annual
A REPRINT OF THE REPORTS

OF THE

COUNCIL ON PHARMACY AND CHEMISTRY

OF THE

AMERICAN MEDICAL ASSOCIATION

WITH THE

COMMENTS THAT APPEARED IN
THE JOURNAL DURING 1911

PREFACE

The reports of the Council on Pharmacy and Chemistry of the American Medical Association have appeared from time to time in more or less complete form in THE JOURNAL of the American Medical Association. However, in some cases, the more technical and scientific parts of the reports, both from lack of space and because of their technical nature, have been abstracted or entirely omitted from the published reports. Believing that these scientific investigations should be available to scientists in general, especially to chemists, pharmacologists, etc., interested in medicine, this volume, containing the complete reports of the Council for 1911, as well as the comments which appeared at the time of publication, has been prepared.

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Reports of the Council on Pharmacy and Chemistry

FORMUROL

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., Jan. 21, 1911, p. 210)

Formurol, Citrocoll and Aspirophen were submitted to the Council by the Cellarius Company of San Francisco. The manufacturers having failed to substantiate the claims they make for these products, the Council has voted that the preparations be refused recognition. The Council also authorized the publication of the following report, which deals particularly with one of the preparations—Formurol.

W. A. PUCKNER, Secretary.

Formurol is the product of the Chemische Fabrik Falkenberg, Falkenberg-Gruenau, near Berlin, Germany. The Cellarius Company, San Francisco, acting as selling agents for the United States, submitted Formurol (along with Aspirophen and Citrocoll, also made by the same firm) to the Council, with the statement that it is "hexamethylentetraminsodium-citrate," and that it has the following composition: "$C_6H_7O_7Na.C_6H_{12}N_4$."

Zernik,[1] who examined these products, reported that Aspirophen, Citrocoll and Formurol do not have the composition that is claimed for them by the Fabrik Falkenberg. Formurol, he states, is not a definite chemical compound, but a mixture of hexamethylenamin and sodium citrate. The agents were advised of this fact by the Council and were asked to submit evidence to substantiate their claims. No such evidence was submitted.

Since a compound having the composition that is claimed for Formurol is theoretically possible, the Council requested that the product be examined in the Association Laboratory to determine whether it still was the simple mixture reported by Zernik, or whether, perhaps, it now possessed the formula claimed for it. The following report was made by the Association chemists:

1. Zernik: Arb. a. d. Pharmazeut. Inst. d. Univ. Berlin, 1907, iv, 46.

Formurol, as submitted to the Council, was in the form of tablets weighing about 1 gm. each and appeared to be composed of a fine white substance interspersed with some transparent particles. The tablets were readily soluble in water, were odorless and possessed a slightly acid taste. The aqueous solution responded to tests for hexamethylenamin, citrate and sodium. To determine whether hexamethylenamin was present in the free or the combined state, the method of Zernik was employed. This consists in the extraction of Formurol with chloroform, which dissolves out hexamethylenamin, leaving insoluble sodium citrate. As the use of the solvent, chloroform, would seem to preclude decomposition of such a hypothetical compound as "hexamethylenamin-sodium-citrate," the extraction of hexamethylenamin from Formurol may be taken to demonstrate its presence in the free state.

That Formurol is not a compound of hexamethylenamin, but a mixture of hexamethylenamin and sodium citrate, was further indicated by the appearance of the crushed tablets described above. Further, under the low-power microscope the powder was found to be composed of transparent crystals and white opaque particles which appeared to be masses of minute crystals. When treated with chloroform the transparent crystals dissolved, leaving the white masses intact, demonstrating the presence of two distinct substances, one soluble and the other insoluble in chloroform. It having been demonstrated that the residue obtained by evaporation of chloroform could not be weighed as hexamethylenamin, due to enclosed chloroform, the amount of this substance in the residue was determined.

The method used has been described in the Report of the Chemical Laboratory of the American Medical Association, Vol. I, p. 55, and depends on the decomposition of hexamethylenamin by means of sulphuric acid to form ammonium sulphate and formaldehyd. From this solution the ammonia is liberated, distilled and determined[2] by titration and from the ammonia found the amount of hexamethylenamin is calculated. By this method Formurol was found to contain (*a*) 35.42 per cent. and (*b*) 35.32 per cent., or an average of 35.37 per cent. hexamethylenamin. The residue insoluble in chloroform was shown to consist essentially of disodium hydrogen citrate

2. Determinations were made, following the details of the method described in the report of the Chemical Laboratory of the American Medical Association, Vol. I, p. 55, with the following results: (*a*) 1.0769 gm. Formurol yielded an amount of ammonia requiring 10.96 c.c. normal sulphuric acid for neutralization, indicating the presence of 0.3815 gm. or 35.42 per cent. hexamethylenamin. (*b*) 1.1178 gm. Formurol required 11.36 c.c. normal sulphuric acid, equivalent to 0.3952 gm. or 35.32 per cent. hexamethylenamin, making an average of 35.37 per cent.

by determining[3] the amount of sodium (Na) contained in Formurol. The percentage of sodium calculated from the amount of sodium sulphate found was (*a*) 11.38 per cent. and (*b*) 11.20 per cent., or an average of 11.29 per cent., equivalent to 62.50 per cent. disodium hydrogen citrate.

As a check on this determination, the amount of material contained in Formurol which is insoluble in chloroform was determined.[4] It was found to be (*a*) 63.23 per cent. and (*b*) 63.49 per cent., making an average of 63.36 per cent., and thus agreeing fairly well with the results obtained when the sodium content was assumed to be disodium hydrogen citrate. From this analysis it appears that Formurol is not a definite compound of hexamethylenamin and sodium citrate, but instead is a mixture of these substances consisting approximately of hexamethylenamin 35.37 per cent. and sodium acid citrate (disodium hydrogen citrate) 63.36 per cent., practically a mixture of 1 part hexamethylenamin and 2 parts sodium acid citrate. These results agree with those reported by Zernik and show that the product now, as then, is not true to claims.

In view of the findings of the laboratory, it is recommended that Formurol be refused recognition. As the exploitation of well-known remedies under false and misleading names is detrimental to the progress of medicine, it is recommended that publication of this report be authorized.

EDITORIAL NOTE: This report illustrates once more the value of the Council on Pharmacy and Chemistry and the Chemical Laboratory to the medical profession. Before the Council was organized there was no agency to protect the physician's interests in the matter of pharmaceuticals. Under the old régime Formurol would have been heralded as a new "synthetic" of the most approved made-in-Germany type—and the claims would have gone unchallenged. To-day its status is made clear and the profession is informed. Only those who have closely studied the question can realize what a wonderful power for commercial probity the Council has

3. Sodium was estimated by converting to sodium sulphate in the usual way, with the following results: (*a*) 1.0319 gm. Formurol yielded 0.3621 gm. sodium sulphate, equivalent to 11.38 per cent. sodium. (*b*) 0.8783 gm. Formurol yielded 0.3035 gm. sodium sulphate, equivalent to 11.20 per cent. sodium; average, 11.29 per cent., equivalent to 62.50 per cent. disodium citrate ($C_6H_6O_7Na_2 + H_2O$).

4. The matter insoluble in chloroform was determined by weighing Formurol to a tared filter, which had been washed with chloroform and dried at 100 degrees, and percolating with chloroform till the dried filter and contents became constant in weight. By this method (*a*) 1.0769 gm. Formurol yielded 0.6826 gm. or 63.23 per cent. matter insoluble in chloroform; and (*b*) 1.1178 gm. Formurol yielded 0.7079 gm. or 63.49 per cent. insoluble matter; average, 63.36 per cent.

proved. Under the *laissez faire* system of the past, many large pharmaceutical firms gave little attention to the accuracy of the claims made for their products. If the advertising gave good "pulling" results, that was all that was asked or expected. Within the past five years a wonderful change has taken place in this regard, and firms of the better class have so modified their advertising as to make it not only conservative in tone, but to approximate scientific accuracy.

BISMUTH IODO-RESORCIN SULPHONATE

Report of the Council on Pharmacy and Chemistry

(*From The Journal A. M. A., Feb. 11, 1911, p. 441*)

A pharmaceutical preparation submitted to the Council was said to contain as its essential ingredient, bismuth iodo-resorcin sulphonate. In accordance with its general procedure, the Council investigated this unofficial constituent when it considered the preparation that was said to contain it. The following report was made to the Council in reference to this constituent:

The Council, having voted to take up the consideration of bismuth iodo-resorcin sulphonate, the Association chemists were requested to investigate the composition of the specimen submitted by the firm whose pharmaceutical preparation contained this substance as an ingredient. The composition of this article, as determined by the chemists, varied widely from the composition that was claimed by the firm. In view of these discrepancies, the Council directed that the chemists' findings be submitted to the firm and an explanation requested. This was done and the firm replied by acknowledging the differences in general, but attacking in many minor ways the findings of the laboratory. The Association chemists now report an exhaustive reexamination of the product in reference to the points involved. This, while showing a slight modification of the previous findings, because more refined methods were used, shows on the whole, that the firm was grossly ignorant regarding the composition of its product. It also shows that the firm's attack on the chemists' work was without justification.

As this furnishes a typical illustration of the many obstacles which are put in the way of the Council and the laboratory, and since it is a good illustration of the lack of reliance which is to be placed on the statements of many firms, the referee has requested the chemists who made the examination to prepare a record of their work. This record is now presented and it is recommended that the Council authorize its publication. As it is not believed that the submission to

the Council of a preparation untrue to claims was deliberate on the part of the firm, and inasmuch as more recently a specimen of bismuth iodo-resorcin sulphonate, containing the amount of iodin claimed, has actually been received, it is recommended that when the report is published, the names of the firm and of the preparation be omitted.

The Council authorized publication of this report and also of the contribution from the chemical laboratory, but in accordance with its regular custom, both reports were sent to the interested firm before publication. The firm, in reply, requested that before publication the report be modified. The referee of the Council submitted this reply to the chemists for comment and then requested that the entire matter be assigned to a second referee for an opinion. This was done and the second referee submitted the following report:

"Your referee has gone over the whole matter of the claims for the composition of the bismuth iodo-resorcin sulphonate. The firm submitting the product gives a formula which calls for the presence of 19.69 per cent. of iodin and 43.17 per cent. of bismuth. A preliminary analysis made in the Association laboratory showed about 10 per cent. of iodin and about 50.6 per cent. of bismuth. When these findings were submitted to the firm they questioned the accuracy of the analyses and presented some analyses of their own, which, however, did not support their own claims for the formula, but do suggest that the product cannot be a definite chemical compound of the composition assumed. A second analysis in the Association laboratory shows now 11.59 per cent. of iodin, as against 14.2 per cent. reported by the firm's chemist. The firm next set up the plea that the discrepancy may be explained by the hygroscopic character of the product, which, they say, the Association laboratory did not take into consideration.

"The present referee is of the opinion that the contention of the firm does not conform to the facts. The formula proposed by the firm gives a ratio of iodin to bismuth of 1:2.19, but according to the firm's own submitted analysis the ratio should be 1:3.19. This situation alone is sufficient to show the absurdity of the claim that the composition of the product is definitely known. It is probably an indefinite mixture, or at any rate a product the composition of which is not accurately known to the firm manufacturing it. The report of the Association laboratory gives the bismuth content even higher, and this would be still further increased if the moisture content were to be calculated out, as the firm finally contended. Such a correction would not help the firm's formula.

"Several of the statements in the letters from the firm are but little more than quibbles, and seem unworthy of consideration. The failure to substantiate a formula is enough to condemn the contention of the firm and to warrant a rejection of its claims. The final report of the Association

laboratory appears to present a perfectly fair statement of the situation, and your referee recommends its publication in full as well as that of the first referee's report and of this report.

"It is worthy of notice, however, that while the Council is unable to accept bismuth iodo-resorcin sulphonate or the proprietary preparation containing it, as submitted by this firm, the firm's products have been materially improved as a result of the Council's investigation."

The second referee's report was adopted by the Council and in accordance with the recommendation, the matter is herewith published.

W. A. PUCKNER, Secretary.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE AMERICAN MEDICAL ASSOCIATION]

BISMUTH IODO-RESORCIN SULPHONATE

W. A. Puckner and L. E. Warren

Some time ago a proprietary preparation (in the form of suppositories) which was said to contain bismuth iodo-resorcin sulphonate as its chief ingredient, was refused recognition by the Council because, among other things, the claims made in regard to its composition were not substantiated by the firm which sold it. Subsequently the results of the examination of this product in the Association laboratory were published,[1] and it was shown that the preparation contained only negligible amounts of iodin and hence could not possibly contain more than very small amounts of bismuth iodo-resorcin sulphonate.

A similar preparation was recently submitted to the Council with the claim that it contained bismuth iodo-resorcin sulphonate as its essential constituent. In accordance with its usual procedure the Council considered this constituent at the same time that the preparation containing it was taken up.

The formula assigned by the manufacturer to this substance is as follows:

$$[C_6H_2(OH)_2ISO_3]_3Bi.3Bi(OH)_3$$

Bismuth iodo-resorcin sulphonate apparently is not described in chemical literature. The manufacturer of the specimen examined stated, however, that the process for the manufacture of the substance was "the subject of a patent applica-

1. Anusol Hemorrhoidal Suppositories: THE JOURNAL A. M. A., Oct. 2, 1909, p. 1112.

tion" by the firm. The potassium salt, from which the bismuth salt is said to be prepared, has been obtained in the form of microscopic crystals containing three molecules of water of hydration.[2]

$$KC_6H_2(OH)_2ISO_3+3H_2O$$

THE QUESTIONS INVOLVED

The points involved in the examination which is here reported have been classified as follows, for the purpose of bringing out the matter more clearly:

1. From the formula submitted by the manufacturer it was calculated that the bismuth salt should contain 19.69 per cent. of iodin and 43.17 per cent. of bismuth.

2. From the formula found in the literature it was also calculated that the potassium salt should contain 31.079 per cent. iodin and 13.22 per cent. of water.

3. In the first examination we reported finding but about 10 per cent. of iodin in the bismuth salt (in which 19.69 per cent. of iodin had been claimed) and about 50.6 per cent. of bismuth, an amount considerably larger than that indicated by the formula.

4. We also reported finding about 28.06 per cent. of iodin in the firm's specimen of potassium iodo-resorcin sulphonate in which, if the formula were correct, there should have been 31.079 per cent.

THE FIRM'S REPLY

These facts, substantially as given, were submitted to the firm which replied to the points raised as follows:

1a.—The theoretical iodin content of the firm's bismuth salt was 20.76 per cent. and its bismuth content was 45.36 per cent.

2a.—The potassium salt contained no water of hydration and theoretically should, therefore, contain 35.84 per cent. of iodin.

3a and 4a.—The method used by the Association laboratory for the determination of iodin was not a standard one in chemical literature since it gave but about 70 per cent. of the total iodin present. After the firm had reexamined a portion of the original specimen, it reported that by its method it had found 14.2 per cent. iodin. According to the formula it should have contained 19.69 per cent. iodin, although the Association chemists had found but about 10 per cent. iodin. The firm stated that in the earlier examinations of its product a

2. Fischer: Monatschr. f. Chem., II, 1881, 340.

reagent had been used which was afterward found to contain large amounts of chlorin. In making the iodin estimations this chlorin was weighed as (silver) iodid with consequent erroneous results, no control estimations, evidently, having been made.

