CONCLUSIONS.

1. When calcium lactate is superimposed for ten days upon an acidotic calcium-deficient but vitamin-containing diet, a quantity amounting to approximately 9.5 Gm. is required to establish calcium equilibrium. Compared with milk, this represents 2.5 or more times as much calcium as is necessary using the latter.

2. The urinary calcium excretion was markedly increased, about 10% of the calcium increment taking this route of excretion. The same tendency is noted in using milk.

3. The urinary phosphorus excretion was decreased and phosphorus retention secured by the ingestion of calcium lactate. In this diet the original Ca:P ratio was 2:9; and the favorable influence upon phosphorus metabolism may be due to the establishment of a more favorable balance of 14:9. However, in the case of milk experiments, a ratio of 5:9 yielded a more decided phosphorus retention.

4. Concerning the effect of calcium lactate upon magnesium metabolism, slightly increased losses were noted in three of the five subjects.

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GOLD COMPOUNDS FOR MEDICINAL USE.*

BY F. R. GREENBAUM.

Gold has been used as a drug for many centuries. Abu Moussa Gafar (1) recommended gold in the middle of the eighth century as a remedy for administration to human beings, animals and plants. He believed that all metals were diseased except gold.

Ebu Sina, (2) better known as Avicenna (Arabia, 978–1036), recommended gold, silver and other metals for internal use as blood purifiers. Pills were coated with gold foil and gold paper.

Bombastus Paracelsus (1493–1541), alchemist and chemist, recommended gold

* Scientific Section, A. PH. A., St. Louis meeting, 1927.

for diseases of the heart. His "elixir of life" is a mixture of gold and mercury. He was the first to recommend gold in the treatment of tuberculosis.

Robert Koch (3) (1890) found that gold cyanide, auro and auri cyanide Au (CN) and $Au(CN)_3$ inhibit the growth of the tubercle bacilli in a dilution of 1:2,000,000 in vitro. In the animal body it does not possess such great bactericidal power.

J. B. White (4) in 1891 recommended gold and sodium chloride ($AuCl_3NaCl$) combined with manganese iodide. Considerable improvement of the symptoms of the disease was noted but it was found to be too poisonous.

From 1912 to 1915, the study of gold was in the hands of German investigators. Men like Arthur Meyer, Oberstadt, Heubner, Bruck and Glueck concentrated their attention on the gold treatment of tuberculosis. Heubner (5) pointed out the capillary poisoning effect of gold and platinum salts.

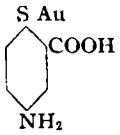
Bruck and Glueck (6) after R. Koch used gold cyanide and found that it healed the tuberculosis lesions but also caused severe poisoning effects. Poor (7*a*) and Geber (7) used potassium gold cyanide successfully in tuberculosis of the skin. Potassium gold cyanide is less poisonous than gold cyanide, though its toxic properties are still high.

Adolf Feldt (8) used gold cyanide intravenously and subcutaneously and found that it caused a local reaction in the tuberculous organs. Feldt believes that the gold salts attack the tubercle bacilli in a selective way, kill them and thus form toxins on the wall of the cells which cause an inflamed hyperæmia.

Arthur Meyer (9) reported similar experiences with gold potassium cyanide.

In 1914, Spiess and Feldt (10) brought out a new remedy; recognizing the high toxicity of gold cyanide on the one hand and its healing effect on tuberculous organs on the other, they tried to find a carrier which would decrease its toxicity. They used cantharidin, which has a marked affinity for tubercular organs. In order to decrease the toxicity of cantharidin, they combined it with ethylenediamine, by which combination the toxicity is lowered 700 times. This monocantharidyl ethylenediamine is used as a carrier for gold cyanide, with which it combines readily. This combination called "Aurocantan" was found to be less poisonous than gold cyanide and represented a marked advance in the treatment of tuberculosis. It was given subcutaneously but caused necrosis when administered for a long time.

A still better and less toxic gold compound was prepared in 1917. Feldt and Spiess (11) once more introduced a new gold preparation in which the gold was introduced into an organic compound. This preparation is called "Krysolgan" and is the gold-sodium salt of an aminothiophenolcarbonic acid

"Krysolgan" has the following formula: 

a compound representing aminothiosalicylic acid in which the gold entered into the linking to the sulphur.

