young adults and that the drop out rate for no response and toxicity was the same in both groups. However, it was noted that serious haematological toxicity only occurred in patients over 42 years of age and nephrotic syndrome only occurred in patients over 52 years of age in that study. The elderly should not be denied injectable gold therapy in the treatment of rheumatoid disease.

There is now an extensive literature devoted to the development of toxicity to injectable gold compounds (and D-penicillamine) and the patients human leucocyte antigen (H.L.A.) types (11). HLA-D4 and HLA-DR4 are present in 25-30% of normals but are found in rheumatoid patients in a ratio of 2:1 over controls, although this is less apparent in Jewish and East Indian groups. However, patients with HLA-DR3 (also claimed to be associated with increased levels of rheumatoid factor) have been shown to be at increased risk of developing toxic reactions to injectable gold sodium thiomalate and also to D-penicillamine. In 1978 Panayi and colleagues reported on 95 patients with rheumatoid arthritis and noted that although there was no increase in HLA-DR3 over controls, 14 out of 18 with DR3 had a toxic reaction to gold or D-penicillamine and that 7 of 8 patients with HLA-DR2 had a toxic reaction (24). HLA-DR2 has been reported to be associated with mouth ulcers (25) but the association between HLA-DR2 and toxicity in general has been disputed. Several reports suggest that HLA-DR2 and also HLA-DR7 may be protective against the development of toxicity and like HLA-DR4, the HLA-DR2 group may be a disease modifier (26). In a follow-up report Panayi and colleagues reported that 79% of patients with HLA-DR3/B8 developed proteinuria while on gold (14 out of 15) or on D-penicillamine (9 out of 13) (27). Subsequent reports reviewed by Ford have claimed an association with HLA-DR3 and thrombocytopenia, HLA-DR3/B8 and proteinuria and HLA-DR3 alone for skin rash (11). The last association is unusual in view of the known linkage disequilibrium between HLA-DR3 and B8 (11). Dequeker and colleagues found no association between gold thiopropanol sodium sulphonate and HLA groups, but they did find an association between HLA-B8 (but not DR3) and proteinuria (28). Again, an unusual outcome in view of the linkage disequilibrium between DR3 and B8. Dr. Ford points out that most studies, if not retrospective, only looked at the first 6 months of therapy, when clearly side-effects due to gold or penicillamine can occur at any time (1,11). In particular it is our experience and that of others that proteinuria occurs predominantly between 6 and 15 months (1,4-7). It is of interest that HLA-DR3 and B8 are rare in Japanese and that in a large Japanese trial of D-penicillamine proteinuria occurred in only 2.2% of patients (29).

Most investigators agree that HLA-DR3 and HLA-B8 are associated with drug toxicity, particularly proteinuria in association with injectable gold therapy and D-pencillamine. However, patients possessing these antigens should not be denied therapy with these agents since the relative risk does not outweight the clinical benefits.

ADVERSE EFFECTS OF AURANOFIN$_{TM}$

Alteration in stool pattern with the development of soft stools, is the most common side effect of Auranofin$_{TM}$ therapy and may occur in over 40% of treated patients (30, 31). The frequency of this side effect is highest in the first month of treatment. It should be noted that the lower incidence of altered stool pattern in later months may be directly related to a pre-selected drop out of those patients susceptible to the diarrhoea. The development of frank watery diarrhoea occurs in 2-5% of patients and is dose related, but some patients are totally intolerant of even 3 mg/day. The postulated mechanism is an elevation in cyclic AMP in the gut mucosal cell with a resultant outpouring of intracellular contents (30).

Rash is also a common side effect of Auranofin$_{TM}$ therapy, occurring up to 20% of patients. Half of these

patients also experience pruritis. Rash is most common in the first 12 months of therapy but can occur at any time. When rash develops, the drug should be withheld until the condition resolves. Approximately 2-3% of patients have to discontinue therapy because of severe skin rash (5).

Stomatitis occurs in 1-12% of patients and may be concomitant with skin rash. The occurrence is greatest in the first month but like other side effects, may occur at any time (5).

Non-specific digestive system complaints account for approximately 20% of all side effects and 2% of all withdrawals (32).

Conjunctivitis occurs in 4% of patients and occurs with equal frequency at any time period throughout treatment.

