

SCIENTIFIC SECTION

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A STUDY OF CALOMEL FROM THE PHYSICAL AND THE CHEMICAL STANDPOINT.*

BY CHARLES H. LAWALL AND JOSEPH W. E. HARRISSON.

The two chlorides of mercury have had a long and interesting history. The mercuric chloride dates from the Arabian period under Geber in the 9th century, while the mercurous chloride seems to have first appeared in the 16th century and is described in the works of Beguin and Crollius, under the name of "dulcified mercury."

It has appeared in more physical forms and under a greater diversity of Latin and common names than any other official chemical salt.

It has appeared in every edition of the United States Pharmacopœia.

In the U. S. P. of 1820 directions were given for the preparation of calomel from "oxymuriate of mercury" (corrosive sublimate) and purified mercury, which was three times sublimed and then levigated and elutriated.

In 1830 the process was changed in that mercuric sulphate was first prepared from mercury and sulphuric acid, and this was then mixed with salt and sublimed and the sublimate subsequently purified with solution of ammonium chloride and boiling water and finally levigated and elutriated.

In 1840 the same process was directed as in 1830 with the addition of a test to exclude soluble chlorides.

No further change was made until 1880 when the formula was discontinued and identity tests were added as well as tests for absence of mercuric chloride.

It was not until 1910 that an assay method was introduced. It was in the 1890 Pharmacopœia that a descriptive requirement was introduced which has remained essentially unchanged for four decades and which reads as follows:

"A white impalpable powder, becoming yellowish white on being triturated with strong pressure, and showing only small isolated crystals under a magnifying power of 100 diameters."

This requirement probably originated in the fact that in European pharmacy two calomels had been recognized, one for sublimed calomel (which was described as distinctly crystalline) and the other for calomel prepared with steam, which was described (as in the paragraph quoted above) as showing under the same magnification (100 diameters) only a few isolated crystals. This same requirement occurs in the 6th edition of the German Pharmacopœia (1926) and in the 4th edition of the Belgian Pharmacopœia (1930).

The reason for this investigation is a rather curious and unusual one.

A private client came to us with the statement that he had suffered from a non-specific urethritis which had been caused by the irritating effect of a prophylactic ointment which had been injected into the urethra.

* Scientific Section, A. P. H. A., Washington meeting, 1934.

Investigation of this ointment showed the presence of a large number of sharp pointed acicular crystals of calomel and as none of the calomels which were easily accessible showed a microscopic appearance, anything like the specimen in question, it was decided to make a complete study of the calomels made by different manufacturers both in America and in Europe.

The American calomels were obtained by corresponding with the respective manufacturers, while the European calomels were obtained through the kind assistance of Dr. Joseph Rosin, of Merck and Company. In this investigation we have examined sixteen specimens of at least seven different origins, as follows:

American manufacturer	A	2 specimens
American manufacturer	B	6 specimens
American manufacturer	C	1 specimen
German manufacturer	A	3 specimens
French manufacturer	A	1 specimen
French manufacturer	B	1 specimen
English	A	1 specimen
Of unknown origin		1 specimen

For many years there have been three different types of calomel described in the literature, differentiated by their methods of manufacture and their titles, and by specific recognition in some of the European pharmacopœias.

These different types are discussed at some length in "Hager's Handbuch der Pharmaceutischen Praxis," the following abstracts being taken from the 5th edition of that famous work, published in Berlin in 1907, where photographs are shown of their comparative appearance when examined under the microscope.

They are distinguished by the following Latin titles:

- A. *Hydrargyrum chloratum præparatum*
- B. *Hydrargyrum chloratum vapore paratum*
- C. *Hydrargyrum chloratum præcipitatum*

Type A is made by subliming a mixture of mercuric chloride and metallic mercury.

This type is first produced in white, glistening masses of crystalline texture, the product being subsequently reduced to a fine powder by levigation and purified with water in unglazed porcelain mortars or in ball mills.

It occurs as a fine, impalpable, yellowish white, dustless powder, which has a tendency to agglutinate and which under microscopic examination is found to consist of broken crystal fragments which are larger in size than those observed in other types.

Type B is made by permitting calomel vapor (obtained by a reaction similar to that described above or by starting with the crude product made as above, before levigation) to come in contact with steam or cold air in a closed vessel or chamber. Under these conditions the calomel condenses in the form of small crystals and crystal aggregates. It is not always necessary to levigate this variety but it is sometimes done.

