HISTORY OF GOLD IN MEDICINE

The presumed magical qualities of gold and its resemblance to the ‘essence’ of the sun made gold and gold potions the natural choice of priests, healers and shamans since the earliest civilizations. Medicinal use of gold and other precious metals was known to the Chinese circa 2500 BC [1], and it is stated that Taoist philosophers of ancient China circa 600 BC [2, 3] used gold and silver to enhance the quality of their medicines. Probably one of the earliest records pertaining to the practice of gold alchemy has to be the dramatic account in Exodus of Moses burning the golden calf, preparing a potion from the ashes, and forcing the Children of Israel to ‘. . . drink of it’ [4]. The Roman physician, Pliny the Elder [5] and the Greek, Dioscorides in the first century AD [6] record the use of gold compounds as medicinal agents for multiple ailments. In the great Persian medical schools founded by the Nestorian Christians, physicians—physicians such as Yabir, Avicenna and Rhazes all advocated the use of gold compounds as panaceae. Yabir is reputed to have discovered and described the formulation of aqua regia, the mixture of nitric and hydrochloric acid, necessary for the dissolution of gold. Knowledge of structured and sophisticated medical practice spread from the Arab cultures into Europe and the British Isles by the 11th and 12th centuries. The Franciscan scholar Roger Bacon (circa 1214–1292 AD) was one of the first known gold alchemists of the British Isles.

He described the synthesis of gold chloride [7] and advocated its use in the treatment of diseases. The renaissance pharmacologist Paracelsus proclaimed gold compounds as a panacea; however, many of his contemporaries refuted his recondite theories.

The modern use of gold compounds in medicine was initiated in the early 19th century by the work of Andre-Jean Chrestien and Pierre Figuier (1765–1817), two professors at the University of Montpellier [8]. Figuier, a pharmacist, described the chemical formulation for the gold compounds, in particular gold sodium chloride, which the clinician, Chrestien, advocated as of value in the treatment of tuberculosis and syphilis. The observation by Robert Koch [9] that gold cyanide was bactericidal to tubercle bacilli in vitro, led European investigators, over the next 40 yr, to experiment with the use of gold complexes in the treatment of human and bovine tuberculosis. The serendipitous assumption by Dr Jacques Forestier [10] 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. The success of this initial experiment was the seed which steered researchers over the next 50 yr to investigate both the beneficial and the toxic effects of anti-arthritic gold complexes. It is important to note that although Forestier’s hypothesis was based on a so-called erroneous assumption, his observations of the histological similarity of ‘reactive’ rheumatoid synovium and tuberculous nodules are now known to bear more similarity to scientific truth than to fiction.

GOLD CHEMISTRY

The element gold is not attacked by oxygen or sulphur at any temperature, hence its unique stability [11]. Gold is present at ~ 0.004 p.p.m. in the Earth’s crust in both metallic and mineral forms. The most common minerals are the tellurides such as calaverite, krennerite (different crystalline forms of AuTe2), montbrayite (Au2Te3) and mixed gold–silver tellurides such as sylvonite (AuAgTe3) [11]. Mineral forms of auriferous sulphides also exist in lesser quantities [12]. Metallic gold and silver–gold mixtures such as electrum, which contains 20% silver, are found in nugget or particulate form. Gold is a Group IB metal in the periodic table with the most common oxidation states as I, II, III and V, although metal–metal bonds exist in complexes in which it is difficult to assign a formal oxidation state to the gold atom. Halides which form the true salts of Au(I) are unstable in the presence of H2O and disproportionate to Au+ (metallic gold) and Au(III). Au(I) can be stabilized by the formation of ‘soft’ ligand complexes [13] with thiolates and phosphines. All current anti-arthritic gold complexes exist as Au(I) thiol or phosphine compounds [14]. The high cellular toxicity of the Au(III) complexes, such as chloro-auric acid (HAuCl4), makes them unsuitable for human ingestion. Studies on laboratory animals treated with gold sodium thiomalate have shown that the gold recovered from the tissues and urine exists in the Au(I) oxidation state (i.e. the same Au(I) oxidation state in gold sodium thiomalate) and not the Au(III) oxidation state [15]. Further, if HAu(III)Cl4 is given to laboratory animals, gold recovered in tissues and urine exists only in the Au(I) oxidation state. The Au(I) oxidation state, therefore, appears to be the primary oxidation state which is stable and exists in the biological milieu and in vitro. Reduction from Au(III)
to Au(I) is most likely caused by the powerful sulphhydryl-containing reducing enzymes present in vivo.

In the late 1970s, aurano_n emerged as a possible alternative gold anti-arthritic agent which had the presumed advantage of oral administration. In order to obtain a stable gold compound which could be absorbed from the gastrointestinal tract, a unique formulation was devised.

Auranofin is a monomeric Au(I) species in which the triethyl phosphine group stabilizes the gold-thiol complex. Its chemical name is 2,3,4,6-tetra-o-acetyl-1-thio-β-D-glucopyranosato-S-(triethyl-phosphine) gold. It is marketed as a 3 mg tablet or capsule which is 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, aurano_n contains ~29% gold and has a molecular weight of 678.5 with a melting point of 112–115°C.

**AURANOFIN PHARMACOKINETICS**

Following oral administration of [195Au]aurano_n, ~25% of the administered dose is detected in plasma bound to albumin through bonds to cysteine and histidine [16]. Peak concentrations of 6–9 μg% are reached within 1–2 h [31, 32]. The plasma half-life of aurano_n is in the order of 15–25 days with a total body elimination rate of 55–80 days [17]. Only ~1% of the 195Au is detectable by 180 days, whereas up to 30% of the 195Au from gold sodium thiomalate may be detected at this time [18].