REEXAMINATION BY THE LABORATORY

Our calculations of the theoretical iodin and bismuth content in bismuth iodo-resorcin sulphonate having been challenged, the values were recalculated. This recalculation showed that the values first reported were correct and that the firm's challenge was unwarranted.

Our findings concerning the iodin content in bismuth iodo-resorcin sulphonate also having been challenged, the iodin in the original specimen was redetermined by several independent methods. The highest result obtained by any method was 11.59 per cent. iodin. Although somewhat higher than that obtained by the method previously used, it is still considerably less than was claimed by the firm in its reexamination, viz., 14.2 per cent. An appreciable quantity of chlorin was also found, which may explain, at least in part, the firm's wrong estimate of its product.

On reexamining the potassium salt we found 32.00 per cent. of iodin and 10.41 per cent. of water—this notwithstanding the fact that the firm had asserted that its product contained no water of hydration.

A review of the above facts shows that the contentions of the firm could not be substantially confirmed. To summarize:

SUMMARY

1. The firm's claim that the laboratory's calculations were wrong is shown to be unfounded.

2. The firm's statement that its potassium salt of iodo-resorcin sulphonic acid contained no water of hydration is shown to be wrong, the salt, in fact, containing more than 10.0 per cent. of water.

3. The contention of the firm that the first method of analysis used by the Association laboratory gives low results is correct. The assertion is, however, not justified that the method gives but 70 per cent. of the iodin present since the amount first reported by us is about 88 per cent. of the amount found later.

The accompanying table gives in graphic form the essential points of the controversy.

	According to firm's formula or formula in literature.	According to analysis of Association chemists.	According to the firm's revised statements.	According to the check analysis of Association chemists.
Iodin content in bismuth salt ...	19.69 *	10.00	{ 20.76 § { 14.20	11.59
Bismuth content in bismuth salt ...	43.17 *	50.60	45.36 §	No analysis made.
Iodin content in potassium salt..	31.079 †	28.06	35.84	32.00
Water of hydration in potassium salt	13.22 †	No analysis.	0.0	10.41

* Based on formula given by firm.
† Based on formula given in literature.
§ These figures were later acknowledged by the firm to be incorrect.

COMPRESSED OXYGEN

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., March 18, 1911, p. 833)

The referee of the Council appointed to report on the composition of compressed oxygen as found on the market and to make recommendations as to its inclusion with New and Nonofficial Remedies submitted the following report:

The Section on Stomatology at the 1909 session of the American Medical Association having recommended the inclusion of compressed oxygen with the U. S. Pharmacopeia, the Council voted to describe this product with New and Nonofficial Remedies until such Pharmacopeial recognition had been secured. This action having been decided on, it became necessary to provide standards of purity for this substance. Correspondence both with firms who make the product as well as with those who use it gave the referee of the Council little information as to what degree of purity should be required for this substance, and it therefore became necessary to examine the product as it was found on the market.

Professor Warren R. Smith of Lewis Institute, Chicago, kindly offered to cooperate with the Council and to make an examination of this product. The referee herewith transmits the very thorough report regarding the composition of commercial compressed oxygen which has been made by Professor Smith in collaboration with Edwin D. Leman. The referee recommends that the Council express its appreciation for the work and that it request publication of the report in THE JOURNAL. The referee further recommends that the descrip-

tion of compressed oxygen submitted herewith be adopted for inclusion with New and Nonofficial Remedies.

This report was adopted by the Council and in accordance therewith the examination of Smith and Leman is published below and the description of compressed oxygen appears with New and Nonofficial Remedies on another page of this issue of THE JOURNAL.

W. A. PUCKNER, Secretary.

The Purity of Compressed Oxygen

PROF. WARREN R. SMITH AND EDWIN D. LEMAN

We have recently examined three specimens of commercial oxygen purchased in the open market, with the results shown in the accompanying table.

Maker	Chicago Oxygen Gas Co., Chicago		Ohio Chemical and Mfg. Co., Cleveland		S. S. White Dental Mfg. Co., Philadelphia	
Per cent. oxygen	94.78	94.80*	97.84	97.85*	96.84	96.76*
	94.78	94.80†	97.84	97.86†	96.84	96.93†
Per cent. nitrogen[1]	5.22	5.20*	2.15	2.16*	3.09	3.17*
	5.22	5.20†	2.14	2.16†	3.09	3.00†
Potassium iodid test	Negative.		Negative.		Negative.	
Per cent. carbon dioxid	Negative.		Negative.		0.06	0.07*
Carbon monoxid methane, etc.	Negative.		Negative.		Negative.	

1. That is, not absorbed by potassium pyrogallate.
* Smith.
† Leman.

The gas from the Chicago Oxygen Co. was claimed to be under a pressure of 16 atmospheres. The amount of nitrogen found in this sample is just about that which would be present if pure oxygen were forced into a container filled with air under one atmosphere pressure until a pressure of 16 atmospheres was reached. The other samples were stated to be under a pressure of 1,600 pounds, so that the amounts of nitrogen found cannot be accounted for by a similar hypothesis.

The potassium iodid test mentioned in the table consisted in passing from 2 to 4 liters of the gas through a solution containing starch and potassium iodid. A negative result in this test shows that the gas is free from chlorin, ozone, oxids of nitrogen, etc. The negative results for carbon dioxid mean that not more than a slight opalescence was obtained by passing 2 to 4 liters of the gas through a solution of barium hydroxid. The carbon monoxid test was made by passing the gas through alkali to remove all carbon dioxid, then over heated platinum, and finally through barium hydroxid solu-

tion. A negative result here shows freedom from carbon monoxid, methane and other hydrocarbons.

PANTOPON REJECTED

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., April 29, 1911, p. 1278)

A referee of the Council reported that Pantopon was not eligible for inclusion with New and Nonofficial Remedies and recommended that the reasons for its rejection be published. The Council voted to adopt this recommendation and in accordance with its regular procedure the facts were reported to the manufacturers before publication. The firm's reply having been received, the Council authorized publication of the report which appears below.

W. A. Puckner, Secretary.

PANTOPON

Under this name, the Hoffmann LaRoche Chemical Works submitted a pharmaceutical preparation of opium, consisting of a mixture of the hydrochlorids of the various opium alkaloids, as extracted directly from the drug, with more or less purification.

The Council holds that this name does not effectively suggest that the preparation is a mixture of opium alkaloids, as is required by the part of Rule 8, which reads:

"In the case of pharmaceutical preparations or mixtures the trade name must be so framed as to indicate the most potent ingredients."

and further explains:

"It is particularly important that actively poisonous or habit-forming drugs be not disguised under an innocently worded title."

The Council maintains that the name "Pantopon" does not sufficiently protect the public against the habit-forming and other dangers inherent in such mixtures. The manufacturers, on being informed of these objections, offered to substitute the name "Omopon." As this is open to the same objections, it could not be accepted by the Council. After much correspondence, the manufacturers refused to consider any other name which would more definitely suggest its composition.

The Council is therefore forced to reject the product and has ordered the publication of this report.

Comment: This is a case in which the rules of the Council are in conflict with the views of the manufacturers and the Council is bound in consistency to stand by its rules, which are framed to protect the public and the profession. Pantopon

is not a definite chemical body, but a mixture of known substances—the several alkaloids naturally occurring in opium—, and the Council's rules require that such a preparation should bear a name indicative of its composition. The name "Pantopon," although it might suggest opium to those well acquainted with Greek, would not do so to all and it would be relatively easy for physicians to fall into the habit of using it indiscriminately without realizing fully the character of the preparation, and the preparation thus becomes a menace to the public.

As to the merits of the preparation itself, it is remarkable what a literature has been built about a simple mixture of the opium alkaloids. The preparation is claimed to be superior to opium because it is more readily soluble. This trifling advantage seems to have been sufficient, however, to justify the publication of a dozen or more pamphlets. But in reality, this preparation is nothing more, therapeutically, than a form of opium and, therefore, should be known to the physician as opium. The reports made of its action seem to indicate a lack of critical sifting of the evidence. Notwithstanding, both its source and the fact that experimental and clinical reports emphasize its close resemblance to opium and morphin, one author (H. Haymann, "Pantopon in der Psychiatrie," *Münch. med. Wchnschr.*, No. 43, 1910) remarks that a habit was not produced, inferring that something in the character of the preparation prevented the formation of such a habit.

The one thing to be kept in mind in considering the claims made in the literature for this preparation is that it represents opium and opium only and any statements of its superiority to opium must be read in the light of the well-known tendency of writers to exaggerate the virtues of proprietary substitutes for official substances.

ERPIOL (DR. SCHRADER)

Report of the Council on Pharmacy and Chemistry

(*From The Journal A. M. A., June 3, 1911, p. 1670*)

The original rules of the Council governing the acceptance of articles have recently been modified, particularly by adoption of Rule 10, which reads:

"Unscientific and Useless Articles.—No article will be admitted which, because of its unscientific composition, is useless or inimical to the best interests of the public or of the medical profession."

In view of these modifications, the Council is reconsidering the articles already accepted with the view of determining their compliance with the rules as amended. In line with this

the Council reconsidered Erpiol (Dr. Schrader), manufactured by the William S. Merrell Chemical Company, and from the evidence given below concluded that one of the constituents, gossypin, is inert and its use unscientific. The Council therefore voted that Erpiol (Dr. Schrader) be omitted from New and Nonofficial Remedies and authorized publication of the following report.

W. A. PUCKNER, Secretary.

In consequence of the more thorough scrutiny now given by the Council to the therapeutic value of the remedies admitted to New and Nonofficial Remedies, the Council has reconsidered Erpiol (Dr. Schrader), previously accepted for New and Nonofficial Remedies. Erpiol (Dr. Schrader) is the name applied to capsules containing apiol, ergotin and gossypin, which are sold as an emmenagogue. The first two ingredients have a recognized value in the treatment of diseases of the female generative organs. The third, gossypin, is a preparation from cotton-root bark, belonging to the somewhat indefinite class of pharmaceutical preparations known as resinoids.

Cotton-root bark (*Gossypii radicis cortex*, U. S. P.) has been credited by some with pharmacologic and therapeutic properties, similar to ergot, especially in its action on the uterus; experiments on pregnant animals do not confirm this view. Most authorities on gynecology either make no reference whatever to the drug or ascribe little or no value to it. The preparations from the dried bark are inert.

From reports made to him, Professor J. U. Lloyd concluded (*Eclectic Med. Jour.*, 1876, xxxvi, 545) that a prime fluidextract of fresh cotton-root bark is an active therapeutic agent and deserving the attention of the medical profession, while that of the dry bark is inert and worthless. The gossypin on the market is made from the dried bark.

Professor Lloyd, who is considered an authority on eclectic medicine, says: "Were it left to me to admit or exclude it by reason of its therapeutical position, I should exclude it, because, in my opinion, it has never been demonstrated, in clinical practice, to be worthy of any therapeutic recognition whatever."

As the available evidence indicates that gossypin is an inert preparation, Erpiol (Dr. Schrader) was considered in conflict with Rule 10 and the Council has therefore voted that it be deleted from New and Nonofficial Remedies.

LIQUID NITROUS OXID

Report of the Council on Pharmacy and Chemistry

(*From The Journal A. M. A., Aug. 12, 1911, p. 576*)

The referee of the Council appointed to report on the composition of liquid nitrous oxid as found on the market and to make recommendations as to its inclusion with New and Nonofficial Remedies, submitted the following report:

The Section on Stomatology, at the 1909 session of the American Medical Association, having recommended the inclusion of Liquid Nitrous Oxid with the U. S. Pharmacopeia, the Council voted to describe this product with New and Nonofficial Remedies until such Pharmacopeial recognition had been secured. This action having been decided on, it was necessary to provide a standard of purity for this substance. Correspondence with those who make liquid nitrous oxid, as well as with those who use it, brought out very little information as to what degree of purity should be required. It therefore became necessary to examine the product as it was found on the market.

Prof. Warren R. Smith of Lewis Institute, Chicago, kindly offered to cooperate with the Council and to make an examination of liquid nitrous oxid. The referee herewith transmits the very thorough report regarding the composition of commercial liquid nitrous oxid which has been made by Professor Smith in collaboration with Edwin D. Leman. The referee recommends that the Council express its appreciation for the work, and that it request publication of the report in THE JOURNAL. The referee further recommends that the description of liquid nitrous oxid submitted herewith be adopted for inclusion with New and Nonofficial Remedies.

This report was adopted by the Council, and in accordance therewith the examination of Smith and Leman is published below, and the description of liquid nitrous oxid appears with New and Nonofficial Remedies on another page of this issue of THE JOURNAL. The increasing use of nitrous oxid gas, not only as the sole anesthetic in minor operations, but as a preliminary to ether or chloroform anesthesia, makes the adoption of a standard of purity for this substance highly desirable. W. A. PUCKNER, Secretary.

The Purity of Nitrous Oxid

PROF. WARREN R. SMITH AND EDWIN D. LEMAN

Nitrous oxid is commonly sold in cylinders containing 25 ounces of the liquid, which is approximately equal to 100 gallons of the gas under ordinary conditions. We have analyzed four cylinders of this material from different makers. Three of these samples were purchased in the open market, and the other was supplied to us through the courtesy of the dealer.

We find that all these samples contain nitrogen as the principal impurity, that two of them contain oxygen and that one contains oxygen and carbon dioxid.

All samples were tested qualitatively by passing from 2 to 4 liters of the gas through solutions of barium hydroxid, litmus, silver nitrate, potassium iodid and starch and Nessler's reagent, with negative results in every case except the one which showed carbon dioxid. These results proved that the samples were free from acids, chlorin, the higher oxids of nitrogen, ammonia and various other less probable impurities. The findings in the quantitative analysis are given below.

These results cannot be taken as representing the contents of the cylinders with the same degree of exactness that can be obtained in the analysis of other materials of different nature, because, aside from the ordinary difficulties in the analysis of a gaseous mixture, the problem is complicated by the fact that the impurities (oxygen and nitrogen) are apparently held in solution in the liquid nitrous oxid and as the gas is drawn off, they tend to escape from the solution at a more rapid rate, proportionally, than the nitrous oxid. The result is that the first portions of gas drawn from the cylinders are much more impure than the later portions. From a product containing originally 96.1 per cent. of nitrous oxid, samples varying as widely as from 87.2 per cent. to 98.5 per cent. have been obtained. The greater part of the nitrogen escapes with the first half of the gas, but the oxygen and a small part of the nitrogen persist throughout.

This possibility of variation in the composition of the gas as drawn from the cylinders should be known and reckoned with in the administration of the gas. It seems, also, to make a difference whether the sample of gas drawn for analysis is that which has been standing for some time in contact with the liquid, or is that which comes from the liquid after the gas in the upper part of the cyinder has been drawn off. This variation complicates the analysis, but is hardly enough to be of significance in the administration of the gas. The results given below are either averages of those obtained from samples drawn at intervals during the escape of the entire quantity of gas from the cylinder or of material drawn directly from the liquid itself, methods which we have proved to give results practically identical.

