Chemotherapy of Tuberculosis*

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INTRODUCTION

It is the intention to focus anew in this paper the attention of physicians, and particularly phthisiologists, upon a type of therapy which, at present, does not play the role in the treatment of tuberculosis which it deserves. Chemotherapy of tuberculosis has been in eclipse for reasons which are understandable, but do not suffice to justify refusal of its possible benefits to a patient afflicted with tuberculosis. Chemotherapy of tuberculosis is essentially gold therapy. Gold therapy is usually identified in this country with the use of Sanocrysin. In reality, this type of treatment is much older. Original experiments with gold salts go back to Robert Koch.

As early as twentyfive years ago, preparations of Aurocanthan, Krysolgan and Triphal gave evidence of a specific effect therapeutically upon tuberculous tissue. However, their high toxicity prevented their use on a large scale.

World-wide interest in gold therapy was reawakened by Moellgard's publication of his and Secher's results with Sanocrysin. Enthusiastic reports were followed by disappointment of other workers who were justified in pointing out the severe damage done in many cases. It is now generally agreed that this was largely due to the administration of too large doses. However, the result was unfortunate in that the majority of the physicians in this country abandoned the use of gold preparations entirely. European workers and investigators in other parts of the world, as well, insisted that they had seen favorable results in cases where other types of treatment proved unsuccessful or could not be administered. In 1933 Henrichsen and Sweany published a comprehensive report about their experiences with Sanocrysin at the Chicago Municipal Tuberculosis Sanitarium. They arrived at qualified but, on the whole, favorable conclusions and confirmed the now general consensus of opinion that reduction of the dosage markedly reduced the complications attributed to Sanocrysin.

Adolf Feldt, one of the pioneers in the field of chemotherapy of tuberculosis, endeavored for many years to develop an organic gold compound having sufficient therapeutic effect without causing

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*Read before the Boston Trudeau Society, Rutland State Sanatorium, Rutland, Massachusetts, May, 1941. From the New Hampshire State Sanatorium, Glencliff, N. H.

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harmful complications. In 1924 Solganal A, an organic sulfur-gold compound, was submitted for trial and Freund and others\textsuperscript{4} reported very remarkable improvement in many cases, although gold exanthemata, some of severe nature, occurred. In 1937 an extensive debate about gold therapy of tuberculosis took place at the German Tuberculosis Congress at Wiesbaden, and it was stated that a literature of about three thousand papers had appeared so far. This confirms a remark in an editorial of \textit{Lancet} in 1932, which reads: "We are by no means at the end of the chapter." Many promising reports were published on the effect of Solganal-B Oleosum, which Feldt developed from his older Solganal A. This preparation has been in use on a large scale in Europe and has been proved only slightly toxic, without loss of effectiveness. After using it previously for many years at other places, the author of this paper has given it a trial of three years at the New Hampshire State Sanatorium,\textsuperscript{*} and is convinced of its usefulness in properly selected cases. Reports about the earlier results appeared in the \textit{American Review of Tuberculosis}.\textsuperscript{6} This paper will deal with the general principles of the method of administration and conclusions derived from further clinical studies.

THEORETICAL CONSIDERATIONS

Solganal-B Oleosum is an aurothioglucose suspended in oil and belongs to the organic gold compounds which are, in their effect upon the tuberculous tissue, different from inorganic preparations. The empirical formula is $\text{C}_n\text{H}_{11}\text{O}_n\text{SAu}$. The "therapeutic index" (Ehrlich), which is defined as the relation between the smallest healing and the largest tolerable dose, amounts to 1:50 for Solganal-B Oleosum and 1:4 for Sanocrysin. Originally it was assumed that gold preparations had a direct bacteriotropic and bactericidal effect upon tubercle bacilli. Early experiments of Robert Koch pointed in that direction and he was able to prove that 1:200,000 dilutions of gold salts sufficed to prevent tubercle bacilli from growing on artificial media. Moellgard believed that his Sanocrysin was bactericidal and bacteriolytic and met the requirements of Ehrlich's "therapia magna sterilisans."