When aurano_n crosses the plasma membrane, the acetyl groups on the thioglucose moiety are lost and some dissociation of the compound takes place [19]. Triple label studies with radioactive 197Au, 35P and 85S show evidence of Au–S and Au–P disruption which occurs across the plasma membrane [20]. Different experimental models have shown different results for radioactive ligand dissociation across the plasma membrane [19]. Since it is unlikely that the gold moiety alone is the active species, in vivo study of molecular gold kinetics has been of little value in the interpretation of the mechanisms of action of gold complexes. Proper design of in vitro and ex vivo experiments must incorporate the expected ligands which occur following the dissociation of the aurano_n. The application of the intact aurano_n molecule to an in vitro or ex vivo experiment may not provide results which reflect the in vivo activity of the dissociated components of the aurano_n [21].

**AURANOFIN PHARMACODYNAMICS**

Chemical structure, biological actions and pharmacokinetic studies indicate that the oral gold compound, aurano_n, differs significantly from the injectable gold-thiol compounds [22]. Walz et al. [23] showed that aurano_n inhibited carrageenin-induced oedema in rats in a dose-related fashion at concentrations of 40, 20 and 10 mg/kg with maximum inhibition of 86% at the highest dose, and a serum gold level of ~10 μg/ml.

The two basic ligands of aurano_n, namely tri-ethylphosphine oxide and 2,3,4,6-tetra-o-acetyl-1-thio-β-D-glucopyranosato were without biological activity and gold sodium thiomalate, gold thioglucose and thiomalic acid did not affect rat paw oedema significantly. Aurano_n was shown to suppress adjuvant arthritis significantly, whereas the ligands were without any effect. Aurano_n inhibited antibody-dependent complement lysis, whereas antibody-dependent complement lysis was enhanced in the serum of rats treated with gold sodium thiomalate [22].

The gold-thiol compounds, particularly gold sodium thiomalate, are ubiquitous inhibitors of cellular enzymes, particularly the serine esterase enzymes such as elastase, cathepsin G and thrombin [24]. No specific inhibitory effect of aurano_n on these enzymes has been recorded, but aurano_n has been shown to inhibit the release of lysosomal enzymes such as β-glucuronidase and lysozyme from stimulated polymorphs [22]. 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 or enzyme inhibition. Aurano_n 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 aurano_n had no significant effect on polymorphonuclear antibody-dependent cellular cytotoxicity. Although results vary depending on the system used to study superoxide production, in general aurano_n 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 aurano_n, which had produced marked inhibition [22]. Walz et al. [22] postulated that aurano_n 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 et al. [25] have shown that aurano_n, like gold sodium thiomalate, inhibits lymphblastogenesis in vitro by 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 aurano_n that are 10- to 20-fold lower than those of the gold sodium thiomalate. The above findings suggest that aurano_n has immunosuppressive activity. In general, patients with active rheumatoid disease have a decreased capacity for either mitogen-stimulated lymphblastogenesis 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 [26]. In contrast, patients who receive aurano_n develop a marked inhibition of lymphocyte responsiveness [27]. Thus, aurano_n has
powerful immunosuppressant effects in vitro and acts at an order of magnitude less than the injectable gold compounds. This may reflect major differences in the pharmacological properties of the oral compound versus the injectable gold-thiol compounds. Indeed, it has been proposed that auranofin could have potential in cancer therapy [28] because of its potent immunosuppressive properties [29]. To date, there have been no reports which cast concern on carcinogenicity or other long-term safety of auranofin treatment with respect to the dangers of prolonged immunosuppressive therapy.

ADVERSE EFFECTS OF AURANOFIN

Loose stool/diarrhoea

A change in stool pattern with the development of loose or soft stools is the most common side-effect of auranofin therapy and may occur in over 40% of treated patients [30, 31]. The frequency of loose stools is highest in the first month of treatment, but 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 can be totally intolerant of even 3 mg/day. The precise mechanism underlying gold-induced diarrhoea is not well defined. The major part of solute and water absorption occurs in the small intestine, with the large intestine, particularly the distal colon, playing the role of a final modifier. This mechanism is similar to that observed in the renal tubule where obligatory reabsorption of salts, solutes and water occurs in the proximal segments, with the distal tubule and collecting duct responsible for facultative reabsorption. By analogy with the renal tubule collecting duct, the reabsorptive capacity of the distal colon is limited. Decreased reabsorption of solutes and water in the proximal segments can overwhelm the reabsorptive capacity of the distal segment and result in diuresis in the case of the kidney, and diarrhoea in the case of the gut [32].

Clinical and experimental studies have suggested that auranofin alters the intestinal transport process to produce diarrhoea. Van Riel et al. [30] studied the occurrence of diarrhoea during the course of a long-term clinical trial. Eleven patients developed diarrhoea and, in eight who were studied, K⁺ ion and dry weight were reduced, but faecal Na⁺ concentration was elevated. The authors suggested that auranofin could have a direct effect on the absorption of salt and water by the colon [33]. In six patients taking auranofin, Behrens et al. [34] found that intestinal transit time was decreased, the concentration of Na⁺ in faecal water was increased with a reduction in bicarbonate, but no significant changes in levels of Cl⁻ or K⁺ were recorded. They also noted that the excretion of ⁵¹Cr-EDTA and lactulose was increased with little increase in the excretion of mannitol. This argued for an increase in intestinal permeability. Whether this implied destruction of the absorptive surface was not clear, but experimental studies in the rat produced evidence of mucosal damage. In contrast to these results suggesting that gold compounds inhibit absorption, a study of a single patient given gold thioglucose suggested that they could produce a secretory type of diarrhoea [35].

