well, as it was the second to the last of any Allied ships to go in.

The crew of our ship was partly British and partly Australian. They served sandwiches and tea to us and I think it was, without doubt, the best meal any of us ever had or ever will have. Dawn found me sleeping in the chief engineer's cabin, which was just below the high angle gun. It was pumping away for all it was worth. We were under attack again. After two near misses for us, and a lot of broken crockery for the *Nizam*, we finally reached Alexandria. All I had left to remember Crete by was a flood of memories, a pair of shorts, a pair of shoes and a cap—just what I was wearing.

GOLD THERAPY IN RHEUMATOID ARTHRITIS*

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WHEN to advise gold therapy for rheumatoid arthritis continues to be a problem for those concerned with the management of this disease. Many believe it to be the most effective single measure now available, while others feel that, because of the serious intolerance to gold shown by many arthritic patients, its use is largely contraindicated. It is not a new drug: its antibacterial properties were demonstrated by Feldt as early as 1914, and in 1924 its use in the treatment of pulmonary tuberculosis was reported by Mollgaard. Reports of the value of gold salts in rheumatoid arthritis appeared in the European literature in 1927, and in 1935 Forestier[1] published an analysis of some 550 treated cases.

By this time an extensive literature in France, Germany and the Scandinavian countries indicated considerable experience with gold therapy. Forestier stated that between 70 and 80% of his cases responded favourably to treatment; 50% of recent cases and 20 to 30% of cases of two or more years' duration apparently were cured. He described the toxic reactions observed in his series of cases and discussed their recognition and prevention. He was among the first to emphasize the significance of the erythrocyte sedimentation rate as an indication both for beginning and for maintaining treatment with gold.

In England reports on treatment of rheumatoid arthritis with gold salts began to appear in 1935. Two years later Hartfall, Garland and Goldie[2] reported their investigations on 900 cases of arthritis, 750 of them being cases of rheumatoid arthritis. Apparent cure or striking improvement occurred in 80% of the cases of rheumatoid arthritis. However, their mortality rate was disturbing: deaths apparently due to the administration of gold were 0.78% as a minimum and 1.1% as a maximum, according to the interpretation of deaths of uncertain origin. Subsequently, Ellman, Lawrence and Thorold[3] carried out a series of carefully controlled observations and provided definite evidence of the beneficial effect of gold salts upon the course of rheumatoid arthritis. Further, they showed that both the efficacy and the toxicity of the drug varied directly with the amount administered.

In the United States gold therapy was viewed with scepticism for some years but recently many investigators have reported favourable results in the treatment of rheumatoid (atrophic) arthritis with gold salts. In 1939 Key and his associates[4] expressed the opinion that gold therapy definitely ameliorates the course of the disease in the majority of cases. Cecil, Kammerer, and de Prume,[5] in 1941 reviewed their studies of 235 patients; 66% of this series showed remission or great improvement and another 19% were moderately improved. They concluded that gold is the best single agent for the treatment of rheumatoid arthritis, but that it is a dangerous drug. Similar views were expressed by Dawson, Boots and Tyson[6] in their report of 100 cases treated at the Presbyterian Hospital, New York.

In Canada, Bagnall[7] expressed his encouragement after two years' experience, when he opened a discussion on aurotherapy before the Canadian Rheumatic Disease Association. He reserves its use largely for the more severe and stubborn cases.

Since 1938 gold salts have been in continuous use for the treatment of rheumatoid arthritis at the Toronto General Hospital, and the present report comprises a study of the first 100 cases

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in which this measure was undertaken.* The series includes a few ambulatory cases, but the majority were patients admitted to hospital suffering from arthritis of more than average severity, most of them presenting a picture of active and advanced multiple joint involvement.

METHOD OF TREATMENT

An attempt was made to provide some measure of medical care and protection to all patients during treatment and for some time afterwards. As most of the patients were in hospital, opportunity was provided to study each case and observe the reaction to bed rest and institutional supervision. Early recognition of toxic reactions was much facilitated and, we believe, the susceptibility to relapse was substantially less if the patient went on to a fair convalescence before discharge from hospital.

All patients were treated with gold sodium thiomalate (myochrysine), an aqueous solution containing 50% metallic gold, which was injected intramuscularly. Two small initial doses were given, a week apart, to detect idiosyncrasy: the first dose was 0.01 grm.; the second, 0.05 grm. Following these preliminary injections, doses of 0.10 grm. were given at intervals of one week for ten weeks. This constituted a course of treatment. Decision as to further courses of treatment depended upon the clinical result and the sedimentation rate. Two or even three courses of gold treatment are sometimes required to ensure maximum benefit, but before commencing a second or third course a rest period of six to twelve weeks should be allowed as the metal is excreted very slowly.

