The Treatment of Rheumatoid Arthritis With Gold

By Gilbert B. Bluhm

The clinical benefit from gold therapy in rheumatoid arthritis was first suggested by Forestier. A recent double-blind study of gold salt administered parenterally for 2 yr to patients with rheumatoid arthritis (RA) reported for the first time that the progression of rheumatoid joint disease as evaluated by x-ray was significantly reduced or arrested. That study and other controlled evaluations of gold therapy have shown by objective and subjective clinical measurements significant relief from joint swelling and pain as well as improved function in patients who receive gold. Because gold therapy offers more than relief of pain, its continued use is appropriate for RA until such time as prevention and cure of RA is discovered.

From 1927 to 1975 a wealth of published reports about gold preparations, tissue distribution, mode of action, selection of patients, regimens for administration, clinical results, and drug toxicity has accumulated. Representative articles are cited for these points and used to outline a practical regimen of gold therapy for the patient with active rheumatoid disease. These guidelines for the physician will hopefully permit the patient to reap the maximum benefit of gold therapy.

GOLD SALTS

Gold compounds were demonstrated to provide antibacterial action by Koch. Consequently, the early clinical application for gold was in the treatment of tuberculosis and syphilis. Because systemic lupus erythematosus and rheumatoid arthritis during the 1920s were believed to be related to tuberculosis and probably due to an infection, gold was used initially for those rheumatic diseases. Toxicity from gold salts deterred widespread use of the compounds. Nevertheless, important metabolic studies were performed by Freyberg et al. about absorption and excretion of gold salts. Gold compounds were found to produce measurable serum levels, whereas colloidal gold compounds were mobilized too slowly from injection sites to be practical for clinical use. An excellent review of the chemistry and pharmacology of gold compounds was published in 1963 by Nineham.

Presently, the most commonly administered water soluble gold salts are aurothioglucose (ATG), or gold sodium thiomalate (GST). Each gold salt by weight is approximately 50% elemental gold. Preparations of gold are administered intramuscularly. Sometimes articles published about gold salts have referred to the dose as “elemental” gold rather than the gold “salt.” In this article preference is given to the dose of the gold salt.

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TRANSPORT AND TISSUE DISTRIBUTION

The gold salt is largely bound to albumin for transport in the blood. Binding to other proteins is negligible.\textsuperscript{12} The drug concentration free in the tissue fluid determines the pharmacologic activity of most drugs. Albumin escapes readily from the diseased synovial vessels and is rapidly metabolized in the rheumatoid joint.\textsuperscript{13} Gold salts concentrate in the synovial membrane, but not in the cartilage.

Study of the tissue distribution of gold in animals shows the greatest concentrations are in the liver and kidney.\textsuperscript{14} The reticuloendothelial system has an affinity for gold that may be related to the macrophage avidity to heavy metals.\textsuperscript{15} Radioautography has complemented earlier histological stains for gold by showing an increased concentration of gold in subsynovial membrane areas, especially in the area of perivascular infiltration of mononuclear cells.\textsuperscript{16,17} Tissue obtained at autopsy from patients with RA who had received gold showed that the distribution and concentrations of gold in human tissues are similar to the pattern reported for experimental animals.\textsuperscript{18}

The blood transport, tissue distribution, and excretion of gold may relate in part to its action and possibly influence the occurrence of undesirable reactions experienced during administration of gold.\textsuperscript{10}

MODE OF ACTION

Precisely how gold salts benefit the patient with rheumatoid disease is unknown. Besides the antibacterial properties cited earlier, recent studies report its lack of influence on the immune response.\textsuperscript{19} A decreased rate of lymphocyte transformation was reported, but plasma cells continued to produce immunoglobulins in unaltered quantities.\textsuperscript{20} In the guinea pig, neither the short-term nor long-term experiments addressed to delayed hypersensitivity responses were found altered by gold therapy.\textsuperscript{21}

Rabbit studies suggest some effect for gold treatment locally at a site of inflammation. It was shown that gold salts inhibited the Shwartzman phenomenon.\textsuperscript{22} Evaluation by skin window technique of inflammatory exudative cells in patients with RA has shown the phagocytic activity of the macrophage and neutrophil is partially suppressed by gold therapy.\textsuperscript{23} Significantly, it seems likely that gold does have anti-injury benefits which may be mediated by stabilizing lysosomal membranes and thus inhibiting enzyme release at inflammatory sites.\textsuperscript{24-26} Regardless of the mechanism of action, gold salts maintain currently a place in the treatment of RA.

