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Gold and its use in rheumatoid arthritis

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HISTORICAL:

Gold was probably first used by the Chinese in 2,500 B. C.[4] Its initial uses were as panaceas and it became a popular therapeautic agent. It was at this time that all chemists were attempting preparation of an "Elixer of Life" using metallic gold. Paracelcus, in 1,500 A. D. recommended gold and mercury as a panacea combination.[4]

The first specific use for gold was apparently in the treatment of tuberculosis. Due to serious accidents, however, it fell into disfavor and it was 1810 before it was revived by Chrestien.[4]

During this period there was practically no disease for which gold was not used, and always with good results.[4] It was commonly used in scrofulex, psoriasis, syphilis, sycosis, cutaneous affections, suicidal melancholia, mercurialism, dropsy, inflammation of the heart, vascular turgesence, cancer and specific indurations.[4]

The first bacterio ogic experiments with gold were conducted by Robert Koch (890) who showed gold cyanide in 1:200,000 dilution to be effective in arresting the growth of tubercle bacilli. He was unable, however, to show a similar effect in vivo using animals.[4] Von Behring further showed that the substance above had, in serum, only one-fourth the effectiveness as in agueous solution. In 1913, Bruck and Gluck[4] administered

gold potassium cyanide I. V. as the treatment of skin tuberculosis and syphilis and reported good results. They were not certain, however, whether it was the gold or the cyanide which may have produced the results. Roov[4] used the same compound in lupus vulgaris with good results. Junker[4] used gold salts in pulmonary tuberculosis with good results.

The increasing use of gold compounds was accompanied by many reactions, however, so that the use in humans was coming again under disfavor. In spite of its toxicity, the reports of beneficial results led to search for less toxic compounds.

Feldt[4], in 1913, showed a significant bacteria-static effect of gold sodium thio sulfate and Möllgaard[4] introduced this compound in 1924 as a specific therapeutic agent for tuberculosis and named it sanocrysin. There was reported low toxicity but high effectiveness in skin tuberculosis and it soon found widespread use in medicine especially in treatment of pulmonary tuberculosis.

In 1917, Feldt, now experimenting with organic gold compounds, prepared the sodium salt of aminoauromercaptobenzol and called it Krysalgan[4]. In animal experiments it was shown to be definitely less toxic than previous preparations, but with a bacteria static effect equivalent to that of gold postassium cyanide. There were later conflicting reports and its eventually proven toxicity caused it to fall from use.

In 1927, Feldt[4] introduced the disodium salf of sulfonmethylamine auromercaptobenzolsulfonic ad (Solganol). With

this introduction, gold again became popular--especially in the treatment of tuberculosis.

Gold apparently found its first (reported)[4] specific uses in arthritis in 1927 when Lamde and Pick[4] independantly reported their results. Gold as a therapeutic agent in arthritis was actually popularized by Forestier when he published his regults in 1929. The rational of Forestier's use of gold was Feldt's demonstration of an anti-infectuous effect of gold and on the mistaken assumption that chronic polyarthritis and tuberculosis were related. His results were good as were those of many other European workers.

There was little interest in this country until 1936 when one of the earliest reports appeared.[4]

In addition to those listed earlier, gold has been used in the treatment of lupus (on mistaken assumption that it was of tuberculosis origin); Reiter's syndrome, osteoarthritis, ankylosing spondylitis, palindromic rheumatism, erythema induratum, psoriasis, epilepsy, asthma and multiple sclerosis. Its greatest use has been in tuberculosis, lupus and rheumatoid arthritis.

The status of gold compounds has again come under scrutiny with the advent of Cortisone, A.C.T.H. and similar steroids, however, as many writers point out[1,6,4] the steroids have their limitations so that gold must not be merely dropped from a plase of therapy of rheumatoid arthritis, but should be given critical careful study.

PREPARATIONS AND CHEMISTRY:

Metallic gold itself is relatively inactive. Gold compounds, however, are quite reactive being easily reduced to metallic gold. Gold may occur as the mono-valent or tri-valent ion in compounds. Most of the clinically used forms contain the mono-valent ion.

Gold compounds are divided into three groups: (1) water soluble, ionized form, an example of which is gold sodium thiosulfate; (2) water soluble, non-ionized--gold sodium thiomalate; (3) water insoluble--calcium aurothiomalate.

Presently used forms and their respective gold content follows:

Sanacrysin - Gold Sodium Thiosulfate - 37% - Soluble in H_2O Aqueous

Crisalline
Aurathion
Myocrisine - Gold sodium Thiomalate - 50% - Soluble in H_2O Aqueous

Aurocalcium - Gold calcium Thiomalate - 50% - Insoluble in H_2O Aqueous

Allachrysine - Gold sodium Thiopropanol Sulfonate 30% - Soluble in H_2O Aqueous

Lauron - Aurothioglycoanilide - 54% - Insoluble in H_2O Oil suspension

Myoral - Gold calcium Thioglycolate - 67% - Insoluble in H_2O Oil suspension

Solganol B-Oleosum - Gold Thioglucose - 50% - Soluble in H_2O Aqueous

Auradextrin - Gold keratin compound - 8.14% - Insoluble in H_2O Oil suspension

Aural sulfide - Auric Sulfide - 87% - Insoluble in H_2O Aqueous colloidal suspension

There are reports[9] that Sanacrysin gives pain at the injection site. Whether one preparation is better than another is not definite. Black and Van Goor[4] state that those compounds with very few toxic reactions are of very little value.

METABOLISM AND BLOOD LEVELS:

Black et al[4] studied the absorption of various gold compounds in the white rat following intramuscular injection and on the basis of these experiments, gold compounds have been generally classified as rapidly absorbable (soluble crystalline forms); slowly absorbable (colloidal preparations) and inter-mediate in absorbability (insoluble crystalline preparations). Water soluble compounds are probably rapidly absorbed and have therapeutic advantages[2]. Colloidal gold preparations are Phagocytized rapidly by the reticulo-endothelial system and are therefore not as effective[2,4].

Conflicting reports have appeared on the rapidity of absorption from intramuscular sites. Lawrence[6] reports that "gold compounds" are slowly absorbed from the intramuscular site. He does not differentiate between soluble crystalline and non-soluble crystalline and colloidal preparations. Drill[15] makes the same statement. Freyberg[4], however, has stated that absorption from intramuscular sites is rapid. Lumiere and Leonet[4] have shown that rate of absorption is re-lated primarily to the solubility in water of the gold compound and that suspending it in an oil to prolong its absorption is without effect. This is contrary to Freyberg's[4] findings. Black's[4] findings tend to support Luniere's and Leonet's findings. He has shown that the rate of appearance of plasma gold follows intramuscular injection parallel to the various preparations. Gold calcium thiomolate showed a slow, but significant absorption.

Block[4] and others[6] have pointed out that the gold is bound to plasma proteins and is found, therefore, in the plasma. This has since been confirmed by studies using radioactive gold. There is a direct ratio of plasma level and the amount of gold injected. Block[4] states that following injection of soluble gold compounds, maximum blood levels appeared in one hour and remained high for twenty-four hours. He states that values for colloidal gold are lower. Mattu[4] injected gold sodium thiosulfate into rabbits and showed a 40% removal from the circulating plasma in forty minutes. The same compound given orally showed a maximum plasma concentration in twelve to sixteen hours, with traces only at the end of fifty hours.