Experiments performed by A. Feldt and other workers led to the conclusion that chemical preparations effective in tuberculosis influence mainly the diseased organism as a whole and have only an indirect bearing upon the disease by stimulating the defense forces of the body. The reticulo-endothelial system, as conceived by Aschoff, acts as a catalyst. The main support for this conception is the experience that very small doses of gold compounds are still effective.

\textsuperscript{*}The Solganal-B Oleosum was supplied through the courtesy of the Schering Corporation, Bloomfield, New Jersey.
in experiments on diseased animals, although they do not exercise any damaging influence upon bacteria in test tubes. On the other hand, reduction or elimination of the action of the reticulo-endothelial system diminishes the healing effect of gold compounds upon protozoic and bacterial infections. The change in the leukocyte picture during gold treatment, and particularly the appearance of monocytosis, are regarded as significant of the reaction of this cell system. A few hours after the administration of gold preparations, the so-called activation of the reticulo-endothelial system in the liver, as well as in the spleen, becomes noticeable. This means a more pronounced visibility and increase in the number of the Kupffer star cells and the formation of fine vacuoles, which sometimes can be dyed with basic dyes. The importance of the reticulo-endothelial system is readily demonstrated by the regular presence of large mononuclear cells which constitute an integral part of the anatomy of the tubercle and are nothing else than Aschoff's histiocytes, or Metchnikoff's macrophages with their phagocytic capacity. Evaluating this fact, it becomes understandable that gold therapy yields the best results in exudative cases which show the most active mutual relationship between the intruder and the defense forces of the body.

**INDICATIONS**

To determine the place of chemotherapy in the treatment of tuberculosis, it stands to reason that in its present form it cannot replace any form of collapse therapy or basic conservative treatment. However, there remains an important field, and in spite of all controversy, the indications for chemotherapy can be well outlined. As already pointed out, exudative cases even of the far-advanced type and with cavities, often respond favorably to gold treatment. Acute infiltrative spreads occurring in old chronic, fibrotic lesions, as well as contra-lateral spreads during pneumothorax treatment or following thoracoplasty, often disappear within two or three months. Frequently gold therapy makes the administration of a pneumothorax on the contralateral side unnecessary, or the patient is spared a second stage of thoracoplasty. I cannot agree with Kayne, who holds, speaking of Sanocrysin, that in the presence of a cavity a pneumothorax should always be induced. It is very much worth while to finish a full course of Solganal-B Oleosum, which should be preferred to Sanocrysin if x-ray, physical examination and blood test indicate a definite improvement within six weeks. The disappearance of cavities solely under gold therapy has frequently been observed and has been reported by the author of this article in the *American Review of Tuberculosis*.6

Only recently, Skavlem and co-workers emphasized that indis-
criminate use of pneumothorax treatment in exudative cases accounts for many cases of empyema, and suggested that a temporary phrenic crushing would transform an acute, exudative case into a more benign productive or fibrotic type, which shows far less complications when pneumothorax is administered. This is undoubtedly true and remains valid when gold treatment is used instead of a phrenic crushing. Although it is not easy to prove this statistically in a sufficiently large number of patients, I feel in full accord with the opinion of Skavlem and his co-workers, after an experience of over fifteen years with gold treatment.

One sometimes witnesses an attempt to improve the results of an incomplete pneumothorax by additional gold treatment. A simple mechanical consideration makes it obvious that no result can be obtained. Adhesions which keep cavities open and under tension counteract the tendency towards fibrosis which could be the final and satisfactory result under gold treatment alone. It is better, therefore, to discontinue a dangerous and useless pneumothorax treatment and turn to gold. After some time, the possible extent of improvement can be surmised; and if no full healing, but only partial improvement is noted or can be expected, thoracoplasty would be the procedure of choice. Smith, of England, believes that gold treatment shows its value in collapse therapy in preventing a spread to the contralateral lung. It is difficult to conceive how this can be proven.

It must be stressed that the so-called acute, benign, exudative lesions of Ornstein's and Ulmar's classification should not be the object of gold therapy. They often heal under bed rest. The type of tuberculosis dealt with above cannot be considered as benign in the presence of cavities.