Although less common than with injectable gold therapy, proteinuria occurs in up to 5% of patients treated with Auranofin$_{TM}$. The drug should be withheld and assessments of renal function made in a manner similar to that for injectable gold toxicity to the kidney.

Rarely thrombocytopenia and bone marrow suppression may occur as a result of Auranofin$_{TM}$ treatment. This type of thrombocytopenia (unlike to more common type seen with gold sodium thiomalate) does not have platelet surface associated auto-antibodies. The treatment of choice is immediate withdrawal of drug therapy. The development of thrombocytopenia or a low white blood cell count is an absolute contraindication to therapy.

Despite the apparent overall lower number of side effects related to Auranofin$_{TM}$ compared to injectable gold compounds, Auranofin$_{TM}$ should not be considered a benign drug. A strict monitoring system as for injectable gold compounds should be undertaken for each patient. Insufficient data is available at present to determine whether there will be any long term side effects related to Auranofin$_{TM}$ therapy. In view of its immunosuppressive properties, particular attention should be paid to effects on immune functions related to long term therapy.

CLINICAL STUDIES OF INJECTABLE GOLD COMPOUNDS

Dr. Jacques Forestier hypothesised that since the manifestations of rheumatoid arthritis were so similar to those of tuberculosis, gold compounds shown to be of benefit against the dreaded bacillus could be effectively employed against a disease of similar evolution, chronic rheumatoid arthritis (33). In his original series, Forestier treated 11 women and four men of mean age 42 years, with 250 mg of gold thio-propanol sodium sulphonate as weekly intramuscular injections. Five patients had an excellent response, five patients were much improved and two were recorded as having a minimal response. In three patients insufficient knowledge of outcome was available but according to the author, none of them was worse (3). Significant improvement was thus recorded in local and general features of a hithertofore progressive, destructive disease.

In February, 1930 Jacques Foresiter supported his initial findings by reporting the outcome of a further 33 patients with symmetrical inflammatory polyarthritis which he believed to be consistent with rheumatoid arthritis. The outcome of this second study confirmed the efficacy and toxicity data of the first but also showed that the use of 100 mg of gold thiopropanol sodium sulphonate weekly was probably less toxic and equally effective to the original higher dose of 250 mg weekly (34).

In 1934, in the Hunterian Address (35), Forestier presented the results of 50 patients with rheumatoid arthritis, treated with gold compounds. He recorded a 70 to 80% success rate. Fifty per cent of patients treated early in the disease state were permanantly improved compared to only 25% of patients with disease of two or more years' duration. In his discussion of gold compounds Forestier stated that gold sodium thiomalate and gold thioglucose were the most useful agents. In this publication, Forestier recorded a fatal case of agranulocytosis, which was his first reported death due to gold therapy.

Over the next 10 years numerous descriptive analysis of gold therapy in rheumatoid disease appeared in the literature. In a series of publications between 1935 and 1937 (21,36,37), Hartfall and colleagues recorded their observations of benefit and toxicity due to gold therapy in patients with rheumatoid arthritis. The final article described the outcome of 900 patients (750 of whom were rheumatoid patients) treated with gold compounds. Striking improvement was noted in approximately 70% of patients and toxicity occurred in 42% of cases, although only 6% were severe. The relapse rate was 21% and the authors stated that the relapse was less common if two courses of gold therapy were given. Hartfall and colleagues also stated that gold therapy was of doubtful value in other forms of arthritis. This has never been challenged by a series of controlled clinical trials although in 1978 Dorwart et al reported a comparative trial of gold therapy with either gold sodium thiomalate or gold sodium thioglucose in patients with psoriatic arthritis compared to patients with rheumatoid arthritis. The authors recorded that the 14 patients with psoriatic arthritis had greater benefit and less toxicity than the 42 patients with rheumatoid arthritis (28). Except for this study and that of Brewer et al (29) on the use of gold therapy in juvenile rheumatism, no other controlled study of injectable gold therapy has been done to examine efficacy nor toxicity in the other rheumatic diseases.