ADMINISTRATION OF GOLD SALTS

Route

Intramuscular administration of gold salt (GS) is used for treatment. An oral preparation was tried successfully in animals, but human experience is lacking.\textsuperscript{27}

Dose and Frequency

The quantity of gold and the frequency of injections best suited to the patient has evolved by the experience of numerous clinicians over the years. Originally gold salts were given in 100–200 mg doses at weekly intervals until an arbitrarily chosen dose of 1 g was administered. This course of injections was associated
with undesirable toxic reactions in nearly one-third to two-thirds of the patients.\textsuperscript{28,29} Those who tolerated the drug did not receive another "course" of GS until the arthritis flared again. When symptoms and signs of arthritis exacerbated, another 1 g course was given. Clinical observations from that type of regimen suggested the arthritis patient who was helped did not have sustained improvement.\textsuperscript{30} Those clinical experiences prompted changes in administration of gold salt. When the weekly dose was reduced to 50 mg, a decrease in the frequency of toxic reactions was noted.\textsuperscript{31} Also, the course of weekly gold injections was sometimes prolonged until a total of 1.5 g of GS was administered. Thereafter, the same 50 mg GS dose per injection was continued, but the interval between injections lengthened to 2 wk, then 3 wk, and finally maintained at monthly intervals. Clinical experience with this "maintenance" gold treatment program after the initial "loading" dosage was believed to produce better results and longer remissions.\textsuperscript{10,11} Since renal excretion of elemental gold amounts to about 4-6 mg per week even after a course of injections, a maintenance therapeutic program is indicated.\textsuperscript{32}

**Maintenance Dosage**

Double-blind studies of gold therapy with data obtained and analyzed similarly reported results of placebo versus a 1-g course\textsuperscript{5} or placebo versus the 1 g course immediately followed by a maintenance program.\textsuperscript{2} Comparison of data from these studies reveals firm evidence that a *maintenance* gold regimen clearly prolongs the improvement in the symptoms and signs as well as retards the progression of arthritis as determined by x-ray evaluation.

**Serum Gold Values**

It has been recommended to individualize gold therapy in order to produce better clinical results of less toxicity.\textsuperscript{16} Application of recent laboratory methods utilizing atomic absorption spectroscopy to measure serum gold levels and urinary excretion rates and equate these with clinical responses may alter this attitude.\textsuperscript{32,33}

Some studies suggested that maintaining serum gold levels above 300 µg/100 ml would produce better clinical effects,\textsuperscript{34} but other data are at variance.\textsuperscript{32,35,36}

At Henry Ford Hospital a prospective study was designed during which serum gold values were measured by atomic absorption spectroscopy.\textsuperscript{33,37,38} Serum samples were obtained serially in 23 patients with classical rheumatoid arthritis who received gold salts for the first time.\textsuperscript{*} The purpose of the study was to establish any correlation between the serum gold levels, clinical response, or the occurrence of gold "toxicity." Serum samples for gold were collected immediately prior to each gold injection. The specimen was dated, coded, and stored frozen. All gold determinations were performed after the response of the patients was determined and classified according to clinical measurements or type of toxicity.