Block's findings do not correlate well with those of Lawrence[6] who reports maximum blood levels of 2 mg% by the fourth weekly injection. He also found that following therapy, blood levels fell slowly reaching one-half the final level by week nine. Gold was still detectable in the plasma four months later. It can be detected up to ten months following injection and can be found in tissues as late as three years following therapy. This agrees with Freyberg's[4] findings that plasma gold can be detected as long as fifteen months following therapy. Of the gold that is absorbed 20% is rapidly excreted and 80% is fixed in the tissues[15].

Crystalline compounds concentrate in greatest degrees in the kidneys, liver and spleen in that order. That found in the heart and lungs is insignificant. Block[4] feels that the

the increased amount in the kidneys represents presence by excretion and not deposition. This feeling was also expressed by Gilg[4].

Elftman[4] studied by histio-chemical methods, the distribution of gold following intra-peritoneal administration (in rats and guinea pigs) of soluble gold chloride and found the highest concentration of gold in the kidneys (protubule) and in the Kupfer cells of the liver. He also found appreciable amounts in lymph nodes, spleen and lungs. He claimed that the histiocytes had an extreme affinity for gold.

Bertrand et al[4] has claimed passage of gold from the blood to the central nervous system and ocular structures of the rabbit. Roberts[4] has also found this to be true. Gilg[4], however, found gold only in the central nervous system's vascular system and found none in the brain substance itself. He also showed a great uptake of gold by the synovial tissues. Bertrand showed a greater uptake of gold by the synovium tendons and articular cortex of patients with arthritis than in these structures of people without arthritis. Freyberg[4,7] found synovial fluid concentrations slightly less or equal to, but never greater than that concentration of gold in the plasma.

Lawrence[6] speculates that since large molecules can leave the vascular system only in the presence of damaged capillaries, higher concentrations of gold are initially found in areas (joint tissues) most affected by the disease.

EXCRETION:

Gold is slowly excreted for many months following the last injection. Freyberg[4] studying the excretion of gold sodium thiomalate, gold sodium thiosulfate and colloidal gold sulfide found excretion to be greatest during the first twenty-four hours following injection. He found a direct ratio, but not a direct proportion of gold excretion to gold administered. He also found that the greater the amount of gold injected, the greater was the tendency for the body to retain greater amounts.

Block[4], Kent and McCance[4] working separately have shown that crystalline gold compounds are largely (84%) excreted in the urine, whereas colloidal preparations are largely eliminated via the feces. Insoluble gold calcium thiomalate is largely eliminated by way of the feces also. The absolute per cent of the excretion in the feces is apparently no different for the soluble crystalline preparations on the one hand and the insoluble or colloidal preparations on the other, but as so much of the colloidal and insoluble forms is retained by the reticulo-endothelial system that that portion that is excreted (small) is excreted via the feces.

Explanation for the greatest excretion occuring in the first 24 hours may be that in these early hours the gold is in an easily excretable or combined in a less excretable form, of course, much of it after the first twenty-four hours has probably been phagocytosed by the reticulo-endothelial system,

hence less is available for excretion. Gold thioglucose suspended in oil showed greater excretion levels as treatment progressed. This was not observed with aqueous preparations. There was also marked retention of this preparation. Insoluble and colloidal preparations of gold compounds showed only scant urinary excretion, most of what was eliminated being done so in the feces.

Block[4] found that those preparations most rapidly absorbed were the ones most rapidly excreted. Freyberg reported the quantitative retention of colloidal preparations as 99% ang that for soluble salts as 77 - 88%. These retention values may explain the occurence of toxic reactions long after treatment has been discontinued.

METABOLIC EFFECTS AND MODE OF ACTION:

Block and Knapp[4] studied the effect of various gold compounds on oxygen consumption of the rat kidney and liver. Soluble ionized compounds (gold chloride and gold sodium thiosulfate) inhibited respiration of both the kidney and liver. Extreme dilutions had no effect. The effect was believed to be due to the action of gold ions. The effect on the kidney was greater than that on the liver (which might be expected from the fact that the highest concentration of tissue-bound gold has been found to be in the kidney. Those compounds which have no inhibiting effect on cellular respiration (sodium succinimide aurate, gold sodium thiomalate, gold thioglucose, produce the least number of side reactions.

Goldalso inhibits cholinesterase in horse serum or leech muscle. This is probably an ionic effect as more dilute solution s produced greater inhibition. Gold chloride and gold sodium thiomalate have been shown to also inhibit brain pyruvate oxidase. Tyrosinase is inactivated by gold chloride and the inactivation of invertase by tyrosine is accelerated by gold ions. The inactivation of tyrosine may be on the

basis of competition against gold. In rats, gold decreases the ascorbic acid content of the plasma, a phenomenon which some feel to be the basis of toxid reactins. It has also been shown that gold decreases ascorbic acid content of guinea pig plasma, In fact the ascorbate content of all tissues is decreased. The liver and adrenals were most affected. The mechanism which is responsible for reducing plasma and tissue ascorbate is not known, but Zwemer and Elftman[4] feel that it may be a part of the generalized toxic reaction.

Cortell and Richards[4] Denko and Anderson have shown cross tolerance with certain of the gold compounds.

As can be appreciated from the numerous metabolic effects exibited by gold, the mode of action is unknown, though there are numerous speculations.

Many[2,5,6], feel that the high concentration of gold in arthritic joint tissues when gold is given, is explained by the escape of the gold through damaged capillarys in these tissues. This is believed since the gold protein molecule is probably quite large and large molecules escape from the vascular system only in the presence of damaged capillaries.

The bactericidal effect of gold when used in the early years for the treatment of tuberculosus was believed by Mollgaard to be the result of a specific affinity of gold for tuberculous foci, though his own products showed no in-vitro effect.

Feldt[4], thought that gold had a catabolic effect, influencing metabolic processes and hence promoting healing. Many, including Feldt, thought that gold stimulated the reticulo-endothelial system and therefore increased the defensive powers of the patient. Russu and Sachet[4] feel that they have demonstrated a reticulo-endothelial stimulating effect of gold. This theory is still popular, but as yet is unproven.

Still others feel that gold has a diuretic effect and produces s ome responses through the increased output of water.

It has been definitely shown by Rathbard et al[4] that gold sodium thiomalate is chemotherapeutic against hemolytic streptococci in mice in vitro, though the in vivo studies are not convincing. Gold protects mice against lethal doses of other forms of streptococci.

Hartung and Catler[4] found the serum of patients being treated with gold to be bacteriostatic for hemolytic streptococci. They found no increase in agglutination titers which would not support the earlier mentioned theory of reticulo-endothelial system stimulations.