Uncontrolled studies on the use of gold therapy in rheumatoid disease suggested that these drugs were of benefit to between 50% to 80% (40, 41) of patients given these compounds, but that a wide range of adverse effects occurred which could be serious and even fatal. In 1939 Sir Stanley Davidson, Chairman of the Scientific Advisory Committee of the Empire Rheumatism Council proposed a multi-centre controlled double blind trial to investigate the compound gold sodium thiomalate in rheumatoid arthritis. World War II disrupted the success of this initial proposal but the late Dr. Thomas N. Fraser of Glasgow completed his section of the multi-centre trial at the Western Infirmary of Glasgow and published his results in the Annals of the Rheumatic Diseases in 1945 (42). Fraser's trial was the first published double-blind controlled trial of any anti-rheumatic drug. It confirmed Forestier's original findings and demonstrated an efficacy rate of 82% in the treated group compared to 45% in the control patients. Fraser emphasised that the results should only be interpreted within the confines of the study group. The control group had a marked improvement rate which was apparently unexpected. He explained, firstly, that all study patients received physiotherapy and secondly, that some spontaneous remissions might have occurred. If this also accounted for some improvement in the myocrisin group, therefore improvement attributable to gold therapy would be reduced to 42%. It is important to note that 72% of the control group recorded a subjective improvement although for the purpose of the study, improvement was only recorded for the 45% who showed objective improvement. This suggests that a considerable psychological factor may have been operative.

In 1947 Waine and colleagues reported on 58 patients treated with either gold sodium thiomalate or gold thiosulphate. All patients received a minimum of 500 mg with an average total dose of 1600 mg. The authors reported a significant improvement in 57% of the treated group compared to 29% of controls. However, the controls were a group of 62 rheumatoid arthritis patients treated with only "supportive" therapy and did not receive a placebo injection (43).

In 1950 Adams and Cecil reported on 106 patients with rheumatoid disease who either received gold sodium thiomalate or aurothioglucose during the first year of their disease (44). The total compound given was between 1000 mg and 1500 mg. There authors recorded a 66% rate of "remission" by their definition in the gold treated group compared to only 24.1% remission rate in the control patients. These figures were non-comparable since the control group only received conventional therapy and no placebo injection. Remission occurred on average 10 months later in the control group than in the gold treated group (17 months and seven months respectively). The average time from remission to relapse was 27 months. The authors thus concluded that gold therapy increases the incidence and accelerates the appearance of remission if given during the first year of the disease.

In contrast to the beneficial effects of injectable gold therapy over conventional therapy so far cited, Merliss and colleagues found aurothioglycolanilide (Lauron) given over six months to 27 patients, to be no better than saline or serum injections given to 44 control patients over a similar period of time (45).

The largest series of data recorded to date is the 47 years of clinical experience with injectable gold therapy documented by Dr. Maxwell Lockie of Buffalo and reported at the VIII Pan-American Congress of Rheumatology in Washington D.C. in 1982. Dr. Lockie recorded the outcome of 1,019 patients with classical or definite rheumatoid disease treated with injectable gold between 1933 and 1980. There were 317 males and 702 females of mean age 46 and 47 years respectively. His patients were assessed as being mild, moderate or severe. At the discontinuation of therapy the mild group had increased by 95% and the moderate and severe had decreased by 35% and 37% respectively. Thirty-eight patients discontinued therapy because of disease remission and 589 (59%) patients discontinued therapy because of a serious side effect (46).