Percentage of	No. 1.*	No. 2.*	No. 3.*	No. 4.*
Nitrous oxid	95.4	93.4	95.8	96.1
Oxygen	0.0	1.4	1.1	00.1
Nitrogen	4.6	5.2	3.1	3.5
Carbon dioxid	0.0	0.0	0.0	0.3

* 1 = Johnson & Lund; 2 = Ohio Chemical and Mfg. Co.; 3 = The Lennox Chemical Co.; 4 = S. S. White Dental Mfg. Co.

Carbon dioxid was determined by absorption with alkali, oxygen with alkaline pyrogallol, nitrous oxid by explosion with hydrogen and nitrogen by difference.

THE BIO-ASSAY OF EPINEPHRIN PREPARATIONS

Report of the Council on Pharmacy and Chemistry

(*From The Journal A. M. A., Sept. 30, 1911, p. 1149*)

The variable quality of epinephrin preparations having been brought to the attention of the Council on Pharmacy and Chemistry, a committee was appointed to determine means of securing uniformity of composition in these products. In particular the committee was to study the keeping qualities of epinephrin solutions and to propose a uniform method for the valuation of preparations depending for their activity on the blood-pressure-raising principle of the suprarenal gland. The report of this committee was submitted to the Council's Committee on Pharmacology and after discussion was adopted by the Council. Its publication having been authorized, it appears below: W. A. PUCKNER, Secretary.

The experiments of Reid Hunt, of Sollmann and Brown, and of W. H. Schultz have shown that the various commercial samples of epinephrin solution differ considerably in activity. It may fairly be assumed that these variations are not due to any intentional difference in composition, but may be attributed, in part, to the spontaneous deterioration with age and exposure and in part to different methods employed in standardizing the solutions at the factory.

Deterioration would naturally depend on the preservative used and on the conditions to which the sample has been exposed. Until the influence of these is better known, it would not be fair to set an age limit. It is better to rely on occasional standardization of samples bought in the open market; and it is herewith recommended that arrangements be made to this end. A variation of 15 per cent. from the claimed strength might be permitted without detriment to the public, and with fairness to the manufacturers. It is highly desirable, however, that manufacturers stamp the age of manufacture on the container, to guard against samples which are obviously over-aged.

As regards the method of standardization there seems to be universal agreement that the preference should be given to the blood-pressure method, the principle of which was first published by E. M. Houghton. In order that different observers

may obtain uniform results by this method, certain details must be observed rigorously, while others may be left to the discretion of the experienced experimenter—and only such should undertake bio-assays. The subjoined method has been elaborated to unify these essential details.

The question of supplying an absolute standard has not yet been solved. This requires the issuance of an absolutely pure epinephrin, or of samples of known, absolute strength. Until arrangements for this can be made, the results will not be absolute; but the unification of methods is desirable even for comparative experiments.

It is recommended, therefore, that the method about to be described be employed in investigations by the Council, and that it be published for the convenience of other investigators and for the information of the manufacturers; it was further recommended that its use by the latter be left optional at least for the present.

BIO-ASSAY OF EPINEPHRIN PREPARATIONS

The strength of epinephrin preparations is to be stated in terms of pure epinephrin, and must not differ by more than 15 per cent. from the strength as determined by the quantity required to produce the same rise of blood-pressure as is produced by a known quantity of pure epinephrin, when both are injected, in approximately the same dilution, and at the same rate, into an homologous vein of the same mammal.

1. *Preparation of Experiment:*—A medium-sized dog (or, less conveniently, a cat or rabbit), weighed and thoroughly anesthetized, is used. The carotid artery is connected with a mercurial manometer, the excursions of which are partly damped by a screw clamp on the connecting tube. It should be made to write on a drum which should revolve slowly—about 1 to 4 inches per minute.

A short cannula of small bore is tied into each saphenous vein close to its junction with the femoral vein and the veins clamped off with small artery clamps. One of these is for the standard solution, the other is for the solution to be standardized. These cannulæ are provided with rubber connections so that the dead space between the opening into the vein and that of the standardized 1 c.c. all-glass syringe does not exceed 0.5 c.c. Two all-glass syringes may be used for making the injections, one marked *A* for the standard solution, and the other marked *B* for the solution to be standardized (or graduated burettes may be used). Both vagi are divided and artificial respiration is performed. Care should be used to maintain a uniform anes-

thesia, complete enough to avoid muscle-movements, throughout the experiment.

2. *Preparation of Solutions:*—The standard solution is prepared by dissolving 1 part of pure epinephrin hydrochlorid in 100,000 parts of 0.9 per cent. sodium chlorid (NaCl) solution.[1] The preparation to be standardized is diluted with normal saline solution to approximately the same strength, as nearly as can be estimated, of that of the standard used.

3. *Determination of Standard Dose:*—One of the syringes (*A*) and its cannular connection are filled with the standard 1:100,000 solution. The blood-pressure tracing is started on a slowly revolving drum, and the standard solution is injected in the dose of 0.1 c.c. per kilo of body weight at such a rate that 1 c.c. passes into the vein in five seconds. Soon after the blood-pressure begins to return to normal the drum may be stopped.

The rise of the blood-pressure should be about 25 to 45 mm. of mercury (equivalent to 12.5 to 22.5 mm. rise of the writing point of a U-shaped manometer), and it should be submaximal. To determine the latter, a second injection of 0.15 c.c. per kilo should be made, with tracing, which should show a higher rise.

If the dose of 0.1 c.c. per kilo does not give a submaximal rise of at least 25 mm.; or if it gives a maximal rise, the dose should be increased or reduced respectively, until the standard effect is obtained, and this dose should be considered the "standard dose" for this animal. The injections should be made at the same rate (1 c.c. in five seconds), and an interval of at least three minutes should elapse after the blood-pressure has returned to the normal, before another injection is made.

4. *Adjustment of Dosage of the "Unknown" Solutions:*—The solution of the "unknown" sample is diluted as directed under No. 2. The unused cannula in the saphenous vein and syringe *B* are filled with the solution to be tested. A "standard dose" (see last paragraph of No. 3) is injected at the rate of 1 c.c. in five seconds, and at intervals of from three to five minutes, while a tracing is being taken. The rise of pressure is compared with that produced by the standard dose of the standard solution. According to the result so obtained, the unknown solution is diluted or strengthened, and the

1. The Hygienic Laboratory, the U. S. P. Revision Committee, or the Council on Pharmacy and Chemistry should issue a standard trituration of ephinephrin hydrochlorid with NaCl 1:900; the standard solution may be prepared by dissolving 0.9 gm. of this in a sufficient quantity of distilled water to make 100 c.c.

results controlled by injections (occasionally making an injection of the standard solution to insure constancy in the reaction of the animal). Final equality is tested by injecting alternately the same dose of the standard and unknown solutions until the average rise from three successive injections is equal within 15 per cent.

5. *Use of Several Animals:*—If an animal reacts abnormally to the standard epinephrin solution, the results from that animal shall be rejected. If the reaction changes during the course of the experiment, or if the blood-pressure falls permanently below 80 mm. of mercury, then the results after this change or fall should be rejected, or at least not compared with those obtained before the changes occurred.

The relation of the unknown solution to the standard solution should be determined on several animals, until the results on three (3) animals agree within 15 per cent., and the average of the three (3) animals shall be accepted as the final result.

QUININ TANNATE

Report of the Council on Pharmacy and Chemistry

(Reprinted, with additions, from The Journal A. M. A., Oct. 14, 1911, p. 1303)

The following report was adopted by the Council and its publication authorized. In accordance with the recommendation, the description of quinin tannate, appearing in New and Nonofficial Remedies department of this issue, requires a quinin content of not less than 29 per cent. and lists, as brands which comply with this standard, the products sold by the Mallinckrodt Chemical Works, the New York Quinin and Chemical Works and the Powers-Weightman-Rosengarten Company.

W. A. Puckner, Secretary.

Quinin tannate, being almost insoluble in water, is practically tasteless and therefore adapted for administration to children in the form of mixtures (suspensions). Although the absorption of this quinin salt is claimed to be somewhat uncertain and its tannin content is an objection, the Council decided to describe it in New and Nonofficial Remedies because of its general availability and its rather general recognition. But in view of the common unreliability of little used substances, the actual description of quinin tannate in New and Nonofficial Remedies was postponed until the market supply could be examined and standards for the preparation formulated.

An exhaustive and critical search of the literature, as well as a chemical investigation of this substance, has been made in the Association's chemical laboratory. The results of this investigation were reported by W. A. Puckner and L. E. Warren in a paper read before the Scientific Section of the American Pharmaceutical Association, and to be published in the Annual Reports of the Chemical Laboratory. In brief the findings are:

Quinin tannate is official in most foreign pharmacopeias, but not in that of the United States. In some of them methods for preparation are given and the official product in all cases is required to contain not less than 30 per cent. of anhydrous quinin alkaloid. The methods prescribed by these pharmacopeias, however, were found in the Association's laboratory to yield products which did not contain the stated amount of alkaloid. As a result of considerable experimentation and consultation with the manufacturers of quinin tannate in this country, a simple method of making the substance was worked out, which will enable anyone at all familiar with pharmaceutical operations to make a preparation of good quality.

Four commercial brands of quinin tannate were examined with the results shown in the accompanying table. From these findings it appears that the quinin tannate of the New York Quinin and Chemical Works is of good quality and contains more than 30 per cent. quinin. The products of the Brunswick Chemical Works (Mallinckrodt Chemical Works, selling agents) and the Powers-Weightman-Rosengarten Co. are satisfactory except that their quinin content is somewhat low. The Merck brand contains about 9 per cent. of free quinin, is bitter and is, therefore, not fit for use. The poor quality of this brand is a further illustration of the need of controlling the quality of medicines, particularly when these are not of much commercial importance.

Inasmuch as the authors have shown that quinin tannate with more than 30 per cent. quinin can readily be made, a preparation with less alkaloid should not be permitted. However, as two brands approach this standard and, as the interested firms will not find it difficult to meet the proposed standard, the referee recommends a temporary standard of not less than 29 per cent. quinin, which standard is to be increased so as to require a quinin content of not less than

30 per cent. by Jan. 1, 1913. It is recommended that the description of quinin tannate submitted be accepted for inclusion with New and Nonofficial Remedies and that the product of the New York Quinin and Chemical Works, of the Brunswick Chemical Works (Mallinckrodt Chemical Works, selling agents), and of the Powers-Weightman-Rosengarten Co. be listed as brands which meet the requirements of this description. It is further recommended that, beginning with 1913, a quinin content of from 30 per cent. to 35 per cent. be required.

In order that physicians may know the facts in the case, it is recommended that publication of this report be authorized.

EDITORIAL COMMENT

In order that pharmacists might be in a position to dispense a good quality of quinin tannate, the examination of the Association's chemical laboratory above referred to was presented to the American Pharmaceutical Association at its recent annual meeting in Boston. While the very simple directions for its preparation which were worked out should make it possible for every pharmacist to prepare his supply of this drug, it was feared that the pharmacist would continue to place his faith in the drug as found on the market and hence the quality of the several available brands was also given in the report. This would have enabled the pharmacist to give preference to those brands which were shown by examination to be of a satisfactory grade. Unfortunately for the pharmacist, as well as for the physician and his patients, those interests which are not in sympathy with the Association's policy of giving publicity to the makers of worthless or adulterated drugs, appear to have been in control when the paper was read and were able to carry a motion that the names of manufacturers be omitted from the paper when it should appear in the American Pharmaceutical Association's publication. In view of this, physicians who use quinin tannate should, in their prescriptions, take the precaution to specify a brand of the drug which was shown to be reliable or, perhaps better still, indicate that they want a brand which corresponds with the standards established by the Council, by appending the letters N. N. R., thus "Quininæ tannas, N. N. R."

Number or Brand.	Water (Loss at 100°).	Anhydrous Quinin.	Ether-Soluble Matter.†	Sulphate.	Chlorid	Taste of Filtrate.
P. W. R.....	7.88	29.30	0.10	Distinct turbidity.....	Noticeable opalescence....	Noticeably bitter.
Brunswick (M. C. W.).	6.50	29.51	0.19	Absent	Very faint opalescence....	Noticeably bitter.
N. Y. Q.....	8.05	33.36	0.36	Distinct turbidity.....	Noticeable opalescence....	Noticeably bitter.
Merck	9.06	33.97	9.02	Very faint opalescence.....	Very faint opalescence....	Very bitter.

† In general, the values given in this column should indicate the presence of uncombined alkaloid, but quinin tannate is slightly soluble in anhydrous ether; hence the test must be carried out under arbitrary conditions and the residue obtained tested for uncombined alkaloid. The three specimens in which the ether-soluble matter amounted to less than 0.4 per cent. contained no uncombined alkaloid.

[Contribution from the Chemical Laboratory of the American Medical Association]

THE PREPARATION, QUALITY AND TESTING OF QUININ TANNATE *

W. A. Puckner and L. E. Warren

Quinin is one of the very few specifics known to medicine. It is probably more used than any other single remedy. Because of the extremely bitter taste of its soluble salts its administration, especially to children, is a perplexing problem. Many attempts have been made to overcome this difficulty, but few of them are without objections. The administration of the alkaloid in capsules or coated tablets is fairly satisfactory, but most children and some adults cannot be induced to swallow these. Suspension of the alkaloid or some of its sparingly soluble compounds in flavored syrup has met with moderate success. Besides the alkaloid itself the most common combinations which are administered in this way are the sulphate, salicylate, tannate and certain esters.

Quinin tannate has been known in medicine for a very long time and the literature concerning it, although chiefly of pharmaceutical interest, is extensive. It is employed chiefly because it exhibits the quinin in an extremely insoluble form, one part of the salt requiring several thousand parts of cold water for solution. The salt is official in the Austrian, Danish, Dutch, German, Hungarian, Russian, Spanish and Swiss pharmacopeias. Numerous methods have been proposed for the preparation of quinin tannate. In most of them quinin sulphate is employed as the starting point. This is dissolved in very dilute sulphuric acid and the solution precipitated with a solution of tannic acid containing a small amount of alkali, usually sodium bicarbonate or ammonia. In other methods the acetate or the hydrochlorid of the alkaloid is employed and in some the precipitation is made in a hydroalcoholic menstruum. The precipitate is then freed from soluble impurities more or less completely by washing.

Since the literature of quinin tannate is so voluminous, and since it deals for the most part with unimportant modifications of processes for making the salt, no attempt is here made to review any except a few of the more important papers.

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* Presented to the Section on Scientific Papers of the American Pharmaceutical Association at the meeting held in Boston, Mass., Aug. 14-19, 1911.

Between the years 1875 and 1885 Rozsnay,[1] a Hungarian pharmacist, perfected a process for preparing quinin tannate which produces a salt of great purity. For a time the method remained a secret, but later the details became known and the process has now been incorporated in several of the pharmacopeias. By the process which Rozsnay introduced the salt is prepared by precipitation in the usual way, is washed with a small quantity of water and is then melted in hot water. By this process the small individual particles coalesce and the substance is thereby rendered less bitter. On pouring off the supernatant liquid the quinin tannate is left as a resin-like mass which soon solidifies and may then be powdered and dried.

A process for preparing quinin tannate which was quite popular a quarter of a century ago deserves mention.[2] Quinin was first prepared by precipitation from the solution of the sulphate of the alkaloid with solution of sodium carbonate. The precipitate was washed and dissolved in alcohol. The alcoholic solution was then poured slowly into an aqueous solution of tannic acid. The precipitate after washing and drying was light in color and practically tasteless. Because of its expensiveness, owing to the alcohol used, and because of the low alkaloidal content of the finished product (about 20 per cent.), the method is no longer used.