A group of pleuro pneumonia-like organisms can produce in mice a polyarthritis similar to--but not identical to--rheumatoid arthritis in man. This induced arthritis is used as an aid in evaluating various possibilities of therapeutic agents and their effectiveness. Sabin and Warren[4] have completely cured mice polyarthritis with gold s alts. Their response occured only if therapy was begun early before cartilage destruction had occured; results were poor if therapy was begun too late. Colloidal gold bismuth salts, arsenic and antimony failed to give such a favorable response. Except for gold chloride, which was found too toxic, almost all other gold prepatations fave a good result. The authors did not feel that the effect of the gold was an antibacterial action as they found that in vitro, organisms (pleuro pneumonia-like) when grown in a media containing gold salts, did not lose their ability to produce the polyarthritis and disease. The effect of counteracting the polyarthritis depends upon the concentration of actual gold in the compound.

Libesen[4] theorizes that gold may tie up sulfhydril groups important in tissue enzymatic processes and hence alter cellular metabolism. This, he feels, may explain some of the feneficial results reported with

gold and some of the toxic reactions.

It had been suggested, as there seems to be a relationship between rheumatoid arthritis and steroid metabolism, that gold may have some effect on the adrenal glands, reflected in 17-ketosteroid output changes. Bruce and Mackay[7] undertook a study to see whether there was any change. They selected 16 cases who by their activity and E. S. R. were expected to respond. Their findings were that gold does not elevate 17-ketosteroid output, but, on the contrary, in some cases the values approached lower limits of normal, findings which supported Hench (1949). Their conclusion was that any improvement in the arthritis with gold therapy cannot be attributed to any alterations of steroid output by the adrenals.

Though felt to be of no signigicance in humans, Brecher and Waxler[4] demonstrated a weight gain in mice receiving gold thioglucose. There was centro-lobular fatty infiltration found in the liver.

Kersley, Mandel and Jeffrey[11] point out that Selye, in 1950, postulated that certain "conditioning factors", both exogenous and endogenous, may affect some of the responses of the General Adaptation Syndrome or target organs themselves. As an example, sodium favors the production of mineralo-corticoids, acting at the adrenal level of the response. Previously Selye had stated that sodium-rich diets favor production of diseases of adaptation, and acidifying salts tend to prevent these changes.

The authors point out that many stresses--toxic drugs, hepatitis, starvation, pregnancy--produce amelioration of symptoms of rheumatoid arthritis and postulate that gold may act in this way, especially since the arthritic symptoms decrease when toxic signs appear.

They conducted an experiment, therefore, to determine if a low salt diet and an acidifying salt would potentiate the effect of gold

therapy in rheumatoid arthritis. The conclusion of the experiment was that the above regimen had no potentiating affect of gold therapy. There was also no correlation of any liver function changes and improvement of the arthritis.

As mentioned above, stress situations are often beneficial to the arthritis. Two such stresses are pregnancy and jaundice, common to both of which is a marked lipemia as noted by Riddell[4]. He could show no plasma lipid changes, however, in gold treated patients. Gunter and Ivy[4] failed to show any liver changes from gold therapy.

The effective portion of the compounds is apparently the gold, as many experiments have tended to show. Some such experiments were those of Preston et al[4], who failed to show that sulfur must be present with the gold for the salt to be effective.

Finally, as Drill points out[15], the major difficulty in establishing the mechanism of gold effect is our lack of understanding of the etiology of rheumatoid arthritis.

DOSAGES:

Gold compounds used in the treatment of rheumatoid arthritis are given by intra-muscular injection, preferably in the gluteal region. The actual amount given, the time over which it is given, and the spacing of individual injection varies considerably, but the programs are divided into three general catagories:

1)Beginning with small amounts, and increasing them progressively until a moderate acceptable dosage is being given.

2) Beginning initially with the moderate dosage and maintaining this.

3) Beginning with relatively large doses and adjusting subsequent dosage to objective responses of the patient.

The first plan is demonstrated by Ramos[10] observation that before 1945 the general plan of treatment was 10 mg gold salt each week for four weeks, then 25 mg each week for four weeks until a total of 1 to 2 grams had been given. A rest period of 2 months was given and the procedure repeated until remission occured. Since 1945 he reports that the routine program is 25 mg of gold thioglucose every four days for six weeks, 25 mg every 2 weeks for six doses, 25 mg every three weeks for six doses, and 25 mg every four weeks for up to two years.

Preuse[1] reports a program beginning with 10 mg myocrisin for the first dose, and then increasing to 20, 30, 30, 40, and 50 mg doses at weekly intervals, the last dose being repeated four times giving a total of 380 mg of salt having been given over a period of 10 weeks.

It has been reported[9,1] that a few authors give 15 to 25 mg of gold salt initially to be followed by a 50 mg maximum weekly dose, but that the most common program today[1,9,4] is 10 mg the first week, 25 mg the second, 50 mg the third, and the 50 mg dose being repeated each week until 1 to 2 grams have been given or until response has been obtained. The patient is then maintained on a dose of 25 to 50 mg every two to four weeks indefinitely. A total dose of over 2 grams without response will probably not yield a response.

In mild cases or in cases of suspected sensitivity, it has been recommended that one not exceed 25 mg each dose. In stubborn cases[1] one may have to go as high as 100 mg each dose.

Black and Van Goor[4] report that if there has been no improvement after a total dosage to 1 gram , there will probably be no response. If response has occured, one continues with individual doses of 50 mg, but gradually spreads the intervals. They feel that under the former practice of stopping the above regimen for a two month test, then

re-starting another course of therapy, gave too high a relapse rate. A present method therefore, following remission, is to continue with 50 mg injections every two weeks for six to ten injections, 50 mg every three weeks for several months, and finally 50 mg every month for six to twelve months. This is one form of maintenance therapy.

Kersley, Mandel and Jeffrey report the use of intra-muscular calcium aurothiomalate beginning with an initial shot of 10 mg.,25 mg. for two doses at weekly intervals and then 50 mg. each week until one gram had been given over a period of five months.

Kaliomaki[14] placed 173 patients on a regimen of 50 mg. initially and every week for ten to twelve weeks. When the total dosage received reached 500 mg., 50 mg. each month was given as maintenance therapy.

Lawrence[6] points out that Sabin and Warren in 1940 showed in animal experiments that the therapeutic effect of gold is proportional to gold dosage. The author feels that the results of Freyberg and Comroe using 50 mg. per week as the effective top dose are poor and favors a program of 100 mg./Kg. given over the shortest possible period. The author placed several patients on maximal dosage based on the erythrocyte sedimentation rate or plasma fibrinogen level. The values for these tests were taken at monthly intervals and subsequent dosage related to these. As an example, a patient with an sed rate of 50 mm./hr. received 200 mg /week until the sed rate fell to 25. If the sed rate was 20, 100 mg./week and if the sed rate was 15 mm. , 50 mg./week gold was given. Therapy was continued until the sed rate was the same value for two cnsecutive months. He found that plasma fibrinogen levels was a better guide to the activity of the disease than the sed rate. The author feels that the incidence of toxid reactions was markedly reduced on this program.

Block and Van Goor[4] however, point out th t there may be cli ical improvement of the disease be fore the sed rate falls, or even without a fall.

As to the total amount of gold that should be given a patient, beliefs vary widely. Cecil believes that no limit should be set. Ra gan and Tyson, however, contend that two grams of gold salt should give a res onse if the patient is going to respond and that this figure should not be exceeded[2]

THERAPEUTIC RESULTS:

During the last twenty rears, gold salts have been used more in the treatment of rheumatoid arthritis than in any other disease. For the evaluation of therapy, the American Rheumatism Association in 1949 established various classifications for standardization[2].

