INVITED ARTICLE

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

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HISTORICAL PROFILE

Elemental gold has been known to man since the dawn of civilisation. The lustre and permanence, coupled with its rarity, has led to the worship accorded this metal throughout history. Gold's presumed magical qualities and its resemblance to the "essence" of the sun made it a natural choice by priests, healers and shaman. Although reference had been made to the medicinal use of gold by the Chinese circa 2500 B.C. (1) the dramatic account of Moses burning the golden calf, preparing a potion from the ashes, and forcing the Children of Israel to "...drink of it", is probably one of the earliest accounts of the practices of alchemy involving gold (2). The medicinal use of gold is also attributed to the Taoist philosophers of ancient China circa 6000 B.C. (3,4) and in later literature, Pliny the Elder (5) and Dioscorides (6) record the use of gold as a medicinal agent. In the great Persian medical schools initiated by the Nestorian Christians, pharmacist-physicians such as Yabir, Avicenna and Rhazes all advocated the use of gold compounds as panaceae. Yabir is attributed to have discovered the formulation of aqua regia. Medical knowledge spread into Europe and the British Isles by the 11th and 12th centuries and perhaps the first gold researcher in the British Isles was the Franciscan scholar Roger Bacon (circa 1214—1292 A.D.), who documented one of the first known descriptions of gold chloride (7).

The revival of gold compounds in medicine occurred in the early 19th century due to the work of Andre-Jean Chrestien and Pierre Figuier (1765—1817), two professors at the University of Montpellier (8). Figuier, a pharmacist, provided the chemical formulation for the gold compounds, in particular gold sodium chloride, which Chrestien advocated as of value in the treatment of tuberculosis and syphilis.

The herald of the modern use of gold compounds in medicine starts with the observation by Dr Robert Koch that gold cyanide was bactericidal in vitro to tubercle bacilli (9). European scientists and physicians over the next 40 years experimented with the use of gold complexes in the treatment of human and bovine tuberculosis. The erroneous but serendipitous assumption by Dr Jacques Forestier that rheumatoid disease was an infectious disease analogous to tuberculosis, led him to use gold thiopropanol sodium sulphonate on 15 patients with inflammatory rheumatoid disease (10). The success of this initial experiment was the seed which has led researchers over the past 50 years to investigate both the beneficial and the toxic effects of anti-arthritic gold complexes.

GOLD CHEMISTRY

Gold is a soft, yellow lustrous metal, with a unique stability since it is not attacked by either oxygen or sulphur at any temperature (11). Solar spectral analysis confirms that gold is present at 0.04 parts per million in the sun, and approximately 0.004 parts per million in the Earth's crust. Gold deposits on Earth exist as the metallic form or in mineral form, either as Tellurides such as calaverite and krennerite (different crystalline forms of $AuTe_2$), montbrayite (Au_2Te_3) and mixed gold-silver tellurides such as sylvonite (Au Ag Te_4) (11). To a lesser extent mineral forms of auriferous sulphides also exist (12). Metallic gold and silver gold mixtures also exist, perhaps the most well-known being electrum, which contains 20% silver.

Pure gold metal has a density of 19.32g cm^{-3} at 20°C: it melts at 1063°C and boils at 2966°C (11). Gold has a atomic number of 79 and an atomic weight of 196.9665. The stable isotope ^{197}Au contains 79 protons and 119 neutrons. There are 29 other isotopes of gold with mass numbers in the 177 to 204 range. The most important of these is ^{198}Au which decays by β-emission accompanied by gamma radiation. The half-life of 2.76 days makes it a relatively safe and useful tool in medical science, in radiotherapy, radiodiagnostic and radiotracer studies.