Lack of firm statistical evidence as to the usefulness of injectable gold compounds led the Empire Rheumatism Council in 1957 to plan a second multi-centre trial (47). This was carried out in 24 centres throughout the United Kingdom and the results were published in 1960 and 1961. Ninety-nine patients in the treated group received 1000 mg of gold sodium thiomalate as 50 mg injections weekly over 20 weeks. One hundred control patients were given 0.01 mg of gold sodium thiomlate as 0.5 ug weekly over a 20 week period (i.e. they received 1×10^{-6} the quantity of gold compound received by the controls). It was unequivocally demonstrated that in most patients given the 50 mg weekly gold sodium thiomalate, there was progressive improvement in a number of objective variables, including the number of joints clinically inflamed, grip strength and sedimentation rate. Although gold therapy was stopped after 20 weeks (1000 mg of compound), improvement persisted for up to 12 months in many patients and was generally maintained up to 18 months. However, by the 30th month (i.e. 24 months after gold therapy had been discontinued) little if any advantage was recorded in the original gold treatment group compared to controls (48). In 1973 the Cooperating Clinics Committee of the American Rheumatism Association reported their double-blined trial of 68 patients with definite or classical rheumatoid arthritis (6). The initial phase of this study compared 36 patients who received gold sodium thiomalate 50 mg weekly for six months and a control group of 32 patients who received sterile water vehicle over the same period. Twelve patients in the gold group dropped out because of adverse effects and eight patients in the placebo group dropped out because of no benefit. The gold treated group showed slight but definite improvement in all parameters measured, although only the change in sedimentation rate was statistically significant. In the second phase of the study, designed to compare the results of maintenance therapy, patients received six 50 mg doses at two-week intervals until a total of two years of treatment had been given. Control patients received the sterile water vehicle in the same fashion. In phase two the gold group showed no increase in the number of involved joints, improved their grip strength and demonstrated a fall in sedimentation rate. During the same time period, the control group deteriorated in all of these measurements. The authors commented that the results of the Cooperating Clinics Committee Trial confirmed the results of the Empire Rheumatism Council Trial and stated that the larger sample size of the latter allowed the differences recorded for grip strength and number of active joints to reach statistical significance as had been achieved by the sedimentation rate. It should be noted that although the Empire Rheumatism Council Trial patients and Cooperating Clinics Committee Trial patients were comparable in almost all respects, there were marked differences in the category of duration of disease prior to therapy. The majority of Empire Rheumatism Council Trial patients had disease of less than three years duration and had an upper limit of five years, whereas the Cooperating Clinics Committee Trial patients had no disease duration limit and almost one third of the patients had rheumatoid arthritis for longer than five years. If injectable gold works better when given early in the disease process, this would explain the greater demonstrable benefit in the Empire Rheumatism Council Trial results.

Two subsequent double-blind trials have added further useful knowledge to the management of rheumatoid disease with injectable gold compounds. The first is that of Dr John W. Sigler and colleagues (49), and the second is that Dr D.E. Furst and colleagues (7).

Sigler and colleagues reported a two year double-blind study of 13 patients who received gold sodium thiomalate compared to 14 patients who received placebo identical in appearance to the gold compound. Significant improvement in relation to global measurement, ring sizes and grip strength was recorded in the gold treated group. However, the most striking finding was the claim by the authors that radiological examination showed arrest of bone and cartilage destruction in several patients and that the mean progression rate of destruction was significantly slowed for the treated group. In the Cooperating Clinics Committee Trial posteroanterior radiographs of the hands were taken at the beginning and end of phase one (0-27 weeks). The results obtained by a single observer in blindfold fashion detected deterioration in none of 19 controls and three of 20 gold treated patients. The difference ($P = 0.06$) was not significant but favoured gold therapy as being possibly beneficial. In the Empire Rheumatism Council Trial no significant radiological differences were detected between the gold treated and the control groups in terms of joint narrowing, development of new erosions or extension of new erosions in any period of the trial. The minimal

differences that did occur were in favour of the gold treated group. This apparent arrest or even regression of radiological changes recorded by Sigler et al has also been recorded in a much larger but uncontrolled study by Luukhainen et al (50).

The preceding double-blind trials confirmed that injectable gold therapy was of value in the treatment of rheumatoid disease, but this dosage schedule had been achieved by empirical means based on descriptive analyses and poorly controlled comparative studies. The question was raised as to whether 50 mg of gold sodium thiomalate weekly was equally efficacious and less toxic than higher doses. Furst and colleagues attempted to answer the question by comparing the outcome of 23 patients who were given 50 mg of gold sodium thiomalate weekly, to a group of 24 patients who were given 150 mg weekly. Drug administration and evaluations were carried out double-blind. Serum gold concentrations were recorded but did not correlate with efficacy nor with toxicity. The conventional dose — 50 mg weekly was just as efficacious as the high dose — 150 mg weekly. However, side effects were more frequent and severe in the high dose group. These findings are identical to those observed by Forestier in his second publication on the use of gold thiopropanol sodium sulphonate (34).