Classification of Rheumatoid Progression:

Stage	X-ray	Muscle Atrophy	Extra Articular Lesions	Deformities	
1)	Osteoporosis No destructive change	0	0	0	0
2)	Porosis with sl. destruction/Adjacent		May be	0	0
3)	Cartilagenous & bone destruction	Extensive	"	Subluxation, Ulnar dev., Hyperextension	0
4)	As 3) with ankylosis	"	"	"	Fibrosis or ankylosis

Classificatio of Functional Capacity:

1) Complete: - - - - - - - - no handicap.
2) Adequate for norm. activities: - - despite handicap or discomfort.
3) Limited: - - - - Little of none of usual occupation or self care.
4) Largely or Wholly: - - - bedrid en, wheelchair, little or no self care.

It was apparently hoped that future reports on therapy would classify the paitents according to the above chart so that a more standardized,

exact evaluation of therapy could be made.

The first published reports on gold therapy in rheumatoid arthritis appeared in 1927. Lande and Pick reported their results independantly. Lande had treated fourteen patients and with good results; Pick had treated two with poor results.

Forestier appears to be the first to report in 1929, on a large series of cases, and is responsible for the popularization of gold therapy in rheumatoid arthritis.

Following is a chart from Block[4] showing the various authors and their results.

Author:	Yr.	# cases	Cured or markedly improved	Moderate to slight imp.	Somewhat improved	Relapse	Toxicity
Forestier	'35	550	50%	20%			25%
Pemberton	'35	100	50%	38%			
Hartfall	'37	780	67%	19%		21%	42%
Copeman & Tegner	'37	70	58%	13%			26%
Snyder	'39	80	1.3%	48%			
Cecil	'42	245	66%	20%		42%	42%
Price & Leichtentrill	'43	101			60%	55%	38%
Rawls	'44	100	53%	33%			42%
Cohen	'45	259	48%	40%			10.3%
Oren	'46	150			90%		4.6%
Ragan & Tyson	'46	142	50%	39%		75%	34%
Robinson	'46	200			76%		
Cohen	'48	216	53%	27%			27%
Sundelin	'48	2441			90%		50%
Nystrom	'50	620			62%		40%
Gilbert & Moore	'50	21	24%	66%			38%
Our Clinic Patients:		7	43%		86%	66%	70%

From the chart it can be seen that the over all rate of response was:

1 Cured or markedly improved. - - - - - 53% (2533 cases)
2) Moderate improvement - - - - - - - - -27% (2533 cases)
3)Somewshat Improved - - - - - - - - - - 83% (3512 cases)

The average relapse rate was 34% (1238 cases).
The average rate of toxic reactions was 40% (5716 cases)

All of the above studies represent studies in which no control group was used and the figures correspon somewhat to those reported in the Tenth Annual Rheumatism Review[2] in which data was collected on 142 patients who had h d a single course of 500 mg. Their figures were:

1) Marked Subjective Improvement - - - - - - - - 55%
2) Marked Objective Improvement - - - - - - - - 50%
3) No Improvement - - - - - - - - - - - - - - - - -11%
4) Asymptomatic for 45 to 78 months - - - - - - -13%
5) Relapse (in five years) - - - - - - - - - - - 75%

Of these reports, 80% of those who did relapse had a second remission.

Browning et al[4] reporting on forty seven patients followed for at least eighteen months following gold therapy showed 23% had continued improvement and 62% no change. He concluded that gold therapy gave no lasting benefits and that it was in effect no better than general and orthopedic care.

Egelius followed patients up to five to twelve years following their therapy and found that 59% of the males and 39% of the females treated showed lasting improvement. The initial results following therapy were 75% and 80%. He concluded that the initial improvement was no indication of lasting resul s. He also felt that males benefited more than females from godl treatment.

It has been reported[9] that 50% of patients can be expected to be much improved at the end of three months. In one series, 24 of 26 patients improved and in another 26 of 29 improved.

In one study conducted in Sweden, of 620 patients treated, 61% of these responded to treatment. Of these 70% had had the disease five years or more.

Ramos[10] reports loss of pain in 84% of patients under gold therapy following the first two shots. Also following the first two shots, there was noted: Return of complete mobility in 58% and complete rehabilitation in 47%. By at least the twelfth shot, he reports that the majority of

patients found o worsening of their condition by barometric changes. During his study, his paitents all received physio-therapy.

Results reported in American and European literature on 4086 cases shows a 61% arrested or greatly improved rate.

Brown and Currie[3] in assessing at three months and one year, patients who had received gold, failed to find any evidence of benefit from the treatment. This confirmed Short, Bechmand and Bauer's findings of 1946, who had concluded the same.

Fraser in 1945[4] gave 57 patients Myocrisine and a placebo to46. His results were as follows?

Clinical Improvement:	gold - - - 82% control - 45%
Greatly improved:	gol. - - - 42% control - 8%
Moderate improvement:	gold - - - 21% control - 13%
Slight imporvement:	gold - - - 19% control - 24%

Though these results appear very good, Fraser felt that the results were exceptionally high.

Adams and Cecil, however, in 1950, eported on cotrol studies of 189 patients, all early and who's results showed a 66% remissio rate ingold treated patients as compared with 24% in conventionally treated patients. The relapse rate was the same (30%) in both roups. They also found that the gold treated group responded earlier, seven months a s opposed to seventeen months of the control group. Their conclusion was that gold, when given within the first year of the disaase produced more and earlier remissions.

Another study showed 51.4% of 455 patients responded, whereas response rate to conventional me hods w s 15%.

In other studies using control groups, findings are less encourag-ing. Marliss[4] in 1951, studied 72 patients, 28 of whom received gold and 44 a placebo. He reports a subjective improvement of 37% ingold group as compared with 43% of the control group. Objective improvement rates wee 11% and 13% respectively. Another study showed a net improvement in gold treated patients of 23% as compared with a 53% net improvement in the control group. Other authors[9] report similar re-sults whether gold, copper salts, arsenic preparations or conservative therapy is used.

Snorrason of Denmark evaluated gold therap in p: tients with rheu-matoid arthritis after one year and again gain at ten years in 295 patients as compared to 169 who had been treated with conservative management.

He found that in those patients with capsular involvolvement 77% of those treated with gold were arrested at four years as compared to 22% of the control group. At ten years, however, there was not much difference and both groups showed progression.

Of seven cases in our clinics who's charts were reviewed, 6 of the 7 or 86% showed some improvement. Those showing marked improvement, however, was 43%. Of the total patients that did respond, four had relapses during or following discontinuance of therapy. This represents 66% of those that responded.

Lawrence[6] points out that Sabin and Warren in 1940 showed by animal experiments that gold effect is proportional to the dosage.

Results of the effect of maintenance therapy also veries. In one study[2] fifty patients receiving gold were compared with sixty two re-ceiving conservative therapy. There was a 21% arrested rate im the first as compared with 10% in the latter. Marked improvement was 36% and 19% respectively. Unimproved was 19% compared with 44%. Other reports have not been this favorable.

