Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Gold Treatment Of Rheumatoid Disease

olume XIII | Friday, April 17, 1942 | Number 22

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
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INDEX

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William ... [illegible], M.D.

I. LAST WEEK

Date: April 10, 1942

Place: Recreation Room
Powell Hall

Time: 12:15 to 1:15 p.m.

Program: "Post-Irradiation Bone Changes"
E. G. Holmstrom and F. R. Gratzek

Discussion
J. L. McKelvey
K. W. Stenstrom
L. G. Rigler
Wallace Armstrong
W. C. Bernstein

Present: 120

Gertrude Gunn,
Record Librarian

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II. MEETINGS

1. SEMINAR IN PATHOLOGY

12:30 p.m., Monday, April 20, 1942, 104 Institute of Anatomy. Further reports of recent meetings at St. Louis. Dr. E. T. Bell. Visitors welcome.

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2. PHYSIOLOGY-PHARMACOLOGY SEMINAR

12:30 p.m., Tuesday, April 21, 1942, in room 214, Millard Hall. Wallace D. Armstrong - "Mechanism of Parathormone Action."

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3. NEXT WEEK

Because of the conflict with the American College of Physicians meeting the regular staff meeting by the division of internal medicine will be given June 19. Next week there will be a special showing of moving pictures.

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III. GOSSIP

These have been busy days on the campus with the two-week course in internal medicine at the Center, special lectures, and preparation for the meeting in St. Paul next week. During the past two weeks we have had some excellent special lectures for the University family. These have included William S. Middleton (Wisconsin), "Some Rationalized Therapeutic Procedures," Alvin F. Coburn (New York), "Rheumatic Fever," Philip Levine (Newark, N. J.), "Serologic Differentiation of Human Blood with Special reference to Factor Rh," H. B. Andervont (Washington, D.C.), "Recent Trends in Cancer Research," and Charles Huggins (Chicago), "Endocrine Relationships in Prostatic Carcinoma." Other visitors have included Theodore L. Althausen (San Francisco), Willis H. Fowler (Iowa), Thomas T. Mackie (New York), Elmer L. Sevringhaus (Madison), and E. L. Tuohy (Duluth). From the Mayo Foundation we have had Edgar V. Allen, J. A. Bargen, Jesse L. Bollman, John D. Camp, George B. Eusterman, Byron E. Hall, Philip S. Hench, Edward H. Rynearson, Charles H. Slocumb, Elmer G. Wakefield, and Henry W. Woltman. The contributions of all these men, plus those of our own group have made a favorable impression on our campus visitors from all sections of the United States. Minnesota has reached its optimum in state development. We have an ideal distribution of population, interest and activity. There are few Universities in an urban area in a state with such a rich background and so many opportunities for individual self-development. The group in internal medicine under Cecil J. Watson has created a place that is unique in the series of special courses developed by The American College of Physicians. There will be a change in faculty as new groups come to the Center. April 30-May 2, the Obstetric and Newborn nurses will study the latest developments in their field. A group of physical-therapy technologists (Kenny method) started Monday, April 13 for a 2 to 6-months' course. The week of May 11th will have another course in Obstetrics for representatives of medical societies. The Kenny course for physicians will be June 1 to 6. Industrial Nursing and Pre-school Health Problems follows June 8-13....

IV. GOLD SALT TREATMENT OF CHRONIC RHEUMATOID DISEASE

Macnider Wetherby
K. d'A. Andresen

Gold preparations have been used therapeutically to a limited degree for a number of years although much less than many of the other heavy metals. One of the early investigations with gold was the work of Koch in 1890 in testing the effect of a gold cyanide preparation on bacillus tuberculosis. Since that time gold has been used experimentally and therapeutically by a number of investigators in the treatment of tuberculosis. The work of Mollgaard in 1924 on the gold salt treatment of tuberculous veal calves gave added incentive to its use and there have been a number of reports of the use of gold salts in treating tuberculosis since that time. These reports have not been convincing as to the effectiveness of gold salts in treating tuberculosis; however it is still used somewhat in Europe. There have also been a number of reports of the use of gold in the treatment of lupus erythematosis and there have been some clinical trials in the treatment of syphilis.

The first use of gold salts in treating chronic arthritis is ascribed to Landé in 1927, Pick in 1927, and Forestier in 1929. Since that time there have been a number of reports in the European and English medical literature and more recently in the American literature.

Gold Preparations

Gold has been used orally, intravenously and intramuscularly in the treatment of rheumatoid diseases. The use of gold preparations by mouth has largely been abandoned as ineffective. Colloidal gold which was used for a time has also been used little in recent years because of being less effective and probably more toxic. At the present time water soluble salts are used almost entirely and are given either intravenously or intramuscularly with apparently no difference in therapeutic effectiveness. In some instances oil suspensions of solutions of these salts are given intramuscularly.