Experimental studies have provided evidence that both anti-absorptive and secretory mechanisms may be operative. Hardcastle et al. [36] used everted rat colon sacs, and showed that auranofin in the mucosal solution reduced fluid and Na⁺ absorption, whereas it was ineffective from the serosal side. The drug also inhibited the activity of Na⁺/K⁺ ATPase. Similar observations were made in dogs where auranofin caused significant elevations in efferent volume, osmolarity and Na⁺ concentration with significant decreases in K⁺ [37]. These results led to the hypothesis that auranofin and other gold compounds, such as gold sodium thiomalate and chloroauric acid, reduced absorptive processes by inhibiting the Na⁺ pump activity of enterocytes. In contrast, Ammon et al. [38] found that auranofin induced a net fluid and electrolyte secretion across the in vitro perfused rat jejunum. Since gold sodium thiomalate did not produce similar effects, they suggested that it was not the gold moiety but the carrier molecule that was responsible for the effects. Later, these authors showed that prolonged perfusion with auranofin produced mucosal injury, whereas gold sodium thiomalate did not. It should be noted that the structural differences amongst gold compounds, especially between the oral compound auranofin and the injectable compounds, suggest that the gold moiety may not be the active species and may not be chemically available for biochemical interaction with other ligands, except in conjunction with another molecule such as sulphur or with a complete ligand (see gold chemistry).

The colonic epithelium has an extensive neural network and it is possible that gold compounds could alter colonic transport by modulating enteric nerve activity. This was investigated [39] by using two different in vitro preparations from the canine colon: (a) mucosa which had the muscularis mucosa and attendant submucous plexuses present and (b) an epithelium that was functionally nerve free [40]. Both preparations responded to auranofin from the luminal and from the contraluminal (serosal) sides. However, the concentrations required to elicit responses from the luminal side were 100-fold greater. With the mucosal preparation, responses to auranofin were significantly reduced by tetrodotoxin which is a neurotoxin. These results suggest that the effects of auranofin on colonic secretion have a significant neural component, as well as the direct effects noted above. In addition, it appears that auranofin traverses the epithelial lining to modulate colonic activity from the serosal side. The ionic gold compound, sodium aurothiosulphate, altered colonic transport only on serosal application, but had no effects on luminal application. Thus, two chemically distinct gold compounds, auranofin and sodium aurothiosulphate, produced similar effects on serosal application. It should be noted that this suggests that a Au-S complex or Au–ligand or the
ligand alone is the active species. It is not appropriate to assume that ‘free’ gold is the active species since it could not exist in these biological conditions, but would have to be bound to some other species (see gold chemistry). The precise molecular mechanisms responsible for the above effects are not clear.

Snyder et al. [41] suggested that both the therapeutic and toxic effects of auranofin were due to the interactions of the drug with -SH groups, and that auranofin and other gold complexes stimulate the activity of phospholipase C. This leads to the production of secondary messengers such as diacylglycerol (DAG) and inositol 1,4,5 triphosphate (IP3). DAG is hydrolysed to produce arachidonic acid which could, in turn, produce a variety of eicosanoids through the cyclo-oxygenase and lipooxygenase pathways. The prostanoids and leukotrienes have pronounced effects on intestinal transport [42]. Intracellular Ca2+ is released by IP3 and can stimulate Cl− secretion by enterocytes [43]. Snyder et al. [41] also stated that lipid peroxidation could lead to the production of superoxide (O2−) and hydroxyl radicals (OH−), as well as hydrogen peroxide, with disruption of membrane fluidity. It is not known which of these mechanisms is responsible for the effects on the epithelial cells and the enteric nerves, but the activation of phospholipase C does appear to be a possibility.

The above results suggest that gold compounds can produce diarrhoea by inhibition of absorption and/or stimulation of secretion. Altered motility may play a role. In the clinical studies of Behrens et al. [34], the mean transit time decreased from 71.0 h (off auranofin) to 40.5 h (on auranofin) and the authors suggested that much of this could be due to more rapid transit through the colon. However, Fondacaro et al. [37] found that auranofin had no effect on the basal tension of isolated colonic smooth muscle strips and did not alter KCl-induced contractions. Since the responses of the muscle to neurotransmitters or hormones could have been altered, the evidence for an effect on gut motility is inconclusive at present.

Although loose bowel movement or frank diarrhoea are the most common gastrointestinal side-effects of auranofin, non-specific digestive system complaints account for ~20% of adverse reactions and 2% of all withdrawals from auranofin therapy [44]. Stomatitis occurs in 1–12% of patients and may occur concomitantly with skin rash. While occurrence is greatest in the first month, stomatitis can occur at any time [45]. The oral ulceration may or may not be painful. The ulcers resemble aphthous ulcers in the mucous membrane and in the vestibule of the mouth. Occasionally, the lesions are present on the tongue or the hard palate. The development of a mouth ulcer is a definite contraindication to gold therapy until it has resolved. Oral ulceration can precede the development of pemphigoid-like bullous skin lesions. The causes of rash and stomatitis are unknown.