Relapses occur quite frequently. As shown by the chart on page 17, the average relapse rate of many authors w s 34%. Other figures have been 75%[2] , 30% and our own relapse rate being abou 66% of those patients who initially responded to g ld. Various estimates show that a relapse rate of 50 to 80% should be expected when one course of gold therapy is given and then discontinued. Many receive a second remission, possibly as high as 80% of those who relapsed, but the second remi sion may not be as marked as the first.

Short and others in 1948 ha se med to confirm the findings of Browning and other s of 1947 that the relapse rate was greater if too low a dosage were used[6]. Ramos[10] on a program of increasing dosage to maximum of 25 Mg. each month over a period of about 26 months and continuing with 25 mg. every onth up to two years duration, found only three of 36%cases relapsed.

Block and Van Goor[4] put forth several reasons to account for the varied reported results: 1) The cause of rheumatoid arthritis is unknown. 2) There are normally relapses and remissions in the course of rheumatoid arthritis, 3) The ode of action of gold preparations is unknown. 4) The compounds resently used very in physical and chemical properties. 5) The side of the dose varies. 6) Intervals between injects ons vary. 7) The diagnosis may not always be correct. 8) Evaluation of response to therapy is basic ally dependant upon the patients sub-jective improvement.

There are two indications for the use of gold compounds in joint disease. The first is a definite diagnosis of active rheuma oid arthritis and the second, palindromic rheumatism. Many authors[2,9,10] feel that one may treat the rheumatoid patient with conservative measures for only a short period of time b fore using gold, while others feel that gold is a last resort. Ramos[10] feels that gold can prevent crippling if used

early and recommends that in ac ive cases, that they are b st treated within one year from the onset of the disease. Others recommend beginning therapy no later than 2 years from the onset of the disease.

It is interesting that of our own patients treated with gold, a 36 white female who displayed probably more marked response to gold than any of our patients, had had the disease three years, while a 29 year white male, who had had the disease only 11 months received no benefit. Of the patients who showed improvent on therapy, one had the disease 13 years, another 50 years, another 8 years, another 3 years and the last, four months. Of these the 4 month, 8 year and 50 year relapsed.

To help determine activity and therefore the choice of those who should recevie gold, Ramos[10] suggests that the following may be helpful: X-ray is not reliable, the sedarate is usually elevated, there may be decreaset total serum proteins with albumiglobulin ration reversal, increase in plasma fibrinogen and a positive thymol turbidity; 92% of patients wit adult rheumatid arthritis giv. positive aggrutination of sensitized sheep cells and finally there may be an increases serum polysaccharide/protein ratio. Ramos feels that one should be certain that rheumatic activity is present and that one should not subject the patient to years of gold therapy.

There is general agreement that the decision to use gold compounds in the treatment of rheumatoid arthritis is to be made by the doctor and the patient together.

Contraindications to the use of gold compounds are several, but probably the one to always remember first is previous reaction to gold. Other contraindications are severe diabetes melitus, disseminated lupus erythematosis, nephritis, ulcerative collitis, hepatic damage, blood dyscrasia, and hemorragic tendancy, pregnancy (because symptoms decrease dur ng pregnancy). Any diabetic patient should be treated care-

fully. Vascular hypertension and chronic valvular disease are not contra-indications.

The effect o combining gold compounds with steroids was not, for this paper, investigated extensively, Of those reports read, results varied, some authors finding improved results, others not.

TOXICITY:

Ramos[10] states that most reactions occured in his series during the first six weeks or during the administration of the first 250 mg. This is not born out by our own patients who's average toxic dose was 640 mg. or greater. The incidence of toxic reactions varies fro 4.6% to 62%. At least 25% of all cases treated experience some form of reaction. The incidence, depending upon the preparation used, does not vary greatly; the values given as 39% fo sodium thiomalate; 31% for thioglucose and 21% for calcium thiomalate. Reasons for the variation in reports of toxid reactions are probably the preparation used, dosage and program, care-lessness in therapy (especially disregarding warning signs). Also, some authors report only severe reactions.

In 1941 Sundelin published reports containing the ate of toxid reactions in tuberculosis patients receiving gold. He reported n incidence of an average of 53%. In 3002 cases of joint disease receiving gold the toxic reactions occured in 49% of the patients. In 730 patienst of his own, he reported an incidence of 52%. Cecil , in reviewing 245 cases had an incidence of 42%. In one study using a control group, 37% of 49 patients receiving an inert placebo had toxic reactions. Cafea reported an incidence of 10.3% but these were only severe re-actions. In a later report, Sundelin, reporting on 2441 cases, had a toxic incidence of 50%, 415% severe. Suanberg[8] reports an incidence of

The incidence of se ere reacti ons as just mentioned is about 5% Mortality in 1935 was 3%. This has fallen to a present level of 0.4%.

Block and Van Goor[4] classify the types of reactions into three groups: 1) The nitroid or focal , 2) Parenchymatous cell poisoning and 3) Allergic. The first or focal type is charact rized by the development, in from a few minutes to ours, following the intitial injection, of transient vertigo, giddyness, flushing of the face, headache and occassionally, syncope. These reactions may persist for a few hours. The most common focal or nitroid reaction is a mild elevation of body temperature, often with a mild exacerbation of the disease which may last several days and is considered a good prognostic sign. None of the react ons of this group contraindicates continuance of the therapy.

Lawrence[6] reports three instances of urticaria, erythema and fever with aggravation of the disease twelve days after therapy was began and referred to this r act on as a serum sickness-like reaction.

The second group or cell poisoning, usually affects the liver and kidneys. Severe cases of liver damage are rare. Hartfall, in 900 cases had on y 13 cases of severe jaundice and two deaths. One death was due to acute yellow atrophy and he feels probably represented rare susceptability. Many authors have observed jaundice with or without hepatitis; the jaundice being le s severe than that just described. Hartfall had 50 cases of moderate jaundice and 22 with slight jaundice. Of his 900 cases mentioned previously, eventually 85 developed at least some jaundice. However, three of his patients who were not receiving gold also d veloped jaundice. Gunter and Ivy failed to show any liver changes attributable to gold therapy. In his report of reactions in 90 patients Lawrence[6] reported one case of jaundice. Some authors feel that jaundice seemed to aid the remission. Others have found opposite results and deny this.

Severe renal damage is also rare. Wright reported severe proteinuria durng gold therapy and the patient died 18 months later of nephritis. The author points out that the patient was 73 and questions whether the gold really significantly contributed to his death. Rect has also reported deaths from renal pathosis in patients on gold therapy. Freyberg has found renal damage only when large doses of gold were used. Mathers has reported cases of nephritis which have cleared in three weeks. Forestier believes that renal insufficiency occuring during gold therapy is the result of susceptibility of the patient to gold.

Slight, transient allbuminuria is frequently observed during gold therapy and usually clears soon following discontinuance of therapy and leaves no permanent renal damage. Freyberg has reported casts and hr-maturia. Cecil has noted marked albuminuria in three cases which did not develope renal pathosis. Hartfall found that 13 of his 900 patients developed albuminuria and only 2 were sever and persistant. There were no deaths from renal damage.