Gold is classified as a Group I.B. metal in the periodic table with an electronic configuration of (Xe) $4f^{14}5d^{10}6s^1$. The most commonly recognized oxidation states at I, II, III and V, although metal-metal bonds do exist in complexes in which it is difficult to assign a formal oxidation state to the gold atom. The true salts of Au(I) such as the halides are unstable in the presence of water and disproportionate to Au° (metallic gold) and Au(III). However, Au(I) can be stabilised by the formation of complexes with "soft" ligands (13) such as the thiolates and phosphines. All currently used anti-arthritic gold complexes exist as Au(I) thiol or phosphine compounds (14). The high toxicity of the Au(III) complexes such as chlorauric acid ($HAuCl_4$), makes them unsuitable for human use. Elder and colleagues have shown that if gold sodium thiomalate is administered to laboratory animals, the gold recovered from the tissue and urine exists in the Au(I) oxidation state (i.e. the same oxidation state as the gold in gold sodium thiomalatel and not the Au(III) oxidation state (15). Further, if $Au(III)Cl_3$, is administered to laboratory animals, gold recovered in tissues and urine exists only in the Au(I) oxidation state as determined by x-ray absorption near edge spectroscopy (XANES) and extended x-ray absorption fine structure spectroscopy (EXAFS) The Au(I) oxidation state therefore appears to be the primary oxidation state in a biological milieu: reduction from Au(III) to Au(I) is most likely caused by the powerful sulphydryl containing reducing enzymes present in vivo.

A common misconception among members of the medical profession, is the idea that D-penicillamine may be used as a chelating agent for gold, if a toxic reaction occurs during or following the administration of the anti-arthritic gold complexes. There is no theoretical nor biochemical evidence that D-penicillamine chelates Au(I) in vivo. Au(I) compounds normally have a linear geometry in which the AU(I) atom is attached to only two ligand atoms (X) such that the X-Au(I)-X angle is 180°C. Less frequently, and only for rather specific ligands, Au(I) binds to three (X-Au(I)-X angle equal to 120°) or four (X-Au(I)-X angle equal to 109.5) ligand atoms. Thus one would expect D-penicillamine to bind to Au(I) only through the sulphydryl site. Furthermore, Au(I) binds more readily to polarizable (soft) ligand groups such as sulphur or phosphines as opposed to weakly polarizable (hard) ligand groups, and the amine and carboxylate groups of D-penicillamine are "hard". Thus, as supported by the studies of Davis and Barraclough (16), there is no theoretical reason why D-penicillamine should chelate Au(I) (17).

THE ANTI-ARTHRITIC GOLD COMPLEXES AND RELATED STRUCTURES

The current commonly used gold complexes in the treatment of rheumatoid arthritis and in related research work are illustrated in figure 1.

Gold sodium thiomalate has been used in the treatment of rheumatoid arthritis since the early 1930's. It is marketed by May and Baker (U.K.), Rhone-Poulenc (Canada) and Merck, Sharp and Dhome (U.S.A) as vials of 50 mg/ml of compound suspended in sterile water for use as an intramuscular injection. The compound contains approximately 51% gold and 0.3 mols of glycerol per mol of thiomalate. During the manufacturing process glycerol is used in the final purification step. The vials of compound marketed for human use also contain the following preservatives: phenylmercuric nitrate 0.002% (May and Baker preparation): chlorocrescol 0.05% (Rhone-Poulenc preparation), benzyl alcohol 0.5% (Merck Sharp and Dhome preparation). The currently assumed molecular weight of gold sodium thiomalate is 390.12. This value is based on the empirical formula of the compound but clearly this structure is incompatible with the known chemical properties of Au(I) and a more likely explanation of the structure is a polymer or oligomer. According to Shaw (18), gold sodium thiomalate elutes from Sephadex G-100 as a polymeric structure. Ultracentrifuge and hydrogen-1 and carbon-13 nuclear magnetic resonance studies by Sadler and colleagues support this concept of the gold sodium thiomalate structure (19-21). Based on model building, a likely structural formula suggested by Sadler is a hexamer although studies by Elder suggest a pentamer is also a likely structure.

Gold thioglucose (figure 1) was manufactured in the United States by Merck Sharp and Dhome in the early 1930's and is currently manufactured under the brand name Solganol by the Schering Corporation of New Jersey and is administered as an intramuscular injection. Although it is water soluble, it is marketed as 50 mg of gold thioglucose in sterile sesame oil with 2% aluminium monostearate; 1 mg of propyl p-hydroxybenzoate is added as a preservative. Gold content is approximately 50.25% and the molecular weight based on the empirical formula is 392.18, but as with gold sodium thiomalate, the structural formulation of