Proteinuria

The wide variations in the definition or lack of definition of proteinuria in the literature have resulted in a considerable difference in the 0–40% reported incidence for injectable gold compounds [45–49]. Proteinuria occurs in up to 5% of patients treated with auranofin. The drug should be withheld and assessments of renal function made in a manner similar to that for renal toxicity due to injectable gold compounds. Proteinuria in urine in amounts of 1 + by dipstick over 2–3 weeks warrants a 24 h urine protein estimation. If proteinuria is <500 mg/24 h, the drug should be continued. Between 500 and 3000 mg/24 h, auranofin therapy should be withheld until it is established that renal function is normal. Patients with proteinuria >3000 mg/24 h should have the auranofin stopped until the proteinuria resolves. There are no well-documented cases of long-term serious or permanent renal damage due to gold-induced proteinuria. The most common renal histological lesion is membranous glomerulonephritis with deposition of IgG, IgM and C3 on the glomerulus [50], although heavy metal tubular damage does occur during injectable gold therapy [51].

One postulated mechanism of the proteinuria is that the gold or a gold complex damages the renal tubule, analogous to heavy metal damage, and results in release of a ‘neo antigen’ which complexes with immunoglobulin and deposits on the glomerulus to result in a glomerulonephritis. The tubular damage is characterized by the presence of β2-microglobulin in the urine. Electron microscopy has demonstrated the presence of fibrillar particulate gold-containing material within the proximal tubular cells and also the presence of mitochondrial degeneration [51]. Clinical studies have suggested an association between HLA DR3 and the presence of proteinuria [52].

Haematuria should not be considered as a recognized side-effect of auranofin therapy. When microscopic haematuria develops, auranofin should be stopped immediately and a cause for the haematuria sought. Once haematuria has resolved, auranofin may be reinstituted at a reduced dosage.

Thrombocytopenia/bone marrow suppression

Thrombocytopenia and related bone marrow suppression may present as rare side-effects of auranofin treatment. This type of auranofin-induced thrombocy-
topenia (unlike the more common type seen with gold sodium thiomalate) [53] does not express platelet surface-associated autoantibodies. Physicians monitoring auranofin therapy should observe a platelet count of \(<200\,000/\text{mm}^3\) as an indication to discontinue gold therapy temporarily. Most laboratories record a value of \(150\,000/\text{mm}^3\) as the lower level of normal for the platelet count. A falling platelet count, even within the normal range, can be a signal of early thrombocytopenia. A sudden change in a platelet count which has been steady at e.g. \(\sim 400\,000/\text{mm}^3\) weekly to a value of e.g. \(210\,000/\text{mm}^3\) behoves a physician to withhold auranofin therapy until a repeat platelet count confirms a stable value \(>200\,000/\text{mm}^3\) on at least two occasions 1 week apart. When a fall in platelet count results in a value which is persistently \(<200\,000/\text{mm}^3\), extreme caution is advised. Close observation of changes in platelet count even within the normal range may result in earlier identification of some patients who may develop a sudden thrombocytopenia. The treatment of choice is immediate withdrawal of drug therapy. The development of thrombocytopenia is an absolute contraindication to therapy.

Bone marrow suppression due to auranofin is rare, but is sufficiently serious to warrant strict monitoring of blood parameters on a weekly basis [46]. The marrow suppression secondary to injectable gold therapy is postulated to be due to a direct action of the drug on the marrow cells [54]. A fall in either platelet count as recorded above, or a fall in haemoglobin below 10 gram%, and/or a fall in total white count below 4000/\text{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, 1 week apart, have been recorded. If any of the above indicators of haemopoiesis remain abnormal, a bone marrow examination and investigation for autoantibodies to white cells, red cells and platelets are essential before auranofin therapy can be reintroduced. Bone marrow suppression secondary to auranofin is an absolute contraindication to further continuation of therapy.

While auranofin-associated bone marrow suppression could be a direct effect of the gold compound, an alternative postulate is that there is an alteration in the marrow feedback system from monocytes in the peripheral blood due to an action of the auranofin components on these cells or their ‘cell messengers’.

In spite of the potential for gold compounds to induce marrow suppression, successful treatment of Felty’s syndrome has been carried out in a controlled situation where assessment of bone marrow tissue and peripheral blood counts were available [55]. However, one case of Felty’s syndrome, treated with auranofin 6 mg/day for 1 yr, failed to respond. This patient also received prednisone which may have negated the potential effectiveness of the auranofin [56].

**Eye problems**

Conjunctivitis has been reported from collective studies in \(\sim 10%\) of patients treated with auranofin, and occurred with equal frequency at each 3 month time period over 3 yr of treatment. Withdrawal from therapy because of conjunctivitis is rare [57].

**Gold in pregnancy and lactation**

Injectable gold compounds have been implicated in the cause of fetal abnormalities in humans [58, 59], but this has not been substantiated due to the small numbers studied [60, 61]. Since gold levels have been found in the blood of newborns [60, 62, 63], it would seem wise to avoid gold therapy during pregnancy if possible. Usually, rheumatoid arthritis (RA) will decrease in severity or even remit during pregnancy. A small number of patients who received auranofin during pregnancy have been observed with no effect to mother or child [64]. Since auranofin has immunosuppressive-like properties and contains triethyolphosphine, it would seem wise to avoid this medication during pregnancy [65].

Trace amounts of gold derived from gold thioglucose therapy have been detected in breast milk [66, 67], but since gold is not readily absorbed from the gastrointestinal tract, it is unlikely to be a significant problem. To date, there are no data on the concentration of auranofin in breast milk. As noted above, because of its immunosuppressive properties, auranofin should be avoided in breast-feeding mothers.