Twelve patients received aurothioglucose (ATG) and 11 patients gold sodium thiomalate (GST). Patients adhered to the same dosage schedule of 50 mg of gold salt per injection at weekly intervals until 1 g had been given unless the occur-

\textsuperscript{*}Supported by a Research Grant from Michigan Chapter, Arthritis Foundation (1973).
Table 1. Patients With Gold Toxicity

<table>
<thead>
<tr>
<th>Patient</th>
<th>Theoretical Accumulated Dosage Gold Salt (mg)</th>
<th>Weeks of Injections</th>
<th>Serum Gold Values (μg/100 ml)</th>
<th>Weeks before reaction</th>
<th>Weeks after reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8  6  4  2  1  R  1  2  4  6  8  9  16</td>
<td></td>
</tr>
<tr>
<td>G. S.</td>
<td>A - 430</td>
<td>10</td>
<td>105  109  205  216  250  149  213  167</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. G.</td>
<td>G - 400</td>
<td>9</td>
<td>458  553  222  259  304  221</td>
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<td></td>
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<tr>
<td>H. K.</td>
<td>A - 300</td>
<td>7</td>
<td>149  78  340  321  264  235  149  362  140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. D.</td>
<td>A - 50</td>
<td>2</td>
<td>125  167  192  148</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. H.</td>
<td>G - 875</td>
<td>21</td>
<td>533  923  537</td>
<td>646  557  318</td>
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</tr>
<tr>
<td>R. T.</td>
<td>A - 775</td>
<td>19</td>
<td>152  176  211  200  200  115  115  71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. S.</td>
<td>G - 675</td>
<td>15</td>
<td>326  333  371</td>
<td>442  500  415</td>
<td></td>
</tr>
</tbody>
</table>

A = Aurothioglucose
G = Gold Sodium Thiomalate

rence of "unwanted reactions" interrupted treatment. Seven patients were withdrawn from therapy—four because of dermatitis and three because of albuminuria. Onset of these complications occurred between 2–21 wk after starting gold treatment (Table 1). One other patient had gold discontinued after 1550 mg because of profound anemia. The other 16 patients continued gold salt injections according to the recommended protocol (Table 2). After the patient reached a total theoretical accumulated dosage of 1800 mg, 50 mg of gold salt was given once a month until the last patient completed the study period. Both ATG and GST produced similar serum gold levels after the initial few weeks of administration (Fig. 1). Neither drug was more advantageous in producing a remission, improvement, or lack of a measurable clinical effect. Furthermore, neither drug was more likely to be associated with toxic dermatitis or albuminuria. The serum gold values before toxicity were similar to the values in those patients without toxic reaction (Table 1).

The Henry Ford Hospital (HFH) data support the results of others that serum gold levels (SGL) fail to predict the clinical response. When serum gold values are grouped for evaluation by type of clinical response (remission, significantly improved, and unimproved or worse), similar means and ranges that overlap widely are evident (Fig. 2). A recent investigative group suggested that an individualized gold dosage used to maintain a SGL above 300 μg/100 ml may provide the best clinical response. Those patients in the HFH group who were unimproved clinically by gold therapy maintained consistently SGL over 300 μg/100 ml; on the other hand, the group of patients who developed a re-

Table 2. Recommended Dosage Schedule for Gold Salts in Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Injection interval</th>
<th>Weekly</th>
<th>Weekly</th>
<th>Biweekly</th>
<th>Triweekly</th>
<th>Monthly</th>
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<tr>
<td>Duration of interval</td>
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<td>19 wk</td>
<td>20 wk</td>
<td>18 wk</td>
<td>52 wk plus</td>
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<td>50 mg</td>
<td>50 mg</td>
<td>50 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Theoretical accumulated dosage</td>
<td>50 mg</td>
<td>1000 mg</td>
<td>1500 mg</td>
<td>1800 mg</td>
<td>2400 mg plus</td>
</tr>
<tr>
<td>Weeks since initiating therapy</td>
<td>1 wk</td>
<td>20 wk</td>
<td>40 wk</td>
<td>58 wk</td>
<td>110 wk plus</td>
</tr>
</tbody>
</table>

*Some patients note increased symptoms at monthly intervals but become relatively free of complaints when the dose is resumed at 2 or 3 week intervals.
TREATMENT OF RHEUMATOID ARTHRITIS WITH GOLD

Mean Serum Gold Values in RA
(Gold Sodium Thiomalate (G) vs. Aurothioglucone (A))

