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OF THE

COUNCIL ON PHARMACY AND CHEMISTRY

OF THE

AMERICAN MEDICAL ASSOCIATION

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PREFACE

This volume—the Annual Reprint of the Reports of the Council on Pharmacy and Chemistry of the American Medical Association—contains the reports of the Council that have been adopted and authorized for publication during 1920. It includes reports of the Council previously published in THE JOURNAL, along with such editorial comments as have accompanied them. In addition, the volume contains reports of the Council which, because of their lesser importance, were not published in THE JOURNAL, and which as a matter of record are included here. That the Council's official reports may be made available to physicians, chemists, pharmacologists and others interested in medicine, the Council authorized publication of this volume.

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REPORTS OF THE COUNCIL ON PHARMACY AND CHEMISTRY

EUMICTINE

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Feb. 21, 1920, p. 542

The Council has adopted and authorized publication of the report which appears below. This report declares "Eumictine" ineligible for New and Nonofficial Remedies because (1) it conflicts with Rule 10 in that it is unscientific, (2) it conflilts with Rule 6 in that it is sold under unwarranted therapeutic claims, (3) it conflicts with Rule 4 against indirect advertising to the public in that the name "Eumictine" is blown in the bottle for the obvious purpose of bringing the product to the attention of the public when it is prescribed in the original package and (4) because the name is therapeutically suggestive and not in any way descriptive of its composition.

W. A. PUCKNER, Secretary.

Eumictine is a preparation from the laboratory of Maurice Le Prince, Paris, France, and is marketed in this country by George J. Wallau, Inc., New York. It is claimed that the product is "a balsamo-antiseptic preparation composed of Santalol, Salol, and Hexamethylene-Tetramine, in the form of gluten-coated capsules." Nowhere in the advertising are the amounts of the ingredients given. According to the American agent, however, "each capsule is supposed to contain 20 centigrams of Santalol, 5 centigrams of Salol, 5 centigrams of Hexamethylene-Tetramine."

Eumictine is advised "in treating genito-urinary diseases (urethritis, cystitis, prostatitis, pyelitis, etc.)." It is claimed to be "both an antiphlogistic modifying agent, a well-tolerated diuretic" which "may be administered for long periods without ill effects."

The Council declares Eumictine ineligible for New and Nonofficial Remedies because it is exploited in conflict with the following rules:

It is unscientific (Rule 10). Eumictine is composed of hexamethylenamin, salol and santalol in fixed proportions. Hexamethylenamin may serve a useful purpose in some forms of infection of the urinary tract, but neither it nor

salol is of any considerable value in gonorrhea. It is now known that the balsamic preparations, formerly so widely used, do not have the curative effects in gonorrhea and associated conditions that used to be ascribed to them. To combine three substances, none of which has any distinct therapeutic value in the conditions for which Eumictine is proposed, does not enhance their value. There is nothing original in the combination used in Eumictine, or in the manner of dispensing it.

It is sold under unwarranted therapeutic claims (Rule 6). These claims are made not only for the components of Eumictine but for the combination itself. Though santalol has certain advantages over the somewhat variable oil of santal and other balsamic resins, it is not true that santalol "does not cause congestion of the renal epithelium" or that it does not "produce exanthema as do copaiba, cubebs, and the ordinary santal oil." It is not true that salol is "devoid of toxicity." Neither is it correct to say that salol "asepticizes and disinfects the bladder, the prostate and the urethra." The claim that hexamethylenamin "is of value when any acute symptoms or tendency to inflammation subsist" is not justified. The claim that hexamethylenamin "renders soluble the uric acid and urates" is also without foundation. The following paragraph is characteristic of the claims made for Eumictine:

"Anti-gonorrhoic by its Santalol, diuretic, urolytic and analgetic by its hexamethylenetetramin (Urotropin) antiseptic and antipyretic by its Salol, Eumictine represents a real therapeutic advance in the scientific treatment of diseases of the urinary passages."

Instead of being "a real therapeutic advance" in the treatment of diseases of the urinary passages, Eumictine presents one of the complex combinations that have long retarded the scientific treatment of these diseases. Eumictine also conflicts with Rules 4 and 8 of the Council.

PLATT'S CHLORIDES

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., March 27, 1920, p. 903

The Council has authorized publication of the following report on "Platt's Chlorides." It also declares the preparation inadmissible to New and Nonofficial Remedies because its composition is uncertain and indefinite and because the claims made for it are exaggerated and misleading.

W. A. PUCKNER, Secretary.

"Platt's Chlorides," marketed by Henry B. Platt, New York, is sold as a disinfectant and germicide. Only incomplete and contradictory statements have been made in regard to its composition. Many years ago (about 1899) the composition of Platt's Chlorides was given as "The Chlorids of Zn 40 per cent., Pb 20, Ca 15, Al 15, Mg 5, K 5." The statement that the preparation contained 20 per cent. of lead chlorid, is interesting in view of the fact that lead chlorid is soluble in water at ordinary temperatures to the extent of less than one per cent. In a booklet, also issued a number of years ago, the following "Formula of Platt's Chlorides" was given:

"A saturated solution of Metallic Chlorids combined in the following proportions:

"Sol. Zinc Chlorid	40 per cent.
"Sol. Aluminum Chlorid	15 per cent.
"Sol. Lead Chlorid	20 per cent.
"Sol. Calcium Chlorid	15 per cent.
"Sol. Magnesium Chlorid.....	5 per cent.
"Sol. Potassium Chlorid	5 per cent."

The label on a bottle purchased in 1911, describes Platt's Chlorides as:

"A Highly Concentrated Solution of the Chlorids of Aluminum, Calcium, Lead, Zinc, etc."

The label of a bottle purchased in 1919, reads:

"Contains Inert Material: Water 84.0%. Sodium Chlorid 4.8%. Calcium Chlorid 0.3%."

This statement is obviously made to meet the requirements of the federal Insecticide Act. This law requires either that the identity and the amounts of potent ingredients in disinfecting preparations be declared or else that the percentage of the inert ingredients of such preparations be given. The omission from the label of all statements with regard to the potent ingredients of the preparation and the absence of such a statement in recent advertising matter suggests either that the older statements about its composition were false or else that the composition has been changed.

Tscheppe published (Pharmaceutische Rundschau **8**:109, 1890) an analysis of Platt's Chlorides which has been quoted in other publications as indicating the composition of the preparation. He reported that he found each quart of the preparation to contain aluminum sulphate 6 ounces, zinc chlorid 1⅓ ounces, sodium chlorid 2 ounces, calcium chlorid 3 ounces.

Some years ago (about 1911) the company made the following statement relative to the germicidal power (phenol co-efficient) of Platt's Chlorides:

". . . for some time the carbolic acid co-efficiency of our output has been from 2.5 to 4.3; the average being about 3; namely about three times stronger than pure carbolic acid."

In 1912, the U. S. Public Health and Marine Hospital Service reported (*Bulletin 82,* Public Health and Marine Hospital Service, p. 69) that the phenol coefficient of a sample of Platt's Chlorides was so low that it could not be determined and also that the sample was found to contain some mercuric chlorid. In 1913, the North Dakota Agricultural Experiment Station reported (*Bulletin,* July, 1913, p. 292), that Platt's Chlorides contained principally zinc chlorid, also some aluminum chlorid, calcium chlorid, and traces of mercuric chlorid. The phenol coefficient, determined by the Hygienic Laboratory method, was found to be 0.05.