Cortell and Richards[4] showed, th their satisfaction, that albuminuria diappears wit the development of gold tolerance. They felt that the tolerance was the result of the development of epitheliar resistance to the damaging effect of gold salts. Kalliomaki had an incidence of 1 to 8% of patients showing proteinuria. There is general feeling that mild transient albuminuria does not contraindicate re-instution to gold therapy fol owing a rest period which allows the uring to become negative for the protein. They feel that this way about all of the mild reactions.

By far the most common reactions are the allergic. These may be cutaneous, mucous membrane, gastro-intestinal tract, hematologic, or central nervous manifestations.

The cutaneous are the most frequent of all reactions to gold salts. This may vary from a mild erythema to a severe exfo liative dermatitis.

Skin manifestations are almost always preceded by a mild or severe, generalized or focal pruritis. Cutaneous reactions may appear and disappear during therapy and usually do not appear until 300 to 400 mg. had been given. The skin reactions may resemble pityriasis,rosea, seborrheic dermatitis, urticaria, lichen planus, lichen ruber, lichen spinulosus, herpes labialis and simplex and zoster. Hyperkeratosis, folliculitis and exzematoid dermatidides have also been reported. Changes usually occur first over the neck, arms, axillae, gro ns, chest and back. A collar of scaley, greasy appearance is not uncommon. Pigmentation of the skin from depositior of gold (crysiasis) may actually occur but is rare and is usually a residual from some previous skin disorder. Temporary alopeci may occur. Skin changes may spread to a generalized exfolliative dermatitis whic with pemphigoid reactions are the most serions of the skin disorders of gold therapy. These skin reactions persist forweeks even after therapy is discontinued. Kalliomaki[5] had an incidence of 35 to 44% skin reactions, He concluded that as the skin reactions (and eosinophile reaction) showed no relation to the sed rate that they were both allergic phenomena. Lawrence[6] had a 20% incidence of dermatoses. Suanberg[8] had an 30% incidence and most of these occured during therapy and a ter several doses.

Stomatitis may occur. In mild cases, this may be merely a superficial erosion,shile in the more severe reactions, there may be ulcerations. Temporary loss of tast may occur. Conjunctivitis, iritis and c corneal ulceration have all been reported, Barrow and Stone have noted vulvovaginal eruption, stomatitis and generalized cutaneous eruption. Anal ulceration has been reported. Lawrence had an incidence of 14% stomatitis. Suanberg showed an 15% incidence of mucosal reactions, five cases of which were metallic taste in the mouth.

Nausea, vomiting, epigastric distress, hiccough, and diarrhea have all been reported frequently. These are usually of short duration and respong to mere discontinuance of gold therapy. A few cases of severe colitis have been reported. Anderson and Palmer[4] reported a fatality from ulcerative colitis following a total of 200 mg. gold sodium thio-sulfate. Cecil has also reported such a case.following only 25 mg. , but the patient here, had a history of intestinal symptoms. Severe distur-bances are rare and Freyberg has yet to see such a reaction in ten year s experience with gold. Suanberg reports a 7;5% incidence of gastric complaints, all occuring during therapy.

Hematologic co plications are the most serious, but fortunately are the most rare reactions. These reactions account for almost all of the reported fatalities and fall into three major classifications: 1) Thrombocytopenia 2) Granulocytopenia and 3) Aplastic anemia. Wintrobe and Peters have reported several cases of granulocytopenia and others have been reported. Marriott and Peters found, up to 1948, 60 cases of thrombocytopenia in the literature. This is the most frequent of the hematologic reactons to gold. Sorensen had a fatal case of thrombocytopenia develope ten months following therapy. The purpura may be confined to the skin or may involve the viscera. There have ben some fatalities from subdural and intracerebral hemorrage. Leukopenia and secondary anemia have been reported. Some feel that a pre-existing secondary anemia has been helped by small doses of gold, but aggravated by large doses. Eosinophiles may predede or accompany therapy and may be a warning of impending reaction. Kalliomaki had as hig as a 9% incidence of leukopenia and an 8% eosinophilia. Lawrence had only one case of granulocytopenia in 90 cases.

Bowerll reported that to 1948, 20 cases of aplastic anemia had been reported. He reports the case of a 47 yr. man who on 50 mg. gold

each week , received relief from arthritis symptoms after one gram gold had been given. One month following therapy he developed a rash and bl eding gums and was placed on B.A.L., liver shots and penicil in but to no avail. He had numerous petechii and ecchymoses at autopsy and there was degeneratin of the distal convoluted tubule.

Watson[12] reports an incidence of 1.5% of all patients developing thrombocytopenia. In his review of the literature he reports 28 cases of purpura, ten of whom died; ten cases of granulocytopenia wit two deaths and 19 cases of aplastic anemia with 14 deaths. Suanberg[6] showed an ncidence of 9% hematologic reactions, 13 cases of which were leuko-penia.

Bjorkman[13] reports a very interesting case. The patient received 0.3 g. of one gold preparation but because of a rise in eosinophils, was switched to another preparation for a total dose of 2.6 g. over a period of two months. On his first day home, he had fever and chills for which he received penicillin without improvement. He became dyspneic, threat and mouth became dry and he developed a non-productive cough. A chest film showed bilateral blotchy areas near the bases. Penicillin, streptomycin, terramycin gave no response. The E.K.G. showed myocardial damage. Laboratory work was normal except for a 92mm.sed rate an a total eosinophile count of 1200/cu.mm. She failed to respond to cardiac therapy. On the suspicion that the basis may be gold toxicity, B.C.T.H. was given and in a few hours responded mrakedly and in a few days, res-pirations were easy. Chest film showed clearing, temperature fell to normal, E.K.G. was normal, sedate fell to ill, eosinophiles to 78. She was discharged in good health at the end of three weeks. Miscel-laneous reactions which habe been seen include bronchitis, hemoptysis, epistaxis; follicular hyperplasis, polyneuritis, meningitis and central nervous symptoms. There has been one death believed due to meningp-

encephalitis . Nervous symptoms ranging fro depression to frank psychosis have been described. These are the rarest react ons (2.5% in Suanberg's reports.

Many of the metabolic effects of gold compounds mentioned under that headi g have been suggested by many authors to be also responsible for toxic react ons. Such effects include inhibition of cellular oxygen consumption by gold, inhibition of cholinestera es, inhibition of brain, pyruvate oxidase inactivation of tyrosinase and normal inactivation of invert se by tyrosine being accelerated by gold preparat ons and decreased tissue and plasma ascorbate.

Libesen[4] has theorized that gold may tie up sulfhydril groups important i tissue enzymatic proceddes and therefore alter tissue metabolism.

Heubner had early, felt that gold compounds act as capillary poisons. This is not a commonly held view now. Feldt thought that the reactions are due to non-specific metal poinoning. Mollgaard believed that toxicity was due to release of bacteriolysis of tubercle baci li (in uberculous patients). This of course is not cceptable in patients other thatn tuberculous. Milan believed in the biotropism theory which says that cer-tain chemical, physical or bacterial agents are capable of stimulating microorganisms present in the body to produce unexplained complications and that the complications are therefore, regarded as activated latent diseases. It is interesting with this in mind that Parr found 2 cases of rheumatoid arthritis treated with gold in whom clinical syphilis became apparent only ollowing gold therapy. This theory at present is not too unpopular.