Fig. 1. Henry Ford Hospital Study. The "accumulated" dosage refers to the amount of gold salt (GS) that had been administered when the three serial serum gold samples were obtained. Therefore, points on the graph represent the mean gold value of 18, 21, or 27 different serum samples from six, seven, or nine patients. The elapsed time between the last GS injection and when the sample for analysis was drawn is designated "Days after last injection." Gold sodium thiomalate (G) tends to produce higher serum gold levels during the initial weeks of therapy, but little difference exists thereafter. Lower serum gold values are evident as the interval between injections is lengthened.

mission showed a trend for an average SGL slightly under 300 µg/100 ml. Unfortunately, there is an apparent lack of discrimination by SGL to predict the clinical response and thus provide a means to adjust the gold dosage for a patient. Hence, the empirical regimen used to administer gold salt for RA formulated by trial and error over the years must yet remain the practice!

When to Start Gold

Before giving gold treatment, the physician should be sure the diagnosis is RA and not another connective tissue disease. To best benefit the patient, initiate gold therapy at the earliest possible stage of rheumatoid disease, but signs of active synovitis should be evident. Gold therapy will not correct residual joint deformity, yet it can be helpful for active synovitis in joints already showing deformity. A sufficient period of observation (usually 4-6 mo) prior to starting gold treatment assures the physician the disease is unrelentingly progressive. During observation, a record of baseline assessments of the number of joints involved and other objective measurements to evaluate disease activity is obtained. X-rays are helpful too when obtained of the hands, feet, and any other joint with
Fig. 2. Henry Ford Hospital Study. "Remission" was defined as no evidence of swollen joints by clinical examination and a normal sedimentation rate. "Significantly improved" was assessed by a joint count reduced greater than 50%. Ranges of serum gold levels between the three groups overlapped. The mean of serum gold level (SGL) of four patients in remission remained below 300 μg/100 ml. The mean SGL and the six patients in the significantly improved group was nearly the same as the four patients who were unimproved or worse, but both were well above 300 μg/100 ml.

persistent involvement. Preliminary blood studies advised include CBC, platelet count, sedimentation rate, alkaline phosphatase, SGPT, SGOT, bilirubin, BUN, creatinine, and urinalysis. Whenever there is a history to suggest previous urinary tract disease, an intravenous pyelogram may be of assistance before selecting gold therapy. Information from subsequent examinations compared to the initial data base permits the physician to evaluate objectively the progress and response of the patient to gold therapy.

Contraindications

Any patient with a confirmed history of gold sensitivity or intolerance to previous treatment should not be challenged again with a gold salt. Patients with active hepatitis, serious renal disease, or a blood dyscrasia would not be given gold. It is not advisable to initiate gold treatment in a pregnant woman. Furthermore, discontinue the gold therapy if conception occurs during the course of treatment.

The Regimen

The program of administering gold recommended at this time has evolved through experience and is supported by a double-blind study. The recommended schedule for gold therapy is summarized in Table 2. The blood count and urinalysis is monitored within 24 hr of the next scheduled injection of gold salt. The practice at Henry Ford Hospital is for the physician to briefly interview the
patient about symptoms such as pruritus, rash, metallic taste, stomatitis, bruises, or diarrhea which might herald a toxic reaction. An examination is performed if indicated. In the absence of signs of intolerance, the injection is given.

The accumulated amount of gold salt administered after each dose will be called the "theoretical" accumulated dosage (TAD). The first two weekly doses of gold salt (GS) are 25 mg per injection. The next 19 doses of GS are 50 mg per injection. Therefore, after 21 wk of gold therapy the TAD is 1000 mg, providing the recommended schedule was not interrupted.

By this time, lab studies as well as a progress x-ray study of joints which were obtained immediately prior to the start of gold therapy are usually repeated. An articular evaluation and limited general medical exam is advisable about every 3 mo during the first year of gold therapy and at 6-mo intervals as long as gold therapy continues.

A biweekly interval for injections of 50 mg GS are usually begun after 21 wk of therapy. This part of the regimen continues until the TAD equals 1500 mg. By this time, 40 wk has elapsed since starting the gold salt, and objective signs of improvement may be evident. Nevertheless, at this point in the schedule, tri-weekly injections of 50 mg of GS is started for the next 18 wk. At the end of that period the TAD is 1800 mg.