Some of the gold preparations are: Gold sodium thiosulphate (crisalbine, sanocrysin, aurocidin) Abbott, Merck, Searle; gold sodium thiomalate (myochrysine, myocrisin) Merck; gold thioglucose (Solganol B) Schering; gold sodium thiobenzimidazole cerboxylate (Triphal); gold calcium thioglucose (Myoral) Tongere and Company; sulphonate of gold sodium thiopropanol (allochrysine); gold naphthyl trisulphocarbonium derivatives (aurocein); and others.

The two preparations used most frequently in this country are the water soluble salts, gold sodium thiosulphate and gold sodium thiomalate. Gold sodium thiosulphate contains 37.4 per cent gold and is used both by the intravenous and intramuscular route. Gold sodium thiomalate (myochrysine) contains approximately 50 per cent of gold and is given by the intramuscular route.

Clinical Reports of Gold Therapy for Chronic Arthritis

Some of these clinical reports are: Secher '33; Fehlow '33; Bourderon '34; Forestier '34 and '35; Pemberton '35; Griffiths and Race '35; Buckley '36, Crosby '36; Phillips '36; Owen '36; Copeman and Tegner '37; Hartfall, Garland and Goldie '35, '36, and '37; Sashin and Spanbock '37; Parr and Shipton '37; Dawson '37; Key Rosenfeld and Tjoflat '39; Snyder Traeger, and Kelly '39; Ellman, Lawrence and Thorold '40; Tarsy '40; Logefiel and Hoffman '41; and Sundelin '41.

The most extensive clinical reports are those of Forestier (550 cases), Hartfall, Garland and Goldie (900 cases), and Sundelin (730 cases).

There is rather general accord by most authors as to the therapeutic effectiveness of gold in a high percentage of cases designated as rheumatoid arthritis. The experience with patients having osteo-arthritis has been variable although improvement has been claimed in many of these cases also.

Spondylitis has apparently responded less frequently than other rheumatoid manifestations. There are of course the usual difficulties and uncertainties in attempting to classify patients with symptomatic arthritis into such distinct groups as rheumatoid arthritis, osteo-arthritis and other designations. Some patients with gonorrheal arthritis have received gold therapy with improvement reported in a number of cases.

Hartfall, Garland and Goldie in 1937 reported the use of gold therapy in 900 cases. (Rheumatoid arthritis 750, osteo-arthritis 68, chronic villous arthritis 23, spondylitis ankylopoietica 18, gonococcal arthritis 6, peri-articular fibrositis 17, unclassified arthritis 18). They used 4 different gold preparations (1) Crisalbine (gold-sodium thiosulphate), (2) Lopion, (3) Myocrisin (gold sodium thiomalate), (4) solganol B (gold thioglucose). Injections were given once per week and in the first 100 cases the large dose of 200 milligrams was given for 10 weeks and a total dosage of 2 grams. Later they reduced the initial dose to 50 milligrams and still later to 25 milligrams and a total of not more than 1 grain with a course of about 12 injections. They then repeated the course after a 12-week rest period depending on the degree of clinical response. Toxic reactions were often a reason for interrupting or terminating treatment. Their results in the treatment of 750 patients having rheumatoid arthritis were as follows:

Results - Hartfall, Garland & Goldie

	No.	Percentage
Apparent cure	68	9.9
Marked improvement	392	56.8
Moderate improvement	90	13.0
Slight improvement	43	6.2
No improvement	61	8.9
Worse	17	2.5
Died (various causes)	19	2.7
Total	690	
Defaulted	60	
Total	750	

Forestier reported the use of gold salts in the treatment of 560 patients, apparently the majority with rheumatoid arthritis, but also some described as Still's disease, focal arthritis, tuberculous arthritis and ankylosive spondylitis. He used several gold preparations including allochrysine (sulphonate of gold sodium thiopropanol), myochrysine (gold sodium thiomalate), myoral (calcium gold thioglycolate), and solganol B (gold thioglucose). The starting dose of allochrysine was usually 50 milligrams and then 100 milligrams at weekly intervals for a total of 1.5 to 2 grams per course. The same or slightly higher dosage of myochrysine was used. Solganol B was given with a starting dose of 50 milligrams and up to 200 to 300 milligrams as weekly intervals for a total of 2.5 to 3 grams per course. Forestier stated that the interval between the first and second course should not exceed 6 to 8 weeks but that later the interval between courses may be from 3 to 4 months if the patient is making good progress. He emphasized the importance of continuing therapy and not suspending after 1 course.