The preceding suggests that the composition of Platt's Chlorides had been changed (without notice to the consumer) and that it had been fortified by the addition of mercuric chlorid. Years ago part of the advertising of this product was a testimonial from a health official which declared that, for disinfection, "bichlorid of mercury is useless in disinfecting sputum or discharges from the bowels, being rendered inert by the albumen present" and it lauded Platt's Chlorides as devoid of such drawbacks.

RECENT ANALYSES OF PLATT'S CHLORIDES

To determine the present composition of Platt's Chlorides and to compare it with that sold formerly, the A. M. A. Chemical Laboratory has made an analysis of a specimen purchased in 1919 and also of one that was purchased in 1911 and since kept unopened in the files of the Council on Pharmacy and Chemistry. The following table contains the results of these analyses (all quantities given are Gm. per 100 c.c.):

	1911 Specimen	1919 Specimen
Color	Colorless	Straw Color
Odor	None	None
Specific Gravity at 25 Cc.	1.1229	1.1313
Total Solids (residue at 100 Cc.)	16.49	18.33
Chlorid (Cl^-)	7.60	10.74
Sulphate (SO_4^{--})	1.11	.16
Aluminum (Al^{+++})	.22	.90
Calcium (Ca^{++})	.19	.13
Zinc (Zn^{++})	5.11	3.93
Lead (Pb^{++})	.046	Traces
Mercury (Hg^{++})	.....	.0086
Sodium (Na^+)	1.01	1.39

These quantities transposed to hypothetical combinations would indicate that Platt's Chlorides has the following composition:

	1911 Specimen	1919 Specimen
Aluminum Sulphate	1.32	.18
Aluminum Chlorid	.07	4.29
Calcium Chlorid	.54	.37
Zinc Chlorid	10.66	8.19
Lead Chlorid	.06	Traces
Mercury Chlorid	.....	.0116
Sodium Chlorid	2.57	4.81
Hydrogen Chlorid	.43	None

In the past, the advertising has suggested, more or less directly, that, as chlorinated lime (bleaching powder) may be made to give off chlorin gas which disinfects, so the air in a room may be disinfected by evaporating Platt's Chlorides. Thus the label of the 1911 specimen contains the following:

"For Store Rooms, Refrigerators, and Closets, keep a sponge saturated with the pure liquid in a saucer on an upper shelf."

On the label of the 1919 specimen, the statement reads:

"Refrigerators and Storerooms—As a disinfectant wash regularly with one part Chlorides to eight of water. As a deodorant, keep in an open vessel a sponge or cloth saturated with the Chlorides full strength."

That the owner of Platt's Chlorides really believes that the vapors of the preparation have disinfecting properties is seen from a letter over the name of Henry B. Platt printed in the New York *Tribune* in 1916. This read, in part:

". . . by keeping in a dish or saucer on radiators Platt's Chlorides diluted one-half, the hot solution will evaporate and purify the air, thus destroying the grip germ which is the cause of all the trouble."

From the analysis of Platt's Chlorides, it is evident that when the preparation is evaporated, water vapor only escapes.[1] Whatever disinfecting or germicidal action the preparation may possess is exercised only when the solution is brought in direct contact with the substance to be disinfected.

The aluminum and zinc salts present may be useful as deodorants but they are not effective as germicides. The presence of mercuric chlorid in a concentration of 1 to 10,000

1. It is well known that when a solution of mercuric chlorid in water is evaporated, mercuric chlorid passes off with the water vapors, but under any condition the amount is but a fraction of the whole. As in Platt's Chlorides other metallic chlorids are present, the formation of complex mercuric compounds which is bound to have occurred, should retard or prevent the volatilization of mercuric chlorid. That this actually occurs was confirmed by the following experiment: When 1 gm. mercuric chlorid was dissolved in 1 liter of water and the solution distilled, the distillate contained a very small amount of mercury. Then the experiment was repeated after adding sodium chlorid to the solution to simulate the conditions in Platt's Chlorides. In this case no mercury was found in the distillate. Even were all the mercury in a bottle of Platt's Chlorides volatilized in a room 10 by 12 by 9 feet, this would be equivalent to only about $\frac{1}{500}$ grain mercuric chlorid per cubic foot.

is hardly to be considered as materially increasing the efficiency. The directions recommend the use of a mixture of 1 part of Platt's Chlorides to 10 parts of water for rinsing the hands, and a mixture of 1 part to 4 parts of water for the disinfection of discharges. It is further stated that 1 quart makes 2 gallons sufficiently strong for general use. It is evident that such dilutions decrease considerably the feeble germicidal action of the original fluid.

ANTI-TUBERCULOUS LYMPH COMPOUND (SWEENY) AND ANTI-SYPHILITIC COMPOUND (SWEENY)

Reports of the Council on Pharmacy and Chemistry

From The Journal A. M. A., April 3, 1920, p. 965

The Council has authorized publication of the reports which appear below, declaring Anti-Tuberculous Lymph Compound (Sweeny) and Anti-Syphilitic Compound (Sweeny) ineligible for New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

Anti-Tuberculous Lymph Compound (Sweeny)

"Anti-Tuberculous Lymph Compound (Sweeny)" is put out by the National Laboratories of Pittsburgh, Dr. Gilliford B. Sweeny, "Medical Director." Sweeny has claimed at different times that he became interested in the subject of von Behring's efforts to immunize cattle to tuberculosis at a time when he was an assistant in von Behring's laboratory. He claims to have conceived the idea while there of transferring bovine immunity to tuberculosis to the human subject and later to have evolved his "treatment" at the Pasteur Institute in Paris.

Just how Anti-Tuberculous Lymph Compound is made today is not stated—at least so far as one is able to learn from recent advertising. Some years ago Sweeny declared that his "Anti-Tubercular Lymph" (as it was then called) was derived from a bullock which had been immunized to tuberculosis. Then:

> "The immunized animal having been slaughtered, the contents of the lymph reservoirs are carefully collected and an aqueous extract is made from the grey cerebral substance, spinal cord and the lymph glands. It is then filtered under high pressure and de-albuminized by succussion. To this, the lymph, together with a definite proportion (50 per cent.), of the naturally phosphorized brain fats is added, with a small amount of chloride of gold (about 1-60 gr. to the dose), the latter as a preservative."

It is a fair assumption that however the preparation may have been made originally, it is not now made in such a manner as to bring it under the federal laws governing the preparation of serums and similar preparations. The claims made for Anti-Tuberculous Lymph Compound are of the usual uncritical and unscientific type. Mainly, of course, they are of the testimonial class. The physician is told that the preparation has been carefully tested by men whose judgment is worthy of consideration; that the verdict has been altogether favorable to the "Compound." Thus:

". . . the remedy was submitted to a selected body of skilled physicians, recognized for their skill and care in making therapeutic observations. These men represented widely varying conditions, climatic and otherwise. Those who said ten years ago that Anti-Tuberculous Lymph Compound has a specific immunizing influence upon the tuberculosis patient, find the same to be true today."