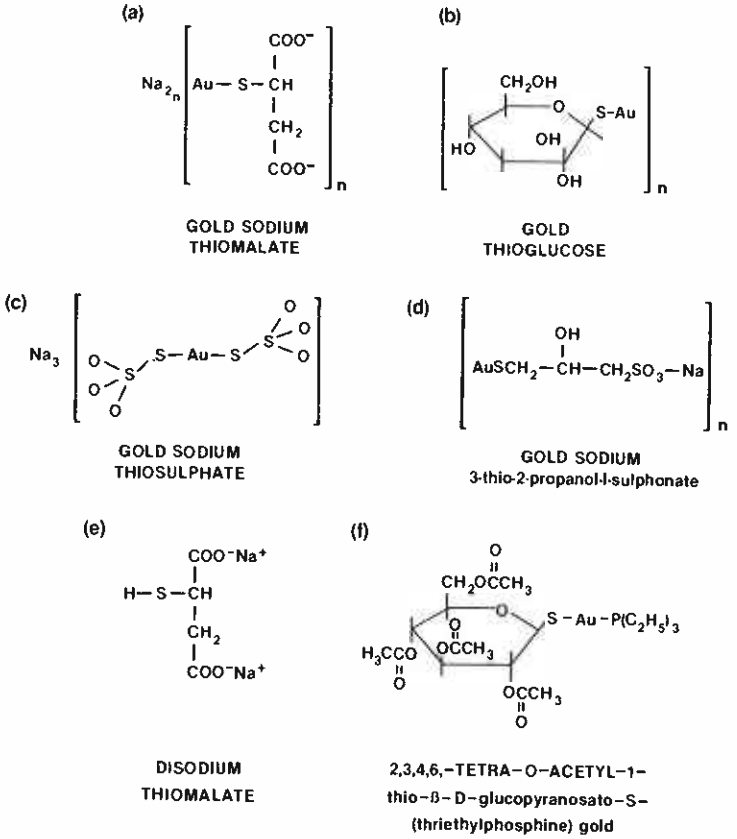

Fig. 1(a):The formula of gold sodium thiomalate depicted as a polymer

Fig. 1(b): The formula of gold thioglucose depicted as a polymer

Fig. 1(c): Gold sodium thiosulphate, structural formula. The anion contains two thiosulphate moieties bound to gold through the sulphur atoms

Fig. 1(d): The formula of gold sodium 3-thio-2-propanol-l-sulphonate depicted as a polymer

Fig. 1(e): Disodium thiomalate formula. The disodium thiomalate salt is a monomeric species

Fig. 1(f): 2,3,4,6-Tetra-o-acetyl-l-thio-β -D-glucopyranosato-S-(triethyl-phosphine) gold is characterised as having a gold-phosphine bond as well as a gold thiol bond, and is a monomeric species

gold thioglucose based on the known chemistry of gold, is most likely an oligomer (figure 1).

Gold sodium thiosulphate (Figure 1) is marketed as Sanochrysine in Europe by Nordiske in Denmark, in vials of 100 mg of compound/ml for use as an intravenous injection. It has been available since 1924 when it was first introduced by Mollgard. The compound has a molecular weight of 490.21 and contains 40.19% gold. The anion contains two thiosulphate moieties bound to gold through the sulphur atoms. Gold sodium thiosulphate is one of the few Au(I) compounds whose structure is known and which has been studied crystallographically.

Gold sodium 3-thio-2-propanol-1-sulphonate (Figure 1d) is marketed in Europe as Allochrysine lumiere by Laboratoires de Therapeutique Moderne France. The manufacturers list the gold content as being 30% but some analysts place the value as high as 52.9%. This variation may be dependent upon associated H_2O molecules or variations in the structural formulation of the gold compound during the manufacturing process (see discussion on gold sodium thiomalate). This compound, like gold sodium thiomalate, is most likely a small polymer. It was the original compound used by Forestier in 1928/29 and is still widely used in France, Switzerland and other parts of Europe.

2,3,4,6-Tetra-o-acetyl-l-thio-β -D-glucopyranosato-S-(triethyl-phosphine) gold (figure 1) is manufactured as auranofin$_{TM}$ by Smith Kline and French, Philadelphia, USA. It is a monomeric species with a gold phosphine bond as well as a gold thiol bond. It is marketed as a 3 mg tablet administered orally. The compound is a white, odourless crystalline solid which is insoluble in water. The powder is unstable and must be protected from light and heat. On a weight basis it contains approximately 29% gold and has a molecular weight of 678.5 with a melting point of 112°—115°.