Forestier reported that 70 to 80 per cent of the patients treated has responded favorably to treatment and that 50 per cent of recent cases and 20-30 per cent of older cases (above 2 years' duration) have been clinically cured by 2 to 5 series of injections, and remained so after discontinuing treeatment for 2 or 3 years.

Sundelin of the University of Uppsala in 1941 wrote a monograph reviewing the extensive literature dealing with gold therapy and including a report of his experience, in the treatment of 750 patients, 530 cases termed chronic infections (rheumatoid, atrophic). He also used a number of gold preparations including sanocrysin (gold sodium thiosulphate), Solganol, Neosolganol, Aurodetoxin and Myoral. Sanocrysin (gold sodium thiosulphate), which was used most frequently was given in single doses varying from 50 to 750 milligrams, with an average of 8.4 injections at weekly intervals.

The other gold preparations were used in correspondingly large doses. A course varied from a few injections to 20 injections, depending on reactions and clinical response. The interval between courses was apparently irregular and dependent on the same factors.

Sundelin reported some degree of clinical improvement in 93% of patients treated with gold. (44 per cent much improved, 49 per cent improved, 6 per cent unimproved, and 1 per cent worse). There was little significant variation in the clinical results of those treated with various gold preparations. Sundelin in reviewing the literature cited 3800 chronic arthritic patients treated with gold with a variation from 40-95 per cent improvement reported, and with an average improvement of 81 per cent of cases.

In the United States the tendency has been to use smaller doses of gold than those used by most European and British physicians. Snyder, Traeger, and Kelly using gold sodium thiosulphate gave an average of 14 injections at bi-week intervals beginning with 5 milligrams and increasing so that the last 8 injections were 100 milligrams for a total of 990 milligrams per course. After a rest period of 6-8 weeks a second course was given at 1 week intervals and in many instances further courses were given as indicated after longer intervals. They reported some degree of clinical improvement of 48 per cent of cases termed rheumatoid arthritis, 45 per cent of cases of osteoarthritis, and 26 per cent of mixed cases.

Sashin, Spenbock, and Kling using gold thiosulphate gave 25 to 50 milligram doses once or twice weekly, according to reaction, until 1 gram had been given. They reported very marked improvement in 43.75 per cent of cases, moderate or slight improvement in 38.75 per cent of cases and no improvement or worse in 12.5 per cent of cases. The clinical reports of Key, Rosenfeld and Tjoflat, of Tarsy, of Logefiel and Hoffman have also reported much the same favorable experience with gold salts.

Pharmacological and Therapeutic Basis for Gold Salts

The basis for the use of gold salts has rested largely on their therapeutic effectiveness. There have been few extensive studies of the exact pharmacological action of gold. The intangible factor "shock therapy" has been suggested as a basis. Many authors have mentioned the frequent correlation of significant improvement with toxic manifestations. Hartfall, Garland, and Goldie however made a statistical comparison of the incidence of clinical improvement in groups of patients with and without toxic reactions and found no significant difference. It was also of interest that Hartfall, Garland and Goldie reported that the clinical improvement was less marked in a group of patients who were jaundiced than in those not jaundices. This is in contrast to the clinical observations that patients with arthritis are frequently clinically improved when jaundiced.

There has been recent stimulation to the study of the distribution and secretion of gold in animals and patients reported from the University of Michigan. Block and Buchanan reported an accurate photoelectric colorometric micromethod for the determination of small amounts of gold in urine, plasma, body fluids, and tissues. Block, Buchanan, and Freyberg using the water soluble gold salts, gold sodium thiosulphate, and gold sodium thiomalate and colloidal gold and colloidal gold sulfide in rats, found certain significant differences in the use of crystalline salts and colloidal gold preparations. The colloidal gold and colloidal gold sulfide were poorly absorbed at the site of injection, after a series of daily injections. Another difference was that after colloidal gold or colloidal gold sulfide, more gold was found per gram of tissue in the liver than in the kidney. Those receiving wate water soluble gold salts had much more gold per gram of kidney than per gram of liver. Gold was found to be excreted both in urine and feces. The urine contained much more gold than did the feces in the case of those preparations (crystalline) with which the kidney gold

content was greater than the liver, while the feces were the chief route of excretion in the case of those substances (colloidal) producing liver gold content greater than kidney. They also found gold only in the plasma of blood.