Careful reading of the matter just quoted will reveal its ambiguity and inherent lack of frankness. The inference conveyed is that the "selected body of skilled physicians" have unqualifiedly endorsed Anti-Tuberculous Lymph Compound (Sweeny)—but it does not say so!

It is the history of all such preparations, introduced to the medical profession with the usual blare of trumpets, that a certain number of favorable testimonials can be obtained. It is also the history of such products that one has but to wait a few years and the physicians who had written most enthusiastically regarding the preparation—in the first flush of their optimism following its use and the perusal of the manufacturers' literature—will acknowledge that they were mistaken in their original estimate and are no longer using the agent. In this connection an investigation of some of the old testimonials for Anti-Tuberculous Lymph Compound by the Propaganda department of THE JOURNAL is instructive.

In a somewhat elaborate booklet published in 1907 by Sweeny, an Indiana physician was said to have reported favorable results following the administration of the "lymph." A letter written to this physician in October, 1919, asking for his present opinion on the product brought this reply, in part:

". . . it being twelve years since using the serum and no reference or repeated orders since should surely suffice as evidence of my lack of faith in the serum. . . ."

An Illinois physician was reported in the same booklet to have described a case of a young man with an active tuberculosis, who was given injections of the "lymph" in February, 1907. The patient, it was claimed, showed immediate improvement and the Sweeny booklet (published in August, 1907) stated that "improvement in this case con-

tinued and terminated in complete recovery." A letter written to the physician in October, 1919, brought out the fact that the young man in question, after receiving "Anti-Tuberculous Lymph Compound" and *other treatment* was removed "on a stretcher" "to New Mexico, where he remained for three or four years" and recovered. The doctor adds:

"I do not think that the Anti-Tuberculous Lymph had anything to do with the man's recovery, although I realize the difficulty of definitely analyzing just what did effect the cure. I did since that time use that preparation in several other cases without beneficial results so that I gave it up a good many years ago adding it to that large heap of pharmaceutical material 'weighed and found wanting.'"

A physician in Texas also reported in the 1907 booklet as having had very satisfactory results with the Anti-Tuberculous Lymph Compound in one case of pulmonary tuberculosis was written to in October, 1919. He replied:

"I will state that subsequent use of this compound did not bear out the apparent good results from its use in the first case or two."

In a "Bulletin" issued by the Sweeny concern in 1912, a Pennsylvania physician was quoted as having treated three cases with Anti-Tuberculous Lymph Compound with resultant cures. This physician was written to in October, 1919, and he replied:

"I have no knowledge of the use of my name by any Pittsburgh concern and know nothing of a lymph of the name of Sweeny; neither do I recollect ever curing three cases of tuberculosis with any lymph."

The same "Bulletin" quoted the alleged statement by a Delaware physician to the effect that he believed Anti-Tuberculous Lymph Compound to be the most successful treatment of tuberculosis extant. This in 1912. To an inquiry sent in October, 1919, this physician briefly replied:

"Am not using it now."

The result of the Propaganda department's questionnaire was what might have been expected. Every physician who answered the inquiry regarding his previous and present opinions of Anti-Tuberculous Lymph Compound (Sweeny) declared, in effect, that he had long since ceased to have faith in its value or efficacy.

According to claims made in the Sweeny literature, "Anti-Tuberculous Lymph Compound exercises its immunizing power through a specific action upon the blood cells." The statement that "it destroys the tuberculosis germ when this is present in the system of the patient" is untrue. The facts are, no serum or lymph has thus far been proved to have any value in the treatment of tuberculosis even when fortified by "a small proportion of chloride of gold and soda" as one circular tells us the "lymph" is. In spite of

years of research by competent investigators, we are still without any aid in the form of a serum in the treatment of tuberculosis.

Anti-Tuberculous Lymph Compound (Sweeny) is one of those preparations that need no elaborate laboratory tests, nor even exact therapeutic research, to convince any clear-thinking person that it is patently and obviously worthless. One would hesitate before asking any reputable clinician to test a preparation of this sort. It is a constant source of surprise that some physicians allow themselves to be persuaded by advertising literature that is obviously uncritical and unscientific, to use preparations which have no more reasonable foundation than this one.

The Council declares Anti-Tuberculous Lymph Compound (Sweeny) not acceptable for New and Nonofficial Remedies.

Anti-Syphilitic Compound (Sweeny)

This preparation also is made by or under the direction of the same Dr. Gilliford B. Sweeny whose researches (?) led to the production and evolution of the Anti-Tuberculous Lymph Compound (Sweeny). According to the data at hand, this preparation is made by suspending benzoate of mercury in lymph from the bullock. Case reports are given of alleged cures of syphilis after two months of treatment; indeed, the circular exploiting the agent makes the statement that it is seldom necessary to continue the treatment beyond two months, which, if one chose to be credulous, would indicate extraordinary power for the mercury.

Mercury of course has a proper place in the treatment of syphilis, but that any physician could be induced to place his trust in this preparation is almost unthinkable though testimonials—which the "National Laboratories" claim to have received from physicians—are published. They all stamp the writers as not only gullible but also incompetent. The tenor of the claims is on a par with those made for the Anti-Tuberculous Lymph Compound; they do not justify the time required for detailed consideration.

The Council declares Anti-Syphilitic Lymph Compound (Sweeny) not acceptable for N. N. R.

SYRUP LEPTINOL (FORMERLY SYRUP BALSAMEA)

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., June 5, 1920, p. 1591

The Council has authorized publication of the following report on "Syrup Leptinol" (formerly "Syrup Balsamea"). The product is inadmissible to "New and Nonofficial Reme-

dies," first, because the manufacturers fail to give the profession information regarding either the amount of the potent ingredient or the method of determining its identity and uniformity; second, because of the unwarranted recommendation for its use in such infectious diseases as pneumonia and epidemic influenza and for lack of satisfactory supporting evidence of its alleged therapeutic efficacy in other diseases and, third, because the recommendations for its use appearing on and in the trade package constitute an indirect advertisement to the public.

W. A. PUCKNER, Secretary.

Syrup Leptinol is sold by the Balsamea Co. of San Francisco. It was first introduced as Syrup Balsamea. In recent advertising, Syrup Leptinol is also referred to simply as "Leptinol."

According to the statements of the Balsamea Co., Syrup Leptinol is prepared from the root of a species of Leptotaenia (a plant belonging to the parsnip family) which grows in Nevada and which has heretofore not been used in medicine. The manufacturer states that the botanists who have been consulted have been unable to agree on the botanical classification of the plant. The dried root of this unclassified species of Leptotaenia is extracted with alcohol and from the extract so obtained the syrup is made, but no information has been furnished to show how the alcohol-soluble material is incorporated in the syrup. Further, the manufacturer has not announced tests whereby the identity and uniformity of the finished preparation may be determined.

