REVIEWS AND COMMENTARIES FROM CURRENT LITERATURE

THE ACTION OF GOLD IN THE TREATMENT OF RHEUMATOID ARTHRITIS.

SINCE Forestier first advocated the use of gold salts in the treatment of arthritis the method has rapidly grown in popularity until it has come to be regarded as the most promising method at present at our command, but a method attended with considerable risk of serious toxic effects. Reports from the clinical aspect have been numerous, but hitherto biochemical investigation has received but little attention, and the appearance of a series of articles bearing on this point deserves serious consideration.

R. H. Freyberg, Walter D. Block and S. Levey have published a preliminary report of their researches under the title "Metabolism, Toxicity and Manner of Action of Gold Compounds used in the Treatment of Arthritis" (*Journ. Clin. Inv.*, xx., 4, pp. 401-412). The fate of gold after injection, the tissues and tissue fluids affected, the route and speed of excretion, are chiefly dealt with in this report. They have used a photoelectric colorimetric micromethod specifically designed for this work by Block and Buchanan (*Journ. Biol. Chem.*, 1940, **136**, 379). The research was first directed to analysis of the blood, the urine, and the synovial fluid before and after the injection of gold salts in a series of cases of typical rheumatoid arthritis. The salts used were gold sodium thiomalate (myochrysine), gold sodium thiosulphate (*e.g.*, crisalbine, sanocrysin), and colloidal gold sulphide (aurol sulfide), the two former by the *intramuscular* route and the latter both intramuscularly and orally. The two former gave fairly uniform results, but those obtained by the use of colloidal gold were variable. The figures given throughout are the amounts of metallic gold and not of the gold salt employed.

Gold was found in the plasma in increasing amounts as the amount of gold injected increased; the course started usually with a small dose and gradually increased to 50 mg. of gold at weekly intervals. In a typical instance, after the first dose of 50 mg. given on the twenty-first day had been injected, the amount of gold in the plasma averaged about 0.8 mg., the daily values fluctuating somewhat, tending to increase after each

increase of dose; in this case the weekly dose was reduced to 25 mg. of gold, after which the average plasma content was lower and did not increase as more gold was administered.

The excretion of gold in the urine increased as larger amounts of gold were given, though the increase was not directly proportional. Excretion does not keep pace as the amount injected increases, and this retention is important. In one case when the dose of 50 mg. was reached on the twenty-first day an average of only 1 mg. was excreted daily during the week following before the next dose of 50 mg. was due on the twenty-eighth day; when the dose was reduced to 25 mg. excretion showed a definite diminution. After a course of 500 mg. in one case, the plasma contained gold for thirteen weeks after the last injection, and it was found in the urine for sixteen weeks; in other cases the urine contained gold seven, nine and ten months after the treatment ended. Fæcal analyses were done in some of the cases, and indicated that the urine was the chief route of excretion.

Five out of six cases who received large weekly doses of gold had significant toxic reactions, while none of the eight who received weekly doses of 25 mg. had any evident toxic reaction. Another type of reaction noted occasionally shortly after a dose of the drug, not necessarily a large one, was headache, flushing of the face, a sense of tightness in the throat and occasionally a purpuric dermatitis. This appeared to indicate sensitivity to gold, and when it occurs may be a warning of possibly serious effects if the treatment is continued.

When colloidal gold sulphide was used either orally or intramuscularly, the plasma and urine values varied greatly in different patients; some absorbed gold and had plasma and urinary values comparable to those obtained with the other salts studied, but most of the patients had very low plasma gold concentration and excreted little gold in the urine, even though the colloidal gold sulphide was given in amounts providing much more gold than was supplied in the crystalline forms.

Further investigations are being carried out in the endeavour to discover the tissues in which gold is deposited and also to determine, if possible, whether benefit depends upon the circulation of a certain minimal amount of gold for a minimal length of time.

Hartung, Cotter and Gannon report similar investigations which they have carried out (*Journ. Lab. and Clin. Med.*, xxvi.,

11, pp. 17-50). The method they used was that described by Pollard (1937) (*Analyst*, **62**, 597) and Jamieson and Watson (1938) (*Analyst*, **63**, 702) with some modifications. All the subjects were cases of rheumatoid arthritis, and observations were made during routine treatment with gold sodium thiomalate administered *subcutaneously*. The average dose varied from 25 mg. of gold sodium thiomalate once a week to 50 mg. every other day; results were recorded as metallic gold. In the case receiving 50 mg. of the salt (equivalent to 25 mg. gold) on alternate days, the daily excretion in the urine during the thirteen days of the observation reached a maximum of 12.83 mg.=9 per cent. roughly. The serum level during this time varied from 0.22 to 0.50 mg. per cent.; the synovial content was parallel. The amount of gold excreted in the stools in a three-day period was 0.66 mg.; in two other cases in which the faecal excretion was measured it ranged from 0.22 to 0.65 mg. per day. In another case in which 330 mg. of the gold salt had already been given observations were made during a fortnight in which 25 mg. of gold salt were given every seven days. She excreted a total of 4.35 mg. of gold, equal to 17.2 per cent. of the intake; but this proportion does not take note of the 330 mg. previously given.