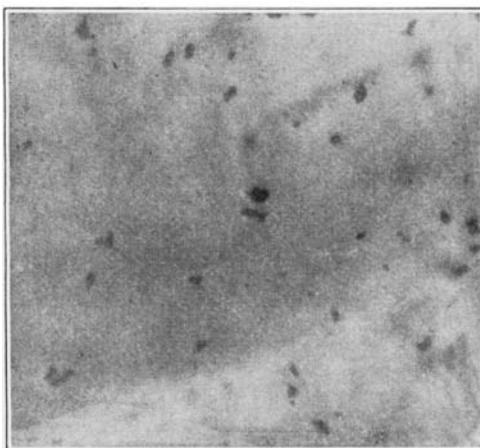
It occurs as a dusty powder which does not show a tendency to cohere when pressed between the fingers. Under the microscope it shows translucent prismatic crystals of a great variety of sizes and shapes and of which the individual particles are smaller than in A.

Type C is made by precipitation. There is a choice of a number of methods of which the two following are typical. In one method a dilute solution (1 in 30) of mercuric chloride is saturated with purified sulphur dioxide. After several hours standing to complete the reduction and precipitation, the precipitate is collected, washed and dried. In another method mercurous nitrate solution is precipitated with a diluted hydrochloric acid and the precipitate subsequently collected, washed and dried.

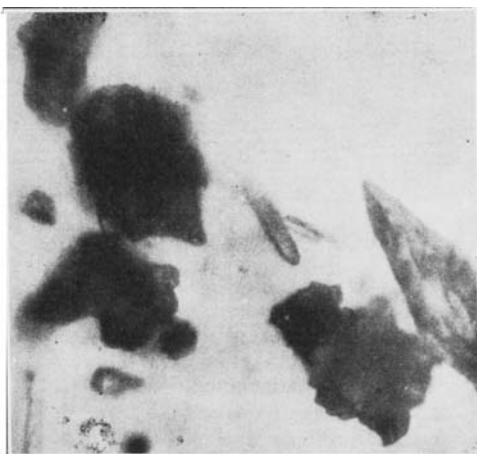
Precipitated calomel is a heavy, fine, amorphous, white powder, greasy to the touch and very adherent to the fingers. It is the finest of all of the types in the size of the particles when subjected to microscopic examination.

All three of these types are light sensitive in the presence of moisture and must be dried and handled in the dark before finally packaging for the market.

Types A and C have the property of agglutinating and both varieties are unsuitable for dusting purposes.



Calomel specimen No. 1. (Specimens Nos. 4, 10, 12 and 15 were of similar appearance.)



Calomel specimen No. 2. (Specimens Nos. 3 and 14 were of similar appearance, No. 14, however, contained more acicular crystals.)

Type B does not agglutinate and is suitable for dusting, and according to Hager is *the variety to be dispensed when "calomel" is ordered.*

Type A is known by the following Latin names:

Hydrargyri subchloridum
Hydrargyrum chloratum
Hydrargyrum chloratum mite
Hydrargyrum chloratum mite sublimatum paratum
Hydrargyrum chloratum mite praeeparatum seu levigatum.

Type B is known by the following Latin names:

Hydrargyri chloridum mite
Hydrargyrum chloratum vapore paratum
Calomel vapore paratum.

Type C is known by the following Latin names:

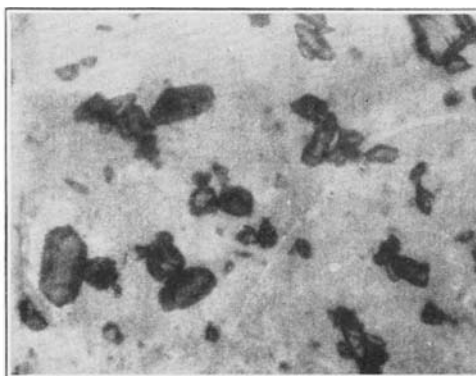
Hydrargyrum chloratum via humida paratum
Hydrargyrum chloratum mite praecipitatione paratum.

The specimens were labeled as follows (omitting the name of the manufacturer):¹

1, Calomel, U. S. P. special, finely powdered; 2, Calomel, mercurous chloride, C.P.; 3, Calomel, U. S. P., mercurous chloride; 4, Calomel, U. S. P. X special, fine powder; 5, Calomel, mild mercurous chloride, U. S. P.; 6, Calomel, reagent; 7, Calomel, mild mercurous chloride, U. S. P. X; 8, Hydrarg. chlor. mite, sublimatum; 9, Hydrarg. chlor. mite, vapore paratum; 10, Hydrarg. chlor. mite, precip., *via* humida paratum; 11, Protochlorure demercure, calomel a la vapeur; 12, Protochlorure de mercure, pricipite blanc; 13, Calomel; 14, Calomel; 15, Calomel, U. S. P. special, fine powder; 16, Calomel, sublimed, not powdered.