Freyberg, Block and Levey further investigated the metabolism, excretion, toxicity and manner of action of gold used in rheumatoid arthritis. They used gold sodium thiosulphate, gold sodium thiomalate, and colloidal gold sulfide in patients. They found that gold sodium thiosulphate and gold sodium thiomalate (crystalline salts) injected intramuscularly in amounts supplying equivalent amounts of gold result in similar plasma gold concentrations and urinary excretion of gold. The urine and plasma gold concentrations and urinary excretion of gold. The urine and plasma gold values varied with the size of the weekly dose given but were not proportional to it. Patients receiving a series of weekly injections of 50 mg. of gold (100 mg. myochrysine) with total doses of 500-800 mg. gold, were examined at intervals after discontinuing gold injections and were found to have gold in the urine from 6 to 10 months later (6 cases). If the weekly dose of gold was 25 mg. (50 mg. myochrysine) the gold was found in the urine for somewhat shorter periods and with 12.5 mgm. gold (25 mg. myochrysine) the gold in the urine was not present after a month with 1 patient. Gold similarly was found in blood plasma for a period of time after discontinuing, in proportion to the doses given.

They also found that gold is not concentrated in synovial fluid but is found in an amount equivalent to or less than that found in the blood plasma.

In considering the frequent toxic effects of gold therapy it is important to appreciate that gold is retained in body tissues for a long period of time. If crystalline gold salts are given in large doses they may be excreted very slowly and largely in the urine. Gold given as a crystalline water soluble salt has been estimated as 75-80 per cent excreted in the urine.

Hartung and Cotter have recently studied the effect of gold sodium thiomalate (myochrysine) administration on the bacteriostatic properties of the serum in patients with rheumatoid arthritis. The organism used was a beta hemolytic streptococcus (strain Greene) isolated from an acute mastoid infection. The serum from patients with rheumatoid arthritis, before and after receiving from 60 mg. to 92 mg. of gold sodium thiomalate in divided doses, was found to show a marked increase in the bacteriostatic power against this organism after receiving gold. The bacteriostatic effects were in rough proportion to the dose of gold sodium thiomalate given, the maximum effect being attained after 147 to 155 mg. had been administered. The bacteriostasis disappeared after stopping the administration for 3 to 6 months. Colloidal gold, as given, and bismuth were found to have no significant bacteriostatic effect. Gold sodium thiomalate was also found to be bacteriocidal in vitro against streptococcus hemolytic strain grain in dilutions through .000001 per cent and bacteriostatic in higher dilutions. This was also true with other common laboratory organisms and was roughly in proportion to the concentration of gold salt.

The Toxic Manifestations of Gold Therapy

Nearly all publications concerning gold therapy have dealt with the toxic manifestations as much as with the therapeutic effectiveness. These toxic effects are many and varied and offer a serious objection to the clinical use of gold therapy. Hartfall, Garland, and Goldie reported toxic reactions in 41.9 per cent of 900 patients treated with gold salts. They reported 7 deaths in this series in which gold was considered as the principal cause (.78 per cent). These consisted of 3 cases of purpura, 1 of agranulocytosis, 2 of subacute necrosis of the liver, and 1 of exfoliative dermatitis. Sundelin has published a thorough review of the literature concerning the reactions from gold therapy as well as a careful study of 730 patients treated by him. In this group he noticed toxic reactions in 39.9 per cent of the men and

in 58.2 per cent of the women. He reported 6 deaths, 5 frm purpura hemorrhagica, 2 from encephalitis and 1 from bronchopneumonia. Various gold preparations have been tried but apparently have shown little difference in toxicity if the same gold content is given. Sabin and Warren have reported on the use of gold calcium thiomalate. In mice it seemed more effective and less toxic and is undergoing clinical trial in man at this time. Calcium salts and vitamine C have been tried in conjunction with gold therapy although there is little positive evidence that their use has reduced the toxic effects.

A more detailed discussion of the various toxic reactions to gold will be included in the report of our own experiences with reactions.

Clinical Analysis of the Treatment of Patients with Gold Salts

Our experience with gold salts in the treatment of chronic rheumatoid disease extends over the past 2 years and the treatment of more than 100 patients. Of this group, 74 have received at least 10 injections or were discontinued sooner because of toxic reactions, and were subjected to clinical analysis.

The form of gold salt that we have used has been almost entirely gold sodium thiomalate (myochrysine, Merck). There is probably little difference in using this and other of the available water soluble gold salts if used in dosage of comparable gold content. The dose that we have used, 25 milligrams (12.5 milligrams gold content), would be considered small according to the usual doses given by European and British authors. The planned routine has been to give 20 injections of 25 mg. of myochrysine at 1 week intervals and to then allow a rest period of 2 months and repeat a similar course of therapy or in some instances a smaller number of injections. In some instances we have given as much as 50 milligrams in some of the later doses although we believe now that the dose of 25 milligrams may be preferable. Following the second course of treatment we have usually given a rest period of from 2 to 6 months depending on the clinical response and have then given further shorter courses of gold therapy 8-10 weekly injections of 25 milligrams as seems clinically indicated. Few of our patients have yet received more than the second course of gold. Regardless of any fixed plan of therapy there are many minor or questionable toxic reactions that seem cause for temporarily postponing gold therapy and obviously altering any set plan. Some of these reactions are such as a sudden drop in hemoglobin or in the leucocyte count, bladder irritation, mild stomatitis, marked pruritus, etc. The estimation of the significance of these minor reactions is important and calls for close observation of the patient with temporary or permanent interruption of treatment. We have adopted a conservative course and have interrupted treatment at least temporarily when such symptoms have appeared. All patients have had a sedimentation rate, hemoglobin, white blood count and urinalysis prior to treatment and have had a hemoglobin and white blood count prior to each successive gold treatment. The urinalysis is also followed at times, and a platelet count should be taken if there seems any indication.