**Adverse effects—comment**

Despite the apparent overall lower number of side-effects related to auranofin compared to injectable gold compounds, auranofin should not be considered a benign drug. A strict monitoring system, as for injectable gold compounds, should be undertaken for each patient. Insufficient data are available at present to determine whether there will be any long-term side-effects related to auranofin therapy. Particular attention should be paid to effects on immune functions related to long-term therapy.

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 or biochemical evidence that d-penicillamine chelates \(\text{Au(I)} \text{in vivo}\). \(\text{Au(I)}\) compounds normally have a linear geometry in which the \(\text{Au(I)}\) atom is attached to only two ligand atoms (X) such that the X–\(\text{Au(I)}\)–X angle is 180°. Less frequently, and only for rather specific ligands, \(\text{Au(I)}\) binds to three or four ligand atoms. Thus, one would expect d-penicillamine to bind to \(\text{Au(I)}\) only through the sulphhydryl site. As supported by the studies of Davis and Baraclough [68], there is no theoretical reason why d-penicillamine should chelate \(\text{Au(I)}\) [69]. D-Penicillamine and other chelating agents should NOT be used for the treatment of auranofin (gold)-induced toxicity.
CLINICAL OVERVIEW

Methodology

By definition, the disease-modifying anti-rheumatic drugs (DMARDs) are thought to impact on the progression of RA by (i) favourably altering the (short-term) natural history of the disease and (ii) slowing the development of radiologically demonstrated joint erosions or joint destruction [70, 71]. However, because of the often unpredictable course of RA, it is often difficult to determine the real (and unconfounded) impact of DMARDs, or other interventions, on disease outcome.

When evaluating the effectiveness of a specific therapeutic agent, much depends on the robustness of the instruments that are used to measure outcome. While it is generally agreed that multiple measures of clinical outcome are helpful in determining the effectiveness of a particular intervention, it needs to be acknowledged that such measures may be duplicative and vary in their relative sensitivity to change [72]. Moreover, although radiological assessments can satisfactorily demonstrate the extent of joint damage at any given time, there is little correlation between the radiological progression of disease and functional impairment [73].

What therefore becomes apparent is that any scrutiny of the available literature on one or another of the DMARDs needs to include a meticulous appraisal of the potential imprecisions of clinical outcome measurement and radiological interpretation. In addition, the broader context of study design and general methodological robustness also need to be considered carefully. There is an expectation that rigorously conducted studies and their reports should lead to better and more realistic estimates of treatment effects, more accurate and reproducible predictions of treatment efficacy, and greater acceptance of their results within the health care community [74, 75].

The quality of evidence in published research can be assessed according to various critical appraisal criteria, but for the specific purposes of this overview, the general guidelines developed by Sackett et al. [76] on the effectiveness of therapy provide the basis for judging the merits of particular studies. In evaluating each report, the following questions were addressed:

1. In randomized controlled studies (RCTs) was the assignment of patients really randomized?
2. Were clinically important outcomes assessed objectively?
3. Was there at least 80% follow-up of subjects?
4. Were both statistical and clinical significance considered?
5. If the study was negative, was power assessed?

As a further stage in the ‘quality filter’, a level of evidence can be attributed to the selected studies, and a hierarchy for grading recommendations (for application of the research conclusions) can be assigned [74]. The relationship between the levels of evidence and grades of recommendation is summarized in Table I [77]. This framework, although less rigorous than a precursor advocated by Sackett [78], is a useful medium for categorizing treatment recommendations.

This overview will focus primarily on studies demonstrating Grade I evidence (according to the criteria in Table I) but, to provide context and clarification, a small number of selected reports, reflecting Grade II evidence, will also be included.

To retrieve the relevant studies on the use of auranofin in the management of RA in adults, a MEDLINE search was conducted on the available English language literature for the period between 1980 and 1996. Additional studies were identified through reference lists contained in some of the searched reports and those contained in textbooks of the rheumatic diseases.

The notion of a possible oral gold preparation took root in 1972 with a report by Sutton et al. [79] that orally administered alkylphosphine gold co-ordination complexes exhibited anti-inflammatory properties when administered to adjuvant arthritic rats. In the same year, it was demonstrated that triethylphosphine gold chloride was equipotent to parenterally administered gold sodium thiomalate for suppression of inflammatory lesions in these rats [80]. Because triethyl gold chloride is extremely toxic in humans, further studies of its potential usefulness were not attempted. However, a related compound, 2,3,4,6-tetra-0-acetyl-1-thio-β-D-glucopyranosato-5-(triethylphosphine) gold, later known as auranofin, was also shown to exhibit anti-arthritic properties and was considerably less toxic than its precursor [81].

Grade II evidence favouring the use of auranofin in humans began to emerge following open studies by Finkelstein et al. [82–84] and Bernhard [85]. In the first clinical study on auranofin, Finkelstein et al. [82] described eight patients with RA treated 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 nine at week 15. Clinical improvement was recorded at 5 weeks and in general the drug was well tolerated. Rheumatoid factor titre, IgG levels and α2-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