Calomel specimen from ointment (a).



Calomel specimen No. 5. (Specimens Nos. 8, 9, 11, 13 and 16 were of similar appearance.)

TABULATION OF RESULTS OF EXAMINATION OF CALOMEL SPECIMENS, APPLYING U. S. P. TESTS.

No.		Assay. %	Other U. S. P. Tests.
1	American manufacturer A	99.96	O. K.
2	American manufacturer B	99.67	O. K.
3	American manufacturer C	99.51	O. K.
4	American manufacturer B	99.95	O. K.
5	American manufacturer A	100.09	O. K.
6	American manufacturer B	99.91	O. K.
7	American manufacturer B	100.05	O. K.
8	German manufacturer A	99.42	O. K.
9	German manufacturer A	99.39	O. K.
10	German manufacturer A	99.69	O. K.
11	French manufacturer A	98.93	O. K.
12	French manufacturer B	99.13	O. K. except 0.15% residue on heating
13	English manufacturer	98.78	O. K.
14	American manufacturer (identity unknown)	99.13	O. K.
15	American manufacturer (identity unknown)	100.06	O. K.
16	American manufacturer (unpowdered)	100.36	O. K.

A small portion of the calomel was mixed on a microscope slide with a 60% aqueous solution of glycerin.

An examination was first made with a 10 X eyepiece and a 4-mm. objective, referred to as "low power." Further examination was then made with a 20 X eye-

¹ Five illustrations of photomicrographs of Calomel specimens are shown.

NOTE: The word "number" is omitted preceding specimen.

piece and a 4-mm. objective, referred to as "high power." The measurements were made with a stage micrometer under 8-mm. objective with a 20 X eyepiece.

No. 1.—American manufacturer *A*. Under low power this specimen appeared crystalline but on examination under high power the particles are seen to be round or oval and do not show a crystalline structure. The largest particles are less than 0.1μ in length.

No. 2.—About half the total number of particles are clear columnar crystals about 2μ in length with the width from one-fourth to one-eighth of the length. There are a few slender acicular crystals. About half the number of particles are rosettes and crystal aggregates ranging in diameter from 0.5 to 1.5μ .

No. 3.—This specimen is very similar in appearance to No. 2 except that some of the rosettes are 2μ in diameter.

No. 4.—This specimen is very similar in appearance to No. 1.

No. 5.—This specimen shows more crystal fragments than rosette aggregates, although they are not acicular.

The crystal fragments range in size from 0.25μ to 1μ and a few even as large as 2μ . The rosettes average from 0.5 to 1μ in diameter.

No. 6.—This specimen is composed almost entirely of rosettes ranging in size from 0.5 to 2μ in diameter. There is an occasional sharp pointed columnar crystal about 3μ in length.

No. 7.—This specimen is almost identical with No. 6 except that the range in size of the rosettes seems to be slightly greater, the smaller being 0.25μ and the larger 3μ .

No. 8.—This specimen is composed of fairly round rosettes mostly uniform in size, a few as small as 0.25μ in diameter and a few as large as 1μ . The separate crystals are very few in number.

No. 9.—This specimen consists entirely of small rosettes and crystal aggregates mostly ranging from 0.25 to 0.5μ in diameter, a few reaching 1μ in size. There are no acicular crystals in this specimen.

No. 10.—This specimen consists almost entirely of very small blunt cylinders of uniform diameter, which show no evident crystalline character under any magnification.

The length of these particles is about 0.1μ and the diameter is about one-fourth of the length.

No. 11.—This specimen is composed mainly of rosettes and crystal aggregates ranging from 0.25 to 1μ in diameter. There are a few separate columnar or prismatic crystals, some more than 2μ in length, and a number of smaller particles, probably broken fragments of these columnar crystals.

No. 12.—This consists of many small irregular-shaped particles ranging from 0.2μ down to 0.05μ in size. The larger particles may be aggregates of the smaller ones. There are very few columnar or prismatic crystals.