The selection of patients to receive gold therapy is an individual problem. We have selected in this series, only patients with long standing serious rheumatoid disease. While doubting the advisability of attempting to place all individuals with clinical chronic arthritis into distinct classes, the patients treated in this series could all be termed as having rheumatoid arthritis. They had been under observation for some time, many for several years or more and had nearly all received a thorough trial of intravenous streptococcic vaccine with inadequate or no clinical improvement. Nearly all had very rapid sedimentation rates. All had some significant destructive joint changes as well as evidence of an active disease process and a number were seriously crippled. The dangers of gold therapy were emphasized to them and each agreed to assume the risks of treatment. Treatment seems contraindicated in pregnancy, nephritis,

known liver disease, purpura, and in other conditions that would seem likely to be aggravated by gold. It is also said to be inadvisable to treat diabetic patients with gold.

Clinical improvement was estimated on the basis of subjective improvement and also of such objective findings as less joint swelling, greater motility of joints and the ability of patients to do more than before. Sedimentation rates were taken on patients before and after gold therapy and in general there was a lowering of the sedimentation rate; however, this was not always true even with marked obvious improvement at times. The sedimentation rate is of interest but is by no means a reliable guide of improvement in many cases. In chronic rheumatoid disease the estimation of clinical improvement because of any specific therapy is difficult. In a previous blindfold control series studied who received intravenous streptococcic vaccine and sterile saline solution we reported apparent improvement in 50 per cent of those receiving sterile saline as compared with 82 per cent of those receiving vaccine. Many of the patients in that group had less severe disease and were not followed here previously with other therapy. There would be few if any in the group receiving gold that would have shown apparent improvement on saline solution. A similar group of severely involved patients have been treated with other methods with the following results.

Table 1
Other Therapy on Patients with Severe "Rheumatoid Arthritis"

Method of Therapy	No. Treated	Improved	Unimproved
Colloidal sulfur	35	0	35
Chaulmoogra oil	25	3	22
Vitamine D (200,000-300,000 units per day)	17	1	16
Bee venom	13	1	12

The essential negative results from such methods furnish a control group for our series receiving gold therapy.

Table 2
Clinical Results of Gold Salt Therapy

	Number	Per Cent
Marked Improvement	19	25.7
Moderate Improvement	26	35.1
Slight Improvement	10	13.5
No Improvement	19	25.7
Total	74	100.0

An improvement in 75 per cent of a series of patients with severe rheumatoid disease under long previous observation seems significant to us of the efficacy of gold therapy. Obviously the degree of improvement in such cases is limited by the amount of permanent damage present. This improvement is maintained for a variable period after therapy, in some apparently remaining for a long time and in many others subsiding within 1 to 4 months after discontinuing gold. The follow-up therapy is important at least for a second course of gold and probably for further courses as indicated by the clinical response.

Reactions

Unfortunately there are many undesirable and at times serious toxic effects from gold therapy as have been previously mentioned. In our experience there was some type of toxic reaction in 50 per cent of the 74 patients who received adequate treatment. It is of interest that using relatively much smaller doses than reported by many others, we still had about as high an incidence of reactions. It is probable however that these reactions were in general of a less serious nature. There are numerous deaths reported in the literature ascribed to gold therapy. In our experience here we had no deaths due to gold although 2 died while under treatment (1 from repeated coronary thrombosis and 1 from appendicitis with peritonitis).

Table 3

Toxic Reactions

	No. of Cases	Number with re-actions	Per Cent with re-actions
Men	28	9	32.1
Women	46	28	63.4
Total	74	37	50.0

Many reactions reported by us were minimal, however it is difficult to tell when a minimal reaction may be the forerunner of a serious reaction, if gold injections are continued. We have frequently interrupted therapy for a few weeks to several months because of such manifestations as a sudden drop in hemoglobin or the leucocyte count, minimal or questionable dermatitis, pruritus or bladder irritation.

In our experience there was a significant increased incidence of toxic reactions in women as compared with men (about twice as frequent in women). These reactions were also relatively more serious in the women. This may be partly explained by using similar doses for all patients regardless of weight, however that alone hardly seems to explain this striking difference.