If at this point there are no convincing objective signs of improvement, the gold therapy should probably be discontinued! About 15%-25% of those who tolerate GS therapy will not be helped. However, most patients (about 75%) will be sufficiently improved so that the 50 mg GS injection will be continued at monthly intervals. Sometimes a patient notes recurrent symptoms of disease when placed on a maintenance monthly dosage, but again becomes relatively free of complaints when the dose is resumed at biweekly to triweekly intervals.

PREDICTION OF RESULTS

Ideally, one would like to predict which patient may benefit most from gold therapy. Unfortunately, no clinical signs, lab tests or even serum gold levels can help make these predictions. Before embarking on gold treatment, the patient must understand the chances of improvement as well as the risks. Only limited double-blind data are available. In the Henry Ford Hospital 2-yr double-blind study of gold therapy, 3 of 12 patients with RA who received and tolerated gold salt experienced a remission, and in the prospective serial serum gold evaluation 4 of 16 patients. (Remission rate of 25%). Improvement (excluding remissions) occurred in another 15 of the 28 patients, and 10 of those 15 experienced marked improvement, which was defined as a joint count reduced more than 50% and x-ray progression apparently arrested. Interestingly, 6 of 28 patients experienced no significant effect from treatment (21%).

From these experiences and the general experience of my colleagues* in the Rheumatology Division at Henry Ford Hospital, the patient with RA about to be advised to submit to gold therapy is informed as follows. Usually one out of six

Fig. 3 (A and B). Patient C.P. The earliest radiographs (A) of the hands and feet were taken in 1967. Note progression of disease by 10/5/72, which was immediately prior to gold treatment (B).
Fig. 3 (C and D). X-ray changes appear stable in this patient who developed a remission during gold treatment when comparing films of 1/25/73 (C) to those of 1/30/75 (D).
patients given GS will have to suspend or discontinue it because of adverse reaction; of the five who tolerate gold injections, one will not benefit, one will achieve a remission and three will markedly improve. The case reports that follow illustrate the clinical responses just referred to for gold therapy.

CASE REPORTS

Patient Illustrates Remission

C. P., a 75-yr-old male with progressive rheumatoid arthritis present for 5 yr was started on gold therapy in 1972. Prior to gold administration intermittent doses of prednisone and other nonsteroidal, anti-inflammatory drugs were utilized unsuccessfully. He had been well indoctrinated in a physical therapy program and was following the basic management of RA. By x-ray, articular erosions involving carpal bones as well as cartilage space narrowing had occurred in both wrists (Fig. 3). Several of the metacarpophalangeal and proximal interphalangeal joints of the fingers revealed similar findings. He was rheumatoid factor positive, but LE cell and antinuclear antibody (ANA) negative. Rheumatoid nodules were absent.

Clinical evaluation of his progress followed the assessment program used in the 2-year double-blind study of gold therapy. Details of interval evaluation scores as gold therapy proceeded are tabulated (Table 3). Although subjective improvement was evident after 12-wk of gold salt (500 mg), objective improvement was delayed until after 23 wk of GS (1100 mg).

Remission defined as absence of joint swelling and a normal Westergren sedimentation rate occurred by 91 wk of gold salt (2200 mg). He has maintained the remission for 9 mo with a monthly injection of gold salt (50 mg). He uses no other medication, not even an aspirin. X-rays show no further joint changes, since 1972 (Fig. 3).

Patient Illustrates Significant Improvement

A. S., a 45-yr-old female, who first experienced an episode of migratory polyarthritis in 1969, was seen in June 1972 with a 3-mo history of continuous symptoms and signs of symmetrical arthritis involving 26 of the peripheral joints (wrists, MCPs and PIPs of hands, knees, ankles, and feet). A Baker's cyst was present in association with a right knee effusion. Antinuclear antibodies and LE cell tests were negative. Rheumatoid factor (RF) by latex fixation titer was positive 1:2560; she did not exhibit rheumatoid nodules. Westergren sedimentation rate was 50 mm/hr. Synovial fluid examination revealed turbid fluid with many exudative neutrophils, no crystals, and RF latex titer of 1:1280. Radiologic changes observed in June 1972 included early erosive changes as well as mild cartilage space narrowing of several carpal bones, the ulnar styloid process and some of the MCP joints. The PIP joints were spared. The feet revealed prominent hallux valgus metatarsus primus varus deformities, subchondral bone cysts, and moderate erosive changes around some of the metatarsophalangeal joints (Fig. 4).