In our series a few patients received 2.0 grm. of gold over a period of eleven weeks, but the majority were given 1.06 grm. according to the schedule outlined above. A study of the results obtained by the larger dosage did not appear to warrant the additional risk involved.

TOXIC REACTIONS

It is unfortunate that the toxic dose of gold appears to be very close to the effective therapeutic dose. It is probable that there is no drug in use today which causes such a high incidence of toxic manifestations. Our experience has been similar to that of other observers who report some complication in over 50% of their patients. Although the majority are mild, very severe and even fatal reactions do occur. There were no deaths in our series.

Toxic manifestations involving the mucous membranes, skin, gastrointestinal tract, kidneys, hæmatopoietic and central nervous systems, occurred in 54% of our cases (Table I). It would appear that reactions are most likely to occur during the first half of the course of treatment and, in some cases, as early as the second or third dose.

TABLE I.

TOXIC MANIFESTATIONS FOLLOWING THE USE OF MYOCHRYSINE IN 100 CASES OF RHEUMATOID ARTHRITIS

	No. of cases
Skin (minor reaction)	19
Mucous membranes	13
Gastrointestinal	11
Joints	8
Kidney	7
Blood	4
Skin (major reaction)	4
Central nervous system	4

Skin reactions vary considerably from mild to very severe. Pruritus, mild erythemas, and more discrete maculopapular eruptions which sometimes desquamate are minor reactions which clear rapidly when treatment is discontinued. Major skin reactions were the most serious toxic manifestations encountered in our series. Four patients developed a severe, exfoliating type of dermatitis, one with marked œdema of the lower extremities. Such severe reactions gave us much concern, but in these cases dramatic quiescence of the arthritic process was usually observed.

Mucous membrane.—Small areas of ulceration may occur on the lips, buccal mucous membrane, under the tongue or under dentures. In two cases these lesions were sufficiently painful to make mastication almost impossible for a period of two weeks. The patient may complain only of a burning or sore mouth without ulceration, which is sufficient warning to discontinue the drug immediately. One of our patients developed a similar type of ulceration in the vaginal mucous membrane. If the gold is stopped when these lesions appear, they clear rapidly and often do not recur when the treatment is resumed.

Gastrointestinal symptoms occurred frequently but were not serious. Loss of appetite, nausea, vomiting and diarrhœa were all observed and some patients complained of epigastric pain.

* A report on Gold Therapy in Chronic Arthritis presented by A. A. Fletcher and J. W. Graham at the Annual Meeting of the Canadian Medical Association, Winnipeg, June, 1941, reviewed the treatment of the first 60 cases of this series.

There were no cases of jaundice but in four instances urobilin was found in the urine.

Joint reactions of pain, and sometimes swelling, occurred in eight cases with each injection of gold and lasted for twenty-four to forty-eight hours. Treatment was not discontinued.

Kidneys.—The presence of occasional traces of albumin in the urine was not considered of sufficient import to include these cases in the toxic kidney reactions cited in Table I. It would appear to be safe to continue treatment in the presence of a *trace* of albumin, but the patient should be kept under careful observation, as this finding may signal the onset of true nephritis. In seven cases, albumin, red blood cells or casts were found and treatment was discontinued. The urine cleared within a few weeks.

Blood changes in our patients were limited to a decrease in white blood cells. In four cases the treatment was discontinued when the white blood count fell to approximately 2,000. The average initial hæmoglobin content in this series was 71% and in the majority of cases the hæmoglobin rose during treatment. None of the patients developed hæmorrhagic complications. Platelet counts were not done, but other observers have reported a considerable decrease during gold therapy. It has been reported that a single dose of 10 mgm. reduced the circulating platelets 50% in two to four days. Aplastic anæmia, a reaction which has been reported by others, was not observed in our cases.

Central nervous system.—Four patients developed symptoms related to the central nervous system: one, a central scotoma with blurring of vision which cleared in three months; the other three developed loss of taste (quinine, salt and sugar) and the sense of smell was also impaired.

Although the incidence of toxic reactions is high, it must be remembered that few of these reactions are alarming. It must also be borne in mind that rheumatoid arthritis runs a tragic course and that there is justification for using treatment which is associated with some danger. However, wide general use of this drug cannot be advocated unless the physician is prepared to observe every precaution.