A booklet contains the following:

"The species of Leptotaenia from which LEPTINOL is produced was first used in medicine by Dr. E. T. Krebs, who, after thorough laboratory investigation and clinical application over a period of several months, which resulted in the perfecting of LEPTINOL, prescribed the preparation for Influenza during the epidemic of that disease in 1918 with remarkably good results. Since this first use, LEPTINOL has been exhaustively tested by clinicians in private practice and in hospitals in the treatment of Pneumonia, Influenza, Bronchitis, etc., and has been universally endorsed."

In a circular letter it is asserted that the use of "Leptinol" during the "influenza epidemic" of 1918-1919 "demonstrated its almost specific action in respiratory affections"; that "during this epidemic it proved to be five times as efficacious as any other treatment in pneumonia . . ."; and that "it is now as firmly fixed in the mind of many doctors for respiratory diseases as quinine is for malaria and the salicylates for rheumatism."

In the booklet it is further stated that the therapeutic action of the preparation is primarily that of a "stimulating expectorant" and secondarily as a "sedative expectorant"; that "its antiseptic action in the respiratory tract is prompt"; that it "is an effectual cardiac tonic where the tone of the heart muscle is impaired by fever"; that "in acute pulmonary conditions it effectively improves the respiratory action and allays cerebral irritation due to fever and toxins"; that it acts "as a vital stimulant and nerve sedative"; that "it stimulates the excretion of acid by the skin and in fever it has a strongly diaphoretic and antipyretic action without depressing the circulation or the central nervous system"; that it is "mildly diuretic" and "slightly augments the biliary flow" and that "it increases the gastric and intestinal secretions and allays intestinal fermentation."

No evidence has been presented to the Council which shows that Syrup Leptinol has the actions ascribed to it. The reports of clinical trial are little more than chance observations and lack all control. This applies also to the following, stated to be a quotation from the report of the Tonopah Mines Hospital Association:

"In the spring of 1919 a recurrence of the Influenza epidemic of the previous winter was experienced. During the first period of this second epidemic, prior to April 15th, there were treated one hundred sixteen cases of Influenza, fourteen of which developed Influenzal Pneumonia, with six deaths. The Pneumonia was of the very virulent type which prevails in this high altitude . . . After April 15th, when the clinical use of Leptinol was inaugurated, three hundred and sixty-eight cases of Influenza were treated and not a singel case developed Pneumonia. Twenty-two cases of Influenzal Pneumonia were received and treated with LEPTINOL, with a consequent one hundred per cent. recovery. . . .

"In the cases where LEPTINOL was used the treatment was the same as had been previously followed, as to diet, fresh air, etc., but the medication was confined to LEPTINOL. Syrup LEPTINOL was started immediately in one-dram doses at one-hour intervals, in cases with high temperatures, and this was continued until temperature and pulse subsided. It was then used in one-dram doses at three-hour intervals as recovery progressed. On admission to the hospital, calomel in ¼ grain doses, was given at fifteen minute intervals for eight doses. The last calomel was followed in six hours by ½ ounce Magnesium Sulphate in saturated solution. The second day 1/10 grain of calomel was given at one-hour intervals for ten doses. . . ."

Medical journals are replete with reports of remarkable results obtained with the most varied forms of treatment instituted at the time that the "influenza epidemic" had been reached. In these cases it is more than probable that the lessened virulence of the causative factor of the disease, the gradually established resistance of those stricken with it in the latter period and the improved management resulting from experience deserve the credit for the successful out-

come of the treatment, rather than the particular form of medication employed.

The report of the Tonopah Mines Hospital Association directly implies that Syrup Leptinol prevents the development of pneumonia in practically all cases of influenza in which it would develop and that it entirely abolishes the mortality of that disease. However, it is well known that innumerable remedies have been recommended as specifics in the treatment of pneumonia on the basis of the treatment of a limited number of cases which recovered, and that eventually these asserted specifics have been discarded as of little value. In the present instance, the recovery of twenty-two cases in succession afford *prima facie* evidence that those cases were not the virulent type of pneumonia in which the death rate is very high under any methods of treatment. While no effort appears to have been made to determine the nature of the infecting organism, the records show fairly conclusively that they belonged to those causing the milder type of pneumonia.

The Council finds Syrup Leptinol (formerly Syrup Balsamea) inadmissible to New and Nonofficial Remedies because: (1) the information in regard to composition does not state the amount of potent ingredient, nor permit the determination of its identity and uniformity; (2) the recommendation for its use in such infectious diseases as pneumonia and epidemic influenza is unwarranted and its claimed therapeutic efficacy in other diseases is without satisfactory supporting evidence; and (3) the recommendations for its use which appear on the label and the circular wrapped with the trade package constitute an indirect advertisement to the public.

The Council accepts the explanation of the manufacturer that he has been unable to obtain a satisfactory classification of the plant from which Syrup Leptinol is made. It would be undesirable to exclude from therapeutic use a valuable drug simply because its botanical character has not been determined or because an exhaustive chemical examination had so far not been made. However, in the absence of such information the manufacturer should give full information with regard to the preparation or standardization of his remedy and the therapeutic claims made for it should be accompanied by indisputable, thoroughly controlled clinical evidence. In the case of Syrup Leptinol, there is no satisfactory evidence available showing that the preparation has any value in the treatment of epidemic influenza, pneumonia, whooping cough, etc. While it is probable that a balsamic syrup, such as Syrup Leptinol, has palliative properties in

coughs, such action does not at all justify the claim that it is useful in the contagious diseases for which it is proposed. The Council cannot recognize a syrup presenting an unknown plant in uncertain proportions which is recommended in a variety of dangerous contagious diseases in which it ultimately may be harmful, even though in early stages of these diseases, it may serve to allay some of the milder symptoms.

Concerning the composition of the plant from which Syrup Leptinol is prepared, the Balsamea Company states that it contains "Alkaloids, acids, glucosides, volatile and fixed oils, gum and resins." This information is valueless since no information is given concerning the character, amounts or pharmacologic action of the ingredients. Further, it is unreliable as far as the presence of alkaloids is concerned since the A. M. A. Chemical Laboratory has been unable to find any alkaloids in the specimen of the crude drug furnished by the manufacturers.

In accordance with its regular procedure, the Council submitted the preceding statement to the manufacturer.

In reply the Balsamea Company stated that it is more than ever of the belief that Syrup Leptinol is deserving of recognition by the Council, basing this opinion on further clinical experience with it in the treatment of influenza.

The manufacturer stated that the use of the words "Leptinol" and "Syrup Leptinol" interchangeably was due to an oversight and promised to limit the use of the word "Leptinol" to an alcoholic extract of the plant.

Concerning the method of preparation of this alcoholic extract and the amount used in the preparation of Syrup Leptinol the Balsamea Company replied as follows:

"The alcoholic extract of the Leptotaenia, which we have termed 'Leptinol' is a preparation of definite and uniform strength, as determined by two methods: (a) the gravity test using the U. S. Hydrometer Scale for spirits, by which Leptinol registers 52 degrees at 60 degrees F., and (b) by gentle evaporation of the alcohol content and the measuring of the active constituents, which measures twenty-five per cent. by weight.