The therapeutic efficiency of quinin tannate has been questioned. Many years ago Hager[3] reported that from the results of experiments on his own person and on others, he had concluded that this salt has only about one-tenth of the value of quinin sulphate. His conclusions, however, cannot be considered authoritative, since he states that nine-tenths of the alkaloid may be recovered from the urine and feces. He evidently assumes that the alkaloid eliminated by the urine is inert, a conclusion which in the light of present knowledge is not justified.

Some years after Hager's report was published, Field[4] experimented with the solubility of quinin tannate in gastric juice. He prepared artificial gastric juice and also collected the natural secretion from a healthy dog. He attempted to dissolve the quinin tannate in these solutions, but found that the

1. Pharm. Zentralhalle, 1875, xvi, 106; New Remedies, 1883, xii, 274.
2. Pharm. Zentralhalle, 1882, xxiii, 250; Am. Druggist, 1887, xvi, 68.
3. Pharm. Zentralhalle, 1872, xiii, 247; Proc. Am. Pharm. Assn., 1873, xxi, 379.
4. Phys. Surg., 1883, v, 353; Pharm. Rec., 1884, iv, 5; Proc. Am. Pharm. Assn., 1884, xxxii, 308.

salt was practically insoluble. From the results of his experiments, which also included the administration of the drug to the human subject, the author concluded that quinin tannate is practically inert as a medicinal substance. It would appear that this conclusion, so far as it is based on the solubility of the salt in gastric juice, is untenable because the salt is prepared by precipitation from a slightly acid solution, and it could not, therefore, be expected to dissolve appreciably in gastric juice. Field pointed out that even if the salt were absorbed in the stomach of the patient, the ingestion of such large proportions of tannic acid might be very undesirable.

On the other hand, Zeig[5] contends that the salt is active. He states that if a grain of the salt be dissolved in an ounce of very dilute hydrochloric acid at a temperature of 140 F. (60 C), the solution will possess a taste as bitter as that of a control using an equivalent amount of quinin sulphate.

Christian[6] working in Koch's clinic has studied the efficiency of some of the difficultly soluble quinin salts and esters. He administered known quantities of the alkaloidal combination, collected the urine of the patients and extracted the alkaloid therefrom, the percentage of alkaloid excreted being considered as the efficiency criterion. While a number of experiments were carried out with such compounds as euquinin and saloquinin only two tests with quinin tannate were recorded. From one of these 13.18 per cent. of the alkaloid given was recovered and from the other 23.79 per cent.

From the conflicting results of these inadequate and for the most part unscientific experiments, it can be seen that the question of the therapeutic efficiency of the salt is still an open one. It is to be hoped that the value of quinin tannate will be determined by scientific experimentation.

But few reports of examinations of commercial quinin tannate have appeared. In 1878 Jobst[7] examined several specimens of the preparation, the method of manufacture of which was unknown to him, and at the same time several factory specimens of known origin were studied. The examination revealed great variations in composition, not only in respect to the content of water and total alkaloid, but also in the kind of alkaloid, as several of the commercial specimens con-

5. West. Druggist, 1893, xv, 361; from Proc. Cal. Pharm. Assn., 1892; Proc. Am. Pharm. Assn., 1894, xlii, 651.

6. Deutsch. Wchnschr., 1903, xxix, 216.

7. Arch. Pharm., 1878, ccxii, 331; Proc. Am. Pharm. Assn., 1878, xxvi, 578.

tained mixtures of the cinchona alkaloids. His findings are tabulated below:

Method of Manufacture.	Water (Loss at 120 C.) per cent.	Quinin, per cent.	Quinidin, per cent.	Cinchonidin, per cent.	Cinchonin, per cent.
Known	7.2	31.37	....	....	....
Known	9.7	22.72	....	....	....
Known	10.7	10.00	....	....	....
Known	11.4	7.40	....	....	....
Unknown	9.1	4.46	11.97	7.33	....
Unknown	9.8	4.93	2.43	13.10	3.35
Unknown	10.2	6.23	trace	20.80	trace

He assigns the formula, $C_{20}H_{24}O_2N_2.2C_{14}H_{10}O_2 + 4H_2O$, as the most probable one for the salt having the highest quinin content, viz., 31.37 per cent. The total alkaloidal content was determined by mixing with freshly slaked lime, drying and extracting the pulverized mass with chloroform. As the author's methods for the qauntitative separation of the several alkaloids are not given, no estimate of the accuracy of the recorded results can be made. Water was determined by drying at 120 C. From the results of his experiments, he concluded that tannic acid is capable of forming very variable compounds with quinin according to the proportion and manner in which it is employed in the manufacture of the combination. To obtain products of even an approximately constant composition, definite quantities of tannic acid and of quinin must always be employed.

In 1889 Neumann[8] examined four commercial specimens of quinin tannate while testing a method which he had worked out for the assay of the product. The quinin content varied between 13.9 per cent. and 28.8 per cent., three of the specimens assaying more than 25 per cent. of the alkaloid. These results, however, could not be considered as authoritative, as controls indicated that the method gave values about 3 per cent. too high.

In 1892 Zeig[9] stated that he had found the alkaloidal content of commercial specimens of quinin tannate to vary between 10 and 25 per cent., but he gave no information concerning the number of specimens examined nor of the names of the brands studied.

8. Zeit. anal. Chemie, 1889, xxviii, 663; Proc. Am. Pharm. Assn., 1890, xxxviii, 673.

9. West. Druggist, 1893, xv, 361: from Proc. Cal. Pharm. Assn., 1892; Proc. Am. Pharm. Assn., 1894, xlii, 651.

Quinin tannate having been considered by the Council on Pharmacy and Chemistry of the American Medical Association, the Association laboratory took up the examination of the several brands of the product on the American market. At the same time specimens of the salt were prepared by various methods, and these were included in the examination. Tentative academic standards for the substance were prepared and submitted for criticism to several manufacturers of pharmaceutical chemicals whom it was thought might be interested.

LABORATORY SPECIMENS

The method of manufacture first employed was that of the Swiss Pharmacopeia. Briefly, the method is as follows:

> Nine parts of quinin sulphate are dissolved in a mixture consisting of 16 parts of diluted sulphuric acid and 300 parts of water. Twenty-one parts of tannic acid and 3.5 parts of sodium bicarbonate are dissolved in 300 parts of water without the application of heat. This solution is poured with constant stirring into the solution of quinin sulphate. The resultant precipitate is washed with water until the washings, after acidification with nitric acid, cease to give a turbidity with barium nitrate solution.

In preparing the salt by this method it was found impracticable to follow the directions concerning the washing to completion, as the precipitate was of such bulk that the sulphate could not be completely removed. Although the standard of the Swiss Pharmacopeia requires that the salt shall contain from 30 to 35 per cent. of quinin, the laboratory specimen prepared as above contained but about 25.8 per cent. of alkaloid. Quinin was determined by suspending the salt in weak ammonia water, shaking the mixture with successive portions of chloroform until extraction was complete, evaporating the solvent, drying the residue at 100 C. and weighing the alkaloid.[10] Water was determined by drying at 100 C. This specimen lost 7.6 per cent. of its weight on drying. In the appended table of analytical results it is designated as "No. 1."

The New York Quinin and Chemical Works, a leading manufacturer of quinin salts, having criticized the Swiss method of manufacture (the method included in the tentative academic standards which were submitted to the manufacturers), in respect to the proportions of the several ingredients used, a specimen was prepared in the laboratory by the Swiss method, but using the quantities suggested by this manufacturer, which were as follows:

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10. This method is described in greater detail in the tentative description for Quinin Tannate given elsewhere in this paper.

Quinin sulphate	8.4 parts
Diluted sulphuric acid	15.0 parts
Tannic acid	15.0 parts
Sodium bicarbonate	3.0 parts

The manufacturer stated that these proportions would yield a product corresponding very nearly to the formula, $C_{20}H_{24}O_2N_2(HC_{14}H_9O_9)_2 + 4H_2O$, and containing 31.16 per cent. of anhydrous quinin, 61.91 per cent. of tannic acid and 6.93 per cent. of water. The laboratory specimen prepared according to the manufacturer's suggestion contained 31.3 per cent. of alkaloid and lost 9.0 per cent. of its weight on drying. This specimen is designated as "No. 2" in the table of analytical results.

Quinin tannate was prepared by the method of the Hungarian Pharmacopeia, aliquot parts of the prescribed quantities being used. The following is the method as used:

Ten parts of quinin sulphate are dissolved in 150 parts of distilled water by the aid of the smallest necessary quantity of diluted sulphuric acid. Twenty parts of tannic acid are dissolved in 140 parts of water and the filtered solution poured with constant stirring into the solution of quinin sulphate. A mixture of 5 parts of tannic acid, 80 parts of water and 5 parts of ammonia water is filtered and poured slowly and with constant stirring into the quinin-tannin mixture prepared as above described. The resultant precipitate is collected on a filter and washed with 80 parts of water. The mass is then gently expressed and warmed with 40 parts of water until it melts to a resin-like mass. It is then dried and pulverized.

Although the Hungarian Pharmacopeia requires that the salt shall contain from 30 to 32 per cent. of anhydrous quinin the laboratory specimen prepared as above described contained but about 25 per cent. of alkaloid. The loss on drying amounted to about 10.0 per cent. of the weight of substance taken. In the table of analytical results this specimen is designated as "No. 3."

The salt was then prepared by the method of the Hungarian Pharmacopeia except that the quantities of the several ingredients used were modified to conform to the proportions employed in the preparation of "No. 2." Ammonia water was used as the precipitant. The following quantities were used:

Solution 1:		
Quinin sulphate	8.4	gm.
Diluted sulphuric acid	15.5	c.c.
Water	150	c.c.
Solution 2:		
Tannic acid	10	gm.
Water	70	c.c.
Solution 3:		
Tannic acid	3	gm.
Ammonia water	5	c.c.
Water	50	c.c.

This laboratory specimen prepared as above contained 28.7 per cent. of alkaloid and lost 10.0 per cent. of its weight on drying. The specimen is designated as "No. 4" in the table of analytical results.

Another specimen was prepared exactly like "No. 4" except that sodium bicarbonate was used as the precipitant instead of ammonia water, 3 gm. being used. This specimen contained 33.3 per cent. of alkaloid and lost 7.2 per cent. of its weight on drying. It is designated as "No. 5" in the table of analytical results.

Quinin tannate was prepared by the method official in the German Pharmacopeia. Essentially this is the Rozsnay method, official in the Hungarian Pharmacopeia, but it has been modified in one important particular. It is directed that after the salt has been dried in a warm place, it is to be dried at 100 C. The preparation of a specimen by this method was begun and completed through the stage of drying at 30 C. to 40 C. The air-dried specimen was then divided into two equal portions and one of them was dried at 100 C. as directed. The two subdivisions were then compared. The air-dried specimen was a drab colored, moderately bulky powder which did not adhere to the surfaces of glass or paper. It contained 25.8 per cent. of quinin and the loss on drying at 100 C. amounted to 9.8 per cent. The portion which had been dried at 100 C. was somewhat darker in color than the other, was slightly less bulky, and adhered to glass and paper in a very troublesome way. It contained 27.8 per cent. of quinin. These specimens are respectively designated in the table of analytical results as "No. 6" and "No. 6-a." The German Pharmacopeia requires that the salt shall contain at least 30 per cent. of quinin.

Another specimen was prepared by the following method:

Ten gm. of quinin sulphate are dissolved in a mixture of 15 c.c. of diluted sulphuric acid and 300 c.c. of water. Twelve gm. of tannic acid are dissolved in 100 c.c. of water and the filtered solution poured slowly and with constant stirring into the solution of quinin sulphate. Six gm. of tannic acid are then dissolved in 50 c.c. of water and 2 gm. of sodium bicarbonate dissolved in the solution. This solution is filtered and the filtrate poured slowly and with constant stirring into the quinin-tannate mixture, prepared as above described. The precipitated quinin tannate is allowed to stand for twenty-four hours. It is then poured on a muslin filter, washed with 100 c.c of water and expressed with moderate pressure. The expressed mass is then transferred to a porcelain dish, 100 c.c. of water added and the mixture heated on the water bath until the quinin tannate melts to a resin-like mass. The supernatant liquid is poured off, the mass dried in the air and pulverized.

This specimen contained 29.3 per cent. of alkaloid and lost 7.9 per cent. of its weight on drying. It is designated as "No. 7" in the tabulated analytical results.

As it seemed probable that the amount of sodium bicarbonate was too small to obtain a salt containing the maximum amount of alkaloid, the experiment was repeated with some variations. Three gm. sodium bicarbonate were employed instead of two and the amounts of solvent in some cases were changed. The details of the variations may be seen by consulting Table 1. This process yielded 22.2 gm. ofthe salt (from 10 gm. of quinin sulphate), and the specimen ("No. 8" in Table II) contained 29.1 per cent. of alkaloid and the loss on drying amounted to 7.3 per cent.

In the hope of obtaining a salt with a higher alkaloidal content another specimen was prepared by the same method as was used in "No. 8" except that 4 gm. of sodium bicarbonate were used as the precipitant. The quantities of the several ingredients used may be seen by consulting Table I. This specimen was very dark colored and otherwise objectionable in appearance. The yield was less than that obtained by some of the other methods and the product was less bulky. It contained 34.2 per cent. of quinin and lost 8.1 per cent. of its weight on drying. This specimen is designated as "No. 9" in Table II.

Another specimen was prepared by a method which is very similar to that used in the preparation of "No. 8," the quantities of the several ingredients used being given in Table I. This specimen contained 33.7 per cent. of alkaloid and lost 7.7 per cent. of its weight on drying. It is designated as "No. 10" in Table II.

A general idea of the variations in the processes used in the preparation of the several specimens may be gained by a study of Table I. In this table the composition is given of the several "solutions" used in the manufacture of each specimen. It is to be understood of course that precipitation is brought about by mixing the several solutions.

From the results of the experimental work it is concluded that it is easily possible to obtain quinin tannate containing over 30 per cent. of anhydrous quinin but that this desideratum is not attainable if the substance be prepared by any of the methods now official in the pharmacopeias. Sodium bicarbonate is more satisfactory as a precipitant than ammonia water but it is essential that an excess of the alkali be avoided. While the observations and experiments are too few to warrant a positive conclusion it appears that if ammonia

water be used as the precipitant the yield of the finished product will be larger than is the case when sodium bicarbonate is employed. The quinin content, however, is proportionately smaller. The observation of Jobst that in order to obtain products of even an approximately constant composition it is necessary to employ definite proportions of tannic acid and of quinin has been confirmed by our experiments.

COMMERCIAL SPECIMENS

Four specimens of quinin tannate bearing the labels of as many manufacturers were purchased and examined with particular reference to the alkaloidal content and to the loss on drying at 100 C. The specimen bearing the label of the Powers-Weightman-Rosengarten Co. contained 29.3 per cent. of anhydrous quinin, and the loss on drying the specimen amounted to 7.9 per cent. of the original weight. The specimen put up under the label of the Brunswick Chemical Works, but bearing the label of the Mallinckrodt Chemical Works as selling agent, contained 29.5 per cent. of quinin and the loss on drying amounted to 6.5 per cent. The specimen bearing the New York Quinin and Chemical Works label contained about 33.4 per cent. of alkaloid and the loss on drying amounted to 8.0 per cent. The Merck brand contained about 34.0 per cent. of total alkaloid and the loss on drying amounted to 9.0 per cent. This specimen contained a considerable quantity of uncombined alkaloid, reference to which will again be made.