Since the results of Fraser's trial and subsequent confirmation by the Empire Rheumatism Council Trial, gold sodium thiomalate has become the most widely used injectable gold compound in the treatment of rheumatoid arthritis although gold thioglucose is used in the United States and gold thiosulphate is still used in Europe. In 1972 Sutton and colleagues reported that orally administered alkylphosphine gold coordination complexes exhibited anti-inflammatory properties when administered to adjuvant arthritic rats (51), and in the same year the same group reported that triethylphosphine gold chloride was equipotent to parenterally administered gold sodium thiomalate in suppressing the inflammatory lesions of adjuvant arthritis (52). Triethylphosphine gold chloride is extremely toxic in man and further studies were not evaluated. However, a related compound 2,3,4,6-Tetra-o-acetyl-l-thio-β-D-glucopyranosato-S-(triethylphosphine) gold was shown to exhibit antiarthritic properties (53). Subsequent studies have shown that this compound has some benefit in the treatment of rheumatoid arthritis (5, 54).

CLINICAL STUDIES ON AURANOFIN$_{TM}$

In the original clinical report by Finkelstein and colleagues (54), 8 patients with rheumatoid arthritis were treated with Auranofin$_{TM}$ for 3 months followed by a 3 month period on placebo. During the treatment period the total number of active joints fell from 60 to 17 at week 12 and to 9 at week 15. Clinical improvement was recorded at 5 weeks and in general the drug was well tolerated. Rheumatoid factor titer, IgG levels and α-macroglobulin levels fell during the treatment period. During the following 3 month placebo period, IgG levels rose and patients experienced a flare-up in disease activity, suggestive of a cause and effect action of the drug.

In the study reported by Calin and colleagues 137 patients were administered either 1 or 9 mg of Auranofin $_{TM}$ in a double-blind fashion (55). At the first three month period approximately 60% of the 1 mg group and 33% of the 9 mg group broke the code because of insufficient therapeutic effect. It was also noted that reduction in immunoglobulins IgM and IgG and the reduction in ESR was greater for patients receiving the 9 mg dose. Conclusions for this interim report showed that 1 mg was insufficient for therapeutic effect but 9 mg caused sufficient diarrhoea io make this dosage unsuitable. The majority of studies since conducted have involved the use of either 3 or 6 mg per day. Most investigators have found that a dosage of 6 mg per day is significantly better than placebo, although a higher frequency of diarrhoea is noted with this dosage than at the 3 mg dosage.

A multicentre double-blind controlled trial of Auranofin$_{TM}$ versus gold sodium thiomalate has been reported at various meetings and published at different stages of evolution (56). All patients were given appropriate placebo injections or placebo tablets. In a 1983 interim report 121 patients were assessed, 59 on Auranofin$_{TM}$ and 62 on gold sodium thiomalate. There was an equal distribution between the groups for age, duration of disease, age at onset of disease, A.R.A anatomical stage (majority stage II), and functional class. There were slightly more patients in the higher functional class (class III) in the Auranofin$_{TM}$ group. After 12 weeks of therapy improvement in pain score was greater for the gold sodium thiomalate group compared to the Auranofin$_{TM}$ group, although the score was approximately the same by 24 weeks. In a group of 46 patients who had received 48 weeks of therapy, pain score was better in the gold sodium thiomalate group at both 12 and 24 weeks but had equalised to the Auranofin$_{TM}$ group by week 48. The authors concluded that gold sodium thiomalate influenced pain more rapidly than Auranofin$_{TM}$. Similarly the decrease in Lansbury Articular Index and Lansbury Activity Index was more rapid and more pronounced in the gold sodium thiomalate group. Improvement in ESR values was better for the gold sodium thiomalate group at both 24 and 48 weeks. Improvement in grip strength was faster with gold sodium thiomalate but better in the Auranofin$_{TM}$ group at 24 weeks. The overall benefit in grip strength was the same at 24 weeks. Morning stiffness reduction was faster in the gold sodium thiomalate group at 24 weeks but the overall reduction in duration was equal at 48 weeks. Twenty-one patients in the gold sodium thiomalate group but none of the Auranofin$_{TM}$ group were able to reduce the dosage of the drug at 24 weeks because of "striking improvement".