Table 4

Reactions - Men - 9 cases -- 10 types of reactions

Skin	Mucous Membranes	Gastro-int. Tract	Urinary Tract	Blood	Resp. Tract	Nervous System	Immediate
Slight Dermatitis	Stomatitis	-	-	Hbg. Drop	-	-	-
Slight Dermatitis	-	-	-	Hbg. Drop	-	-	-
Chronic Dermatitis	-	-	-	Hbg. Drop	-	-	-
Pruritus	-	-	-	Hbg. Drop	-	-	-
				Purpura (no thrombopenia)			

Table 5

Reactions - Women - 28 cases -- 42 types of reactions

(In a series of 46 women)

Skin	Mucous Membranes	Gastro-Int. Tract.	Urinary Tract	Blood	Resp. Tract	Nervous System	Immediate
I. Exfoliative Dermatitis	Stomatitis	Diarrhea	Bladder irritability	Leucopenia & Hbg. drop	-	Mental disorient-ation	Vasomotor flushing
2. " "	"	"	"	"	-	"	"
3. " "	"	"	Drop serum albumen, edema feet	"	-	-	"
4. " (with alopecia)	-	-	BUN 54	Leucopenia	-	-	-
5. Dermatitis	-	-	-	"	-	-	-
6. "	-	-	-	"	-	-	-
7. "	-	-	-	"	-	-	-
8. "	-	-	-	Hbg. drop	-	-	-
9. "	-	-	-	"	-	-	-
10. "	-	-	-	Purpura (no thrombopenia)	-	-	-
11. "	-	-	-	"	-	-	-
12. "							
13. Pruritus							
14. "							
15. "							
16. "							
17. "							

This difference was further borne out when it was found that in 15 cases we discontinued treatment because of reactions in women and in no instance for the men.

The detailed reasons for permanently discontinuing treatment are given in Table 6.

Table 6

Reasons for Discontinuing Gold Therapy (15 cases)

	Sex	No. of injections	Milligrams Myochrysine	Improvement	
1.	F	13	325	++	Recurrent stomatitis, pruritus, and hbg. drop.
2.	F	18	450	-	Persistent diarrhea, duration several months.
3.	F	6	150	-	Stomatitis, exfoliative dermatitis 5-6 months duration.
4.	F	2	50	-	Hbg. drop 66-47 and wbc. 6100 to 2800.
5.	F	19	475	+++	Dermatitis.
6.	F	25	625	++	Stopped after 5, second course, dermatitis.
7.	F	15	375	-	Severe persistent pruritus.
8.	F	6	150	-	Purpura (no thrombopenia).
9.	F	4	100	+++	Severe dermatitis.
10.	F	16	625	++	Purpura (no thrombopenia).
11.	F	11	275	++	Exfoliative dermatitis and diarrhea.
12.	F	3	150	+++	Exfoliative dermatitis, hbg. drop, wbc drop to 2400.
13.	F	7	175	++	Exfoliative dermatitis and alopecia.
14.	F	12	475	-	Severe dermatitis with pigmentation.
15.	F	22	725	-	After 10 injections 2nd course persistent diarrhea and severe mental disorientation.

(Improvement: +++ Marked, ++ Moderate, + Slight, - None)

It is difficult to explain the exact basis for toxic reactions. Consideration has been given to the possibility of toxic effect alone or of gold sensitivity. There is certainly a wide range in the manner in which gold affects different people. An individual may also go through one extensive course of gold therapy without reaction and in some instances have a severe reaction in a second course given several months later. We have also seen some delayed reactions coming on several weeks or months after treatment is ended. One patient who received 12 intravenous injections of gold thiosulphate from another physician, developed an exfoliative dermatitis after consulting us four months after receiving gold salt therapy There is a report of a patient who received colloidal gold injections developing a severe stomatitis two years later. The reactions reported by others and observed by us can be classified in groups as follows:

1. Immediate Reactions. These may vary also, perhaps the most frequent being a sensation of body warmth, paresthesias, and flushings of the skin. This is the only type of immediate reaction seen by us and present in 4 cases. Urticaria and marked edema may develop in local tissues as in the skin, larynx, or lungs. Occasionally an anaphylactoid reaction has been reported with clinical

shock, weak or imperceptible pulse and unconsciousness, such as is occasionally seen following liver injections.

2. Focal Reaction. This refers to an exacerbation of joint pain and swelling and is said by some to be a favorable sign of the probable effectiveness of gold therapy. We have seen few or no such reactions in our experience, and in view of the variations in joint symptoms from time to time would consider such symptoms as difficult to interpret.