Gold keratinate is manufactured in Germany as Aurodetoxin by Beecham-Walfing. It is basically a gold thiol structure attached to a polypeptide with the graphic representation of Au-S-R where R represent the polypeptide. The compound contains approximately 13% of Au(I). Gold distribution studies indicate that the gold from this compound binds predominantly to albumin (90%) with approximately 5% bound to macroglobulins. It is still widely used in Germany as an anti-arthritic agent.

Many other active Au(II)-thiol, anti-arthritic agents have been developed in this century but the majority of research, both basic science and clinical, has been carried out on those listed above.

PHARMACOKINETICS OF INJECTABLE GOLD COMPOUNDS

Since the basic chemical structures of the commonly used injectable gold complexes such as gold sodium thiomalate and gold thioglucose, are not known, knowledge of their pharmacokinetic profiles is largerly centred on the measurement of the Au molecule. These compounds are not monomeric Au(1)

salts but are most likely small polymeric structures. For these reasons extrapolation of the pharmacokinetics of the Au molecule as an interpretation of drug activity is not useful.

The Au moiety of the injectable gold complex is rapidly absorbed into the circulation after intramuscular injection. After each 50 mg injection peak serum levels of 700—1000 ug% are achieved in 2-6 hours. In the succeeding 6 days the serum levels fall to around 300 ug% demonstrating a 40% excretion of Au over the week. Approximately 75% of the Au is excreted via the kidney and the remainder in the faeces. During chronic dosing, 33% of this excreted dose is derived from the most recently administered injection (22). More than 95% of the administered gold is bound to albumin via the sulphur group on cysteine number 34. The remainder of the gold is bound to the macroglobulin layer (Fraction I of electrophoresis) (23). During radioactive labelling studies of gold sodium thiomalate it has been demonstrated that 50% of the ^{14}C label will appear in the urine in 24 hours. Although it is unlikely that this represents intact thiomalate, studies from the UK have shown that even when "purified" gold sodium thiomalate has been produced, as much as 13% "free thiomalate" may be detected in serum following an injection of gold sodium thiomalate (24). No one has yet determined what the active species of the compound is, either for efficacy or toxicity. Although there are good studies suggesting that serum gold relates to effectiveness, the majority of authors do not find this to be the case. The active species of the gold complex probably work at a cellular level, which would explain this apparent discrepancy.

The gold from the injectable gold compounds is widely distributed throughout the reticulo-endothelial system, particularly in the phagocytic cells of the liver, bone marrow, lymph nodes, spleen, and also in the synovium. Electron microscopic studies in our laboratories and those of others demonstrated that Au and S located within the lysosomes of phagocytic cells has a fibrillar like appearance (25). Gold deposition in the skin is predominantly in the dermal area and there is a quantitative correlation between the amount of gold in the dermis and the total dose given (26). Electron dense deposits of gold are also seen in the tubular cells of the kidney, another site rich in sulphydryl containing enzymes, but the presence of gold associated with the glomerulus is extremely uncommon (27).

Gold levels have also been detected in the milk of lactating mothers and in the serum and red blood cells of the nursing infant. The presence of the gold in the serum and red blood cells of the infant indicate that the chemical composition or binding of the Au as presented to the infant is in an orally absorbable form (28).

PHARMACOKINETICS OF AURANOFIN

Phosphines are usually non-bridging ligands and this accounts for the monomeric structure of Auranofin$_{TM}$. Like the gold-thiol compounds, Auranofin$_{TM}$ only contains Au(I) and also binds to albumin via cysteine 34 the only sulphydryl group in albumin. However, when the sulphur atom is blocked, theoretically the Auranofin$_{TM}$ should still bind to albumin via nitrogen with displacement of the chloride (29). Approximately 50% of the whole blood Au content of Auranofin$_{TM}$ is the result of intracellular penetration in the red cells, the rest being associated with albumin (23). This membrane penetration of the red cells and lymphocytes is due to the lipophilic nature of the Auranofin$_{TM}$ molecule.