Patients on Auranofin$_{TM}$ experienced 192 adverse reactions, 34% being diarrhoea and a further 34% other gastro-intestinal side effects. Aphthous ulcers, skin rash and pruritis accounted for 22%, 12% and 25% of all side-effects. Conjunctivitis occurred in 9% and alopecia occurred in 9%. Nine of the 59 patients on Auranofin$_{TM}$ dropped out of the study because of adverse reactions. Seven had serious mucocutaneous reactions but 1 had herpes zosters and 1 had a haemorrhagic cystitis. There were 177 side-effects recorded in the 62 patients who received gold sodium thiomalate. Diarrhoea (n = 11) and other gastro-intestinal side-effects (n = 11) accounted for the total of 34% of all side-effects. This is an unusually high incidence for diarrhoea or for gastro-intestinal upset and has not been recorded with such frequency in any other double-blind controlled trial of the drug. Rash, pruritis, alopecia and conjunctivitis occurred in 42%, 7% and 11% respectively. Again it should be noted that alopecia and conjunctivitis are rarely recorded in other studies of gold sodium thiomalate. Eleven patients dropped out of the gold sodium thiomalate group because of severe adverse reactions; 4 had skin rash; 1 eosinophilia; 3 had injection reaction; 1 abnormal liver function; 1 had dysuria and 1 had osteomyelosclerosis. Dysuria and osteomyelosclerosis are not recognized side-effects of gold sodium thiomalate and are most likely incidental findings.

The overall outcome of the above report suggests that gold sodium thiomalate acts faster than Auranofin$_{TM}$ and probably is clinically superior.

In 1982 Katz and colleagues reported a randomized

double-blind controlled study of 242 patients who received 3 months of therapy and 144 patients who received 6 months of therapy with either 3 mg b.i.d. of Auranofin$_{TM}$ or placebo. Significant improvement in the treated group was recorded for the number of tender joints at 3 months and 6 months and for the number of swollen joints and increase in grip strength at 6 months. The investigators global assessment of efficacy was recorded as significantly improved at 3 months and 6 months in the Auranofin$_{TM}$ group for those patients recorded as having a marked improvement. The authors concluded that the addition of Auranofin$_{TM}$ to NSAID therapy added to the benefit derived from the latter in the treatment of rheumatoid arthritis (57).

In 1983 Van Riel and colleagues reported a single-blind trial of 26 patients treated with Auranofin$_{TM}$ compared to 26 patients treated with Aurothioglucose (58). The authors felt that Aurothioglucose was superior to Auranofin$_{TM}$ in that the index of disease activity measured showed clinically significant benefit of Aurothioglucose over Auranofin$_{TM}$ at 4 months and 9 months. The 10 patients who dropped out of therapy because of no response to Auranofin$_{TM}$ developed a beneficial clinical response when started on D-penicillamine. More side effects were recorded for Aurothioglucose (N = 21) over Auranofin$_{TM}$ (N = 14). This was the major reason (20% of total) for drop out from therapy from Aurothioglucose.

In 1983 Ward and colleagues who comprised the Cooperative Systematic Studies of Rheumatic Diseases group reported a prospective, controlled, double-blind multi-centre trial which compared placebo, Auranofin$_{TM}$ and gold sodium thiomalate (5). Of the 208 patients who fulfilled the entry criteria, 193 were eligible for study. 161 patients completed 20 weeks of therapy. When gold sodium thiomalate was compared to placebo, there was a significant improvement over placebo for number of tender joints, joint tenderness score, joint swelling score, increase in haemoglobin, fall in ESR and fall in platelet count. Skin rash was the most common cause for withdrawal from therapy (10%) followed by stomatitis 5%, nitritoid reactions (4%), abnormal liver enzymes (4%), thrombocytopenia (2%), proteinuria (2%) and individual patients with diarrhoea, leukopenia and pneumonitis. Three patients had rash plus either thrombocytopenia, leukopenia or stomatitis.

When Auranofin$_{TM}$ was compared to placebo significant improvement was recorded for number of tender joints, pain tenderness score, physicians global assessment of disease activity and decrease in ESR. Adverse reactions accounted for the withdrawal of 6% of patients from the Auranofin$_{TM}$ group due to 1 each of rash, diarrhoea, stomatitis, eosinophilia and leukopenia.