The amount soluble in anhydrous ether under specified conditions was determined, not only in the specimens purchased but also in those prepared in the laboratory. Tests for chlorid and sulphate were also carried out and an attempt was made to obtain some idea of the relative bitterness of the several specimens examined.

Ether-Soluble: Preliminary tests indicated that one of the specimens contained considerable amounts of uncombined alkaloid. Accordingly the amount soluble in dry ether was determined as follows:

> Two gm. of quinin tannate were placed in a beaker, 25 c.c. of anhydrous ether poured upon it and the mixture stirred with a glass rod. After allowing the suspended salt to settle the supernatant liquid was poured through a dry filter into a tared flask. The insoluble residue was similarly treated twice more with 25 c.c. portions of dry ether and the filter finally washed with 10 c.c. of the solvent. The united filtrates were distilled, the residue dried at 100 C. and weighed. As quinin tannate is slightly soluble in anhydrous ether, a weighable residue may always be expected.

When tested by the above-described method the several specimens with a single exception gave residues varying not

TABLE I

Solution		1	2	3	4	5	6	7	8	9	10
1	Quinin sulphate..	9	8.4	10 gm.	8.4 gm.	8.4 gm.	4 gm.	10 gm.	10 gm.	10 gm.	10 gm.
	Dil. sulphuric acid.	16	15.0	q.s.	15.5 c.c.	15 c.c.	q. s.	15 c.c.	15 c.c.	15 c.c.	15 c.c.
	Water	300	300	150	150 c.c.	150 c.c.	120 c.c.	300 c.c.	150 c.c.	150 c.c.	150 c.c.
2	Tannic acid	...	...	20 gm.	10 gm.	10 gm.	8 gm.	12 gm.	12 gm.	12 gm.	12 gm.
	Water	...	...	140 c.c.	70 c.c.	70 c.c.	50 c.c.	100 c.c.	100 c.c.	75 c.c.	75 c.c.
3	Tannic acid.	21	15	...	...	3 gm.	.....	6 gm.	.....	.....	.....
	Sodium bicarb...	3.5	3	...	...	3 gm.	.....	2 gm.	.....	.....	.....
	Water	300	300	...	...	50 c.c.	.....	50 c.c.	.....	.....	.....
4	Tannic acid	...	...	5 gm.	3 gm.	.....	2 gm.	.....	.....	.....	.....
	Ammonia water..	...	...	5 c.c.	5 c.c.	.....	2 c.c.	.....	.....	.....	.....
	Water	...	...	80 c.c.	50 c.c.	.....	32 c.c.	.....	.....	.....	.....
5	Sodium bicarb...	...	...	...	...	.....	.....	.....	3 gm.	4 gm.	3 gm.
	Water	...	...	...	...	.....	.....	.....	40 c.c.	50 c.c.	50 c.c.
6	Tannic acid	...	...	...	...	.....	.....	.....	3 gm.	3 gm.	3 gm.
	Water	...	...	...	...	.....	.....	.....	25 c.c.	50 c.c.	50 c.c.

far from 0.1 per cent. to 0.3 per cent. One specimen (Merck brand) contained about 9 per cent. of ether-soluble matter, which latter appeared for the most part to consist of free alkaloid.

Chlorid and Sulphate: One gm. of quinin tannate was thoroughly shaken with 100 c.c. of water and the mixture allowed to settle. The supernatant liquid was poured through a filter, the filtrate acidified with diluted nitric acid and the usual tests for chlorid and sulphate applied. With one exception each specimen contained appreciable amounts of sulphate and traces of chlorid. In this one exception sulphate was absent but considerable amounts of chlorid were present, thus indicating the probable source from which the salt had been prepared.

Bitterness: One gm. of the salt was shaken with 100 c.c. of water and filtered. The filtrates from several specimens were then compared by tasting. While none of the filtrates were free from bitterness in general the relative bitterness was found to coincide with the relative turbidity found in the tests for chlorid or sulphate. The Merck specimen which contained a large amount of free alkaloid, was much more bitter than any of the others although it is described on the label as "Neutral-Tasteless."

The results found from the several specimens examined are tabulated on page 41.

From the results of the examination it is seen that commercial quinin tannate varies somewhat in composition. Doubtless this is due to slight differences in the manufacturing methods of the various makers. However, with the exception of the Merck specimen, which bears evidence of careless manufacture, the several makes of quinin tannate on the American market may, on the whole, be regarded as of sufficiently uniform composition for practical purposes.

Based on the provisional academic standards as first prepared but modified as found necessary by the results of the experimental work, and by the suggestions offered by those to whom the provisional description was submitted for criticism, tentative standards for quinin tannate have been prepared. Our thanks are due to those manufacturers who have made suggestions and criticisms in the preparation of these provisional standards for quinin tannate. The description and standards suggested are as follows:

QUININ TANNATE—Quininæ Tannas.—Quinin tannate is the tannate of the alkaloid, quinin, containing from 30 to 35 per cent. of quinin.

Quinin tannate may be prepared as follows:

Ten gm. of quinin sulphate are dissolved in a mixture of 15 c.c. of diluted sulphuric acid and 150 c.c. of water. Twelve gm. of tannic acid are dissolved in 75 c.c. of water and the filtered solution poured slowly and with constant stirring into the solution of quinin sulphate. Three gm. of tannic acid are then disolved in 50 c.c. of water and 3 gm. of sodium bicarbonate dissolved in 50 c.c. of water. These solutions are filtered, the filtrates mixed, and the mixture poured slowly with constant stirring into the quinin-tannin mixture prepared as above described. The precipitated quinin tannate is allowed to stand for twenty-four hours. It is then poured onto a muslin filter, washed with 100 c.c. of water and expressed with moderate pressure. The expressed mass is then transferred to a porcelain dish, 50 c.c. of water added and the mixture heated on the water bath until the quinin tannate melts to a resin-like mass. The supernatant liquid is poured off, the mass cooled, dried in air and pulverized.

Quinin tannate is an amorphous, pale lemon-yellow to yellowish-white, odorless powder without taste, or at most slightly bitter, and with scarcely any astringency. It is slightly soluble in water, ether and chloroform, but somewhat more soluble in alcohol. The aqueous and alcoholic solutions are colored bluish-black by ferric chlorid test solution. Quinin tannate melts on heating in a glass tube to a purplish, tar-like material.

If 1 gm. of quinin tannate be shaken with a mixture of 50 c.c. of water and 1 c.c. of nitric acid and the mixture filtered, a portion of the filtrate should not become more than slightly opalescent after the addition of 1 c.c. of silver nitrate test solution; nor should there by any darkening after the addition of 1 c.c. of hydrogen sulphid test solution; nor should a portion be rendered turbid immediately by barium chlorid test solution.

If from 0.5 gm. to 1 gm. of quinin tannate be mixed with 25 c.c. of water and an excess of ammonia water, the mixture extracted with three successive portions of 20 c.c. each of chloroform, the total solvent washed with water and evaporated, the weight of residue obtained after drying at 100 C. should correspond to from 30 to 35 per cent. of anhydrous quinin. If this residue be dissolved in 30 c.c. of water by the aid of a few drops of diluted hydrochloric acid and 1 c.c. of the solution be mixed with 20 c.c. of water and 2 or 3 drops of bromin test solution, the mixture should assume a green coloration on the addition of ammonia water.

If 0.2 gm. of quinin tannate be ignited no weighable residue should be obtained.

If from 0.5 gm. to 1 gm. of quinin tannate be dried at 100 C. to constant weight the loss should not correspond to more than 10 per cent. of the weight of substance taken (absence of an undue amount of *water*).

If 2 gm. of quinin tannate be shaken with three successive portions of 25 c.c. each of anhydrous ether, the solvent poured through a filter, the filter washed with 10 c.c. of the solvent, the several filtrates united, evaporated and the residue dried to constant weight at 100 C. the weight of the residue should not exceed 0.005 gm. (limit of *uncombined alkaloid*).

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TABLE II.

Number or Brand.	Anhydrous Quinin.	Water (Loss at 100 C.)	Ether Soluble.	Sulphate.	Chlorid.	Taste of Fltrate.	Yield (in gm.) Calculated from 10 gm. quinin sulphate	Remarks.
1	25.75	7.64	0.17	Very marked turbidity.	Noticeable opalescence.	Noticeably bitter..	....	
2	31.33	9.01	0.08	Very marked turbidity.	Very faint opalescence.	Noticeably bitter..	....	
3	25.02	9.96	0.10	Faint turbidity...	Very faint opalescence.	Slightly bitter....	....	
4	28.70	9.96	0.05	Marked turbidity.	Very faint opalescence.	Slightly bitter....	31.0	
5	33.31	7.20	0.11	Faint turbidity...	Very faint opalescence.	Slightly bitter....	....	
6	25.85	9.78	0.08	Faint turbidity...	Very faint opalescence.	Slightly bitter....	28.8	
6-a	27.82	....	0.09	Faint turbidity...	Very faint opalescence.	Slightly bitter....	26.0	Adheres to glass and paper.
7	29.33	7.94	0.09	Faint turbidity...	Very faint opalescence.	Slightly bitter....	....	
8	29.12	7.35	0.12	Faint turbidity...	Very faint opalescence.	Slightly bitter....	23.2	Dark color.
9	34.25	8.12	0.09	Faint turbidity...	Very faint opalescence.	Slightly bitter....	20.0	
10	33.72	7.74	0.08	Faint turbidity...	Very faint opalescence.	Slightly bitter....	20.6	
P. W. R. ..	29.30	7.88	0.10	Distinct turbidity.	Noticeable opalescence.	Noticeably bitter..		
Brunswick (M. C. W.)	29.51	6.50	0.19	Absent	Very marked opalescence.	Noticeably bitter..	....	Evidently prepared from quinin hydrochlorid.
N. Y. Q....	33.36	8.05	0.36	Distinct turbidity.	Noticeable opalescence.	Noticeably bitter..	....	
Merck	33.97	9.06	9.02	Very faint opalescence.	Very faint opalescence	Very bitter.....		

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1872—Klever: Chem. Zentralhalle, xliii, 434; from Pharm. Ztschr. Russ (1872). States that 100 gm. of glycerol dissolve 0.25 gm. of quinin tannate.

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CALCIUM PHENOLSULPHONATE (CALCIUM SULPHOCARBOLATE)

Report of the Council on Pharmacy and Chemistry

(*From The Journal A. M. A., Oct. 21, 1911, p. 1383*)

A subcommittee of the Council submitted this report:

The Council having voted to consider the eligibility of calcium phenolsulphonate (calcium sulphocarbolate) for inclusion with New and Nonofficial Remedies, the product as it is found on the market was examined in the chemical laboratory of the American Medical Association, with a view of establishing standards for this substance. The laboratory now submits its findings in the matter which show that, largely as a result of its efforts, a product of satisfactory quality is now on the market.

The phenolsulphonates (sulphocarbolates) are, probably, not very valuable as therapeutic agents. Calcium phenolsulphonate has little to recommend it over the official sodium phenolsulphonate, and it may be held as an unnecessary duplication of an official substance; yet its provisional inclusion in New and Nonofficial Remedies is recommended since it contains two radicals (the calcium and the phenolsulphonic) often given in certain conditions, and it may for that reason be found to have some advantage over sodium phenolsulphonate. Further, if the product be described in New and Nonofficial Remedies and standards of purity for it provided, this will have the effect of improving the quality of the product on the market.

It is recommended, therefore, that calcium phenolsulphonate (calcium sulphocarbolate), with the description herewith submitted, be accepted as a non-proprietary article, and that the products of the Abbott Alkaloidal Co. and of the Mallinckrodt Chemical Works be listed.

In order that physicians may appreciate the work of the Association's chemical laboratory and recognize the influence which it exerts on the improvement of the quality of medicines, it is recommended that publication of this report and of the report of the chemical laboratory be authorized.

This report was adopted and in accordance therewith the description of calcium phenolsulphonate appears on another page of this issue and the report of the chemical laboratory is published below.

W. A. Puckner, Secretary.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE AMERICAN MEDICAL ASSOCIATION]

CALCIUM PHENOLSULPHONATE

W. A. Puckner and L. E. Warren

The examination of calcium phenolsulphonate (calcium sulphocarbolate) was taken up at the request of the Council. Tentative standards for the substance were prepared and after the examination of the specimens had been completed, these standards were submitted for criticism to several manufacturers of chemicals. At the same time the findings (for each manufacturer's product) which were not in accord with the proposed standards were submitted to the manufacturers interested.

The product was examined with reference to the residue on ignition, loss on drying at 100 C., freedom from arsenic and heavy metals, sulphates and uncombined phenol. Some of the specimens studied were purchased on the open market while others were furnished by the manufacturers. The tests for purity to which the product was subjected are as follows:

TESTS

An aqueous solution of the salt (1-100) should not respond to the time-limit test for *heavy metals* prescribed by the United States Pharmacopeia, 8th Revision.

An aqueous solution of the salt (1-100) acidified with a few drops of diluted hydrochloric acid should give no immediate turbidity after the addition of 1 c.c. of barium chlorid test solution (limit of *sulphate*).

If 5 gm. of the salt be percolated with 25 c.c. of ether in a small filter, the solvent allowed to evaporate spontaneously and the residue, if any, dissolved in 5 c.c. of water, the solution should not give a white precipitate on the addition of a few drops of bromin test solution (absence of *phenol*).

If dried at 100 C. (212 F.) for 1 hour the salt should not lose more than 2 per cent. of its weight (absence of an undue amount of *water*).

If from 0.5 to 1 gm. of the salt be dried to constant weight at 100 C. (212 F.) and the dried substance be slowly ignited in an uncovered crucible (care being taken that the contents be freely exposed to the air) until the weight becomes constant, the residue should amount to not less than 35.0 per cent., nor more than 36.0 per cent. of the weight of the dried substance.

The results of the examination are tabulated on page 46.

These results show that commercial calcium phenolsulphonate varies somewhat in purity and uniformity of com-

Brand.	Water (Loss at 100 C.).	Residue on Ignition (Calculated from Dried Specimen).	Color.	Odor.	Phenol Test.
M. C. W.[2]...	0.42	35.18	Noticeably pinkish..	Somewhat phenol-like..	Distinct precipitation.
M. & Co.[3]...	0.45	35.28	Very faintly pinkish	Distinctly phenol-like..	Distinct precipitation.
A. A. Co.[4]..	15.13	35.24	Faintly yellowish..	Distinctly acetone-like.	None.
P. W. R.[5]...	0.41	35.42	Faintly pinkish....	Odorless	Distinct precipitation.

2. M. C. W. = Mallinckrodt Chemical Works.
3. M. & Co. = Merck & Company.
4. A. A. Co. = Abbott Alkaloidal Company.
5. P. W. R. = Powers-Weightman-Rosengarten Company.

position. The formula commonly assigned to the salt in most text-books of pharmaceutical chemistry is $Ca(C_6H_5O_4S)_2 + H_2O$. Theoretically such a salt should contain 4.45 per cent. of water and should yield 33.68 per cent. of residue on ignition. The above formula is given in Merck's Index (1907), yet the market product bearing the label of this firm was found to contain only 0.45 per cent. water and was therefore, not the monohydrated salt indicated by the formula.