"The alcoholic extract 'Leptinol' is glycerinated in a machine, using one part of the alcoholic concentration to four parts of glycerin. This is then added to eleven parts of a heavy syrup, containing 7½ pounds of sugar to the gallon of syrup, and thoroughly mixed in an agitating machine. Leptinol is the sole active ingredient of Syrup Leptinol. Syrup Leptinol is a preparation of uniform strength. It is far more uniform in strength than most of the syrups of the U. S. P. made from fluid extracts which are made from crude drugs which are not uniform in strength."

This claim cannot be allowed as meeting the conflict with Rule 1. It is well known that plants vary in their composition at different times of the year; under different conditions

of cultivation and growth; and under other conditions; hence the claim that alcoholic extracts of equal specific gravity insure uniformity of composition in active principles must be considered entirely illogical, especially since the exact nature of the active principles, if any be present, is unknown. If these are known their nature should be stated and tests for their identity be given. If they are unknown it is manifestly misleading to state that the preparation is of uniform strength.

It is evident that the Council cannot approve of the use of a preparation of unknown composition without satisfactory evidence of its value, especially when it is recommended in a variety of serious infectious diseases such as influenza and pneumonia. The mere fact that a small number of patients who have received the drug recover is no evidence of its curative value, and until carefully controlled clinical tests of the preparation are made, it is not entitled to the consideration of physicians.

FORMITOL TABLETS, II

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., June 19, 1920, p. 1730

The Council has authorized publication of the following supplementary report on Formitol Tablets.

W. A. PUCKNER, Secretary.

In the Council report (THE JOURNAL A. M. A., Oct. 4, 1919, p. 1077) on the ineffectiveness of lozenges claimed either to contain formaldehyd or to liberate formaldehyd in the mouth, the composition of Formitol Tablets of the E. L. Patch Co. was briefly discussed in the following terms:

> "The A. M. A. Chemical Laboratory reported that Formitol Tablets contained formaldehyd (or paraformaldehyd), an ammonium compound, and some hexamethylenamin. It is probable that the formaldehyd (or paraformaldehyd) was produced by the decomposition of hexamethylenamin originally present in the tablets but decomposed by long contact with the acid."

At the time this report was published, the label and the advertising matter contained but vague and indefinite statements with regard to the composition of Formitol Tablets. In the October, 1919, issue of *Patchwork*, the house organ of the E. L. Patch Co., it was denied that these tablets contain

hexamethylenamin since none had ever been used in their manufacture. It was also claimed that the company had a "printed sheet giving the formula of these tablets."

The Council advised the E. L. Patch Co. that it desires to publish only facts about the products which it examines and that if the report on Formitol Tablets was inaccurate in any way the Council would want to correct any error it might have unintentionally made. As the Formitol advertising in the files of the Council contained no information as to the composition of the tablets, the firm was also requested to send the printed sheet giving the "formula."

When this printed "formula" came it was found to be a sheet used by the E. L. Patch Co. for the purpose of giving its salesmen information regarding Formitol tablets, to be passed on to the physician. This printed sheet conveyed the information that Formitol Tablets contain ammonium chlorid, benzoic acid, citric acid, guaiac, hyoscyamus, menthol, paraformaldehyd and tannic acid, but it gave no information in regard to the amount of any of the ingredients except that it declared that each tablet represents the equivalent of 10 minims of a 1 per cent. formaldehyd solution.

Because of the nonquantitative, and, therefore meaningless printed "formula" and because, also, of its complexity, it was thought desirable to make a more complete analysis of Formitol Tablets. Experience has shown that frequently the real formula of a thing is quite different from the alleged formula published by the manufacturer. The details of the laboratory's later analysis will appear in the Annual Reports of the Chemical Laboratory or may be had on request.

The result of the laboratory's additional experimental work, especially when taken in connection with investigations made elsewhere on the interaction of formaldehyd and ammonium chlorid justifies the conclusion that Formitol Tablets do contain some hexamethylenamin, even though the amount may be very small. As the E. L. Patch Co. declare that no hexamethylenamin is put into Formitol Tablets the conclusion drawn in the Council's original report to the effect that the formaldehyd probably was formed by the decomposition of hexamethylenamin was evidently an error. The hexamethylenamin present is doubtless produced by the action of the paraformaldehyd on the ammonium chlorid present.

The analysis also showed that more than 78 per cent. of the weight of Formitol Tablets was made up of sugars and about 16.5 per cent. was starch and other material, some of which was talcum or similar material. This means that about 94 per cent. of the total weight of the tablets is sugar and starch neither of which is mentioned in the printed

"formula." The significance of this is apparent when it is considered that there are eight ingredients listed in the "formula" for which therapeutic effects are claimed. Since a tablet weighs about 13.5 grains, the combined weight of all the claimed active ingredients is less than 1 grain per tablet!

The amount of ammonium chlorid found, as indicated by the total nitrogen, was not more than 1.0 per cent. or about ⅛ grain per tablet. The amount of benzoic acid found was 0.34 per cent. or 1/25 grain per tablet. Yet these two drugs are said to exert their peculiar expectorant action. (The U. S. P. lozenge of ammonium chlorid contains 1½ grains ammonium chlorid or twelve times the amount of this drug in a Formitol Tablet.)

The tannic acid contained in the tablets could not be determined with accuracy but it was much less than 1 per cent. (or ⅛ grain per tablet) yet it is said to add valuable astringent qualities to Formitol Tablets! (The U. S. P. lozenge of tannic acid contains 1 grain of tannic acid.)

The quantity of guaiac (as resin) is but a fraction of 1 per cent. Yet it is said to impart to Formitol Tablets "stimulant resolvent" properties and it is intimated that there is sufficient to be of value in "cases of abscess of the throat and inflammation of the tissues."

The total acidity indicates the presence of about 2 per cent. of citric acid or ¼ grain per tablet. Yet this amount is said to be "antiseptic" and "aids in the general results."

While the presence of the drug hyoscyamus (henbane) was not positively identified by microscopic examination, alkaloids were present.

The manufacturers claim that the tablets contain menthol yet only a suggestion of menthol could be obtained from the odor. However the odor of methyl salicylate—a constituent *not* declared in the "formula"—predominated throughout the operations of analysis.

Formitol Tablets furnish a good illustration of some well established but often ignored truths:

1. "Formulas" that are nonquantitative are valueless or worse than valueless.

2. The fact that a manufacturer puts certain drugs in a mixture, is no proof that these drugs are there when the mixture reaches the patient. The physician must be assured that they are there when he prescribes them.

3. Complex mixtures should be avoided. It is absurd to expect, as is claimed in the case of Formitol Tablets, anodyne, antiseptic, astringent, expectorant, and resolvent action all at the same time.

SUKRO-SERUM AND APHLEGMATOL

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Aug. 21, 1920, p. 556

Two years ago, American newspapers contained accounts of an alleged cure for pulmonary tuberculosis "discovered" by Prof. Domenico Lo Monaco of Rome, Italy. At that time no reference to the "cure" could be found in medical journals which had come from Italy and other European countries (THE JOURNAL A. M. A., July 13, 1918, p. 142). Later, reports were published of experiments carried out in Italy, according to which the intramuscular injection of solutions of sugar (saccharose—cane sugar) diminished pulmonary secretion and was of considerable value in the treatment of tuberculosis (THE JOURNAL A. M. A., Sept. 28, 1918, p. 1083). On the whole, the reports of the trial of what has been called the Italian Sugar Cure for Consumption have been unfavorable. At a meeting in Paris in October, 1918, Drs. Louis Rénon and Mignot reported that they had found that the disease in guinea-pigs was not modified by the treatment and with humans, the results were also negative (Paris Letter, THE JOURNAL A. M. A., Nov. 23, 1918, p. 1760).