<table>
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<th>Grade</th>
<th>Definition</th>
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<tr>
<td>I</td>
<td>Evidence from at least one properly randomized, controlled trial</td>
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<tr>
<td>II</td>
<td>Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies, preferably from more than one centre, from multiple time series, or from dramatic results in uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities on the basis of clinical experiences, descriptive studies, or reports of expert committees</td>
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TABLE I
Categories for quality of evidence on which treatment recommendations are made
cause and effect action of the drug. In addition to establishing efficacy and toxicity profiles for oral gold, the early studies focused on determining the optimal dosage of the new preparation. In one larger study, Calin et al. [86] were able to demonstrate that auranofin at a dose of 1 mg/day was insufficient to exert therapeutic benefit, while the 9 mg/day dose was efficacious but provoked toxic side-effects that necessitated dose reductions in a significant number of study patients. At the first 3 month period, ~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 reduction in erythrocyte sedimentation rate (ESR) were greater for patients receiving the 9 mg dose. Conclusions from this interim assessment were that 1 mg was insufficient for therapeutic effect, but 9 mg caused sufficient diarrhoea to make this dosage unsuitable. In a separate study that compared different dosage schedules [87], a 9 mg dose was again found to cause excessive toxicity while 1 mg (or 2 mg) per day appeared to be inadequate. Since the publication of these data, most investigators opted for dosages of 3–6 mg/day; but even within this range differences were evident, with generally greater benefit at the higher dosage that was offset by higher incidences of adverse effects (primarily diarrhoea and skin rashes) that often necessitated a reduction to the lower dosage schedule. Using multivariate analysis, Champion et al. [88] demonstrated that little was to be gained by increasing auranofin dosage above 6 mg/day.

These early studies were followed by several RCTs of generally high quality that (i) compared auranofin to placebo, (ii) examined similarities and differences between auranofin and i.m. gold injections, and (iii) tried to identify a specific place for auranofin in the overall management of RA by comparing its properties, effectiveness and side-effect profile with various other traditionally used DMARDs.

Auranofin vs placebo

Grade I evidence favouring the preference of auranofin over placebo has been provided by several RCTs. While variations in study design and differences in the selection of outcome measures have precluded any firm consensus on the effectiveness of oral gold, trends inferred from each of the studies have, in general, demonstrated the superiority of auranofin over placebo.

Under the aegis of the Cooperating Systemic Studies of Rheumatic Diseases (CSSRD), Ward et al. [45] compared auranofin, gold sodium thiomalate (GST) and placebo in 193 patients with RA. Results after 20 weeks of treatment showed a statistically significant improvement in pain/tenderness scores for patients on either auranofin or GST (but not for those on placebo). No significant differences were detectable for joint swelling, patient assessment or physician assessment [45].

Three separate studies have compared auranofin with placebo over a 6 month time period. In 1982, Katz et al. [89] 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 or placebo. Significant improvement in the treated group was recorded for the number of tender joints at 3 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 and 6 months in the auranofin group for those patients recorded as having a marked improvement. The authors concluded that the addition of auranofin to non-steroidal anti-inflammatory drug (NSAID) therapy added to the benefit derived from the latter in the treatment of RA [89]. In the 340 patients studied by Wenger et al. [90], significant improvements were demonstrated in grip strength, early morning stiffness, number of swollen joints, number of tender joints and physicians’ assessments of global response. Bombardier and the Auranofin Cooperating Group [91] utilized a comprehensive spectrum of clinical, functional, pain and global impression measures in their follow-up of 303 patients. Significantly greater improvement in the auranofin group (vs placebo) was recorded for the composite scores computed for the clinical, functional and global impression measures. Improvements were demonstrated for all of the clinical variables (i.e. number of swollen joints, number of tender joints, 50 feet walking time, early morning stiffness and grip strength).

One 24 month follow-up study has been reported. Borg et al. [92] followed 138 patients with ‘early RA’ (as defined by joint symptoms for < 2 yr). Improvements at the end of this time period were recorded for number of swollen joints, the Keitel Functional Test, the Stanford Health Assessment Questionnaire and the Beck Depression Scale. However, no differences were detectable for grip strength, early morning stiffness or number of tender joints.

Auranofin vs i.m. gold injections

Grade II evidence from two open comparative studies [93, 94] suggested that auranofin was less effective than (i.m.) GST over a 2 yr period. Also, except for a higher frequency of gastrointestinal side-effects (especially diarrhoea), the authors concluded that GST was more toxic than the oral gold preparation, based on the number of adverse responses noted.

Various RCTs (providing Grade I evidence) have compared the effectiveness and relative toxicities of auranofin and GST. In 1983, Ward and colleagues who comprised the Cooperative Systematic Studies of Rheumatic Diseases group [45] reported a prospective, controlled, double-blind multicentre trial which compared placebo, auranofin and gold sodium thiomalate. Of the 208 patients who fulfilled entry criteria, 193 were eligible for study. A total of 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, leucopenia and pneumonitis. Three patients had rash plus either thrombocytopenia, leucopenia or stomatitis.

When auranofin was compared to placebo, significant improvement was recorded for number of tender joints, pain tenderness score, physician’s global assessment of disease activity and decrease in ESR. Adverse reactions accounted for the withdrawal of 6% of patients from the auranofin group due to one each of rash, diarrhoea, stomatitis, eosinophilia and leucopenia.

A comparison of auranofin vs gold sodium thiomalate in the above study by Ward et al. demonstrated that the injectable GST was superior to the oral gold drug for improvement in anaemia and thrombocytosis. Both auranofin and GST were superior to placebo for improvement in number of tender joints, joint pain/tenderness score, physician’s overall assessment and ESR. Although statistical significance was not achieved, the authors indicated that GST 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 GST over auranofin for these variables. Ward et al. concluded that GST does have a therapeutic advantage over auranofin, although the oral gold preparation has less side-effects leading to cessation of therapy. An overall assessment of trials of auranofin vs placebo and auranofin vs injectable gold compounds would support these conclusions by Ward et al. In many patients treated with injectable gold, individual observers will discontinue the drug following the development of rash, mouth ulcer or proteinuria <1000 mg/24 h. In contrast, many observers will merely temporarily withhold the gold drug until the side-effect has cleared or modified and then reintroduce the drug. Thus, inter-observer variations and clinical variations have to be considered, especially in multicentre 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 GST-treated patients over the auranofin patients. Following a 12 month open study that was initiated after completion of the RCT by Ward et al., it was suggested that auranofin had a long-term use profile that was similar to other DMARDs. Moreover, it appeared that auranofin could sustain an initial response to GST [95].