The results of our examination were then transmitted to the firms whose products had been examined.

The Mallinckrodt Chemical Works, in replying, wrote that its manufacturing department was experimenting in an attempt to produce a phenol-free salt at moderate cost. Some time later a specimen of this firm's latest product was sent to the laboratory for examination. This specimen lost 0.44 per cent. of its weight on drying and the dried material yielded 35.24 per cent. of residue on ignition, results that were well within the limits suggested in the standards proposed. The specimen did not respond to the bromin-water test for phenols and both in color and odor was superior to the first specimen of this firm's that was examined.

The Abbott Alkaloidal Co., in submitting its brand of calcium phenolsulphonate, gave the same formula to indicate the composition of its product as is found in Merck's Index, namely, $Ca(C_6H_5O_4S)_2 + H_2O$. When the specimen was dried at 100 C., however, it lost about 15 per cent. of its weight, showing that it had a much larger water-content than was claimed by the manufacturer. This result was verified also by the amount of residue found on ignition, which amounted to 30 per cent. of the weight of the undried specimen instead of 33.68 per cent. as is required by the formula of the salt containing 1 molecule of water. These laboratory findings were sent to the firm. No acknowledgment was received for nearly six months and then the company wrote questioning the chemists' results and asserting that its product contained "about 4.5 per cent." (theoretically 4.45 per cent.) of water instead of the 15.1 per cent. as had been reported by us. This, of course, was a reiteration of the claim made at the time the product was submitted to the Council. In its letter, the company stated that it was sending another sample of calcium phenolsulphonate for further experimentation. This specimen lost 1.93 per cent. of its weight on drying and the dried material gave 35.15 per cent. of ash on ignition; it did not respond to the bromin-water test for phenol. These later results indicated that, although

the firm was ignorant of the composition of its own product, the second specimen complied with the proposed standard.

As the table shows, the products of Merck and Powers-Weightman-Rosengarten were both found to contain free phenol. These firms were advised of the laboratory's findings, but, beyond acknowledging the letters that were sent, they have taken no further action.

The results of the examination of calcium phenol-sulphonate illustrate what other examinations in the Association laboratory have so often shown, viz., that commercial products which are but little used and for which there are no authoritative standards for strength and purity, are also invariably unreliable in composition.

CINERARIA MARITIMA

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., Nov. 11, 1911, p. 1630)

Occasional inquiries in regard to the therapeutic value of *Cineraria maritima* caused the Council to consider the drug with reference to its fitness for inclusion in N. N. R. among non-official, non-proprietary remedies. The following report, having been submitted to the Council by a subcommittee, was adopted and its publication authorized.

W. A. Puckner, Secretary.

To the Council:—The juice of a plant referred to as *Cineraria maritima* was at one time supposed to be of value in the treatment of cataract and certain other affections of the eye. No scientific evidence is available to show that the drug is therapeutically active, and its value is no doubt correctly estimated by Dr. Casey Wood, who ("Ophthalmic Therapeutics," p. 446; Cleveland Press, Chicago, 1909) says:

> "Still, a few respectable names have been associated with its [*Cineraria maritima*] employment in that capacity and it only remains to be said that the instillation into the conjunctival sac of a preparation of this or any other member of the *Senecio* family has about as much effect on the resolution or dispersal of opacities due to organic changes in the lens as pouring the same down the back of the patient's neck!"

The plant from which *Cineraria maritima* juice is claimed to be prepared is commonly referred to in literature as *Cineraria maritima*, but is more correctly described as *Senecio cineraria*, D. C.

It may be considered a matter of indifference whether a remedy like this be advertised for the treatment of such disease as cataract, providing its application could do no harm,

but it must be remembered that it is recommended also for other diseases of the eye in which its use, by postponing efficient treatment, would be the means of serious damage or even loss of vision.

Since there is no evidence to show that this drug is of any therapeutic value, it is recommended that it be not admitted to the list of non-official, non-proprietary remedies in N. N. R., and that the Council formally express its opinion that the drug, as judged by the evidence which is available, is without value in the treatment of cataract or similar diseases of the eye.

EDITORIAL COMMENT: *Cineraria maritima* would long since have been relegated to the limbo of discarded and discredited drugs had it not been given a semiproprietary character by a St. Louis nostrum house—the Walker Pharmacal Company—which, like the Manola Chemical Company, is, we understand, practically a subsidiary concern of the Luyties Homeopathic Pharmacy Company. The Walker concern exploits this drug under the name Succus Cineraria Maritima (Walker). Its method of exploitation consists in publishing testimonials, which it dignifies with the name "clinical reports," from men whom it designates as "representative physicians." As indicative of what constitutes representative physicians, we find that of the seven testimonials given in their pamphlet the names of three of the signers are not to be found in any medical directory.

The exploitation of Succus Cineraria Maritima (Walker) is the oft-repeated story of the resurrection of discarded and worthless drugs for the purpose of creating proprietorship in a nostrum. *Cineraria maritima* is worthless; its therapeutic value is *nil*. By the prodigal use of printers' ink, the attempt has been made to humbug the medical profession—and through it the public—into believing that Cineraria possesses curative value.

REPORT OF THE COMMITTEE ON PATENTS AND TRADE-MARKS

(*From The Journal A. M. A., Nov. 25, 1911, p. 1780*)

The Council appointed a committee to discuss the abuses connected with the patenting and trade-marking of medicines. This committee submitted its report, which was adopted by the Council. In order that physicians may become familiar with these matters, the Council authorized its publication.

W. A. PUCKNER, Secretary.

To the Council on Pharmacy and Chemistry: Your committee, after reviewing the existing abuses in connection with patents on medicinal substances, recommends that the Council on Pharmacy and Chemistry request the cooperation of the Council on Health and Public Instruction in a thorough study of the various questions that are involved, with the view of endeavoring to inaugurate a more wide-spread interest in the possible injury to the public from a misapplication of the laws relating to patents on medicinal preparations.

As an illustration of the abuses that may arise and the injustice that can be done at the present time, it may be well to call attention to some of the variations in the laws relating to patents in different countries.

The duration or life of a patent varies from a minimum of three years in some of the South American republics to twenty years in Mexico, Belgium and Spain; our own country limits the life of a patent to seventeen years.

In Germany, Austria and Hungary food products and chemical products as such cannot be patented, although the processes by which such products are produced may be patented. In France no patents are granted for medicines and pharmaceutical compositions, and added precautions are taken to prevent the creation of a monopoly in the manufacture and sale of medicinal products. In Denmark medicines and food products are not patentable, and in Switzerland neither the product nor the process for making a chemical substance can be patented.

In our own country both product and process patents are granted for useful inventions quite irrespective of the uses for which the product is intended.

The rights and privileges conferred on individuals under our American laws relating to patents and trade-marks have been repeatedly discussed in so far as these laws are thought to interfere with or to hamper rational progress in sciences relating to materia medica, and attention has been called to many of the more or less apparent abuses.

At the Chicago (1908) meeting of the American Medical Association a special committee of five was appointed by the House of Delegates to study the questions involved, and to cooperate with the committee on medical legislation in preparing and securing the enactment of a bill which would correct the abuses thought to be connected with the enforcement of our patent laws. (THE JOURNAL A. M. A., June 13, 1908 p. 2003).

This committee presented a comprehensive report at the Atlantic City (1909) meeting of the American Medical Asso-

ciation (The Journal A. M. A., June 19, 1909, p. 2063). The committee, recognizing the fact that questions relating to patents and trade-marks are in a state of great confusion, suggested that redress from existing abuses be sought in court rather than by a change in the existing patent laws.

At the St. Louis (1910) meeting of the American Medical Association (The Journal A. M. A., June 18, 1910, p. 2079) the committee presented a report in which it was suggested that the subject be left to the Committee on Legislation and that the special Committee on Patents and Trade-Marks be discharged.

Other organizations have discussed the abuses arising from our present system of patent laws and their enforcement, and it is generally agreed that both for the public as well as for the inventor our laws and our system of patent law jurisprudence could be improved on. One well-known attorney in discussing this question from the point of view of the patentee (Louis C. Raegener, *Jour. Ind. and Eng. Chem.*, 1909, i, 203) asserts that this country gives the worst protection possible to the patentee seeking to enforce the rights plainly given him by the statutory law; on the other hand, by trick and device not found in the statutory law or in the patent laws of any other country, it enables him to hamper trade in the most effective manner possible.

The relation of our patent laws to our trade-mark laws and to corresponding laws in other countries is not generally appreciated and much educational work is needed. For instance it should be pointed out that names that are free in one country may be protected in another so that the publicity given to scientific investigations made in one country may be used for advertising purposes in connection with a proprietary article in another country.

In this connection it might be well to state that in France the word "adrenalin" has been denied registration for fear that a monopoly in the manufacture and sale of a pharmaceutical product might be created if an exclusive right were given to the name by which such product is generally known, while in our own country the same name is applicable only to the product of one firm. On the other hand, the word "antipyrin" which is now included in the Pharmacopeia of the United States and generally accepted as a generic name for a well-known chemical, appears to be protected in some of the countries of Europe and applicable only to the product put out by the original manufacturers.

The abuses arising from this variation in the trade-mark laws of different countries should be studied with a view of

suggesting means for overcoming the troublesome questions arising in connection with the nomenclature of synthetics and other new remedies for which arbitrarily coined words are being used.

One other point that is worthy of serious consideration is the fact that practically all of the abuses that are evidenced in connection with patents or trade-marks and new remedies are due to the *abuse* rather than the rational use of the remedies under consideration. For a patent establishes a monopoly; a monopoly permits of excessive profits; excessive profits lead to extensive advertising; extensive advertising leads to misuse of the patented article.

To recapitulate briefly the observations and suggestions herein offered your committee would recommend:

1. That for the present at least no effort be made to test the validity of a product patent which has been declared valid in one or more courts.
2. That the inadequacy of our present patent laws in so far as they pertain to drugs and medicines, and particularly their enforcement, be brought to the attention of the medical profession with the view of securing the interest and cooperation of physicians in an improvement of present conditions.
3. That the Council on Pharmacy and Chemistry request the cooperation of the Council on Health and Public Instruction in a comprehensive and comparative study of the patent laws of the leading countries of the world and subsequently to aid in bringing to the attention of the profession and of the public the abuses arising from proprietary rights in names or in products used in connection with the healing art.

ADRIN AND ITS PREPARATIONS

Omitted from New and Nonofficial Remedies

Report of the Council on Pharmacy and Chemistry

The H. K. Mulford Company having requested that its Adrin preparations be omitted from New and Nonofficial Remedies, the following report was made to the Council. The report was adopted and its publication authorized.

W. A. PUCKNER, Secretary.

The H. K. Mulford Co. advised the Council that it has withdrawn Adrin and its preparations from the market. It also makes the following comments:

"Our reason for requesting the withdrawal of these preparations is not because of any conflict with the rules of the Council, but because the United States Court for the Southern District of New York has declared valid the Takamine Patents covering the active principle of the suprarenal gland and thereby making it impossible for us to legally manufacture or sell these products.

"We expect, in the near future, to be able to submit for approval, suppositories, ointments and lozenges in which the former adrin content is supplanted with a purified Adrenal Extract. The submission of these products will follow in the regular way."

The referee recommends that the withdrawal be accepted and that the report be authorized for publication.

BARIUM CHLORIDE

Omitted from New and Nonofficial Remedies

Report of the Council on Pharmacy and Chemistry

The Council voted that Barium Chloride be omitted from New and Nonofficial Remedies because it was held to be of little value and dangerous. As a matter of record the description which appeared in New and Nonofficial Remedies, 1911, was referred to the Reports of the Council and appears below.

W. A. PUCKNER, Secretary.

BARIUM CHLORIDE—Barii Chloridum.—Baryum Chloratum (Pharm. Germanica, edit. 4; Pharm Helvetica, edit. 4). Barium Chloride ($BaCl_2 2H_2O$) is the barium salt of hydrochloric acid.

Barium chloride occurs as colorless trimetric plates or glistening scales, odorless, non-efflorescent and having an unpleasant, bitter, sharp, saline taste. It dissolves in 2.5 parts cold and in 1.5 parts boiling water, forming a neutral solution; but is insoluble in alcohol. Barium chloride becomes anhydrous when dried at 120° C. (248° F.).

An aqueous solution of the salt yields, with diluted sulphuric acid, a heavy white precipitate, insoluble in strong acids, and with silver nitrate a curdy, white precipitate, insoluble in nitric acid but readily soluble in ammonia water. Diluted alcohol, after remaining in contact with the salt for several hours, should, on ignition, give a pure yellowish-green flame free from red (absence of traces of strontium). An aqueous solution of barium chloride should not be precipitated by ammonium sulphide nor should any residue remain after adding excess of diluted sulphuric acid to the solution, filtering, and evaporating to dryness. Twenty Cc. of the aqueous solution (1 to 20) must not turn blue on the addition of 0.5 Cc. of potassium ferrycyanide T. S.

Actions and Uses.—Barium chloride is a toxic substance, its most striking effects being exerted upon muscle tissue, especially unstriped and heart muscle. In large doses it affects

the spinal cord and medulla. By actively stimulating peristalsis, through action on the muscle wall, and by its direct irritant action, it readily produces vomiting and purging. It strengthens the cardiac contraction by direct action on the heart muscle, and by this means and still more by direct action on the vessel walls it greatly increases blood-pressure, acting like digitalis. It acts on the muscles like veratrin. It first greatly excites and then paralyzes the spinal cord and medulla. Given in very dilute solution, absorption is small and the barium is deposited in the bones. Injected intravenously it causes tonic and clonic spasms, because of stimulation of the spinal cord and medulla.

In fatal doses it causes hemorrhages into the stomach, intestines and kidneys.

Its clinical use has been attended with little success, chiefly because of the gastrointestinal irritation and high toxicity. It has, however, been used in cardiac disease with insufficient blood-pressure, as a general "tonic," and with less reason in tremors, in scleroses of the central nervous system, internally and locally in varicose veins, etc.

In poisoning the most direct antidote against the portion remaining in the gastrointestinal tract is sodium sulphate, which produces insoluble barium sulphate.

Its use is attended with considerable danger.

Dosage.—0.006 to 0.003 Gm. (1/10 to ½ grain) or 2 to 4 Cc. (30 to 60 minims) of a 1 per cent. solution (5 grains to the fluidounce). Fatal, 0.80 to 0.90 Gm. (13-15 grains). It should always be well diluted before giving.

Internally used in syphilis, scrofula and tumor albus in doses of 0.03-0.10 Gm. (½ to 1½ grains) 3 to 4 times per day; for heart disturbances 0.2-0.4 Gm. (3 to 6 grains) per day. Maximum dose per day 0.6 Gm. (9 grains). Externally employed as an eye-wash in scrofulous eye affections in 10 per cent. solution.

CONDURANGO

Report of the Council on Pharmacy and Chemistry

The Council in voting that recognition be refused to Condurango, authorized the publication of the following statement.