Excretion was found to persist for long periods after administration had ceased. In the case which received 140 mg. of gold in thirteen days 0.01 mg. was found on the 300th day afterwards.

No excretion in the saliva was discovered in two cases in which this was investigated.

The researches are being continued.

Tarsy (*Journ. Lab. and Clin. Med.*, xxvi., 12, p. 1918), impressed with the value of gold in the treatment of arthritis and at the same time with the frequency of toxic reactions, made a search for some similar or related agent which might incorporate the beneficial therapeutic qualities of gold salts without their serious toxic effects. He and his colleagues found gold sodium thiomalate not quite so reactive as the thiosulphate, and that it could be used in larger doses, although it may be noted that the thiomalate contains 50 per cent. of metallic gold as compared with 37 per cent. in the thiosulphate. In view of the alteration in the activity of colloidal silver as compared with the salts, it was thought that colloidal gold offered definite possibilities, and

in addition colloidal platinum, colloidal bismuth and selenium were at first included in the study, but later abandoned as not giving sufficient promise of usefulness.

Colloidal gold consists of innumerable particles of metallic gold, and indications have been noted in other researches that even in very dilute solutions colloidal gold exerts a definite analgesic action. Colloids when injected into the bloodstream induce a mild shock similar to that which usually follows injection of a non-specific protein.

Thirty-six cases were treated with gold colloid, varying from early mild cases to chronic bedridden patients, and two cases of generalised fibrositis of many years' standing were included. Nineteen, or 52.7 per cent., showed definite improvement, while 9, or 25 per cent., failed to show any amelioration; these figures compared with the statistics of 1,600 cases treated with gold salts with an average marked improvement of about 54 per cent. and total lack of improvement in 13 per cent. The improvement with the colloid was rather slower in developing than with gold salts, but the two cases of fibrositis showed a quick and excellent response.

The technique was three series of injections, each series comprising 1 gm. of metallic gold, an interval of six weeks elapsing between each series. There was an almost complete lack of toxic effects. One case developed enlargement of axillary lymph glands, an effect which has also been noted after the injection of gold salts. There was an improvement in the sedimentation rate parallel with the clinical improvement. There was no evidence of any renal damage. An essential difference was the lack of any bacteriostatic action with colloidal gold contrasted with the very active bacteriostatic effect shown by the sera of patients treated with gold salts.

Study of the reticulo-endothelial system with trypan blue carried out by Kuhns and Weatherford (*Arch. Surg.*, 1936, **33**, 68) indicated that the colloid particles were deposited in the histiocytes of the synovial membrane, the bone marrow, the intermuscular septa and articular fat pads, and it is suggested that the particles of colloidal gold may be similarly deposited.

While no dramatic therapeutic claims are made, it is felt that a case has been made out for further investigation, especially in fibrositis and rheumatoid arthritis of milder types.

"The Effect of Gold Sodium Thiomalate Administration on the Bacteriostatic Properties of the Serum in Patients with Rheumatoid Arthritis" (*Journ. Lab. and Clin. Med.*, xxvi., 8, pp. 1274-84), F. Hartung and Joyce Cotter. These observers studied the bacteriostatic properties of the serum before and after the parenteral administration of gold salts, and also the effect on the agglutinin titres. The patients were cases of rheumatoid arthritis and were treated by weekly injections of 5, 10, 25, and occasionally 50 mg. doses, until a total of 1 gm. had been given. Toxic reactions were frequent—of minor degree in at least a half and of more serious character in 15 per cent.