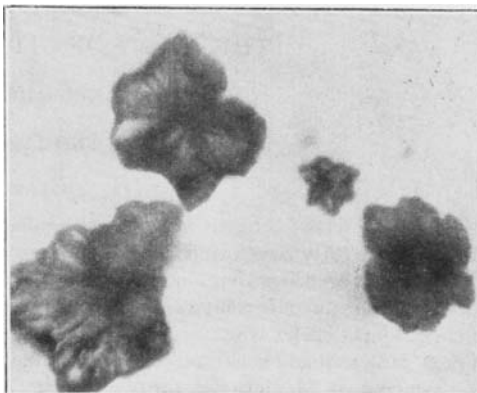
No. 13.—This specimen is composed entirely of rosettes and crystal aggregates, averaging from 0.25μ to 0.75μ with a few as large as 1μ .

No. 14.—This specimen, which is of unknown origin, contains the largest proportions of acicular or columnar crystals of any specimen examined.

The acicular crystals range from 0.5 to 2.5μ in length, the width being from $\frac{1}{8}$ to $\frac{1}{4}$ the length.

The rosette aggregates which constitute the remainder of the specimen are rather uniform in size, averaging 0.75μ in diameter.

No. 15.—This specimen consists of small particles mostly cylindrical or rod shaped, some few of which show a crystalline structure. The largest rod-shaped particles are about 0.2μ in length, but there are many particles less than 0.1μ in diameter.



Calomel specimen No. 6. (Specimen No. 7 was of similar appearance.)

No. 16.—This specimen shows a variety of forms of particles. There are some isolated crystals (not acicular), a few rosettes, a number of crystalline aggregates and some very small particles. The range in size is from 0.05 to 0.1 μ .

No. 17.—(a) and (b) is a specimen of the calomel extracted from the ointment which led to the investigation.

In these specimens large and pointed crystals, some of which appear to have been eroded, are in evidence.

None of the commercial calomels are identical with this specimen in appearance, and it is possible that some alteration in the physical condition of the crystals in the ointment sample may have resulted as a consequence of the action of the fat of the ointment base on the calomel after the ointment was prepared.

The results of the survey are interesting as showing the high quality to which the specimens conformed and also as illustrating the wide variance in size and type of particles as shown by the photomicrograph illustrations, all of which are on the same basis of magnification.

THE ASSAY OF CITRINE OINTMENT.*

AN EXPERIMENTAL STUDY.¹

BY THOMAS G. WRIGHT.

INTRODUCTION.

The Citrine Ointment of to-day is an ointment which is essentially a mixture of mercuric nitrate with a fatty base formed by the action of nitric acid upon lard. An ointment by this name first appeared in the London Pharmacopœia of 1650 and since that date there has been a wide difference of opinion as to its composition, stability and assay. The original preparation was a mixture of coral, limpet shells, white marble, white lead, quartz and tragacanth, incorporated with a base of hogs' lard, suet and hens' grease; but contained no mercury.

Nitrate of Mercury Ointment, approximating in composition the present Citrine Ointment, first appeared in the Edinburgh Pharmacopœia of 1722 and was introduced, according to Christison's Dispensatory, as a substitute for a then popular proprietary remedy, "Golden Eye Ointment," an ointment of yellow oxide of mercury. It was not until 1746 that a similar ointment was admitted to the London Pharmacopœia. A milder ointment, one made with twice the quantity of lard, was made official in the Edinburgh Pharmacopœia of 1792. An ointment composed of mercury, nitric acid, lard and olive oil was included in the Dublin Pharmacopœia of 1807. This ointment was admitted to the British Pharmacopœia of 1864, and one of similar composition was admitted to the French Pharmacopœia at a later date. In this country, the ointment received official recognition as early as 1820, when it appeared in the Pharmacopœia of the United States under the title of *Unguentum Hydrargyri Nitratis*. It was readmitted at each succeeding revision of the Pharmacopœia until that of 1920 when it was dropped. Its official status, however, was not changed as it was immediately given a place in the National Formulary.

From the date of its introduction into the Edinburgh Pharmacopœia to the present time, many different formulas have been suggested for the preparation of the ointment, the principal objectives being to simplify the preparation of the claidin base and to improve the keeping qualities of the ointment. This phase of the subject, in so far as it pertains to the work reported in this paper, will be discussed in detail under the composition of the ointment.

* Scientific Section, A. P. H. A., Washington meeting, 1935.

¹ From the laboratory of A. G. DuMez, Professor of Pharmacy, School of Pharmacy of the University of Maryland. Compiled from a thesis submitted to the Faculty of the Graduate School of the University of Maryland in partial fulfilment of the requirements for the degree of Master of Science.