In view of the exploitation of this treatment in the United States by the Anglo-French Drug Co., which offers "Sukro-Serum," and by G. Giambalvo & Co., which sells "Aphlegmatol," and because of inquiries received, the Council has authorized publication of the statement which follows.

W. A. PUCKNER, Secretary.

A circular issued by the Anglo-French Drug Co. describes "Sukro-Serum" as a "Sterilized Solution of lacto-glucosaccharose." By reading the circular to the end, however, one learns that "Sukro-Serum" is not a "serum" in the ordinary sense but apparently it is a solution of ordinary sugar (sucrose). "Sukro-Serum is a sterilized, specially prepared solution of Saccharose."

Sukro-Serum has been advertised (*N. Y. Med. Jour.*, Sept. 6. 1919) as an "INTRAMUSCULAR INJECTION FOR TUBERCULOSIS" ". . . ready for use in cases of Pulmonary and general Tuberculosis" with the assertion that "It is quite certain that in the near future Sukro-Serum will be largely used and its value fully recognized." The circular received from the Anglo-French Drug Co. contains quotations from an article by Professor Lo Monaco in the *British Medical Journal* (Aug. 24, 1918) setting forth the merits of intramuscular injections of sucrose in tuberculosis. It is recom-

mended that "Néocaine-Surrénine" (which the Anglo-French Drug Co. supplies) be used for the control of pain when Sukro-Serum is injected.

The circular enclosed with a package of "Aphlegmatol," purchased from G. Giambalvo & Co., contained the following with reference to the composition of this preparation:

"A solution of Hydrats of Carbon After the formula of Prof. D. Lo Monaco, Director of the Institut of Physiological Chemistry of the University Of Rome. Contents: *Sucrose* ($C_{12}H_{22}O_{11}$) *Glucose and Galactose* ($C_6H_{12}O_6$)."

The package contained ampules of thin, fragile, brown colored glass, containing approximately 2½ c.c. of light, clear, amber colored, thick, sticky fluid, having a distinct caramel odor. Reaction $p_H = 5.0$. A reducing substance (probably glucose) amounting to 7.4 per cent. was found by using Benedict's method for estimating glucose quantitatively; after hydrolysis with hydrochloric acid, 55.5 per cent. glucose was found. There was no reaction for albumin. No attempt was made to identify the sugars, as it seemed probable that in the preparation caramel had been produced.

The circular which accompanied the package of Aphlegmatol contained the following information (spelling and composition as in original) about its use and effects:

To be emploied wherever a large bronchial secretion is present in the respiratory branches disease. The secretion will diminuish and, in non complicated cases, it will completly disappear.

Fever, cough, hemottisis, night prespiration, vomiting and difficulty of breating are, in the meantime, diminuished.

Aphlegmatol acts also as a riconstituent, being itself a nurrishing composition, improves the digestive function of the body and increases the arterial pressure.

5 c.c. (2 Phials) of Aphlegmatol per day must be injected intramuscularly in the Gluteus.

If the patient wishes two injections may be made, one at the right immediatly followed by a second one at the left.

The cure must not be interrupted untill sometime after expectoration has desappeared, which result may be obtained only after fifty or sixty days, in the meantime the patient must be controlled by his home physician, especialy when thermal elevation of the body takes place.

Improvement will be manifested on or about the tenth day of the first injection.

In the advertising circular, which is apparently intended for general distribution, much the same information is given as in the sheet enclosed with the ampules, except that in the directions we find: "If the injections are painful—especially in cases where patients are very emaciated—physicians are advised to inject together with *Aphlegmatol,* as an anaesthetic, a vial with 1 c.c. solution of Stovain at 3%." The advertising for Aphlegmatol contains many misspelled words and

appears to be the work of those ignorant of the English language.

Tuberculosis is a widespread disease and a majority of the uninformed are only too willing and ready to try such a "cure." The preparations appear to be nothing more than concentrated solutions of sugar. It is probable that a small amount of the cane sugar might be inverted to glucose and fructose, but experiments have shown that cane sugar subcutaneously administered in the small amounts used in this instance is largely excreted in the urine unchanged. Less is known about galactose, but the evidence available would indicate that galactose is largely excreted in the urine unchanged when given subcutaneously. Glucose would be absorbed as such, and in the amounts under consideration, used by the system much the same as when given by mouth.

SUPSALVS NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Oct. 30, 1920, p. 1219

The Council has authorized publication of the following report declaring Supsalvs (Anglo-French Drug Company) inadmissible to New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

Supsalvs are advertised by the Anglo-French Drug Company as "stable suppositories of '606' (of French manufacture)" with the claim that by the rectal administration of these suppositories the effects of arsphenamine may be obtained. The asserted efficacy of Supsalvs medication is based in part on the claim that for these suppositories an excipient was found which mixes with the cocoa butter base "to form an assimilable emulsion."

> "The active principle and the vehicle being bound to one another, the mucous membrane is able to absorb both simultaneously and progressively in the form of an organic emulsion."

As no information was furnished the Council by the Anglo-French Drug Company on the origin or quality of the arsphenamine used in the preparation of Supsalvs or the character of the vehicle which was "bound" to the arsphenamine in such a way as to permit the absorption of this combination in the form of an "organic emulsion," the firm was requested to furnish: (1) Evidence that the arsphenamine used in Supsalvs complies with the N. N. R. standards and that

deterioration of it does not occur in the preparation of the suppositories or on keeping. (2) The identity of the ingredients composing the suppository.

The Anglo-French Drug Company did not supply the requested evidence and consequently the Council judged the preparation on the basis of the information received from the company, and that contained in the available advertising and circulars. It found Supsalvs inadmissible to New and Nonofficial Remedies, first because the quality of the medicament contained in the suppositories has not been established, and second because the claimed efficacy of this preparation as a means of securing the effects of arsphenamine lacks substantiating proof.

During the past few years some French physicians have reported favorably on the intrarectal administration of arsphenamine. Boyd and Joseph at Panama published (THE JOURNAL, Aug. 17, 1918, p. 521) an enthusiastic report on intrarectal injection of arsphenamine but did not refer to its use in the form of suppositories. In a comprehensive report, on the "Treatment of Syphilis" (*Quarterly Journal of Medicine,* July, 1917) L. W. Harrison stated that arsphenamine (Salvarsan) in the shape of an enema is definitely less effective than intravenously and that "Neisser and the vast majority of workers can see no value in the rectal method." Schamberg and Hirschler (A Safe and Efficient Intensive Method of Treating Syphilis, *Therapeutic Gazette,* November, 1919, p. 761) have given a rather thorough trial of this method; the results were most disappointing: "A certain or rather uncertain amount of arsphenamine is absorbed into the blood, but the quantity is obviously too small to be at all comparable in its effect with the intravenous administration. Our conclusions are that the rectal administration of arsphenamine or neoarsphenamine is an extremely feeble method of administering these drugs."