3. Febrile Reactions. These have been described by some as occurring quite frequently. Sundelin reported fever at some time in 12.6% of the courses of gold therapy. Febrile reactions have been minimal and infrequent in our experience, perhaps due to the smaller doses of gold given.

4. Skin and Mucous Membrane Reactions. These reactions are more frequently seen than any other type. Pruritus is very often seen and may occur alone or be the forerunner of a dermatitis. Skin reactions may be of varied types. Urticaria are occasionally seen and erythematous reactions either transitory or more persistent are not uncommon. Lesions may be either discrete or confluent and often appear over the extremities and may be over the entire body. Exfoliative reactions of various severity are not uncommon and may persist over a long period of time. Four patients in our series had an exfoliative dermatitis. Alopecia may be associated and was present in 1 case in our group. At times pigmentation may persist after subsidence of the active phase of dermatitis and we have 1 patient with a marked pigmentation in discrete areas previously involved with red scaling lesions. We have considered a severe dermatitis either with or without exfoliation, as a reason for permanently discontinuing gold treatment. Stomatitis, glossitis and gingivitis are less often seen although we have had 4 cases of stomatitis in our series which were of moderate severity. Lesions of the vulvae and about the rectum have been described.

5. Blood Reactions. Next in frequency after skin reactions are blood reactions. These may assume several serious forms and are the most frequent fatal manifestations of gold toxicity. Significant rapid drops in hemoglobin are often seen and were seen by us in 9 patients. This was seldom alone a basis for stopping gold but was often a cause of interruption of the treatment. Giving ferrous chloride seemed of distinct value in these cases. Aplastic anemia following gold therapy has been reported. A significant sudden drop in the white blood cell count is often seen with gold therapy and was present in 6 of our cases to a level of 3,000 or below. Agranulocytosis has been reported quite frequently and cited as the cause of death in a number of cases (Sundelin 21 cases literature). None of our cases had a true agranulocytosis and we were able to continue treatment in most cases after an interruption of several weeks. In the case of one girl with a sudden drop of hbg. from 66% - 44% and of the wbc to 2800 after but 2 injections of a total of 50 milligrams of myochrysine, we considered it inadvisable to treat further. Purpura is a common serious toxic effect from gold. We have observed moderate clinical purpuric reactions in 3 cases and in none of these was thrombopenia present. There are many cases reported in the literature of thrombopenic purpura associated with gold therapy. Sundelin reported 24 deaths from the literature ascribed to purpuric reactions in patients receiving gold treatment for all types of diseases (tuberculosis, arthritis, skin diseases, etc.). Eosinophilia is not uncommon following gold therapy.

6. Gastro-Intestinal and Liver Reactions. The most common symptom of a gastro-intestinal reaction is diarrhea. This may be persistent and difficult to control. A diarrhea persisting from 4-8 weeks was present in 5 of our cases. There are reports of gross bleeding from the gastro-intestinal tract. Liver damage with jaundice clinically similar to catarrhal jaundice is reported as one of the serious reactions present. Hartfall, Garland and Goldie reported jaundice in 9.4 per cent of 900 patients treated with gold salts. They reported 2 deaths due to liver necrosis. Their experience with jaundice is much more fre-

quent than that of other authors and is difficult to account for. We have experienced no jaundice in over 100 cases treated to date.

7. Urinary Tract Reactions. Albuminuria is reported as an occasional but infrequent occurrence with gold therapy. There have been some reports of more serious complications, such as suggesting a nephritis, although such findings may have been coincidental. A few of our patients have had a transitory albuminuria of small amount. In 3 cases there were symptoms of persistent urinary burning urgency and frequency. These patients had no albuminuria but had some increase in red and white blood cells in the urinary sediment. One patient developed severe edema of the ankles, a lowered blood serum albumen, and a transitory elevation of blood nitrogen to 54 milligrams per cent.

Respiratory Reactions. These are mentioned as bronchitis and in some cases as an inciting factor in bronchopneumonia. Edema of the larynx has also been reported. We have encountered no respiratory symptoms ascribable to gold therapy.

Nervous System Reactions. These are reported as being relatively infrequent. There have been some cases reported of peripheral neuritis due to gold and some of gold encephalitis with death. Two patients in our experience had marked mental confusion and disorientation which may have been due to gold therapy. In 1 case this came on 6 weeks after a course of gold and with an accompanying dermatitis. In the other case there was a persistent diarrhea.

The Prevention and Treatment of Complications from Gold Therapy

Several methods have been employed to reduce the number of toxic reactions from gold and to arrest toxic manifestations after they are present. The two most popularly used are: (1) the use of calcium salts, and (2) the use of cevitamic acid. While these methods are still advocated by many, there is little information confirming their definite value. The treatment otherwise is supportive treatment to meet each type of reaction present.