The basic management for RA was continued and in July 1972 gold therapy was initiated. After 13 wk of gold therapy (550 mg), a nonpruritic skin rash occurred. Gold salt was suspended for 4 wk until the rash disappeared. Gold was resumed without recurrence of the rash or onset of other toxic reactions except for a mild nitritoid reaction (flushing) after a single injection of GST in January 1973.

Her response is considered one of marked improvement and findings are tabulated through 83 wk of observation (Table 4). X-rays of the hands and feet in March 1974, after 20 mo of gold therapy, showed progress of the disease had been retarded (Fig. 4).

Patient Illustrates Progression

S. A., a 59-yr-old female employed as a dietary aide developed rheumatoid disease in January 1972. She was hospitalized in August 1972 with swelling of both knees. Rheumatoid factor, ANA, and LE cell tests were negative. Westergren sedimentation rate of 45 mm/hr. Turbid synovial fluid from the knees showed numerous exudative neutrophils, no crystals, and a friable mucin clot. Although she improved temporarily with rest, salicylates, and physical therapy, the progression of symptoms and signs warranted institution of gold treatment by October 1972. X-rays showed very early erosive and cystic bone changes in the carpal areas and MCP joints of the hands, but none in the feet (Fig. 5). The objective measurements indicate progression over the 71 wk of GS therapy (1950 mg) except for activities of daily living (ADL) which did improve (probably attributable to physical therapy and motivation) (Table 5).
Table 3. C. P.—Remission

<table>
<thead>
<tr>
<th>Weeks/quantity of gold salt (mg)</th>
<th>0/0</th>
<th>12/500</th>
<th>23/1100</th>
<th>35/1300</th>
<th>53/1650</th>
<th>71/1950</th>
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<tr>
<td>Joint count (maximum 44)</td>
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</tr>
<tr>
<td>Ring sizes (total of PIP joints and DIP joints of thumbs-jeweler’s band)</td>
<td>136 1/2</td>
<td>124 1/2</td>
<td>123</td>
<td>124 1/2</td>
<td>122</td>
<td>120 1/2</td>
<td>116 1/2</td>
</tr>
<tr>
<td>Grip strength each hand expressed in ounces of water/sq in) *</td>
<td>R 175</td>
<td>295</td>
<td>290</td>
<td>275</td>
<td>285</td>
<td>360</td>
<td>290</td>
</tr>
<tr>
<td></td>
<td>L 75</td>
<td>205</td>
<td>170</td>
<td>220</td>
<td>215</td>
<td>275</td>
<td>245</td>
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<tr>
<td>Westergren sedimentation rate (mm/hr)</td>
<td>63</td>
<td>25</td>
<td>15</td>
<td>34</td>
<td>10</td>
<td>9</td>
<td>1</td>
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<td>Activities of daily living (best score—30)</td>
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<td>27</td>
<td>27</td>
<td>29</td>
<td>29</td>
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*To convert to mm Hg, multiply by 3.23.

Table 4. A. S.—Significant Improvement

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<th>Weeks/quantity of gold salt (mg)</th>
<th>0/0</th>
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<th>23/800</th>
<th>37/1100</th>
<th>53/1375</th>
<th>71/1600</th>
<th>83/1625</th>
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<td>Joint count (maximum 44)</td>
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<tr>
<td>Ring sizes (total of PIP joints and DIP joints of thumbs-jeweler’s band)</td>
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<td>65 1/2</td>
<td>64 1/2</td>
<td>63 1/2</td>
<td>66</td>
<td>57 1/2</td>
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<td>Grip strength each hand expressed in ounces of water/sq in) *</td>
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<td>115</td>
<td>226</td>
<td>232</td>
<td>195</td>
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<td>L 134</td>
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<td>190</td>
<td>210</td>
<td>86</td>
<td>210</td>
<td>274</td>
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<tr>
<td>Westergren sedimentation rate (mm/hr)</td>
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<td>5</td>
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<td>6</td>
<td>5</td>
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<td>Activities of daily living (best score—30)</td>
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<td>18</td>
<td>22</td>
<td>29</td>
<td>28</td>
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*To convert to mm Hg, multiply by 3.23.