W. A. PUCKNER, Secretary.

Condurango, the bark of *Gonolobus Condurango*, was brought out by Friedreich as a curative remedy in gastric cancer. The testimony of numerous impartial observers as recorded in

recent works on therapeutics is that it is without specific action, and valueless for this purpose. It contains two glucosids which, when used experimentally on animals, according to Cushny, produce ataxia, incoordination, convulsions and death. It has been used as a bitter stomachic, but its value for this purpose is not sufficient to accord it recognition, there being many bitters now recognized of equal or greater value.

CONIINE HYDROBROMIDE

Omitted from New and Nonofficial Remedies

Report of the Council on Pharmacy and Chemistry

The Council voted that Coniine Hydrobromide be omitted from New and Nonofficial Remedies because there appeared to be no rational indication for its use and because it was held to be dangerous. As a matter of record the description included in New and Nonofficial Remedies, 1911, was referred to the reports of the Council and appears below.

W. A. Puckner, Secretary.

CONIINE HYDROBROMIDE—Coniinæ Hydrobromidum.—Coniine hydrobromide is the hydrobromide, $C_8H_{17}N.HBr$, of an alkaloid found in conium.

Coniine hydrobromide occurs as colorless, transparent, glistening rhombic crystals, or as a white crystalline powder, melting at 210-214° C. (410-417° F.). It is soluble in two parts of water, in three parts of alcohol and in ether-alcohol, but insoluble in ether. The solutions are colorless and neutral. The salt contains 61.09 per cent. of coniine.

Evaporated with an excess of sulphuric acid, coniine hydrobromide becomes red, violet, blue and finally brown. An aqueous solution of the salt mixed with magnesium carbonate or oxide, and shaken with carbon bisulphide, colors the latter yellow. Addition of silver nitrate solution to a solution of coniine hydrobromide causes precipitation of yellow silver bromide; iodine test solution precipitates a reddish-brown body and tannic acid a yellowish-white compound. Coniine hydrobromide should burn when ignited, leaving no residue.

Actions and Uses.—Coniine hydrobromide paralyses the peripheral endings of the motor nerves, producing an ever-increasing muscular weakness. To a less degree it affects the sensory nerves. With lethal doses consciousness is retained to the last. It probably depresses the spinal cord feebly and usually dilates the pupils. In therapeutic doses it is said to increase the temperature but in lethal doses it lowers it; convulsions may appear and death results from paralysis of respiration.

Coniine hydrobromide may be used for the same purpose as conium. It has been tried in chorea, paralysis agitans, whooping cough, and is said to produce a condition of calm and relaxation in maniacal and hysterical excitement. It is a dangerous remedy.

Dosage.—0.001-0.003 Gm. (1/60 to 1/20 grain) three times a day. Maximum single dose 0.005 Gm. (1/12 grain); maximum daily dose 0.015 Gm. (¼ grain). For hypodermic use a 5 per cent. solution is used.

DIGITONIN

Omitted from New and Nonofficial Remedies

Report of the Council on Pharmacy and Chemistry

Digitonin was not included in New and Nonofficial Remedies because of any therapeutic value, but because of the unfortunate confusion regarding the nomenclature of the digitalis bodies. Now, on recommendation of a referee, it has been voted that the description for Digitonin be omitted from New and Nonofficial Remedies and that instead a suitable explanation be made in connection with the description of German Digitalin.

As a matter of record the description of Digitonin which appeared in New and Nonofficial Remedies, 1911, is given below.

W. A. PUCKNER, Secretary.

DIGITONIN.—Digitonin is a glucoside $C_{27}H_{46}O_{14} + 5H_2O$ derived from the seeds of digitalis purpurea and belonging to the saponins.

Digitonin is separated from German digitalinum purum by the addition of ether to the alcoholic solution (see digitalin). The precipitate is dissolved in 10 parts of 85 per cent. alcohol and the solution put into water at 45° C. After standing from six to eight hours the greater part of the digitonin will crystallize out.

Digitonin crystallizes in colorless needles or thick warty masses which dissolve in 600 parts of cold water and 50 parts of warm water to a turbid solution, but dissolves to a clear solution in 50 parts of 50 per cent. alcohol. Its solutions are levorotatory. When heated in alcoholic solution with hydrochloric acid it is split into dextrose, galactose and digitogenin.

Concentrated sulphuric acid dissolves it with a red color which is intensified by the addition of a drop of bromine water.

Concentrated hydrochloric acid dissolves digitonin without color, but the solution becomes yellow and finally reddish violet on heating or on long standing.

Keller's reaction gives a rose red zone which soon fades.

Actions and Uses.—Digitonin acts as a heart depressant when introduced into the circulation, but it is not absorbed from the alimentary canal, and therefore exerts no action on

the circulation when taken by the mouth, but it renders digitoxin more soluble whether in infusion or when the leaf is taken by the mouth.

GELSEMINE HYDROCHLORIDE

Omitted from New and Nonofficial Remedies

Report of the Council on Pharmacy and Chemistry

The following report was adopted by the Council:

"Gelsemine has little physiological activity; New and Nonofficial Remedies states that the activity of the commercial preparations seems to be due to the gelseminine which they contain in varying quantities. Under the circumstances it seems better to use the U. S. Pharmacopeia preparations of gelsemium. There seems to be no good reason for retaining a drug which owes its activity to a contamination. It is recommended that Gelsemine Hydrochloride be omitted from New and Nonofficial Remedies."

As a matter of record, the description for Gelsemine Hydrochloride appearing in New and Nonofficial Remedies, 1911, was referred to the reports of the Council and appears below.

W. A. PUCKNER, Secretary.

GELSEMINE HYDROCHLORIDE—Gelseminæ Hydrochloridum.—Gelsemine hydrochloride is the hydrochloride of an alkaloid, $C_{24}H_{28}N_2O_4$,HCl (Gerrard) ($C_{22}H_{26}N_2O_2$ by Spiegel, Ber. d. deut. Chem. Ges., vol. 26, p. 1054) derived from Gelsemium (Gelsemium sempervirens (L) Ait. f. Fam. Loganiaceæ).

Gelsemine hydrochloride occurs in prismatic crystals or a white crystalline powder. Soluble in water, but difficultly soluble in alcohol.

With concentrated sulphuric acid it gives a yellowish and with concentrated nitric acid a green coloration. If potassium dichromate is introduced into a solution of gelsemine in strong sulphuric acid a cherry red coloration shading into violet which soon becomes green is produced at the point of contact.

Actions and Uses.—Pure gelsemine appears to have a very slight toxic action, increasing reflex action in frog, to some extent, its action resembling strychnine. The effects of the commercial preparations are thought to be due to the gelseminine which they contain in varying quantities.

It has been used in neuralgia, especially trigeminal.

Dosage.—0.0005 to 0.002 Gm. (1/134 to 1/33 grain).

NOTE.—Gelseminine is a very poisonous alkaloid, found in gelsemium, which has an action very similar to that of coniine but is more depressant to the central nervous system, and must be carefully distinguished from gelsemine. Gelseminine is a mydriatic but

is seldom used as such owing to its irritating action. Merck's "gelseminin" appears to consist of gelsemine and not gelseminine.

Gelsemine (Gerrard) is, according to Cushny (Proc. Am. Ph. Assn., Vol. 41, p. 850), the same as the German "crystallized gelsemine."

KERATIN

Omitted from New and Nonofficial Remedies

Report of the Council on Pharmacy and Chemistry

The Council voted that Keratin be omitted from New and Nonofficial Remedies. In accordance with the vote of the Council, the report upon which this action was based and the description of Keratin included in New and Nonofficial Remedies, 1911, appears below.

W. A. PUCKNER, Secretary.

KERATIN

The Director of the Association's Chemical Laboratory has submitted the following report to your referee on Keratin:

"As a member of the Committee on Unofficial Standards of the American Pharmaceutical Association, I was requested, some time ago, to propose tests whereby the quality of commercial keratin might be determined. Accordingly, a description based in the main on that contained in New and Nonofficial Remedies was prepared and submitted to a number of firms for criticism. At the same time these firms were invited to send in specimens of their products for examination. In general no criticisms were received. Lehn & Fink appeared to have given careful consideration to the description sent and even submitted it to their correspondent abroad, and in the end said:

" 'We submitted same to our chemist at our laboratory and also communicated with a prominent manufacturer of peptone and keratin in Germany in regard to this matter. No criticisms or suggestions, however, have been offered and the descriptions have been considered entirely satisfactory.'

"Lehn & Fink supplied a specimen of their product (at $2.75 per ounce). As no other specimen of stated source could be obtained the tests in the provisional description were applied only to this specimen. The acid-pepsin test as given in the provisional description having been carried out and a residue many times larger than was permissible having been found, the method was checked by estimating the acid-pepsin indigestible portion, i. e., the portion insoluble in the acid-pepsin solution. The value for the digestible portion was then obtained indirectly by the subtraction from 100 per cent. The results are given herewith:

Ether-soluble	0.51 per cent.
Ash	1.02 per cent.
Ammonia insoluble	1.73 per cent.
Acid-pepsin (indigestible) residue	1.27 per cent.
Acid-pepsin (digestible) residue	1.2295 Gm.*

* The acid-pepsin (digestible) residue is obtained by evaporating the filtrate from the pepsin digestion of 1 Gm. of keratin and contains therefore the residue of the pepsin added as well as the material dissolved from the keratin. Hence this factor cannot be expressed in percentages as are the others.

"The results show that the specimen examined does not comply with the tests proposed. Past experience shows that in such matters the protestations of interested parties are only too often unreliable. Particular attention is called to the fact that the specimen is almost entirely (98.73 per cent.) digestible in acid-pepsin solution. The findings of the experiments are in accord with those of Martindale and Westcot (extra Pharmacopeia, ed. xiv, 540, 1910), who investigated the efficiency of keratin as a coating for pills and showed its worthlessness."

In view of the report of the Chemical Laboratory, it is recommended that Keratin be omitted from New and Nonofficial Remedies and that this report, as well as the description of Keratin included in New and Nonofficial Remedies, 1911, which appears below, be included in the annual Council reports.

KERATIN—Keratinum.—Keratin is a proteid substance which forms the chief part of horns, hoofs, feathers, wool, etc.

To prepare keratin horn shavings are macerated for some days in a mixture of equal parts of ether and alcohol, decanting the liquid and washing the residue with warm water. The washed shavings are then treated with an acid solution of pepsin at 40° C. (104° F.). After further washing with water the residue is dried and powdered.

Keratin occurs as a brownish yellow powder or in transparent white or grayish white scales, tasteless and odorless. It is soluble in concentrated acetic acid, caustic alkalies and ammonia, but insoluble in water, alcohol, ether, dilute acetic acid or acid pepsin solutions. It is decomposed by long boiling under pressure, forming a turbid solution with the liberation of hydrogen sulphide. Boiling with dilute sulphuric acid converts it to leucine, tyrosine and other products. On ignition it emits the odor of burning feathers and the remaining carbon is very difficultly burned. On complete combustion the ash should not exceed 1 per cent. Twenty-four hours' digestion with 15 times its volume of ammonia or glacial acetic acid solution at 25°-40° C. (77°-104° F.) should not leave more than 0.3 per cent. insoluble matter.

Uses.—For coating pills to pass the stomach unchanged.

SANGUINARINE NITRATE

Omitted from New and Nonofficial Remedies

Report of the Council on Pharmacy and Chemistry

The following report was adopted by the Council:

"It seems to be generally accepted that Sanguinarine Nitrate is of practically no value; the referee believes that the inclusion of drugs which have not even a presumptive value serves no useful purpose and recommends its omission."

As a matter of record, the description appearing in New and Nonofficial Remedies, 1911, was referred to the reports of the Council and appears below.

W. A. Puckner, Secretary.

SANGUINARINE NITRATE — Sanguinarinæ Nitras.—Sanguinarine nitrate is the nitrate ($C_{20}H_{15}NO_4.HNO_3$) of the alkaloid sanguinarine, obtained from sanguinaria canadensis and other plants.

Sanguinarine nitrate occurs in orange-yellow crystalline needles or deep-orange colored powder. It is soluble in water and in alcohol.

Actions and Uses.—Sanguinarine is a violent poison producing in mammals vomiting, purging, convulsions with loss of reflex activity and cardiac depression. The blood-pressure is said to be raised by small doses.

The principal use of sanguinarine nitrate is as a stimulant expectorant in chronic bronchitis and in the later stages of acute bronchitis. It is said to be an emmenagogue and may be used in functional amenorrhea.

Dosage.—0.004 to 0.06 Gm. (1/16 to 1 grain); as an expectorant 0.004 to 0.008 Gm. (1/16 to ⅛ grain); as an emetic 0.015 to 0.06 Gm. (¼ to 1 grain); average dose 0.015 Gm. (¼ grain) to be given with caution.

SODIUM CINNAMATE

Omitted from New and Nonofficial Remedies

Report of the Council on Pharmacy and Chemistry

The Council voted that Sodium Cinnamate be omitted from New and Nonofficial Remedies because it is not used. As a matter of record, the description for Sodium Cinnamate appearing in New and Nonofficial Remedies, 1911, was referred to the reports of the Council and appears below.

W. A. Puckner, Secretary.

SODIUM CINNAMATE.—Sodii Cinnamas.—Sodium Phenylacrylate. Sodium cinnamate, $C_6H_5.CH:CH.COONa = NaC_9H_7O_2$, is the sodium salt of cinnamic acid (benzene-propenoic) acid, $C_6H_5CH:CH.COOH$.

Sodium cinnamate may be prepared by saturating a hot aqueous solution of sodium carbonate with cinnamic acid, evaporating and crystallizing. Cinnamic acid is obtained from balsam of tolu or may be produced synthetically by heating together benzoldehyde, sodium acetate and acetic anhydride. By the latter method of preparation a purer product is produced, which it is claimed is free from any by-effects of the acid from natural sources.

Sodium cinnamate is a white, crystalline powder, soluble in water, 1 part in 20, the solution being faintly alkaline. On boiling the alkalinity becomes stronger on account of the decomposition of the cinnamic acid forming sodium carbonate. Solution of sodium cinnamate (1 to 25) yields on the addition of ferric chloride a yellow precipitate. On adding it to potassium permanganate solution the red color of the permanganate is destroyed

and the odor of benzaldehyde developed. If a solution of sodium cinnamate is treated with dilute sulphuric acid a precipitate of cinnamic acid appears, which after purification should melt at 133° C. (271.4° F.).

It is incompatible with acids and with oxidizing agents, e. g., potassium permanganate.

Actions and Uses.—Balsam of Peru, cinnamic acid and sodium cinnamate are recommended by Landerer for the treatment of phthisis, the drugs being injected intravenously under strict aseptic precautions. The effect is referred by him to an inflammatory reaction, localized about the tuberculous foci which leads to cicatrization. He records very favorable results in well-selected early cases, and other clinicians have also reported some successes, although the treatment fails very often. The synthetic cinnamate is preferred on account of its greater purity.

Dosage.—0.001 Gm. (1/60 grain), gradually increased to 0.02 Gm. (⅓ grain), in 1 to 5 per. cent. solution, injected intravenously thrice weekly for long periods (3 to 18 months).

RED GUM

Omitted from New and Nonofficial Remedies

Report of the Council on Pharmacy and Chemistry

This article, with the description given in the British Pharmaceutical Codex, was accepted for inclusion with New and Nonofficial Remedies because it formed a constituent of "Tabloid" Benzoic Acid Compound, B., W. & Co., submitted by Burroughs, Wellcome & Co. As these tablets contained cocaine and codeine as essential constituents, it was held that the name was misleading, disguising the presence of these habit-forming drugs, and hence the article, Tabloid Benzoic Acid Compound, B., W. & Co., was refused recognition.