Summary

The paraenteral use of water soluble gold salts is apparently of clinical value in the treatment of chronic rheumatoid disease. It is probably more effective in producing clinical improvement than any treatment in use at this time. (75 per cent improved in our series of patients who had received other therapy prior to gold salts).

It is not effective in all cases nor does it usually bring about permanent cure in patients with a well established disease process.

The exact optimal method of use, as to dosage, length of treatment, and number of courses to be given, is not yet established; and probably varies with different patients.

There are many mild, moderate, and severe toxic reactions from gold, that may occur regardless of the technic employed (50 per cent in our series). There is some definite danger to life in its use which is probably greater when using larger doses. We have as yet had no deaths due to gold in more than 100 patients treated. Toxic reactions have been more frequent in women than in men (63.4 per cent of the women, 32.1 per cent of the men). They have also been more severe in women than men in our experience. Treatment was permanently discontinued in 15 women and in no men in our series.

We have most frequently used a dose of 25 milligrams of gold sodium thiomalate (12.5 mg. gold) and given 20 such intramuscular injections at 1 week intervals in the first course. Treatment has been frequently interrupted and at times discontinued because of toxic manifestations. We have usually given a second course of 10-20 weekly injections after a 2 month rest interval, and further courses as seemed indicated in each case.

In patients with less severe [illegible]

toid disease, we prefer to use intravenous streptococcic vaccine which seems frequently effective and not dangerous to use. In some patients we have combined the use of intravenous streptococcic vaccine and gold salts.

Patients with severe active rheumatoid involvement with destructive changes or in serious danger of crippling were given gold salts under these circumstances.

1. They have first been given an adequate trial of intravenous streptococcic vaccine with either no improvement or moderate improvement.

2. The dangers of gold therapy are explained to the patient who is willing to assume the risk of toxic reactions.

3. There is no obvious condition present which would contraindicate treatment.

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V. PROGRAM OF CLINICS

American College of Physicians

Tuesday, April 21, 1942

Todd Amphitheatre, University Hospitals

9:00 - 9:40 Effects of Emotion on Digestive Processes.
James E. Paullin, Atlanta, Ga.

9:50 - 10:30 Hodgkin's Disease.
Ernest H. Falconer, San Francisco, Calif.

10:40 - 11:20 Undulant Fever.
Wesley W. Spink.

15 Medical Science Building

9:00 - 9:40 Adrenal and Pituitary Diseases.
David P. Barr, New York, N. Y.

9:50 - 10:30 Allergy.
A. H. Hoge, Bluefield, W. Va.

10:40 - 11:20 Nephritis.
Edwin G. Bannick, Seattle, Wash.

Wednesday, April 22, 1942

Todd Amphitheatre

9:00 - 9:40 Acute Porphyria.
Cecil J. Watson.

9:50 - 10:30 Osteogenesis Imperfecta.
Charles T. Stone, Galveston, Tex.

10:40 - 11:20 Gastro-enterology and Gastroscopy.
J. B. Carey.

15 Medical Science Building

9:00 - 9:40 Cardiovascular Disease (In an Elderly Patient).
Reginald Fitz, Boston, Mass.

9:50 - 10:30 Cardiovascular-renal Disease.
George Morris Forsel, Philadelphia, Pa.

10:40 - 11:20 Polycythemia Vera.
Moses Barron.

Thursday, April 23, 1942

Todd Amphitheatre, University Hospitals

9:00 - 9:40 Obesity and Menstrual Irregularity.
Elmer L. Sevringhaus, Madison, Wis.

9:50 - 10:30 Pancreatic and Adrenal Diseases.
E. H. Rynearson, Rochester, Minn.

10:40 - 11:20 Electrocardiographic Changes in Acute Coronary Disease.
Olga S. Hansen.

Medical Science Building, Amphitheatre (Room 15)

9:00 - 9:40 Adrenal Disease, Relative Insufficiency.
Jonathan C. Meakins, Montreal, Que.

9:50 - 10:30 Chronic Pulmonary Heart Disease.
Philip Hallock.

10:40 - 11:20 Hypertensive Vascular Disease in Relation to Pregnancy.
John L. McKelvey.

Friday, April 24, 1942

Todd Amphitheatre

9:00 - 9:40 Acute Infections.
Francis G. Blake, New Haven, Conn.

9:50 - 10:30 Cardiac Clinic.
S. Marx White.

10:40 - 11:20 Convulsive Orders of Childhood.
Irvine McQuarrie.

Medical Science Building, Amphitheatre (Room 15)

9:00 - 9:40 Coronary Heart Disease.
William D. Stroud, Philadelphia, Pa.

9:50 - 10:30 Congenital Heart Disease.
M. J. Shapiro.

10:40 - 11:20 Duodenal Ulcer.
Owen H. Wangensteen.

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