METABOLISM, PHARMACOLOGY AND THERAPEUTIC USES OF GOLD COMPOUNDS

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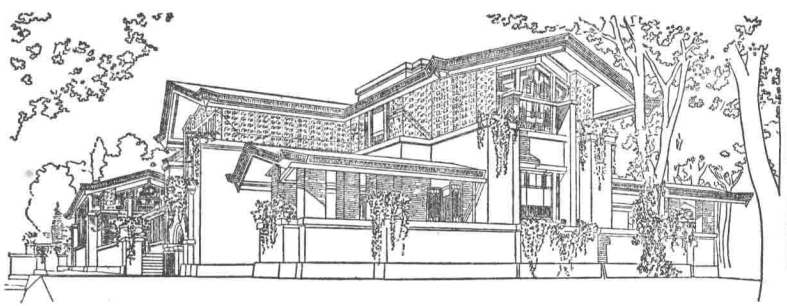

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This book
I affectionately dedicate
to my wife, Thelma
and my children, Bobby and Mimi

W. D. Block

Foreword

THE PRESENT work is limited to a discussion of the use of gold compounds in therapy, and to problems of toxicity and metabolism resulting from gold therapy. The work presented here is not intended to represent a comprehensive review of the literature. Rather, representative references have been included to cover the more important points within the scope of this work. The reader is referred to these articles for a more detailed description of various aspects of the subject. Several obvious and deliberate omissions have been made. Neither the colloidal gold test, nor the work with radioactive gold have been included. These omissions do not reflect a lack of recognition of the importance of these subjects. These topics lie outside the intended scope of the book. The colloidal gold test was omitted since its importance is in diagnosis, rather than in therapy. The work with radioactive gold was omitted because its therapeutic value depends on its properties as a source of radiation rather than on any inherent properties of the gold molecule itself.

W. D. B.
K. V. G.

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I

Historical

THE USE OF GOLD in medicine dates back very early in the records of man. It was probably first used by the Chinese about 2500 B. C. (1). During the period of its earliest use, gold was regarded as a panacea, capable of favorably affecting the course of all diseases. In the 8th century, Abn Moussa the Wise recommended gold as a cure-all for every known disease (2). At about this same time the alchemists were attempting to prepare from metallic gold an "elixir of life," which would cure all diseases, and confer eternal youth. Although the attempt was obviously doomed to failure, gold in the metallic state gradually became popular as a medicinal agent. Dioscorides and Avicenna used metallic gold as a remedy (3) and about 1500 A. D., Paracelsus recommended a universal panacea composed of gold and mercury (3). Gold was first used for the treatment of tuberculosis in his time (2). Due to serious accidents resulting from its use, however, the treatment was discontinued until 1810, when it was revived by Chrestien (4).

The idea that gold represented a universal cure for disease was revived in a modified form by the homeopaths of the late 18th and early 19th centuries. There was almost no condition or disease in which gold was not used, always with favorable results (3). Among the diseases against which gold was reported to be effective were: "scrofulex, psora, syphilis, sycosis, cutaneous affections, suicidal melancholea, mercurialism, dropsy, angina pectoris, inflammation of the heart, vascular turgescence, cancer, and specific indurations" (3).

The earliest bacteriological experiments on gold were

carried out by Robert Koch in 1890 (5). Koch found that a gold cyanide compound arrested the growth of the tubercle bacillus *in vitro* in a concentration of 1 part in 2 million. Koch was unable to show any effectiveness in infected animals. This work was confirmed by v. Behring (6). In addition, v. Behring showed that the bacteriostatic action of this gold compound in blood serum was only about one-fourth its effectiveness in aqueous solution.

In 1913, several workers attempted to apply Koch's discovery clinically. Bruck and Glück (7) administered gold potassium chloride intravenously in several cases of skin tuberculosis and of syphilis, and reported good results. These authors did not know, however, whether the gold or the cyanide portion of the molecule was responsible for the beneficial effect. v. Poor (8), using the same compound in 12 cases of lupus vulgaris, also reported good results. Junker (9) used gold salts in the treatment of pulmonary tuberculosis. His patients reacted with fever, but were somewhat improved.

The use of these inorganic gold salts was accompanied by reactions of such frequency and severity that extensive use in human beings was not practicable. Although the gold compounds used at that time were very toxic, the therapeutic effects were encouraging enough to prompt a search for other gold compounds of low toxicity. Attempts to find such a compound have never been completely successful, but great improvements were made. In 1913, Feldt showed that gold sodium thiosulfate has a growth-inhibiting action on bacteria (10). In 1924, Møllgaard (11) introduced this compound as a specific therapy against tuberculosis, calling it sanocrysin. According to Møllgaard, the compound had almost no toxic properties, and was especially effective in skin tuberculosis. The compound soon found widespread use in medicine, especially in the treatment of pulmonary tuberculosis.

Feldt began to experiment with the use of organic gold compounds, and in 1917 prepared the sodium salt of aminoauromercaptobenzol, which he called krysolgan (12). In animal experiments this compound appeared to be definitely less toxic than the preparations used previously, with the same bacteriostatic effect on tubercle bacilli as gold potassium cyanide. Other workers (13, 14) were unable to confirm Feldt's results on the effectiveness of this compound. Reports appeared which did confirm its effectiveness (15), but which warned against serious complications resulting from its use. Because of its toxicity, the compound gradually disappeared from use.