It is manufactured by the Hoechster Farbwerke, Hoechst am Main, and is available in German markets. Feldt pointed out that "Krysolgan" acts as a catalyst only and as such is used in very small doses (a few mg.). In acting upon the tuberculous tissues, "Krysolgan" causes a scarification and through

this, the tubercle bacilli are killed. Feldt recommends very small doses at very long intervals. The drug was found to be very effective in pulmonary tuberculosis. "Krysolgan," in combination with the hygienic-dietetic treatment, is very advisable for those patients who can give up their occupations. In those who cannot do so, "Krysolgan" should be given in large doses. Unlike arsphenamine and neoarsphenamine which have a direct action upon the spirochetes, the gold preparations act upon the tubercle bacilli indirectly.

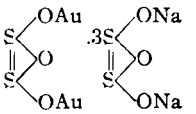
"Krysolgan" causes reactions such as exanthema, nephritis, icterus, hemorrhagia, etc. Heubner and Gelpke (12) proved that gold, like other heavy metals, has an injurious effect on the capillary walls. But Spiess and Feldt insist that these reactions are confined to the tubercular tissues.

"Krysolgan" cannot be used in cases of advanced tuberculosis or in cases with continuous high temperature.

In 1924, Professor Mollgaard (13) of Copenhagen, Denmark, introduced another gold compound which he called "Sanocrysin." It is by no means a new compound. Chemically speaking, it is gold-sodium thiosulphate, a complex gold salt, in which the gold is in the aurous form or monovalent form. It was found that the aurous form of the gold is less toxic than the auric form.

Gold-sodium thiosulphate was used in the middle of the nineteenth century in the photographic process, for which purpose it was employed in a mixture containing 2% gold chloride and 2% sodium thiosulphate. Fordos and Gelis (14) French chemists, investigated this mixture in 1845 and succeeded in isolating gold-sodium thiosulphate of the formula: $Au_2S_2O_3.3Na_2S_2O_3.4H_2O$. This drug is not yet available on the market but it is used in certain hospitals and sanitariums in England, America, Denmark and Germany.

"Sanocrysin" has the structural formula somewhat like this:



A number of methods of preparation have been elaborated since its introduction by Professor Mollgaard. Lucille Eichelberger and K. McCluskey (16) have published an excellent method which, however, is too expensive. A. T. Gelarie and F. R. Greenbaum (17) and H. Brown (18) have published methods of preparation of "Sanocrysin" which are very simple and efficient in yield.

If injected intravenously, "Sanocrysin" causes reactions only in the tubercular tissues but it is harmless and non-poisonous in the normal body. It has a somewhat sweet taste. Professor Mollgaard believes that it affects the tubercle bacilli but at the same time liberates harmful toxins. It order to prevent these reactions, he recommends a specific antitoxin serum which he injects simultaneously with or following an injection of "Sanocrysin."

The number of patients treated with this product in England and Denmark is still too small to warrant definite conclusions. It is certainly not as sure and potent a remedy in tuberculosis as arsphenamine is in syphilis.

Of 134 cases of pulmonary tuberculosis treated with "Sanocrysin" in Denmark, twenty died as a result of the drug, nineteen became worse, thirty improved and only twenty-five (six severe) were cured. (14*a*).

The specific resistance of the tubercle bacilli is due to their layer of fatty sub-

stances by which they are surrounded and protected. Professor Mollgaard's chemotherapeutic considerations which are presented in his book entitled "Chemotherapy of Tuberculosis" are as follows:

"Any drug capable of destroying the *T. bacilli* must penetrate their fatty layer. Tuberculosis tissues are very poor in blood vessels. The bacilli can be reached by diffusion only. The compound must there be rapidly diffusive and sufficiently stable within the organism to remain unaltered when reaching the bacteria. The gold as has been mentioned before, should be in the aurous form and in a real complex." "Sanocrysin" answers all these requirements.

In 1925 another gold preparation was proposed. It is known as "Triphal" and is manufactured by the Horchst Farbwerke Hoechst am Main. "Triphal" is the sodium salt of aurothiobenzimidazolcarbonic acid. It is very readily soluble in water and is injected intravenously.