The report of the Special Committee on the Manufacture, Biological History and Clinical Administration of Salvarsan and Other Substances of the British National Health Insurance Medical Research Committee contains the following: "The rectal method of administration, either in the form of solution or as suppositories, has been advocated by a few observers mainly for cases in which there is difficulty in the adoption of the intravenous method. The experiments made by Mills at Rochester Row show that three enemata of '606' (0.6 Grm. in each) on successive days failed to produce any effect on the spironemes in the lesions. The general opinion of experienced workers is that the rectal method is ineffective, and in this view the Committee concur."

PARATHESIN NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Nov. 13, 1920, p. 1358

The Council has authorized publication of the following report. W. A. PUCKNER, Secretary.

The local anesthetic ethyl paraminobenzoate was first introduced as "Anesthesin" or "Anæsthesin." Ethyl paraminobenzoate is not patented in the United States and it may be manufactured, therefore, by any firm which chooses to do so. In order that a common name by which to designate the drug might be available, the Council coined the name "Benzocaine," as being short and easily remembered, but yet suggestive of its composition and character ("benzo" to indicate its derivation from benzoic acid and "caine" to indicate its cocaine-like properties). As the term "anesthesin" had become a common name for the drug, the Council recognized this as a synonym for benzocaine.

One of the accepted brands of benzocaine is "Anesthesin" manufactured by the H. A. Metz Laboratories, Inc. (see New and Nonofficial Remedies, 1920, p. 33). However, on April 19, 1920, the Metz Laboratories requested that its product be recognized under the designation of "Parathesin." As the use of one substance under several names causes confusion and retards rational therapeutics, the Council's rules provide against the recognition of proprietary names for nonproprietary, established drugs. In view of this and because the legitimate interests of the manufacturer may be safeguarded by appending his name or initials to the common name, benzocaine or anesthesin, the Council voted not to recognize the designation "Parathesin."

HYPODERMIC SOLUTION NO. 13, IRON, ARSENIC AND PHOSPHORUS COMPOUND NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Nov. 13, 1920, p. 1358

The Council has authorized publication of the following report. W. A. PUCKNER, Secretary.

Hypodermic Solution No. 13, Iron, Arsenic and Phosphorus Compound (Burdick-Abel Laboratory) is said to contain in each c.c.:

Ferrous citrate	0.06 Gm.
Sodium cacodylate	0.06 Gm.
Sodium glycerophosphate	0.1 Gm.
Chloretone	0.005 Gm.

The preparation is advertised as "the old reliable hematinic" which is "indicated in all forms of anemia, where both red and white cells are low." It is for hypodermic or intramuscular administration. The product is inadmissible to New and Nonofficial Remedies because:

1. It does not contain ferrous citrate as claimed. Instead the iron is in the ferric condition, apparently in the form of the unofficial and unstandardized "iron citrate green" for which there is no evidence of superiority over the official iron and ammonium citrate.[1]

2. Its name gives no information on the form in which the iron, the arsenic and the phosphorus occur therein. The term "arsenic" does not indicate whether the mild cacodylate or the potent arsenous oxid is being administered nor does the term "phosphorus" tell the physician that he is administering the practically inert sodium glycerophosphate.[2]

CHLORLYPTUS

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Nov. 27, 1920, p. 1512, with additions

The condensed report on Chlorlyptus which follows and also a complete detailed report was sent to the proprietor, Jan. 9, 1920. In reply he requested that publication be postponed pending the submission of further clinical evidence. As after nine months this evidence had not been received the Council has authorized publication of its report.

W. A. PUCKNER, Secretary.

Chlorlyptus is manufactured by Chas. A. Weeks, trading as the Weeks Chemical Company, Philadelphia. It is prepared by chlorinating eucalyptus oil until it has bound 30 per cent. of chlorin, the chlorin being in relatively stable combination. It is claimed that Chlorlyptus is a new "chlorinated antiseptic," highly efficient as a wound antiseptic and at the same time nonirritant and nontoxic. Chlorlyptus is

1. Iron Citrate Green, THE JOURNAL A. M. A., Jan. 12, 1917, p. 135; Reports Council Pharm. and Chem., 1916, p. 42.
2. Glycerophosphates, THE JOURNAL A. M. A., Sept. 30, 1916, p. 1033; Reports Council Pharm. and Chem., 1916, p. 32. Sodium glycerophosphates. Reports Council Pharm. and Chem., 1916, p. 52.

offered for use in the treatment of local infections of all types, as well as of burns, and also as an antiseptic in the alimentary and genito-urinary tracts.

The claims were based largely on reports of investigations made by Phillip B. Hawk and his collaborators. These reports the referee of the committee in charge of Chlorlyptus considered incomplete and unconvincing. Being advised of this, Mr. Weeks caused further investigations to be made. Some of the information was checked and extended by the A. M. A. Chemical Laboratory and by the referee.

The laboratory side of the investigation may now be considered as complete. The results show that Chlorlyptus is a feeble antiseptic of the aromatic oil type, considerably weaker than eucalyptus oil, both as to the therapeutic and toxic qualities. The chlorin contained in it is bound too firmly to have any action; in fact, the chlorination appears to have accomplished nothing more than a considerable destruction or weakening of the eucalyptus oil. As far as the referee can judge, this object could have been accomplished just as effectively by diluting ordinary eucalyptus oil with some indifferent solvent.

The manufacturer of Chlorlyptus contends that if the experimental findings are against his product, it should be judged by the clinical data. The clinical evidence, however, is not decisive. It shows that wounds healed and infections were prevented or successfully combated in cases in which Chlorlyptus was used in combination with good surgery, but it does not show how much of the result was due to the surgery and how much, if any, to the use of Chlorlyptus. Even were it granted as probable that the Chlorlyptus contributed to the favorable outcome, it would still be a question whether it equals other established antiseptics, or whether it possesses any material advantages over diluted eucalyptus oil. Until these points are established the clinical reports cannot offset the unfavorable results of the laboratory investigation.

The manufacturer has endeavored to obtain more convincing clinical reports, but the lack of success in this direction during the past nine months gives little encouragement that acceptable clinical evidence will be available within a reasonable time.

Believing that the information which has been obtained should be made available to the profession, the Council authorized publication of this statement and also of the detailed report. The Council voted not to accept Chlorlyptus for New and Nonofficial Remedies because of the unfavorable results of the laboratory investigation, but with the agreement that the product would receive further consideration should more convincing clinical data become available.—

I. DETAILED REPORTS

SUMMARIZED REPORTS

CHEMICAL NATURE OF CHLORLYPTUS

Chlorlyptus is prepared by chlorinating eucalyptus oil until it has bound 30 per cent. of chlorin. "Chlorlyptol" is prepared in an analogous manner from eucalyptol. There has been some confusion as to the composition; but the principal constituent is now stated to be "a dichloride of eucalyptus oil," to which the formula $C_{10}H_{16}OCl_2$ has been assigned. It differs from the "chlorinated eucalyptus oil," as ordinarily used for making dichloramin-T solutions, and which contains only ⅔ per cent. of chlorin.