In 1927, Feldt (16) introduced a new preparation, the disodium salt of sulfomethylaminoauromercaptobenzolsulfonic acid, which he called solganal. With the introduction of this compound, and other new preparations, gold treatment became more popular, especially in the treatment of tuberculosis. Landé (17) and Pick (18), in 1927, reported independently on the use of gold compounds in the treatment of a few cases of polyarthritis. The use of gold in the treatment of arthritis was popularized by Forestier, who published the first results on a large series of cases (19) in 1929. Forestier's decision to use gold compounds in treating arthritis was based partly on Feldt's demonstration of the anti-infectious effect of gold, and partly on the mistaken assumption that a relationship exists between chronic polyarthritis and tuberculosis. Forestier reported good results with gold treatment. His work was later confirmed by a large number of European workers. There was little interest in gold treatment in this country until 1936, when one of the earliest American reports appeared (20). Since that time, a large number of reports have been published on the effects of gold in rheumatoid arthritis.

Gold compounds have been used extensively in the treatment of tuberculosis and rheumatoid arthritis. They

have also been widely used in the treatment of lupus erythematosus, apparently also on the mistaken assumption that lupus erythematosus is tubercular in origin.

In addition to the three diseases just mentioned, gold has also been used in the treatment of Reiter's syndrome, osteoarthritis, ankylosing spondylitis, palindromic rheumatism, lupus vulgaris, skin tuberculids, leprosy, erythema induratum, psoriasis, syphilis, epilepsy, asthma, multiple sclerosis, and many other diseases. Gold treatment was abandoned in many of these diseases because little apparent benefit was obtained. The diseases in which gold therapy has found most widespread use are pulmonary tuberculosis, lupus erythematosus, and particularly, rheumatoid arthritis. For this reason, the discussion on results of gold therapy will be limited to these three diseases.

II

Chemistry of Gold Compounds

GOLD COMPOUNDS used in medicine in recent years are listed in Table I.

Metallic gold, atomic weight 197, is a relatively inactive element. Conversely, gold compounds are quite reactive, and are easily reduced to form metallic gold. Gold in combination with other elements can exist in two valence states, as a monovalent or a trivalent atom. Gold sodium thiosulfate and gold sodium thiomalate are examples of monovalent gold compounds. Gold sulfide is an example of a trivalent gold compound. The majority of gold compounds used clinically are monovalent compounds.

Gold compounds can be divided into three groups, with respect to physical properties. These are: 1) water soluble, ionized compounds, for example, gold sodium thiosulfate; 2) water soluble non-ionized compounds, for example, gold sodium thiomalate and gold thioglucose, and 3) water insoluble compounds, for example, calcium aurothiomalate and calcium aurothioglycolate. It will be seen later that differences in the behavior of gold compounds in the human body are related to these differences in physical properties.

Both organic and inorganic gold compounds have been used clinically. Among the inorganic compounds are colloidal gold sulfide and gold sodium thiosulfate. Examples of organic gold compounds are gold sodium thiomalate, aurothioglycoanilide, gold thioglucose, etc.

TABLE I

GOLD COMPOUNDS USED IN RECENT YEARS

Trade Name	*Chemical Name*	*Gold Content Per Cent*	*Solubility in H_2O*	*Administered as*
Sanocrysin	Gold Sodium Thiosulfate	37	Soluble	Aqueous Solution
Crisalbine				
Aurothion				
Myochrysine	Gold Sodium Thiomalate	50	Soluble	Aqueous Solution
Allochrysine	Gold Sodium Thiopropanol Sulfonate	30	Soluble	Aqueous Solution
Lauron	Aurothioglycoanilide	54	Insoluble	Oil Suspension
Myoral	Gold Calcium Thioglycolate	67	Insoluble	Oil Suspension
Solganal-B-Oleosum	Gold Thioglucose	50	Soluble	Oil Suspension
Aurocalcium	Gold Calcium Thiomalate	50	Insoluble	Oil Suspension
Aurodetoxin	Gold Keratin Compound	8 to 14	Insoluble	Oil Suspension
Aurol Sulfide	Auric Sulfide	87	Insoluble	Aqueous Colloidal Suspension
	Sodium Succinimido Aurate	29	Soluble	Aqueous Solution

It can be seen from Table I that the gold compounds used clinically vary greatly with respect to gold content. Since it is the gold portion of the molecule which is responsible for the therapeutic effects, the total amount of each compound administered must be adjusted proportionately to ensure an equal response. This has not always been done in cases reported in the literature. The failure to adjust dosage levels of different gold compounds to provide equivalent amounts of gold accounts for a part of the earlier confusion concerning the value of gold salts in medicine.

Information concerning the pharmacology and metabolism of gold compounds was somewhat limited until the development of specific, accurate, and sensitive methods for the determination of gold in biological materials. Block and Buchanan developed such a method for the determination of gold in blood and urine (21, 22), and later extended it to the analysis of various organs and tissues (23). The method is based on the reaction between o-dianisidine and auric chloride in a slightly acid, buffered solution. A red color develops as a result of this reaction. Biological materials are converted to auric chloride by acid digestion, the color is developed and read in a colorimeter.

Other methods which have appeared in recent years include a histochemical staining technique (24), and a photographic method (25, 26) for the qualitative detection of gold in tissues. Methods which require specialized equipment include a polarographic method (27), and a method using the emission spectrograph (28).