The use of gold treatment is not so much determined by the extent of the diseased area as by the amount of resistance the patient has. Unfortunately, we do not have any reliable clinical yardstick for determining this, with the exception of a negative tuberculin test, indicating the complete breakdown of resistance. A high sedimentation rate or an unfavorable differential count often change surprisingly fast. Their value rests in revealing the actual activity rather than in permitting a prognosis. Only clinical experience, and to some extent the method of trial and error, will teach the proper selection of cases. For this reason, gold treatment should be administered mainly in clinical institutions, and occasionally in ambulatory cases, if proper safeguards can be taken by the attending physician, who should have experience with this type of treatment.

Productive cases do not show as striking results as the exudative ones. The histo-pathological picture of this type of tuberculosis implies a slower tissue reaction to the toxic agent. However, they
also improve through the development of fibrotic tissue. Whereas recent cavities with a wall of soft exudative tissue answer favorably to gold, no benefit can be expected if the cavity wall consists of fibrotic tissue. This fact has often not been heeded and has accounted for many failures. Not infrequently it is possible to observe the flare-up of an exudative reaction of a cavity wall, through a series of x-rays. Cavities which appeared to be stabilized show a sudden increase of the width of the cavity wall, sometime followed by dissemination of the disease elsewhere. During this period, which also expresses the renewal of the fight between the bacillus and the organism, gold treatment offers an excellent chance. Continuing this line of thought, it becomes clear that old fibrotic cases should not be treated with any hope for a decisive change. Unless conservative treatment suffices, they belong to the surgeon's realm.

SURVEY OF TREATED CASES

In the course of three and one-half years the author has treated 32 cases with Solganal-B Oleosum. In two instances, gold was given, although the hopelessness of the prognosis was fully evident. Both patients died within a few weeks. Seven cases did not show any noticeable improvement, although they received a full course of Solganal-B Oleosum over a period of several months.

Ten patients showed definite improvement. X-ray shadows disappeared. Sedimentation rates decreased. Recent spreads were absorbed, and in some of these cases it was possible to institute collapse therapy, particularly pneumothorax treatment after they had passed the acute stage in which hypersensitiveness to tuberculo-toxins made institution of a pneumothorax dangerous because of possible complications. Sputa conversions could not be achieved in the majority of this group. However, there was definite clinical improvement and the impression was gained that this type of treatment brought the patients beyond the danger zone.

The most important group consisted of 12 patients whose lesions were mostly of the exudative type. In 8 of them, the cavities present at the beginning of the treatment, many larger than half-dollar pieces, disappeared within the course of several months. All patients had, at the end of the treatment, normal sedimentation rates, and showed either a marked diminution or complete disappearance of rales.

It has to be admitted that guinea pig inoculations were not done in these cases. However, roentgenological evidence of improvement and disappearance of cavities was so obvious that the author feels justified in claiming results better than obtainable by other methods of treatment.
CASE REPORTS

The following x-rays and short histories of several cases may prove the value of gold treatment.

Case 1—L. McCl., female, white, age 25, was admitted January 2, 1940, with large cavity in left middle lung field (Fig. 1). Tubercle bacilli present in sputum. Sedimentation rate (Westergren), 45/71. Pneumothorax attempted on the left side was unsuccessful. Thoracoplasty was contraindicated because of high activity.

Under bed rest, the lesion spread (Fig. 2). Patient developed fever and raised large amounts of sputum. Many rales were heard over the diseased area anteriorly and posteriorly. On Feb. 24, 1940, she was placed on Solganal-B Oleosum. Total amount of Solganal-B Oleosum given in seven and one-half months was 8.74 gm. Rapid improvement followed. In February, 1941, there was no cough and no sputum; sedimentation rate, 10/30. X-rays showed disappearance of the cavity. In October, 1941, only a small fibrotic area was left in the left middle lung field (Fig. 3). Sedimentation rate was normal. Gastric lavage showed negative results for tubercle bacilli.

Case 2—C. L., female, white, age 22. On admission in January, 1939, both upper lung fields were involved with a cavity (not well visible on picture) 1 inch in diameter at the level of the clavicle (Fig. 4). Sputum was positive. Sedimentation rate, 35/61.