The Association Laboratory has reported to the referee that at the present time there are no tests available which will permit a distinction of Red Gum from similar bodies. Further, it does not appear to the referee that the substance possesses superiority over the official Kino. As there appears no reason for the retention of Red Gum with New and Nonofficial Remedies, it is recommended that the description for Red Gum included in New and Nonofficial Remedies, 1911, and appearing below be transferred to the Council reports and that this report also be included as an explanation of the action taken.

W. A. Puckner, Secretary.

RED GUM—Eucalypti Gummi.—Eucalyptus gum. Eucalyptus Kino.

Red gum is an exudation from the bark of *Eucalyptus rostrata*, Schlecht., and other species of *Eucalyptus*.

Red gum occurs in small, dark reddish brown, opaque and more or less dusty pieces which yield a pale red powder. It is usually collected from artificial incisions. When chewed it is tough, and colors the saliva red. Water dissolves 80-90 per cent. Its chief constituent is tannic acid, to the extent of 47 per cent.

Actions and Uses.—Red Gum is an active astringent. It is used as an astringent in sore throat, diarrhea and in catarrhal affections of various mucous membranes. Largely used in the form of lozenges where an astringent is needed in throat affections.

Dosage.—0.1 to 0.3 Gm. (2 to 5 grains).

CEPHÆLINE, EMETINE HYDROCHLORIDE, THORIUM NITRATE, QUASSIN, HEMOGLOBIN

Omitted from New and Nonofficial Remedies

Report of the Council on Pharmacy and Chemistry

The Council voted to further consider the following nonproprietary articles accepted for New and Nonofficial Remedies: Cephæline, Emetine Hydrochloride, Thorium Nitrate, Quassin, Hemoglobin.

The referee in charge of these products reported:

> "These substances do not appear to be in sufficiently extensive use to justify their retention in New and Nonofficial Remedies. It appears to me, however, that their descriptions should be preserved as a matter of record, and I recommend that they be transferred from New and Nonofficial Remedies to the annual reports of the Council on Pharmacy and Chemistry."

This recommendation was agreed to by the Council and in accordance therewith the descriptions of the articles referred to will be omitted from New and Nonofficial Remedies and appear below.

W. A. PUCKNER, Secretary.

CEPHÆLINE—Cephælina.—Cephaline is an alkaloid, $C_{11}H_{20}NO_2$, obtained from ipecacuanha root.

Cephæline occurs as snow-white, fine, interlacing needles, which readily turn yellow. It is soluble in ether and caustic soda solutions, melts at 96°-102° C. (204.8°-215.6° F.) and turns brown when heated to 120° C. (248° F.). With Fröhde's reagent, a freshly prepared solution of 0.1 Gm. sodium molybdate in 10 Cc. concentrated sulphuric acid, it gives a purple color which hydrochloric acid changes to prussian blue.

Actions and Uses.—These are identical with those of ipecac. It is relatively more emetic and less nauseant and causes rela-

tively more renal irritation and less cardiac depression. It may be employed as an emetic and expectorant.

Dosage.—0.005 to 0.01 Gm. (1/12 to 1/6 grain) in pills or as a powder triturated with sugar of milk. The hydrochloride is soluble.

EMETINE HYDROCHLORIDE—Emetinæ Hydrochloridum.—Methyl-cephæline. Emetine hydrochloride is the hydrochloride, $C_{15}H_{22}N.O_2.HCl.3H_2O$, of a base found together with cephæline in Cephælis Ipecacuanha.

Emetine hydrochloride occurs as a white crystalline powder, soluble in water and alcohol. A freshly prepared concentrated solution of ammonium molybdate in concentrated sulphuric acid is colored brown by emetine; this color changes to violet when a drop of concentrated hydrochloric acid is added. The general alkaloidal reagents precipitate emetine, even from dilute solutions. Alkalies precipitate emetine from aqueous solutions of its salts.

Actions and Uses.—Emetine acts similarly to Ipecac but is relatively more nauseant and less emetic, and causes relatively less renal irritation but more cardiac depression.

Dosage.—Expectorant, 0.005-0.01 Gm. (1/12-1/6 grain). 0.01-0.02 Gm. (1/6-1/3 grain) causes emesis, but cephæline is preferred as an emetic.

THORIUM NITRATE—Thorii Nitras.—Thorium nitrate, $Th(NO_3)_4 + 4H_2O$, is the thorium salt of nitric acid.

Thorium nitrate occurs as white crystalline granules or lumps. Very soluble in water and alcohol. On calcination yields a voluminous, white oxide, which should amount to 48-50 per cent. of the original salt. The aqueous solution dries over sulphuric acid to a crystalline mass.

An aqueous solution gives a white precipitate with ammonium carbonate, the precipitate being completely soluble in an excess of the precipitant. The aqueous solution gives with caustic alkalies a voluminous precipitate of the hydroxide insoluble in an excess of the precipitant. The presence of tartaric acid prevents the precipitation. Potassium ferrocyanide produces an amorphous precipitate.

Actions and Uses.—The soluble thorium salts bear a close resemblance to alum in their local astringent and irritant properties. They are not absorbed from the alimentary canal. Hypodermically, they cause local sloughing, and intravenously, they kill by coagulating the blood. The non-precipitant double salts are practically non-toxic, even intravenously. They are excreted by the kidneys. Thorium salts are fairly radioactive. They have been recommended for local application in malignant diseases and thorium emanation has been inhaled in phthisis. Reliable evidence as to the therapeutic value of thorium salts is lacking.

Dosage.—A solution of thorium nitrate (1 to 5) is neutralized with ammonia and allowed to stand in a bottle four-

fifths full; the emanation that accumulates in the vessel is inhaled (Br. Codex).

QUASSIN—Quassine (Pharm. Française, 1908)—**Quassinum**—Quassin is a bitter principle found in quassia.

The alcoholic extract of Jamaica quassia wood (Quassia U. S. P.) is neutralized with magnesia, then acidified with tartaric acid and the alcohol distilled off. The residue is shaken up with chloroform and the solution evaporated to syrupy consistency and dissolved in a mixture of equal parts of absolute alcohol and ether. This solution is evaporated and the residue dissolved in as little absolute alcohol as possible, the solution covered with a layer of ether and allowed to evaporate. The crystals which form are recrystallized from alcohol. The product thus prepared consists of two bitter principles *a*-picrasmin ($C_{35}H_{48}O_{10}$) melting at 204° C. (399.2° F.) and *β*-picrasmin ($C_{36}H_{48}O_{10}$) melting at 209-212° C. (408.2° to 413.6° F.).

Quassin crystallizes in oblique rhomboidal needles with a pearly lustre. It is odorless, but has a bitter taste. Its melting point is 210° C. (410° F.) and cooling it forms an amorphous mass. It is soluble in about 400 parts of water at 15° C. (59° F.); in 30 parts alcohol (85 per cent.) and in 21 parts of cold chloroform. It is very soluble in boiling alcohol, in acetic acid and very slightly soluble in ethyl and petroleum ethers. It is soluble in concentrated acids and alkalies, but not in alkaline carbonates. Continued action of alkalies forms resins (Pharm. Française, 1908). It is dextrorotatory in its chloroform solution; 4.22 gm. in 100 Cc. chloroform rotating the plane of polarized light to the right with a specific rotation of plus 38° 8′. Solutions of quassin are neutral.

It dissolves to a colorless solution in concentrated sulphuric acid, which becomes red on the addition of sugar (Pharm. Française, 1908).

HEMOGLOBIN — Hæmoglobinum. — Hæmoglobin, Hæmatocrystallin. Hemoglobin is the red coloring matter of blood.

Hemoglobin is a brownish-red powder, soluble in water. It is decomposed by extremely small amounts of acids, coagulates at 64° C. (147.2° F.) and is dextro-rotatory. It does not give characteristic albumin or iron reactions until decomposed. A solution mixed with a little sodium chlorid, evaporated over sulphuric acid to a syrupy consistence, mixed with 15 times its volume of glacial acetic acid and heated on a water bath for several hours, yields on cooling flat rhombic crystals of hæmatin hydrochloride with a dark violet-red color and metallic luster.

Actions and Uses.—See organic iron. It is converted into hematin in the stomach.

Dosage.—0.3 to 2 Gm. (5 to 30 grains).

XANOL

Report of the Council on Pharmacy and Chemistry

Xanol is a name applied by the Wm. S. Merrell Chemical Co. to its brand of caffeine sodio-salicylate, National Formulary. After consideration the Council held Xanol to be an

unessential modification of an official article, voted that it be refused recognition and authorized publication of this report.

W. A. PUCKNER, Secretary.

Xanol, or caffeine sodio-salicylate, manufactured by the W. S. Merrell Chemical Company, is a preparation of caffeine and sodium salicylate. The manufacturers claim superiority for the preparation because the sodium salicylate is said to be made from the natural salicylic acid derived from the oil of wintergreen or oil of birch. Unless it can be shown that the sodium salicylate made from the natural acid is superior to that made from the artificial acid of the quality required by the Pharmacopeia, the preparation would be in conflict with the rules as an unessential modification of an official preparation. No good evidence has been furnished by the manufacturers to support the claim of superiority of the natural acid, but in submitting the preparation the firm did refer to an article by Dr. F. Forcheimer published in *Jour. A. M. A.*, Oct. 30, 1909, p. 1450. Forcheimer does not mention Xanol, but in referring to the use of caffeine says:

> "I employ the double salts (preferably the caffeine sodio-salicylate, because it is best made in this country), as they are more stable when dissolved in water, more soluble and less irritating when administered hypodermically, than any other salts of caffeine."

Since the manufacturers did not furnish any references, the referee has undertaken to determine the status of the question so far as can be done from the available authorities on pharmacology.

Disregarding instances where authors merely refer to the claim that the natural is superior to the synthetic acid, we find the following statements of opinion or experimental evidence: H. C. Wood (Principles of Therapeutics, ed. 14, p. 446) refers to the work of B. J. Stokvis

> " . . . who reached the conclusion that there is a marked quantitative difference, the natural acid being distinctly less poisonous than the artificial—a circumstance which he thinks is due to the superior osmotic properties of the natural acid, causing it to be more rapidly eliminated." (Atti d. xi Congr. med. Internazionale, 1894, iii.)

Sollmann (Text-book of Pharmacology, ed. 2, p. 374) says:

> "It is sometimes claimed that the salicylates prepared from wintergreen are much superior to the synthetic: but there does not appear to be any strong proof of this assertion."

Stevens (Modern Materia Medica and Therapeutics, ed. 5, p. 398) says:

> "The acid obtained from oil of wintergreen has no advantage over the cheaper synthetic acid if the latter be of official quality."

Potter (Materia Medica and Therapeutics, ed. 9, p. 464) says:

> "The acid prepared from natural sources is purer and more efficient than that prepared artificially and will often be tolerated by a patient who cannot bear the latter."

Cushny (Pharmacology and Therapeutics, ed. 5, p. 468) says:

> "Salicylic acid formed synthetically from phenol is often said to be more poisonous than that obtained from the oil of wintergreen (methyl salicylate) but this is due, not to any difference in the acid, but to the presence of carbolic acid and other impurities in the artificial preparation."

The work of Stokvis is already sixteen years old and appears to lack confirmation. It seems an improbable theory that the mere difference in the physical properties will produce a marked difference in the action of the substance inside the organism. Even if this is true, it would seem that since the difference is only quantitative it would extend also to the therapeutic efficiency, so that we might expect the natural acids to be less efficient than the artificial. Aside from this unsupported experimental evidence, it would appear to be the general opinion that the observed differences are due to impurities in the synthetic acid and do not apply to preparations made from an acid which conforms to the official standard of the Pharmacopœia, which must be pure, whether made from phenol, oil of wintergreen or anything else.

The preceding portion of this report was transmitted to the Wm. S. Merrell Chemical Co., who replied:

> "Your favor of October 31st at hand and also your communication relative to the acceptance of Xanol by your Council on Pharmacy. We have received a paper by Dr. Joseph E. Winters, of New York, Professor of the Diseases of Children, Cornell University Medical College, in which he says:
>
> " 'That there is a positive, chemical antidote elucidates the etiology. This antidote is an *organic*, chemical compound. Synthetic salicylic acid has no effect. The antidote must be from Nature, organic, vegetable.' "

Dr. Winters further states:

> "'Synthetic salicylic acid is not only useless but is injurious—it is dangerous—it is poisonous. Its manufacture should be prohibited by law.'"
>
> "This is the kind of evidence, we understand, that your Council requires at our hands before they will acknowledge the superiority of the natural salicylates prepared from wintergreen or birch oil over the commercial article of the shops synthetically prepared. You will pardon us if we again state that your contention in respect to the natural salicylic acid and its sodium salt is so amazing to us—and to others who have used it—that it is like requiring us to prove an axiom or self-evident truth. We sincerely trust that the eyes of your Council may be opened to see beyond the narrow limits which confine their judgment and accept the testimony of experience as to the truest guide in such matters. In the discussion of all matters of truly scientific interest to the medical profession and in the consideration of any legitimate product brought to the attention of your Council, we are yours to command."

No reference to the source of the quotations is made by the Wm. S. Merrell Chemical Co., but the referee has read a pamphlet (Etiology of Rheumatism) by Joseph E. Winters in which the first quotation cited occurs and is of the opinion that the views there expressed are not such as to entitle the author to consideration as an authority on pharmacology. This is shown not only by the obviously incorrect statement in the quotation that "synthetic salicylic acid has no effect," but by various other dogmatic and unwarranted assertions. As an example the author states "Salicylates liberate their bases in the blood—they never reach the tissue fluids." "Salicylic acid is converted by the alkaline secretions in the intestine into salicylate. In the blood the bases are set free; salicylic acid is at once eliminated, appearing in the urine in a few minutes." The author further states that vegetables are 23 per cent. minerals, mostly compounds of potash.

It is generally held that salicylic acid circulates in the blood as a salicylate (H. C. Wood, Therapeutics; Its Principles and Practice, p. 446; Cushny, Pharmacology and Therapeutics, p. 467), that it probably enters into every liquid of the organism (Wood), and that it has been found in large quantities in the cavities of the joints (Cushny) and that its elimination continues for forty-eight hours. It has been found in the milk, perspiration, and bile. Therefore, the dogmatism of the author who asserts that in salicylates, the base is held in such light chemical union that it is set free in the blood

and never reaches the tissues, while food bases are liberated at the spot where the acids of metabolism are set free, indicates that he cannot be regarded as qualified to furnish evidence on this particular question. There may be room for differences of opinion as to the state in which salicylic acid exists in the blood; but whatever this state may be, there is no reason to assume that the origin of the salicylic acid would affect its fate in the organism, any more than the origin of sodium chlorid or dextrose affects the fate of these substances. There is certainly no evidence for such an assumption; all the evidence points to the logical conclusion that their fate is essentially alike.

In the opinion of the referee, therefore, Xanol is an unessential modification of an official substance and it is recommended that it be not accepted for New and Nonofficial Remedies.

INDEX OF PROPRIETARIES, MANUFACTURERS AND AGENTS