Davis et al. [96] compared the therapeutic benefits and toxicity profiles of auranofin and GST in 120 patients with RA who were followed for 12 months. A similar number of patients (~60%) remained on each of the two preparations until the termination of the study and showed a similar statistically significant improvement in all of the measured clinical variables. No significant differences between the two drugs were detected. However, withdrawal from the study because of lack of therapeutic benefit was twice as frequent in the group of patients receiving auranofin, while attrition resulting from an adverse drug reaction was twice as common and potentially more serious in those receiving GST.

In a 12 month comparative study on 122 patients, Rau et al. [97] did not detect any differences in clinical outcome between patients on auranofin and GST, although the effects on grip strength, articular index and ESR were more pronounced in the GST group. Withdrawals because of adverse effects occurred more frequently in patients on GST.

Auranofin vs other DMARDs

Grade II evidence, based on two small single-blind trials comparing auranofin, GST and d-penicillamine [98], and auranofin and d-penicillamine [99], respectively, demonstrated a trend towards efficacy of all of the target DMARDs, with auranofin producing the least toxicity in both studies. Auranofin and d-penicillamine have also been compared in an RCT that has provided Grade I evidence [100]. In a 12 month study, 90 patients with RA were randomized to receive auranofin, 6 mg/day or a gradually increasing dose of d-penicillamine (to a maximum of 750 mg/day). While patients in both groups completed the study with significant improvements in most measures of efficacy, those in the d-penicillamine group were considered to have done better in terms of physician global assessments, swollen joint counts, swollen joint scores and grip strength. Thrombocytopenia and proteinuria occurred with greater frequency in the d-penicillamine group than in patients on auranofin and, in general, more patients had to withdraw from the study because of adverse effects from d-penicillamine than was evident with auranofin. These results inferred that in the dosage ranges that were used, d-penicillamine was more effective than auranofin, but was also somewhat more toxic.

An open study of sulphasalazine and auranofin in patients with RA (yielding Grade II evidence) has demonstrated comparable efficacy and a similar frequency of adverse effects for the two drugs [101].

When comparing methotrexate and auranofin, convincing Grade I evidence favouring the use of weekly treatment with low-dose methotrexate has been provided by a 36 week RCT [102]. While patients in both groups improved over the study period, responses in those on methotrexate tended to occur earlier and were consistently greater than in those who were on auranofin. Moreover, adverse reactions requiring withdrawal from the study were more common in the auranofin group. Data from this study prompted the conclusion that methotrexate was more effective and less toxic than auranofin. In a further RCT, comparing
methotrexate, auranofin and a combination of the two [103], no statistically significant differences in clinical or laboratory outcome were detected for the three groups, although patients on methotrexate or combination therapy tended to respond more quickly than those on auranofin alone. The frequency of adverse effects was similar for the three groups, but slightly more common in those taking both drugs.

Meta-analyses examining the comparative efficacy and toxicity of DMARDs have been reported [104]. For the efficacy study, tender joint counts, ESRs and grip strength evaluations constituted the target set of outcomes. Sixty-six clinical trials containing 117 treatment groups of interest were identified. For each of the three outcomes, auranofin tended to exert less benefit than injectable gold, d-penicillamine, sulphasalazine, antimalarials and methotrexate. For the purposes of the toxicity studies, 71 trials incorporating 129 treatment groups were examined. Average proportions of study drop-outs and the proportions who were withdrawn because of drug side-effects were calculated for each DMARD. Using this approach, it was found that injectable gold had significantly higher toxicity rates ($P < 0.05$) and higher total drop-out rates than any of the other drugs ($P < 0.01$). Thirty per cent of patients treated with injectable gold dropped out because of side-effects as compared to 15% of all trial patients.

The impact of auranofin on the radiographic manifestations of joint destruction

Whether one or another DMARD actually slows the radiological progression of joint damage is a matter of ongoing debate. The interpretation of most of the studies that have addressed this important issue has been complicated by a pervasive lack of conformity in criteria used to read and report the radiological lesions. As a result, there has been little agreement on the impact of these drugs [70].

Various studies on auranofin have examined possible correlations between drug efficacy and slowing of radiological progression of joint lesions. Grade II evidence by Gofton and O’Brien [105] and Gofton et al. [106], and Grade I evidence by Borg et al. [92] have suggested that auranofin may reduce the progression of articular erosions. In contrast, studies by Caruso et al. [107] and Lopez-Mendez et al. [108] provide Grade II and Grade I evidence, respectively, that auranofin has no effect on the retardation of adverse joint changes.

Auranofin use in children and teenagers

In an open study by Giannini et al. in 1983 [109], 21 children aged 1–17 yr were treated with 0.1–0.2 mg/kg day of auranofin. The authors claimed a significant clinical improvement (25%) in more than half of the children. This included number and severity of joints with swelling, pain on motion and tenderness. The beneficial response was greater in those children taking the higher doses. Only 2/21 had to discontinue therapy: one because of headaches and one 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.