Secker regarded toxicity as an expression of vitamin deficiencies and recommended high vitamin intake with go ld therapy.
are lThe most popular theory at present, of course. is tha toxic reactions

are largely allergic. As we have s en, however, there may be certain results (liver and kidney damage) which r presents actual cell poi-oning. This may occu-, however, only with extremely large doses or in especially susceptible p.tients. Presumably those patients with skin reactions have no higher concentration of gold in their skin than in those patients without reactions. In his revi w of the relation fo the sed rate to complications, Kalliomaki states that authors (Goldie, Ellman, Lawrence) have reported an apparent inverse relationship of complications of gold therapy and the sed rate, The explanation, he feels, may be that when the sed rate is elev ated (active disease) the protein bound gold is releases through damaged capillaries in the area to the diseased joint structures and the concentration in other structures is thereby kept low. When the sed rate drops, however, and the capi-llaries and diseased tissues repair, more gold is deposited in the other structures (skin) and reactions follow. In Lawrences original paper, he reports gold concentration in synovial tissues of an active rheuma-toid to be 18 tiles that of othe tissues. He points out that in Goldie's series, in 8 of 11 patients who developed skin react ons, their sed rate had been below 10 for 2 weeks preceding the reaction. Ramos[10] feels that almost all reactions occur in patients with alergic constitutions and in patients with other allergies.

Reactions are not consistantly related to total dose given to the date of the reaction. In some patients, there is an eosinophilia occurring in some rlation to the reaction, a finding which would strongly suggest an allergic basis at least in these patients. Suanberg had predicted reactions (a cording to skin testing) with a 66% a ccuracy, This will be menti.ned later under treatment of reactions. Some authors feel that the gold itself if possible not the allergen but that it is the gold proteinate.

Bower states that hematologic reactions are possibly the result of a direct effect on the marrow or an effect on the spleen creating a hypersplenic syndrome, with secondary pathologic blood findings.

Cecil[9] has made the statement that toxic manifestations to gold are not preventable, This is an excedingly pessimistic vies in light of reports from other authors. It is somewhat true that there is no reliable method of determining which patientas will react. Suanberg[8], however, in Sweden, reports that no patient at the Noorkoping hospital receives gold until skin testing has been performed in a attempt to determine sessitivity to gold. The testing is carried out using Aurothon in a 1:1, 1:3, 1:5, and 1:10 dilution. A control is run simultaneously using the same dilutions of 6.5% sodium thiosulfate. Skin testing is done by the intradermal tehhnique using all of the dilutions of the gold and the control. A wheal of 0.5 cm. is made and readings are made at thirty minutes. A papule of various sizes is read as varying degree of positive. The readings are made according to the control papule. The tests are repeated every four days on patients receiving gold, Reactions may vary as the test are repeated. Most reactions were found to oocur during therapy and after several injections. In eleven cases, reaction occured immediately following the first injection. In most cases there was a change in the skin test occuring with or following a reaction. A positive skin test may revert to negative following a reaction or following the use of B.A.L. Or, following a reaction, the skin test may become negative, gradually becomming positive again. There were variations on some controls, however: hence, changing skin tests is not primarily associated with the amount of gold given. The testing may also induce sensitivity.

The authors results were as follows:

Skin Test:	Without Complications:	With Complications
Decreased	88%	12%
No Change	54%	46%
Increased	35.5%	64.5%

His cnclusions were three: I the skin test decreases, complicati ns arose in only 12% of those treated. In those showing no change or an increased test, one should procede with cautio or stop until skin test decreases. It is almost impossible to predict on the basis of the skin test which patients will react to the first dose of gold.

It is very interesting to note that in those patients who showed an increasi g skin test, 65% developes complications.

There is general agruement that there are many warning signs and that at the appearance of these, therapy should be proceded with very cautiously, or better, therapy should be interrupted until these symptoms abate before re-instituting therapy. Some of the warnings are ppuritis, purpura, metallic tast of the mouth, sore mouth, diarrhea, mild albuminuria. Prouse, in reportin a death due to gold, feels that he lost the patient in part by not heeding a pruritis which occured prior to the fatal complications. If albuminuria arises to two plus or more, if red cells or casts appear in the urine or if the B.U.N. begins rising, gold therapy should be stopped immediately, Any allergic history sho ld be carefully sought and if obtained, should make one ver cautious of instituting gold therapy.

The patient should be questioned carefully each visit for the occurance of pruritis. The skin and mouth should be examined each visit. A U.A. should be done weekly, a hemoglobin and white count twice a month. If purpura appear, a platelet count may be desired. Eosinophilia should be watched for. When any of the above arouse any suspicion, therapy should be stopped.

As a result of the many metabolic effects attributed to gold, many authors have given substances with the gold injections. At one time it was believed that calcium gluconate given with the inject n wo ld decrease the toxicity but ' is has been discarded. Others have given large doses of vitamins, e. ecially ascorbic acid. Ramos[10] gave 10 ug./c.c. of liver extract with each gold shot. The incidence of reactions has been markedly reduced by the use of less toxic preparations, smaller doses nd careful supervision of the therapy.

Once toxic manifestat ons have occured, therapy rests on one or a combination of B.A.L., steroids or splenectomy. Exce t for the dermatoses, results of treatment of toxic reactions, especial y the hematologic complications has been disappointing. Such compounds as B.A.L., thiomalate, sodium thioglucose and cystine were found by Block to successful y co pete with gold chloride for sulfhydril tissue enzymes. It was found that these compounds reversed theinhibited cellular oxygen consumption induced by gold. The only agent effective against gold sodium thiosulfate was found to be sodium thioglucose. The reversal ef ect is greatest wh n the thiosulfyl gourp/atoms of gold ratio was 3/1. G.A.L. and thiomalate ar themselves inhibitors of oxygen con-sumption but a combination of these and gold chloride or of gold sodium thiosulfate and sodium thioglucose gave less an inhibiting effect tham either alone. Good results have be n reported with thiosulfate and sodium formaldehyde sulfoxylate in gold dermatoses. In 1945 the British introduced B.A.L. effective against heavy metal poisoning and having as its basic role, a stronger affinity for sulfhydril groups than heavy metals.

Cohen, Ragan and Boots[4] were among the first to use B.A.L. for gold toxicity. Cohen reported dramatic results in cases of dermatoses. Some reports are unfavorable, but if the skin reaction is not too far

advanced and not too severe. there is usually good response.
Experiments have shown that B.A.L. can protect rats against lethal doses of gold.

The best protection is secured by giving B.A.L. with the gold. No effect is secured if the B.A.L. is delayed for a matter of d ys following the administration of a toxid dose of gold. If B.A.L. is bigen with the gold there is not even histologic renal damage. It has been sug-gested that B.A.L. when given in this manner competes with the tissues for the circulating gold. The action of B.A.L. is probably through compe-tition with the metal for the sulfhydril substrate and the i creased output of urinary gold. Experiments in rats have shown increased rate and total excretion of gold. It is also rported that following the use of B.A.L. so uch gold is mobilized and excreted that arthritic symptoms may appear in only a short time (one month). B.A.L. can, itself cause toxic symptoms including nausea, vomiting, headache, causalgia, tooth pain, lacrimation, salivati n, muscular aches, increased systolic and diastolic blood pressures. These symptoms are usually only transient and occur within fifteen to twenty minut s following administration of the B.A.L. Sufficient therapy should be carried out.