Table 5. S. A.—Progression

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<th>Weeks/quantity of gold salt (mg)</th>
<th>0/0</th>
<th>12/500</th>
<th>24/1000</th>
<th>37/1300</th>
<th>53/1650</th>
<th>71/1950</th>
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<tr>
<td>Ring sizes (total of PIP joints and DIP joints of thumbs-jeweler’s band)</td>
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<td>125 1/2</td>
<td>107 1/2</td>
<td>118 1/2</td>
<td>117 1/2</td>
<td>107</td>
</tr>
<tr>
<td>Grip strength each hand expressed in ounces of water/sq in) *</td>
<td>R 130</td>
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<td>152</td>
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<td>105</td>
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<td>L 180</td>
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<td>120</td>
<td>95</td>
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<td>Westergren sedimentation rate (mm/hr)</td>
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<td>11</td>
<td>7</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Activities of daily living (best score—30)</td>
<td>19</td>
<td>19</td>
<td>23</td>
<td>25</td>
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*To convert to mm Hg, multiply by 3.23.
Fig. 4. Patient A.S. The films of the hands taken prior to gold treatment dated 7/16/72 show erosive changes as well as cartilage space narrowing of several carpal bones, the ulnar styloid process, and some of the metacarpophalangeal joints (A). The films of the feet taken then exhibit subchondral bone cysts and moderate erosive changes about some of the metatarsophalangeal joints and distal joints of great toes (A). The films 20 mo after the start of gold treatment show the radiologic changes were stable and progression apparently arrested (B).
Fig. 4B. See legend facing page.
Fig. 6. Patient S.A. Radiographs (A) dated 10/18/72 were taken before instituting gold therapy. Early erosive and cystic bone changes in the carpal areas and metacarpophalangeal joints of the hands and some of the metacarpophalangeal joints of the feet are evident. These changes had progressed in the films taken 3/30/74 (B). This patient had not responded favorably to gold salt.
Fig. 5B. See legend facing page.
The incidence of adverse reactions from gold salts (GS) ranges from 4% to 54%. The variable number of reactions appears to relate to the quantity of GS injected per dose and/or the shortened interval between injections.\(^3\) At weekly intervals, a 100-mg dose of GST resulted in 41% toxicity, whereas, a 25-mg dose weekly caused adverse reactions in only 18%.\(^3\) Cautious evaluation of each possible adverse reaction is necessary because toxicity from true placebo injections are reported in one double-blind gold study to be 27%.\(^3\)

It would be helpful if tests were available to predict impending reactions to gold salt. The inability of serum gold levels to do so has been discussed already. Tissue concentrations are similar with or without toxicity.\(^4\) Erythrocyte sedimentation rates were similarly indiscriminating.\(^4\) A recent assessment of peripheral blood eosinophilia in gold treated patients dispelled the idea that its presence might be predictive of toxicity to gold. Blood eosinophilia occurred in one-third of the gold treated patients who never showed signs of an adverse reaction. Yet, it was observed that 11 of 14 patients with toxic reactions manifested a blood eosinophilia.\(^4\)

Some rheumatologists have believed an improvement in the joint disease frequently accompanies a toxic reaction. These coincidences are known to most physicians who have administered gold salts. However, a study addressed to that possibility failed to show such a trend.\(^4\)