An attempt to establish pneumothorax on the left side was unsuccessful. She was placed on Solganal-B Oleosum. Sputum was converted after five months, and has remained negative since. Sedimentation rate became normal in July, 1939, and has remained normal since. Moist rales which were present over left upper half anteriorly and posteriorly on admission have disappeared. A postero-anterior x-ray (Fig. 5) and a special apical picture (Fig. 6) showed the disappearance of the cavity. There has been improvement also in the right first interspace.

Total amount of Solganal-B Oleosum administered between Feb. 8, 1939, and Sept. 6, 1939, was 9.76 gm.

Case 3—S. L., age 35. Admitted June 13, 1940. On admission patient did not raise any sputum. There were very scanty physical findings restricted to some dullness over the right upper 3rd. No rales; normal breath sounds. X-rays showed a cavity one inch in diameter just beneath the right clavicle and a few indistinct foci in its neighborhood (Fig. 7). Sedimentation rate was 7/19. Sputum was not obtainable. A pneumothorax was instituted on the right side but was discontinued because of incomplete collapse. In October, 1940, he began to raise sputum and tubercle bacilli were found. At this time thickening of the cavity wall was noted and shortly afterward a hemorrhage and a spread into the left lower lung field occurred.
In January, 1941, (Fig. 8) the patient was placed on treatment with Solganal-B Oleosum, and in the course of 7 months the cavity as well as the spread disappeared completely. Sedimentation rate went back to normal, 12/4. Total amount of Solganal-B Oleosum given in 7 months was 7.395 gm. At present, 4 months after Solganal-B Oleosum treatment, patient does not raise any sputum, and there are no rales heard anywhere. The original intention to perform a right sided thoracoplasty has been abandoned (Fig. 9).

In this case it ought to be noted that the patient was an extremely nervous man and developed during the treatment a herpes zoster over the right chest. The herpes zoster called for temporary discontinuation of Solganal-B Oleosum treatment. After resumption of treatment no further complications occurred.

Case 4—H. C., female, age 35. Admitted February 9, 1941. She was a former patient at the New Hampshire State Sanatorium from November, 1937 to October, 1938. At that time, the patient had a productive lesion of the upper portion of both lungs without cavitation and sputum. Sedimentation rate was 20 mm. Patient was discharged after treatment with bed rest over 11 months, without showing any improvement. Following discharge, patient was at home, and although at rest, grew slowly worse and reentered the sanatorium on Feb. 9, 1941.

On readmission (Fig. 10) spreading of the lesion into both middle lung fields with formation of a cavity of the size of a half dollar was noted. Sputum contained tubercle bacilli and sedimentation rate was 21/46. Since continuous bed rest at home did not arrest the disease, Solganal-B Oleosum treatment was started shortly after admission (Fig. 11). In June, sedimentation rate became normal for the first time, and sputum did not show any tubercle bacilli. Appearance of a few granular casts in the urine called for a short interruption of the treatment, but resumption was possible and the total amount of Solganal-B Oleosum given was 9.07 gm. Treatment was discontinued in October 1941 (Fig. 12). Serial x-rays showed definite regression of lesion and disappearance of cavity. Urine is now free from pathological elements, and numerous sputa were negative for tubercle bacilli. Sedimentation rate has been normal since June.

MANAGEMENT OF TREATMENT

It goes without saying that the wide divergence of individual cases requires an individual approach in carrying out the treatment. Generally, it can be said that a total dosage of 9 or 10 grams of Solganal-B Oleosum should not be exceeded. Small doses up to 200 mgs. can be given twice a week. During menstruation treatment has to be interrupted. Routine urine examinations for albumen, white blood counts, and sedimentation tests are necessary. Focal reactions are
rarely observed; however, temperatures should be taken every four hours to rule out undesirable surprises. Not infrequently casts are found, although albumen is absent. This fact has impressed the author lately more than in the past. Nevertheless, the casts disappear within 2 or 3 weeks after interruption of the treatment and resumption with smaller doses is permitted. Occasional rashes occur but are transitory. The rashes are treated with cevitamic acid and injections of calcium gluconate. Mirick reported one case of agranulocytosis after administration of Solganal-B Oleosum. I feel that careful clinical observation renders such accidents avoidable.