A comparison of Auranofin$_{TM}$ versus gold sodium thiomalate in the above study by Ward and colleagues demonstrated that the injectable gold sodium thiomalate was superior to the oral gold drug for improvement in anaemia and thrombocytosis. Both Auranofin$_{TM}$ and gold sodium thiomalate were superior to placebo for improvement in number of tender joints, joint pain/tenderness score, physicians overall assessment and ESR. Although statistical significance was not achieved, the authors indicated that gold sodium thiomalate produced a 12% greater improvement in joint pain/tenderness score and a 32% advantage relative to joint swelling score. The authors concluded that Type II error was possible with the small sample sizes thus masking a significant indicator of benefit of gold sodium thiomalate over Auranofin$_{TM}$ for these variables.

Ward and colleagues concluded that gold sodium thiomalate does have a therapeutic advantage over Auranofin$_{TM}$ although the oral gold preparation has less side effects leading to cessation of therapy. An overall assessment of trials of Auranofin$_{TM}$ versus placebo and Auranofin$_{TM}$ versus injectable gold compounds would support these conclusions by Ward and colleagues. In many patients treated with injectable gold, individual observers will discontinue the drug following the development of rash, mouth ulcer or proteinuria less than 1000 mg/24 hr. In contrast many observers will merely temporarily withhold the gold drug until the side-effect has cleared or modified and then re-introduce the drug. Thus inter-observer variations and clinical variations have to be considered, especially in multi-centre studies of toxicity and when two or more trials are compared. It may therefore be a false conclusion that there is an increase in the number of adverse effects resulting in withdrawal in the gold sodium thiomalate treated patients over the Auranofin$_{TM}$ patients.

In an open study by Giannini and colleagues in 1983, 21 children aged 1—17 years were treated with 0.1—0.2 mg/Kg/day of Auranofin$_{TM}$ (59). The authors claimed a significant clinical improvement (25%) in more than half of the children. This included, number of severity of joints with swelling, pain on motion and tenderness. Beneficial response was greater in those children taking the higher doses. Only 2 of 21 had to discontinue therapy, 1 because of headaches and 1 because of haematuria, anaemia and a flare in disease activity. Three other children had side-effects which required dose reduction. These were proteinuria, diarrhoea and one with haematuria and anaemia.

In view of the potent inhibitory capacity of Auranofin$_{TM}$ for DNA synthesis and natural killer cell function in vitro, the administration of this drug to children over the long term will have to be viewed with extreme caution.

SUMMARY OF CLINICAL GUIDELINES

Injectable gold compounds, gold sodium thiomalate, gold thioglucose, gold thiosuplphate and gold thiopropanol sodium sulphonate, are recognised by rheumatologists worldwide as the mainstay of disease modifying therapy in the treatment of rheumatoid arthritis and certain related inflammatory arthritides. Treatment with these agents should be commenced as early as possible after the diagnosis of rheumatoid disease, once it has been established that the disease symptoms are not responsive to adequate treatment with non-steroidal anti-inflammatory agents. In view of the potential for toxicity a strict monitoring system should be applied. Therapy should be conducted as outlined above with the use of a flexible regimen, e.g. if a patient is on monthly maintenance therapy and appears to be developing a flare-up in symptoms, the non-steroidal anti-inflammatory drug regime should be altered if need be and the frequency of gold injections increased to weekly. One important added safety feature of the injectable gold compounds over oral gold and indeed the other oral disease modifying drugs and immunosuppressants, is the fact that drug administration route (the intramuscular injection) is under the control of the physician and not the patient. This benefit limits against excessive use of drugs by the patient and also under-use of drugs.

Auranofin$_{TM}$, the oral gold compound should not be considered as equivalent to the injectable gold compounds as far as mechanism of action is concerned, but more accurately resembles azathioprine, methotrexate and cyclophosphamide. Auranofin$_{TM}$ should therefore be reserved for those patients with

rheumatoid disease who fail to respond to injectable gold compounds, followed by D-penicillamine and the anti-malarials.

The long term outcome of patients treated with gold compounds or indeed any of the anti-athritic agents is unknown. Only a large cohort prospective study will answer the question as to whether disease modifying agents do modify the outcome of the arthritis over the long term. The weight of evidence to date suggests that gold sodium thiomalate does beneficially modify the disease process (49, 50).

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