CONCLUSIONS

Choosing auranofin or i.m. gold

Injectable gold compound 50 mg i.m. weekly is similar in cost to auranofin 3 mg twice daily. When maintenance therapy is started at ~5 or 6 months, the injectable gold is usually given as 50 mg i.m. monthly, whereas maintenance with auranofin is continued at 3 mg once or twice daily. Thus, oral auranofin will have a more expensive maintenance program. Fortunately, for the majority of patients, cost is not a major issue. Effectiveness is probably one of the principal factors influencing decision making in drug administration. If given in high enough dosage of 9 mg/day, the immunosuppressive actions of auranofin compound should result in a faster onset of action over the injectable gold compounds, but toxicity in the form of diarrhoea generally precludes the use of this dosage [32, 86]. Auranofin in a dosage of 3–6 mg/day does not appear to have a faster onset of action than injectable gold compounds [33, 45] and, indeed, the reverse is true: that a faster more meaningful and clinically measured response is achieved with the injectable gold compounds when compared to the oral auranofin [33, 45, 97]. The convenience of oral medication is a much discussed topic, especially in relation to compliance, but the compliance issue is best reserved for non-symptom-driven usage, such as blood pressure control or oral contraception. Patients with pain are usually compliant, those who are not will never be, irrespective of the route of administration. The convenience of oral auranofin is a small concession which is outweighed by the benefits accrued from injectable gold therapy. The process of the patient proceeding to the ‘gold clinic’ to receive the injection increases the insurance that someone with medical expertise will question the patient regarding drug benefit and adverse effects and will test blood and urine for potential abnormalities. Thus, the patient is more likely to have a regular ‘hands-on’ management of their treatment and will perhaps also benefit from the additional placebo effect recorded by the late Dr N. Thomas Fraser [110]. Patient compliance with gold injection treatment is reinforced by physicians and staff keeping a weekly record of the drug administration, clinical response, and blood and urine measurements. The patient is provided with a copy of these results and will thus be more intimately involved in their own care, leading to increase in compliance. Toxicity monitoring with regards to auranofin is usually carried out only on a monthly basis.

Clinical studies have documented a greater frequency of adverse reactions for injectable gold compounds compared to auranofin [33, 34, 97], but the quality and relevance of these side-effects has to be considered. The most common side-effect of injectable gold is rash, and in the context of clinical trials this is
recorded in ~30–50% of those treated. However, in clinical practice, the majority of cases of rash are extremely mild and patients merely require a reduction in dosage or a temporary discontinuation of therapy without major interference or termination of treatment. The most common side-effect of auranofin is diarrhoea [32, 33, 45, 86, 97] which is also dose related. Patients with severe RA, like colchicine-treated gout sufferers, do not thank their clinicians for the diarrhoea side-effect of auranofin. Reduction in the dose of auranofin to reduce the potential for diarrhoea reduces efficacy [86]. Haematological side-effects are uncommon with both injectable compounds and with auranofin. The total quantity of adverse haematological effects is probably less with auranofin than with the injectable gold compounds. The mechanism of auranofin-induced thrombocytopenia is probably central, whereas the most common type of injectable gold-induced thrombocytopenia is peripheral and associated with IgG surface autoantibodies [54]. Bone marrow-induced thrombocytopenia from injectable gold compounds is commonly a precursor to the onset of aplastic anaemia and is fortunately rare. The renal side-effects of auranofin are less common than those of injectable compounds [33, 45, 97], but since the consequences of gold compound-induced proteinuria are almost always of no serious outcome, the difference in side-effect numbers is not relevant.

When the decision is made to treat a RA patient with a gold compound, the greater effectiveness of the injectable compound may therefore take precedence over the quantity of side-effects recorded in favour of auranofin.

Inferences from the clinical studies

Although there is general agreement that high-quality RCTs usually confer satisfactory rigour when determining drug efficacy and toxicity, and while it is encouraging when cumulative Grade I evidence provides consistent results on outcomes of interest, there nonetheless needs to be caution in the application of even the most robust data. When embarking on a treatment programme for patients with RA, it needs to be acknowledged that despite an expanding armamentarium of NSAIDs, DMARDs and newer biological agents, the overall prognosis for a majority of patients remains less than optimal. RA is still a rather severe and progressive chronic disease that has a generally poor prognosis [110].

Pincus has drawn attention to the paradox in the rheumatology literature where apparently effective therapies in clinical trials do not necessarily translate into successful outcomes when longer-term observational studies are scrutinized [111]. Although most clinical trials in RA are completed within a 24 month time frame, their results not only direct long-term therapy, but also dictate the place of specific drugs within the therapeutic hierarchy. In reality, all studies in which patients with RA have been followed for 5 yr or more have demonstrated significant morbidity and accelerated mortality rates, regardless of treatment.

Treatment with auranofin should be commenced as early as possible after the definite 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. Treatment and management should be conducted as outlined above with the use of a flexible regimen. Oral gold therapy in children should be under the supervision of a physician with in-depth knowledge of both paediatrics and gold therapy.

The available evidence, based on relatively short-term trials, seems to infer that auranofin (i) is efficacious when compared to placebo, (ii) is less effective than other DMARDs, (iii) causes fewer serious side-effects than other DMARDs and (iv) its impact on the radiological progression of disease has not been unequivocally determined. A more compelling question, of course, is whether auranofin, alone or in combination with other DMARDs, has any positive impact on disease prognosis in the long term. Only large cohort prospective studies will answer the question as to whether DMARDs do modify the outcome of the arthritis over the long term. To date, this question remains unanswered.

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