Following administration of ^{195}Au labelled Auranofin, approximately 25% of the administered dose is detected in plasma with peak concentrations of 6—9 ug/100 ml being reached in 1—2 hours. The majority of absorption takes place in the upper small bowel. The plasma half life is in the order of 15—25 days with a total body elimination T of 55—80 days. This latter value is considerably less than gold sodium thiomalate. Only about 1% of ^{195}Au Auranofin is detectable by 180 days, whereas up to 30% of ^{195}Au from gold sodium thiomalate may be detected at this time. During single dose kinetic studies, approximately 75-85% of ^{195}Au from Auranofin$_{TM}$ is detectable in the stool. This excretion by the enteral route continues slowly and over a 6 month period the cumulative stool excretion of ^{195}Au may be as high as 88% of the original dose, suggestive of a slow entero-hepatic circulation (30).

Giannini and colleagues reported on whole blood and serum levels in 3 children with juvenile arthritis following a dosage of 0.1 mg/kg of Auranofin$_{TM}$. One child had a sample taken at 24 hours which measured 4.9 ug/100 ml and 7.6 ug/100 ml respectively. The gold disappeared from serum and blood in a linear fashion. The blood and serum half-life was interpolated as 7.1 and 7.5 days respectively (31).

To date the exact fate of the Auranofin$_{TM}$ molecule is not known once it has crossed the plasma membrane of the gut. Triple labelling studies with ^{195}Au, ^{35}S and ^{32}P show that molecule does not remain intact (32). The possibilities are that the Au with or without a S from the drug molecule binds to cysteine 34 on albumin. This would leave some of the molecule to form thioglucose and the phosphine ligand to form triethylphosphine oxide. The Au from Auranofin$_{TM}$ has less of an affinity for tissue distribution in spleen, liver and kidney than the Au from the gold thiol drugs.

MECHANISM OF ACTION OF INJECTABLE GOLD COMPOUNDS

The definitive mechanism of action of the injectable gold compounds is unknown. In vitro, these gold-thiol compounds have been shown to inhibit prostaglandin synthesis, modulate phagocytic cells (24) and to have the capacity to either kill or inhibit the growth of tubercle bacilli (35). The gold thiol compounds are also known to inactivate the first component of complement (c_1) (36) and to inhibit lysosomal enzymes such as acid phosphates, β-glucuronidase (37), elastase (38) and cathepsin G (39). In our own laboratories we have shown that gold sodium thiomalate but no other gold compound inhibits the action of the serine esterase enzyme thrombin, both in vitro and in vivo (40,41). In view of the affinity of Au(I) for sulphur, the ubiquitous action of gold complexes against enzymes is most likely related to the large number of enzymes possessing a SH group near the surface or in an accessible site. Gold sodium thiomalate appears to be particularly active against the serine esterase class, e.g. thrombin which is phylo-genetically related to elastase, trypsin and cathepsin G. The most likely mechanism of action against thrombin is an interaction of gold sodium thiomalate with one or all of the four cysteine-cysteine disulphide bridges of the thrombin molecule (40).

An extensive literature exists on the action of gold compounds in vivo and in vitro on immune response. With regards to effect on humoral immunity, initial studies demonstrated that gold complexes had no effect on humoral immune responses, as shown by the inability to suppress humoral response to paratyphoid vaccine in rabbits (42) and antibody responses to influenza vaccine in patients with rheumatoid arthritis (43). Subsequent studies by Gottlieb and colleagues

(44), and Lorber and colleagues (45) independently demonstrated that gold sodium thiomalate treatment resulted in a fall in all classes of immunoglobulin and also rheumatoid factor titre. Lorber's group showed that the drop in immunoglobulin levels was most significant and correlated best with patients showing the maximum response to gold sodium thiomalate. Gold sodium thiomalate has also been shown to inhibit pokeweed mitogen stimulated, immunoglobulin secreting cells, but only if the gold complex was added to the culture on day 1(46). In terms of cytotoxicity, sodium aurothiomalate has also been shown to inhibit antibody dependent cell mediated cytotoxicity when macrophages are used as effector cells (47), however, no such effect was shown when lymphocytes and polymorphs were used as effector cells (48). At least two groups have shown that Auranofin has an inhibitory effect on antibody dependent cell mediated cytotoxicity in concentrations as low as 0.125 ug of gold per ml. Russell and Davis from Edmonton have shown that Auranofin$_{TM}$ enhanced natural killer (N.K.) cell activity against Ragi cells and human amion cells in concentrations of 0.25—0.5 ug/ml but produced inhibitory effects at concentrations of 1.25 ug/ml and greater (49). In our own unit we studied the effect of Auranofin$_{TM}$ and gold sodium thiomalate on natural killer cell activity in vivo and in vitro in six week old CBA-J Mice (50). In our in vitro study lymphocytes were incubated in a range of concentrations of Auranofin$_{TM}$ (0.25 ug/ml — 1.5 ug/ml) and gold sodium thiomalate (3 ug — ug/ml). Natural killer cell activity was assessed using ^{51}Cr release assay on YAC target cells in a 4 hour assay. The results showed that in vitro gold sodium thiomalate had no effect on natural killer cell activity. Auranofin$_{TM}$ at low dose enhanced natural killer cell activity of the effector target ratios. These results with regards to Auranofin$_{TM}$ are similar to those found by Russell and Davis. In our in vivo study neither Auranofin$_{TM}$ nor gold sodium thiomalate had any effect on natural killer cell activty. It has been shown that killer cell activity is reduced in Sjogren's syndrome and at least one group has reported that patients with Sjogren's syndrome treated with gold sodium thiomalate who improved had an improvement in their N.K. cell activity. It is not possible at present to assess whether this was a direct effect of gold sodium thiomalate on N.K. cell activity in vivo in the human. The authors postulated that gold sodium thiomalate could be having some interferon-like action (51). Further study is required in order to investigate his phenomenon.