In the research a strain of beta hæmolytic streptococcus was used; the gold salt was gold sodium thiomalate in aqueous solution administered subcutaneously. In addition, a 1 per cent. metallic gold in colloid suspension was tried, and also 10 per cent. bismuth salicylate in oil. For the technical details the original paper must be consulted, but the essential point is that the serum of patients with rheumatoid arthritis possessed no more bacteriostatic property than did controls before the injection of gold, but even after a small dose it became definitely bacteriostatic, and this property increased with the amount of gold given to a maximum which was reached after 147 to 155 mg. had been given, and did not materially increase even after many times these amounts had been administered. After gold salts had been withheld for from three to six months the bacteriostatic power was found to have been lost. *In vitro*, gold sodium thiomalate was found to be bactericidal in the stronger dilutions and bacteriostatic in the weaker; the addition of whole blood to the extent of 50 per cent. destroyed the bacteriostatic power. Similar results were obtained with several other common laboratory organisms.

No definite effect upon agglutinin titres was detected. Colloidal gold did not produce significant bacteriostasis, and bismuth salicylate was hardly more effective.

"Toxic Reactions with Gold Salts in Treatment of Rheumatoid Arthritis" (*Journ. Lab. and Clin. Med.*, xxvi., 10, p. 1629). R. M. Lintz. In this discussion of the various toxic reactions following the use of gold salts some points are especially worthy of note. The author found in the earlier cases that in almost

every instance the patient experienced a flushing of the face within one or two minutes after receiving the gold compound: the face became fiery red with a sense of heat and often vertigo; but it is worthy of note that this reaction has almost ceased since the method of producing the thiomalate has been changed. With gold sodium thiomalate, though the usual minor toxic reactions and an occasional severe one have occurred, there have been no fatalities; but among a small number who received gold sodium thiosulphate there were two with very severe reactions, one of whom died. The *intravenous* route appeared to be definitely attended with increased risk. In another series in which the maximum single dose of thiosulphate was 0.05 gm., excellent results were obtained with a minimum of toxic reactions, which were of minor character. The number of cases observed was, however, insufficient to justify any definite conclusions.

There are many points of interest and practical importance in these reports. One of the most important appears to be that smaller doses than those which have hitherto been the practice are not only adequate but much less liable to give rise to toxic effects. The possibility that the interval between doses might also be longer is worth exploring. The length of time after completion of a course during which gold continues to be excreted in the urine points to the desirability of a longer interval between the courses. Examination of the urine for gold at the end of three months and at intervals thereafter would seem to be a wise course. It has been the experience of the reviewer that occasionally the first dose of a second course, though small, has given rise to a marked toxic reaction; probably in such cases the rate of excretion has been slow. The further investigation promised by Freyberg and his colleagues as to the possible necessity of a minimal amount of gold in the circulation for a minimal period promises to be of importance.

Another point to be noted is that toxic reactions after a course in which the maximum dose had been not more than 0.25 mg. of metallic gold in the investigations carried out by Freyberg, Block, and Levy were few and slight in character. In Hartung's cases, however, in which a dose of 50 mg. was only occasionally given, toxic reactions appear to have been more frequent; the only difference in method being apparently that in the former the injection was intramuscular and in the latter sub-

cutaneous; the point appears to be worthy of further investigation.

Lintz's observation that certain reactions followed immediately upon injection in his earlier cases (Freyberg observed similar effects in some cases), but ceased to happen when the method of preparation of the injection was altered, appears to indicate that some other factor than metallic gold played a part. It would be interesting to know if this reaction occurred after a first dose or only after later ones; in the latter case an acquired sensitivity to some constituent seems a possible explanation. If this is so, the administration of calcium with the gold which has been advocated by some would seem to be a good practice.

Gold has not hitherto been tried extensively in fibrositis, and the observations of Tarsy would appear to call for a more extensive trial of the colloidal form in suitable cases, preferably those which are apparently due to toxins of bacterial origin rather than to metabolic or traumatic causes. This is important in view of the probability that the diagnosis of fibrositis is made in cases of widely differing nature and ætiology.

While the bacteriostatic action of gold in the plasma must be regarded as of great importance, the fact that colloidal gold was found by Tarsy to be effective in a good proportion of cases, while no bacteriostatic effect could be detected in the serum, seems to indicate the importance of some other mode of action in addition.

The fact that some of the researches which have been discussed are still being carried on justifies the hope that the value of chrysotherapy will be clearly demonstrated apart from clinical experience, and that sound principles for its use will be established.

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EFFECT OF INFLUENZA VIRUS ON THE HÆMOLYTIC STREPTOCOCCUS.

There would appear to be abundant evidence that streptococcal infection of the upper respiratory tract, especially of the tonsils, may be closely associated with the genesis or recrudescence of rheumatism. Factors influencing the pathogenicity of this streptococcus, therefore, are of special interest because of their possible importance for arriving at a correct interpretation of the present evidence concerning the ætiology of rheumatism.