PRECAUTIONS

It is wise to explain to each patient that gold therapy is not infallible and that severe reactions may occur. There is no certain method of preventing toxic reactions, but their severity may be moderated by early recognition and immediate cessation of gold administration. The urine and blood must be examined frequently. In this series a urinalysis, white blood count, and sedimentation rate (Westegren) were done each week in the hospital cases. The blood examination was done every second week in ambulatory cases.

Further precautionary measures include the initial administration of small doses of the drug to detect idiosyncrasy, the use of an aqueous solution of gold salt, and questioning of the patient each week in regard to skin and other manifestations. Unless specific questions are asked, the patient, in his ignorance of possible consequences, may fail to report minor symptoms which might progress seriously with continued treatment.

There are few contraindications to the use of gold therapy, but diseases of the skin, kidney and liver disorders, and pregnancy should be mentioned.

RESULTS

This series has been classified, according to the results of treatment, in five groups (Table II). Because of toxic reactions, 5 of the 100 patients received only a few doses of gold and, therefore, are not included in the results of treatment. The majority of the remaining 95 patients received only one course of 12 injections. A few received two or three courses.

TABLE II.
RESULTS OF TREATMENT OF 95 CASES OF RHEUMATOID ARTHRITIS WITH AQUEOUS MYOCHRYSINE

Result	*Cases* *Number*	*Percentage*	
Remission (apparent inactivity of arthritis)	15	16	67%
Very much improved	49	51	
Improved	19	20	
No improvement	12	13	
Worse	0	0	

A good result appeared to be definitely related to a fall in sedimentation rate. This fall occurred in the great majority of cases in our series. The average initial sedimentation rate in the 95 cases was 66; the average rate after completion of one course of treatment was 34.

An analysis of the clinical results in relation to the sedimentation rate is shown in Table III. It will be noted that in cases showing recovery or remission of the arthritic process the high initial sedimentation rate fell to a normal level, whereas in cases showing a lesser degree of benefit the fall in sedimentation rate was less marked, and when little or no clinical improve-

TABLE III.

RELATION OF IMPROVEMENT TO FALL IN BLOOD SEDIMENTATION RATE

Result	Sedimentation rate Average initial	Average final
Remission	52	14
Very much improved	64	28
Improved	55	39
No improvement	76	73

ment occurred the initial sedimentation rate was not appreciably altered.

There is some evidence that advanced age diminishes the probability of improvement but this has not been shown in all reports. Snyder[8] found age no contraindication to gold therapy; in fact, his group over 40 years of age responded better than a group of younger patients. In our series best results were obtained in the younger group and in cases of short duration, but gold can be effective even late in the course of the disease (Table IV).

TABLE IV.

RELATION OF IMPROVEMENT TO AGE AND DURATION OF THE ARTHRITIS

Result of treatment	Average age years	Average duration of arthritis years
Remission	33	2
Very much improved	42	7
Improved	37	9
No improvement	49	8

Eight patients with Strümpell-Marie (ankylosing) spondylitis were given one course of treatment with no beneficial results. Here again, as an indication of failure, the sedimentation rate failed to show any significant change. The average initial sedimentation rate in these eight patients was 59, and the average final rate was 62.

MODE OF ACTION

The mechanism of gold therapy has not been adequately explained. Feldt[9] suggested an action upon the reticulo-endothelial system. By others it has been regarded as a chemotherapeutic agent. When injected into experimental animals, the salt is bacteriostatic for hæmolytic streptococci. Dawson and Hobby[10] were able to protect mice against 1,000 lethal doses. According to Hartung[11] the serum of patients under treatment retains increased bacteriostatic power for many months. More significant perhaps are the studies of Findlay, Mackenzie and MacCallum[12] and Sabin and Warren[13] on the arthritis of mice due to a pleuropneumonia-like organism. Sabin and Warren state that, with adequate dosage, gold is curative in almost 100% of animals.

In the metabolism investigations of Freyberg, Block and Buchanan,[14] the metal was demonstrated in the plasma of treated patients at levels roughly proportional to the amount given. No concentration of the salt was found in the synovial fluid, the amount being approximately the same as in the plasma, and excretion was largely by way of the kidney. Specially noteworthy was their statement that traces of gold may be detected in the urine up to thirteen months after the last injection.