If a patient fails to improve after three or four months, further treatment is generally useless. Only cases showing definite clinical and roentgenological improvement beyond the average results of conservative treatment, should serve as proof of the efficiency of gold treatment. It sometimes happens that during the course of the treatment, in spite of initial improvement, a new spread into hitherto healthy areas of the lungs occurs. This confronts us with the decision whether or not to continue the treatment. Without being able to give logical reasons for my decision, I continued the treatment in two cases and succeeded in achieving further improvement of the condition. At present, we are not yet in a position to determine and to analyze the immuno-biological factors having a bearing upon the course of the disease, and have to feel our way, depending upon clinical experience and available laboratory tests. It also must be emphasized that there is no well defined relationship between the amount of gold used and the therapeutic results. Aften a surprisingly low amount suffices to achieve the desired goal.

CONTRAINDICATIONS

As stated above, no success can be expected if the resistance has broken down completely. In addition, certain contraindications against the use of gold must be heeded. Extensive intestinal and kidney involvement rule out its use. Sometimes a subclinical intestinal tuberculosis becomes apparent and calls for discontinuation of the treatment. Laryngeal tuberculosis, however, often answers favorably to gold, and it was originally considered the most suitable type of tuberculosis for this treatment until gradually increasing clinical experience broadened the scope of the indications. Gold therapy is not advisable when diabetes mellitus coexists. I could not gather any information from other sources concerning this question, but in several of my own cases the patients reacted to gold injections with uncontrollable focal reactions and rapid progress of the disease. Cases of hematogenous and extrapulmonary tuberculosis should generally not be treated with gold because of their tendency to develop unexpected spreads (meningitis).
CONCLUSIONS

1) At present, gold therapy is a valuable adjunct in the armamentarium of the treatment of tuberculosis.

2) Predominantly exudative cases give the best results, as proven by the disappearance of large infiltrations, cavities up to a diameter of 2 inches, and tubercle bacilli in the sputum. Recent spreads often disappear in a short time. Conversion of exudative lesions into productive, fibrotic tuberculosis improves the result of collapse therapy and makes complications (empyema) less probable.

3) Renal and intestinal involvement, as well as cases of hematogenous origin, contraindicate the use of gold.

4) There is no fixed relationship between the amount of gold given and the therapeutic results achieved. The amount of 9 or 10 gm. should not be exceeded in one course.

5) At present, Solganal-B Oleosum is considered the least toxic and yet effective gold preparation.

6) Gold therapy is nosotropic and stimulates the immuno-biological activity of the reticulo-endothelial system. The development of bacteriotropic preparations is desired.

7) Frequent urine and blood examinations should be done to exclude possible toxic complications. With such precautions, possibilities of complications are no greater than in other widely accepted forms of chemotherapy.

CONCLUSIONES

1) Al presente la auroterapia es un auxiliar valioso en el tratamiento de la tuberculosis.

2) Casos predominantemente exudativos dan los mejores resultados, como se comprueba por la desaparición de infiltraciones extensas, cavernas hasta de un diámetro de 2 pulgadas, y bacilos tuberculosis en el esputo. Propagaciones recientes desaparecen a menudo en poco tiempo. La conversión de lesiones exudativas en lesiones de tuberculosis productiva y fibrosa mejora el resultado de la colapso-terapia y disminuye las probabilidades de la ocurrencia de complicaciones (empíema).

3) Complicaciones renales e intestinales, también como casos de origen hematogéno, contraindican el uso de oro.

4) No existe conexión fija entre la cantidad de oro administrada y los resultados terapéuticos alcanzados. No se debe exceder la cantidad de 9 o 10 gramos en una serie terapéutica.

5) Al presente se considera que el Solganal-B Oleosum es la preparación de oro menos tóxica y al mismo tiempo eficaz.
6) La auroterapia es nosotrópica y estimula las actividades inmunobiológicas del sistema reticuloendotelial. El desarrollo de preparaciones bacteriotrópicas es deseable.

7) Se deben llevar a cabo exámenes frecuentes de la orina y de la sangre para excluir posibles complicaciones tóxicas. Con estas precauciones, las probabilidades de complicaciones no son más que en otras formas de quimioterapia generalmente aceptadas.

REFERENCES