Gold sodium thiomalate has been shown to have a significant effect on cell mediated immune responses in vitro. The addition of gold sodium thiomalate on day 1 of lymphocyte culture will inhibit lymphocyte transformation to the mitogen phytohaemagglutinin (52) and Conconavlin A (53). It has been shown by Lipsky and Ziff that the direct effect of the gold compound was on the monocyte, thus inhibiting the helper function of the macrophages (53). A similar effect is seen with mixed lymphocyte culture in which gold sodium thiomalate will inhibit the mixed lymphocyte reaction if it is added on day 1 (47). No such effect is seen if the gold compound is added after day 1. The inhibitory effect of the gold sodium thiomalate on the mixed lymphocyte culture can be restored by the addition of fresh peripheral blood monocytes which have not been exposed to gold compounds (53). It is of interest that Percy and colleagues from Edmonton demonstrated that the use of gold sodium thiomalate in their patients was associated with an enhancement of the transformation responses to PHA when compared to pretreatment levels. In this study the return to a normal response to PHA correlated with improvement in clinical variables of disease activity (54).

In summary, gold sodium thiomalate has an indirect effect on human B cell function both in vitro and in vivo, probably due to inhibition of the human monocyte. This latter effect may be mediated through some inhibition of interleukin 1 production and/or function. Gold sodium thiomalate appears to have an effect on natural killer cell activity in vitro but only for certain effector cells. Gold sodium thiomalate inhibits both mitogen stimulated lymphocyte responsiveness and also the mixed lymphocyte culture. In view of the fact that those people who respond to gold sodium thiomalate therapy have a normalization of their mitogen responsiveness and mixed lymphocyte responsiveness, it is difficult at present to fully correlate the in vitro with the in vivo action of the drug. It is of interest that injectable gold-thiol compounds have also been shown to be inhibitory to certain viruses. If, indeed, rheumatoid disease was identified as a chronic viral disease due to Epstein Barr virus or related viruses one would have to consider that the injectable gold-thiol compounds may work through their anti-viral capacity.

There are no known drug-drug interactions with the injectable anti-arthritic gold compounds and other drugs, although it is advisable to avoid using drugs which are potential marrow suppressants, e.g. phenylbutazone, when using gold. Several centres are at present claiming less toxicity and equal benefit when Hydroxychloroquine and gold sodium thiomalate are given together.