DISCUSSION

In general the results of gold therapy in our cases of rheumatoid arthritis have been good, in some cases, dramatic, and we feel that a valuable addition has been made to the treatment of this disease. The incidence of toxic reactions and their occasional severe character are serious considerations, but they are scarcely comparable to the grim prognosis of polyarthritis which is taking a downward course. When arthritis conforms to the classical picture of chronic, progressive, multiple (atrophic) arthritis, in most cases gold will materially shorten the duration and moderate the severity of the active and crippling stage of the disease. In milder cases it would seem advisable to employ first all the usual measures of medical care. In any case, the drug should be regarded not as a cure, but rather as a check to the reactions that are manifest in joint disorders.

There is no justification for the use of gold in any rheumatic or joint affection other than rheumatoid arthritis. It is of no value in the treatment of the various forms of fibrositis, myositis, neuritis, rheumatic fever, gout, the so-called menopausal arthritis or osteoarthritis. Other measures, which are highly efficient, are available for the treatment of gonococcal arthritis; for this reason, in certain cases a careful differential diagnosis should be made. Cases of Strümpell-Marie spondylitis in this series did not respond favourably to gold therapy; this is consistent with the reports of other investigators.

Emphasis has been laid upon the significance of the erythrocyte sedimentation test, which appears to be the most sensitive index of progress, and should influence decision as to when treatment should be commenced or resumed. Untreated cases with a normal sedimentation rate are likely quiescent, and in those with deformity and disability the disease has probably reached an end or burnt-out stage. It would seem unwise to start gold therapy in any such case. A raised

sedimentation rate, however, is met with in many forms of arthritis and is not necessarily an indication for this method of treatment. Ellman, Lawrence and Thorold[3] pointed out that 96% of their reactions occurred in the presence of a normal sedimentation rate and they advise discontinuing gold administration when the rate reaches a normal level. We have noted this tendency to reactions when the rate is low but, on the other hand, have seen many toxic phenomena with high sedimentation levels.

The high toxicity of gold salts remains a serious obstacle to their general clinical introduction. Unconfirmed claims of low toxicity have been made for new preparations which usually prove deficient in clinical value. This has led to the suggestion that toxic reactions and anti-arthritic effects of gold are both parts of the same mechanism and are not likely to be found independently. Copeman and Tegner[15] have pointed out that, while complications are not essential to success, "in those cases in which severe toxic symptoms supervened a great improvement in the arthritis resulted subsequently". In our cases it has been especially true that those who suffered from severe dermatitis almost always underwent striking improvement in their joint lesions and felt no undue regret over this distressing experience. Frequently, however, remissions set in without any toxic complications. Every effort should be made to prevent the occurrence and gravity of reactions by careful adjustment of dosage and by prompt recognition of early symptoms.

From reports made in recent years it would appear that fatal complications are becoming much less frequent, but the possibility of their occurrence cannot be ignored entirely. Cecil and his co-workers,[5] in their series of 235 cases, had one death with ulcerative enteritis, and Dawson, Boots and Tyson,[6] in a series of 100 cases, had one fatal case of aplastic anæmia and one serious reaction with nephrosis. In the series of cases reported here no fatal reactions were encountered, but one death from nephrosis and two from aplastic anæmia have come to our notice.

Disappointment has been expressed in some quarters at the high incidence of relapse after periods of marked improvement following gold therapy.[16] Cecil[5] reported a 40% incidence of relapses in 169 patients who had previously responded to treatment by showing remission, great improvement or moderate improvement, but he stated: "relapses were definitely milder than the original attack". Hartfall[2] observed that most recurrences supervene after the initial course of injections, that they usually clear up readily after a second course and do not recur. In our series there have been comparatively few relapses. The permanence of relief apparently is dependent in part upon the amount of gold administered. It has been our impression that the incidence of relapse is further reduced by continued care of the patient; rest, controlled activity, orthopædic therapy, avoidance of extremes of temperature and the maintenance of good nutrition appear to ensure a more lasting benefit.

SUMMARY

1. Of 100 cases of rheumatoid arthritis in which treatment with gold salt was undertaken, 95 received at least 1.06 grm. Of these 95 cases, 67% underwent remission or were very much improved; another 20% showed moderate improvement.

2. Fifty-four of the 100 patients showed one or more toxic manifestations, the majority of which were mild and cleared up with temporary cessation of treatment. The most severe were four cases of skin reactions with exfoliating dermatitis.

3. Gold appears to be a valuable addition to the treatment of progressive rheumatoid arthritis. The serious dangers incident to its use have been discussed.

4. Dependence was not placed on drug therapy alone. There is evidence that general medical care and protection contribute to favourable progress and lessen likelihood of relapse.

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