The initial dose as prescribed by the Farbwerke is 0.025. The minimum dose is 0.001, the maximum 0.2. N. Galatzer and A. Sachs (15) studied this new compound and obtained good results in thirty cases out of forty. They believe that "Triphal" inhibits the growth of tubercle bacilli and increases the formation of anti-toxin substances. They did not notice any capillary poisoning in the course of the treatment. General reactions with "Triphal" are mild, slightly increase in temperature immediately after the injection, headache, tired feeling and drowsiness. These symptoms disappear after twenty-four hours. Galatzer and Sachs claim that they did not observe any kidney disorders or intestinal disturbances which frequently follow treatment with gold compounds. "Triphal" causes an increase in weight shortly after injection.

This drug seems to be very promising; in very advanced cases, however, it is a failure.

In studying the various gold compounds which have been developed within the past ten years and which are used in medicine as described above, one is impressed by one outstanding fact: that the number of gold compounds containing sulphur exceed those which do not contain sulphur. There is a certain affinity of gold for sulphur and the presence of sulphur in an organic compound practically insures the formation of a gold compound.

GOLD COMPOUNDS CONTAINING SULPHUR.

Gold thiophenol C_6H_5SAu developed and patented by the Farbwerke Meister, Lucius & Brunning, Hoechst of Main, (20), which is a gold salt of thiophenol 

containing 64.3% of gold. It is of interest to note that no corresponding gold compound of phenol is known.

Similar to gold thiophenol is the gold salt of thiosalicylic acid, also developed and patented by the Farbwerke. (21).

The gold-sodium salt of an aminothiosalicylic acid is the before-described "Krysolgan." It is again noteworthy to point that there is no corresponding gold compound of salicylic acid nor of aminosalicyclic acid.

Another group of compounds of which gold salts are known and which at the same time contain sulphur, is as follows:

Thiourea-hydrochlorauric acid, I; thioureahydrochlorauric acid hexamethylenetetramine, II; Thiosinamine hydrochlorauric acid, III; and Thiosinamine hydrochlorauric acid hexamethylenamine, IV.

These compounds can be considered as salts of the base; the thiocarbamide with hydrochlorauric acid, according to the following formulas:

I. $CS(NH_2)_2 \cdot HAuCl_4.4H_2O$ II. $CS(NH_2)_2 \cdot (CH_2)_6N_4HAuCl_4.4H_2O$

III. $CS(NH_2)(NH{-}CH_2{-}CH{=}CH_2) \cdot HAuCl_4.4H_2O$ IV. $CS(NH_2)(NH{-}CH_2{-}CH{=}CH_2) \cdot (CH_2)_6N_4.HAuCl_4 4H_2O$

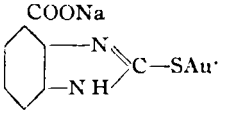
These gold salts of thiourea and thiosinamine, described by H. Brown (22), are insoluble in water. Addition compounds of these with hexamethylenetetramine were prepared which proved to be water soluble. It may also be emphasized in this connection that no gold salt of urea or alkylurea has so far been known. The presence of sulphur seems to be essential for the formation of gold salts.

Another series of gold compounds are the water-soluble gold salts of peptone and albumen, developed and patented by the Farbwerke, vormals F. Bayer of Leverkusen, Germany. (23).

From inorganic sulphur containing gold compounds, the following deserve mention: The various rhodamides, such as potassium aurirhodamide, ammonium aurirhodamide, etc. All of these compounds contain gold as well as sulphur, as the following formulas show: $(K)Au(CNS)_4$ $(NH_4)Au(CNS)_4$.

The toxicity of these compounds is too high, however, thus making them valueless therapeutically. Another inorganic gold compound containing sulphur and also gold, is gold-sodium thiosulphate, introduced in medicine as "Sanocrysin" and described before. This compound contains about 34% of gold and 24% of sulphur.

Another gold compound of very recent date which has been tried out in connection with tuberculosis is the before-mentioned "Triphal." This compound is the gold-sodium salt of thiobenzimidazolcarbonic acid of the following formula:



It also contains a gold-sulphur linking. It is being clinically investigated as a probable remedy for tuberculosis.

NON-SULPHUR CONTAINING GOLD COMPOUNDS.

"Aurocantan" is a combination of cantharidin with ethylenediamine gold cyanide. It was introduced by Feldt and Spiess, as mentioned before and used in tuberculosis. It was found, however, to be too poisonous.

"Goldnapthol Blue" is a gold salt of the dye napthol blue.