MECHANISM OF ACTION OF AURANOFIN

Chemical structure, biological actions, and pharmacokinetic studies indicate that the oral compound, Auranofin$_{TM}$differs greatly from the injectable gold-thiol compounds. Walz and colleagues showed that auranofin$_{TM}$ inhibited the carrageenan induced oedema in a dose related fashion in concentrations of 40, 20 and 10 mg/kg with maximum inhibition of 86% with the highest dose, and a serum gold level of approximately 10 ug/ml. The two basic ligands of Auranofin$_{TM}$, namely triethylphosphine oxide and 2,3,4,6-tetra-o-acetyl-l-thio- β -D-glucopyranosato were without biological activity and gold sodium thiomalate, gold thioglucose and thiomalic acid did not significantly affect rat paw oedema (55). Auranofin was shown to significantly suppress adjuvant arthritis, whereas the ligands were without any effect. Using the same adjuvant arthritis model it was demonstrated that Auranofin$_{TM}$ in a dose of 10 mg/kg caused a significant reduction in 7S haemaglutination titre following immunisation by a single peritoneal injection of 1 ml of 25% sheep red blood cell suspension. These haemaglutination titers were not suppressed by gold sodium thiomalate or by gold thioglucose (32). In a study of antibody dependant complement lysis, anti-L929 immune serum from Auranofin$_{TM}$ treated rats exhibited a marked decrease (80%) in their ability to mediate antibody dependant complement lysis, whereas non-immune serums did not affect these reactions. In contrast antibody dependant complement lysis was enhanced in the serum of rats treated with gold sodium thiomalate. The study of cell mediated immunity using immunosuppressed oxazolone-induced contact sensitivity in C_{57}BL mice, Walz and colleagues demonstrated that Auranofin$_{TM}$ normalised the inhibitory effect of methotrexate on cell mediated immunity. In contrast gold sodium thiomalate had no effect on methotrexate immunosuppression. None of the ligands of Auranofin$_{TM}$ nor of gold sodium thiomalate had any effect (32).

The gold-thiol compounds, particularly gold sodium thiomalate, are ubiquitous inhibitors of cellular enzymes, particularly the serine esterase enzymes such as elastase and cethepsin G (40). No specific inhibitory effect of Auranofin$_{TM}$ on these enzymes has been recorded but Auranofin$_{TM}$ has been shown to inhibit the release of lysosomal enzymes such as β-glucuronidase and lysozyme from stimulated polymorphs (32). Gold thioglucose has no apparent effect on extracellular release of lysosomal enzymes. Similarly the ligands of the above gold complexes have no effect on either release nor enzyme inhibition. Auranofin$_{TM}$ is a potent inhibitor of antibody dependent cellular cytotoxicity exhibited by polymorphs from adjuvant arthritic rats. In contrast gold sodium thiomalate, gold thioglucose and the ligands of Auranofin$_{TM}$ had no significant effect on polymorphonuclear antibody dependent cellular cytotoxicity. Depending on the system used to study superoxide production, Auranofin$_{TM}$ is a much more potent inhibitor of superoxide production than gold sodium thiomalate. In certain systems such as an immune phagocytosis system, gold sodium thiomalate was devoid of inhibitory activity at a concentration of 40 times that of Auranofin$_{TM}$, which had produced marked inhibition (32). Walz and colleagues postulated that the Auranofin$_{TM}$ has also been shown to be more potent than gold sodium thiomalate in the inhibition of cutaneous migration, chemotaxis and phagocytosis by peripheral blood monocytes. Lipsky and colleagues have shown that Auranofin$_{TM}$, like gold sodium thiomalate, inhibit lymphoblastogenesis in vitro by a direct inhibition of mononuclear phagocyte function but also has an inhibitory effect on lymphocyte function not seen with gold sodium thiomalate. The inhibitory action on monocytes is achieved with concentrations of Auranofin$_{TM}$ which are 10—20 fold lower than those of the gold sodium thiomalate (56). The above findings suggest that Auranofin is acting as a potent immunosuppressive. In general, patients with active rheumatoid disease have a decreased capacity for either mitogen stimulated lymphoblastogenesis or for lymphoblastogenesis produced by the mixed lymphocyte reaction. Although patients initially treated with gold sodium thiomalate exhibit a suppression in mitogen stimulated lymphoblastogenesis, those who eventually respond to the drug will have normalization of lymphocyte responsiveness in vitro (54). In contrast within a few weeks of patients receiving Auranofin$_{TM}$, lymphocyte responsiveness is markedly inhibited (57). Thus Auranofin has powerful immunosuppressant effects in vitro and acts at an order of magnitude less than the injectable gold compounds. This may reflect the major difference in the pharmacological properties of the oral compounds versus the injectable gold-thiol compounds. Indeed it has been proposed that auranofin could have potential in cancer therapy (58) because of its potent immunosuppressive properties (59). No data is yet available on the safety of long term auranofin treatment with respect to the dangers of long term immunosuppressive therapy. In contrast gold sodium thiomalate can be given with safety for prolonged periods of time with no recorded evidence of increased mitotic disease.

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