**Skin and Mucous Membranes**

Adverse reactions involve more commonly the skin and mucous membranes. Skin rash from GS may be preceded by localized or generalized pruritus. Some patients experience temporarily a pruritus without developing a rash. The type of rash may be patchy erythema, desquamating eczemoid, pityriasis-rosea-like, morbilliform, scarletineform, vesicular, bullous, urticarial, or exfoliative dermatitis.\(^5\) Many patients who experience a gold dermatitis exhibit an associated blood eosinophilia,\(^5\) but certainly not all of them.\(^5\) The skin rash may become chronic, but usually subsides soon after GS is discontinued. Symptomatic local care including topical adrenal corticosteroids is helpful. An exfoliative dermatitis occurs infrequently, but may require chelation treatment with dimercaprol or penicillamine.\(^6\) Resumption of gold salt after it is suspended as a possible etiology of pruritus or a skin rash is a calculated risk. Sometimes it has been the drug vehicle rather than the gold, so changing to another gold salt suspension may permit continuation of gold therapy.\(^5\) Under those circumstances a small 5–10 mg GS quantity is used as a challenge dose. If it is not followed in a week by recurrent pruritus or skin rash, the injection regimen may be resumed cautiously at a reduced dose and frequency.

Patients receiving GS may experience a rash related to actinic rays. Some seem to become more sensitive to ultraviolet rays and should be cautioned against susceptibility to sunburn.

A stomatitis may accompany a skin eruption due to GS or occur by itself. Sometimes the patient may describe a premonitory metallic taste or sensitivity to condiments. The greatest problem is to distinguish gold stomatitis from recurrent herpangina or other local mouth irritations during GS administration.
Whenever doubt arises as to etiology, it is best to suspend further injections until it clears or the cause becomes evident.

Renal

Serious renal toxicity is infrequently observed, but the nephrotic syndrome due to gold has been reported. Histologic lesions ascribed to toxicity include membranous glomerulitis and lipoid nephrosis. A urinalysis is advised regularly prior to each GS injection so the early possible signs of renal toxicity may be detected by the demonstration of microscopic hematuria and/or albuminuria. Sometimes these signs persist for several weeks after GS is discontinued. When indicated cystoscopy and intravenous pyelography may be performed to eliminate other urinary tract causes of hematuria or albuminuria. The pathogenetic mechanism of renal toxicity is unknown, but it might relate to glomerular deposits of the gold salt.

Bone Marrow

Suppression of blood-forming elements in the bone marrow is probably the most dreaded adverse reaction from gold treatment. A recent survey reported a total of 55 patients with definite marrow suppression or thrombocytopenia. These instances were obtained by contacting the rheumatologic units in Britain where 42 cases had been observed and another 13 cases had been reported to the British Committee on Safety of Medicines. Of the 55 patients, the 15 who died all showed aplasia of the bone marrow. The average total gold salt dose administered was 698 mg, although ten patients developed changes before 200 mg was administered. The true incidence of bone marrow suppression could not be determined in that study.

In some of the early American experience thrombocytopenia was observed in nearly 1.5%, but since 1950 it has been encountered less frequently. The mechanism favored for thrombocytopenia (TCP) in most instances is an immune drug reaction, although in vitro studies do not support that theory. Bone smears often reveal adequate numbers of megakaryocytes in the presence of the thrombocytopenia. Recovery from TCP usually occurs by stopping gold and administering large doses of corticosteroids, and/or chelating agents such as dimercaprol and penicillamine.

The physician must be alert to signs of thrombocytopenia such as ecchymosis without trauma, petechiae, epistaxis, and gum bleeding. Often a granulocytopenia heralds an impending bone marrow depression. Regular monitoring of the hemoglobin and white blood count before administering the next dose of gold is a necessary precaution. An alert physician and patient can prevent or minimize potentially serious adverse reactions during gold therapy.

Isolated case reports often emphasize the unusual reaction derived from gold therapy such as thrombocytopenia delayed 10 mo in onset after a single 50 mg dose of gold salt, enterocolitis, or neuritis complicating gold treatment.

CONCLUSION

Since gold therapy can retard the progression of RA, it is an important supplement to the comprehensive management of the patient. As with any drug
treatment, a calculated risk exists with the use of gold salts. Currently, benefits from gold salt continue to outweigh its risks for the treatment of rheumatoid arthritis.

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