Then there are several addition compounds with hydrochlorauric acid and organic compounds which do not contain sulphur, such as benzamide and acetamide hydrochlorauric acid (24) of the formula: $2C_6H_5CH_2NH_2.HAuCl_4.4H_2O$ and $2CH_3CO$ $NH_2.HAuCl_4.4H_2O$. Then additional compounds with gold-cyanide chloride and hexamethyleneaminomethylchloride and similar compounds are known. (25).

The number of gold compounds that have therapeutic value and which contain sulphur is undoubtedly greater than the sulphur-free combinations. Chemists and chemotherapeutists working along these lines, therefore, seem to be led by the idea of selecting compounds containing sulphur in which gold is then introduced, because a real organic gold compound, a carbon-gold linking, has heretofore not been known. Very recently, however, M. Kharash and H. S. Isbell (26) succeeded in preparing compounds containing carbon-gold linking. The method which they have elaborated is as follows:

Anhydrous gold chloride is prepared by evaporating a solution of the commercial hydrochlorauric acid to dryness, then heated to 160° C. Then a dry current of chlorine is passed over it and finally dried in a curent of air. This anhydrous gold chloride is treated with benzene, the reaction allowed to proceed for only 60 to 90 seconds and is arrested by the addition of ether. The precipitate thus obtained is recrystallized from alcohol. It represents phenylauridichloride and the following reaction takes place: $C_6H_6 + AuCl_3 \longrightarrow C_6H_5AuCl_2 + HCl$. It is a yellow substance, insoluble in water. Instead of benzene, napthalene, diphenyl or toluene can be used. The other method which they employed is based upon Grignard's reactions.

All radicals more negative than phenyl will react. All radicals less negative than phenyl will not react with AuCl. Aurous chloride, which is insoluble in solvents, was made soluble by combining it with carbon monoxide. Aurous chloride was dissolved in H_2O and carbon monoxide was bubbled through. A white crystalline substance, aurous chloride carbonyl, is obtained. It sublimes between 80° and 100° C., and this aurous chloride carbonyl can be used for Grignard's reaction. The disadvantage of the gold compound thus obtained lies in the fact that they are water insoluble, although Kharash (27) claims to have succeeded in making them water soluble by using hexamethylenamine, or sodiumchloride. Each class of organic gold compounds is really a problem in itself and has to be worked out separately. Further research will throw more light on these real carbon-gold compounds and will also prove whether this type of compounds is therapeutically useful.

European investigators, particularly German and French scientists, still adhere to the old theory of gold-sulphur linking and very recently, Charles Lormand, in his Paris letter (28) reported on a new compound of gold which may be used in therapeutics. This compound worked out by Lumière, represents sodiumthiopropanol sulphonate, having for its formula:

$$\begin{array}{l} CH_2\text{—}SAu \\ | \\ CH_2\text{—}OH\text{—}CH_2SO_3Na. \end{array}$$

This compound is obtained by the action of sodium thiopropanol-sulphonate on gold chloride. German investigators of recent date also point out that the gold-sulphur linking offers the best chance for the formation of gold compounds which are therapeutically of importance. It remains to be seen whether the real organic gold compounds, the carbon-gold linking, as elaborated by Kharash and Isbell, offer any advantage over the gold-sulphur linking.

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THE HEMOLYTIC ACTIVITY OF ATRIPLEX CANESCENS.*

BY M. R. MILLER.[1]

DESCRIPTION OF THE PLANT.

Atriplex canescens, James, is a shrub found growing in the desert flats or washes of the Mohave and Colorado Deserts, west to San Bernardino and San Diego; east to Nevada and Dakota and south to Mexico. It appears as a roundish gray shrub, 1 to 5 feet high with linear, entire leaves, narrowed at the base, $^3/_4$ to 1 $^1/_4$ lines long, finely scurfy and canescent. The flowers are mostly dicœcious and very dense in fruit. The fruiting bracts form a thick, hard body, 3 to 4 lines long.[2] The plant has several common names as "saltbush," "chamiso brush," and "shad scale," the latter name being used in reference to the plant in this article.

* Published by permission of the Director of the Nevada Agricultural Experiment Station.

[1] Chemist, Nevada Agricultural Experiment Station.

[2] W. L. Jepson, "A Flora of California," Part IV, H. S. Crocker Co., San Francisco, 1914.