Recommended dosage is 2.5 mg./Kg. body weight every four hours for two days, then the same dosage twice daily for ten days or until toxid reaction responds. The preparation used is B.A.L i a 10% sol-ution of benzyl benzoate in peanut oil. B.A.L. is rapidly destroyed by the body so that there is no accumulation and which, therefore, allows indefinite therapy. B.A.L. should not e used in the presence of liver disease.

Best response to B.A.L. has occured in the gold induced dermatoses. Suanberg reports good results in three patients. There have also been good results reported in stomatitis, conjunctivi tis, hepatitis, menin-gitis and renal irritation.

Lockie[4] had dramatic results with B.A.L. in a case of granulocytopenia and thrombocytopenia. There are reported cases of dramatic response in other cases of these same two reactions, but in general, B.A.L. is not effective in the hematological reactions to gold.

Prouse[1] reports a case of a severe hematologic reaction to gold following 380 mg. over a period of ten weeks. She began with pruritis, soon was bruising easily and finally began bleeding heavily per vaginum. Herpplatelets fell to 2,000, hemoglobin to 48 and white cell count to 3,200. All cells in a marrow biopsy were decreased in number. She was given two courses of B.A.L., but gold was never found in the urine. Steroids also failed. At autopsy all organs were markedly hemorrhagic. The marrow of all bones showed fatty replacement and hypoplasticity.

Aplastic anemia so far as I could find, has never responded to B.A.L.

Steroids may be of value, especially in dermatoses that fail to respond to B.A.L. Steroids may be beneficial in other reactions[10].
The most dramatic response to steroids was probably Bjorkman's case of a severe allergic react on in lungs and heart to gold which cleared on A.C.T.H.[13] This case has been described above.

Hematologic ractions nororiously do not respond to B.A.L. and except for the response obtained in thrombocytopenia and granulocytopenis in the case mentiones previously, steroids also fail to give a response. There have been reports of hematologic reactions responding to splenectomy[1]. One report[9] concerns a patient who's skin reaction cleared on B.A.L. but later developed thrombocytopenic purpura which responded to splenectomy. Watson[12] in a review of six recorded cases of splenectomy for hematologic reaction to gold revealed a response in two and improvement in a third. Mettier and McBride have reported lasting improvement following splenectomy[1]. Marriott and Peters have reported even a case of hypoplastic anemia responding to splenectomy.

The author presents three cases. The first, pancytopenia, re-sponded dramatically and immediately following the surgery. She had failed to respond to transfusions. The second, thrombocytopenia, also failed to respond to transfusions, but gave marked response to splen-ectomy. The last case, thrombocytopenia, refused splenectomy and at her last check had failed to respond to B.A.L.

In hematologic co plications which fail to respond to therapy, or until they do respond, one must give transfusions, try vitamin K for the bleeding and use antibiotics a s prophylaxis against secondary in-fection.

SUMMARY:

The use of gold in medicine dates back to 2500 B.C. and the Chinese. Its early use was a s a panacea. It was first used specifically for the treatment of arthritis about 1927 and the rational for its use in this disease was actually based on Feldt's demonstrat on of its anti-infectous effect. Gold was first reportedly used in ths country for arthritis in 1936.

Gold compounds are generally rapidly absorbed from the intra-muscular site. A small portion is rapidly excreted, soluble preparations i n the urine, insoluble preparations and colloidal gold in the feces, but the larger percentage is concentrated in body tissues, especially the kidneys liver and spleen. The greater the amount injected, the greater the retention.

Gold has been shown to: Inhibit oxygen consumption, inhibit chol-inesterases, inhibit brain pyruvate oxidase, inactivate tyrosinase, to decrease plasma and tissue ascorbate content, all of these in various animal tissues.

The mode of action is unknown. Suggestied possibiities are: bactericidal effect, catabolic effect, reticulo-endothelial system stimulation, tying up of sulfhydril groups and effects through the adrenal steroids.

A common dosage program consists of the intramuscular injection of 10 mg. initially, 25 mg. the second week, 50 mg. the third week, then 50 mg. each week until a total of one to two grams has been given or a response has been obtained. The patient is then maintained on 25 to 50 mg. once or twice monthly. If there has been no response with a total dose of about two grams, it is unlikely that further treatment will yield a response. Lawrence recommends a total dose of 100 mg./Kg. given over the shortest possible period of time. Maintenance therapy may be of value.

Results vary with various authors. The averages from a large ac-cumulation of cases are as follows:

Cured or Markedly Improved: - 55-90%
Moderate Improvement - 27%
Somewhat Improved - 83%
No Improvement -11%
Relapses -34-75%
Toxicity -40-62% (4.5% severe)
Fatalities - 0.4%
Completely Asymptomatic 45-78 months later - - - - - - - - - - - - 13-59%
Second Remission following relapse - - - - - - - - - - - - - - - - 80%

The results of our own clinic patients was:

Response (any improvement)	86%
Marked response	43%
Relapses	66%

The only two indications for the therapeutic use of gold compounds is active rheumatoid arthritis and palindromic rheumatism. Contra-indications are previous reaction to gold, severe diabetes melitus, disseminated lupus erythematosus, nephritis, ulcerative colitis, hepatic damage, blood dyscrasia and pregnancy.

The commonest reactions are cutaneous, the most severe are the hemat-ologic and the most rare are the nervous reactions. Warning signs of tox-icity may be pruritis, purpura, metal ic taste in the mouth, increasing proteinuria. These symptoms should arouse suspicion of impending toxic reaction and should make one procede cautiously with therapy or better,

to discontinue therapy. If react.ons warrant aggressive therapy, B.A.L., steroids or both should be used. Splenectomy may be life saving in hematologic complications.

CONCLUSIONS:

The purpose of this paper was to investigate the rational for the use of a heavy metal, gold, in the treatment of rheumatoid arthritis; and to attempt to decide whether it is actually of any real benefit in this disease. I must conclude that there is no proven pharmacologic explanation for any action of gold in this disease. Some reports show up to an 80-90% remission with gold, but other studies with a control group are not so impressive. The relapse rate is almost as high as the remission rate. Toxic reactions are very frequent with 4.5% of these so severe that the prognosis of the complication may be poor. The chief claims for the use of gold, that it stops the progression of the disease and that relapses do not occur when treatment is stopped, are not born out by the literature and the reports of our own clinic. There are patients in whom gold does seem to produce a remission and in these patients, the effect is dramatic; however, these same patients may be just the on s who would show equally dramatic results with steroids and conservative physio-therapy.

In final conclusion, in a case of rheumatoid arthritis, one might firt tyy gold therapy, but should toxid reactions occur or should re-mission not be achieved with total dose of probably 2 grams. gold should be abandoned as holding any promise for the patient. Prolonged therapy without remissionor with labile and uncertain relief of symptoms, and an off-again, on-again program of therapy should be condemned.

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