AVAILABILITY OF CHLORIN IN CHLORLYPTUS

The chlorin content of chlorlyptus is almost entirely firmly bound, and therefore not "available," in contrast to the group of so-called chlorinated antiseptics (i. e., the hypochlorite and chloramin type). For instance, it does not directly liberate iodin from iodid. It contains a very small quantity of free hydrochloric acid, or perhaps some acid esters, and liberates a little more on prolonged contact with water; but the total quantity liberated under reasonable conditions is very small. According to Hawk's data, they correspond only to ⅛ per cent. HCl even after standing with water overnight, and to only ⅕ per cent. of HCl after two weeks. The referee has shown that this quantity of acid has no therapeutic significance.

The "bound" chlorin of chlorlyptus, being chemically inactive, would have no more practical significance than the bound chlorin in common salt. The "ozone" said to be used during the preparation, to expel the HCl, has also practically disappeared, to judge by the slowness with which iodin is liberated from potassium iodid.

ACID FORMATION

Some constituents of chlorlyptus hydrolyze slowly and to a slight degree with the liberation of a trace of free hydrochloric acid. According to the data of Hawk's report, the free acidity, in term of HCl, is 1/12 per cent. On standing with water over night, this increases to ⅛ per cent.

On this basis, Hawk proposed a theory that the claimed antiseptic effects of chlorlyptus are due to the continuous liberation of hydrochloric acid.

Experiments by the referee show this to be untenable. The traces of acid are neutralized and absorbed by the tissues

so rapidly that an acid reaction is not maintained. These experiments are described in the appendix.

They were submitted to the manufacturers, who in the name of Mr. Weeks (May 9, 1919) concede this conclusion and state that "there is no doubt that the referee's statements as to action in mouth, contact with living tissue and improbability that the acidity is effectively antiseptic is correct, and I am willing to accept the referee's statement as conclusive in this respect."

BACTERIAL CULTURE EXPERIMENTS

Mr. Weeks submitted a statement by Hawk to the effect that chlorlyptus has a phenol coefficient of 2.6, determined by the standard Hygienic Laboratory procedure.

He also quotes Rockefeller War Hospital that chlorlyptus kills *Staphylococcus aureus* in concentrations of 1 dram: 1 gallon (about 1:1,000), but not in more dilute solutions.

More recently, he presented a more comprehensive report by Rivas, which is reproduced in the appendix. The essential results are tabulated herewith. This tabulation shows that chlorlyptus fails to kill the organisms after an hour's exposure of the following concentrations:

Typhoid in bouillon, 10 per cent. of chlorlyptus.
Staphylococci in pus, 5 per cent. of chlorlyptus.
Staphylococci in serum, 1 per cent. of chlorlyptus.

It seems to the referee that a substance that is ineffective with an hour's exposure to these concentrations is not at all likely to kill or check bacteria under clinical conditions. In other words, it is not an antiseptic in the ordinary sense.

The referee is not impressed by the superior power attributed by Rivas to chlorlyptus in the presence of pus. Inefficiency of 10 per cent. for one-half hour or of 5 per cent. for two hours seems a failure rather than a success. The referee also notes the absence of any data as to the relative efficiency of chlorlyptus against staphylococci in pus and in bouillon. The data on serum indicate that chlorlyptus is much weaker than phenol and show that it is *less effective in the presence of pus* than in other mediums.

The referee fails to grasp the bearing of the oil experiments on any clinical condition. Moreover, the inconstant results mentioned by Rivas suggest the possibility that the incorporation of the bacteria in oil may have prevented their effective distribution in the culture medium. If any significance is to be attached to these experiments, they should be checked by controls, without antiseptics.

SUMMARY OF RIVAS' IN VITRO EPERIMENTS

	Minimal Germicidal Concentrations	Maximal Not Germicidal Concentrations
Typhoid Bacilli in Bouillon:		
Chlorlyptus (Exp. 3)	10%, 2 to 4 hours	10% for 1 hour 5% for 2 hours
Eucalyptus oil (Exp. 1)	5% within 5 minutes	No data
Phenol (Exp. 5)	1% within 10 min.	No data
Streptococci and Staphylococci in Olive Oil:		
Chlorlyptus (Exps. 7 and 8)	1%, almost at once, sometimes	No data
Eucalyptus oil	No data	No data
Phenol (Exps. 9 and 10)	1%, almost at once,	No data
Staphylococci in Pus:		
Chlorlyptus (Exp. 11)	10% for 1 hour	10% for ½ hour 5% for 2 hours
Eucalyptus oil	No data	No data
Phenol	No data	No data
Staphylococci in Human Blood Serum:		
Chlorlyptus (Exp. 12)	5% in 1 hour	1% in 1 hour
Eucalyptus oil	No data	No data
Phenol	5% almost at once	1% in 1 hour

INFECTION EXPERIMENTS IN VIVO

Dr. Rivas reports two series of experiments, in each of which three guinea-pigs received staphylococcus suspensions in the peritoneum. One guinea-pig in each series was left untreated; the others received injections of chlorlyptus into the peritoneum at various intervals.

The following results were obtained:

	Chlorlyptus	Results
Exp. 19, No. 1	None	Survived
Exp. 20, No. 1	None	Died
Exp. 19, No. 2	At once	Died
Exp. 19, No. 3	After 24 hours	Survived
Exp. 20, No. 2	After 18 hours	Died
Exp. 20, No. 3	After 24 hours	Died

This shows mortalities of

1 in 2, i. e., 50 per cent., without chlorlyptus.

3 in 4, i. e., 75 per cent., with chlorlyptus.

It is doubtful whether so small a series of experiments on so variable a phenomenon as is infection should receive any serious consideration. So far as they go, they would indicate that chlorlyptus is useless or worse.

TOXICITY

The referee determined the acute toxicity of chlorlyptus

by hypodermic injection of oily solutions into white rats. Comparative experiments were made with ordinary eucalyptus oil. The details are given in the appendix. The end-results may be summarized as follows:

	Chlorlyptus	Eucalyptus Oil
Survived	1.56 c.c. 3.75 c.c. 5.00 c.c. 6.25 c.c. 8.65 c.c.	1.25 c.c.
Died (in days)	12.5 c.c. (1 day) 12.5 c.c. (1 day) 18.75 c.c. (1 day)	2.5 c.c. (3 days) 3.75 c.c. (3 days) 5.00 c.c. (3 days) 6.25 c.c. (1½ days)
M. F. D.	8.75 to 12.5 c.c. per kg.	1.25 to 2.5 c.c. per kg.

Fatality.—The doses are calculated for cubic centimeters of the undiluted drugs per kilogram of rat.

Dr. Rivas reports a series of toxicity experiments on guinea-pigs. Assuming a uniform weight of 400 gm. per animal, his results (details in appendix) may be summarized as:

	Minimal Fatal Dose C.c. per Kg.	Maximal Survived Dose C.c. per Kg.
Chlorlyptus, peritoneal (Exp. 14)	7.5 c.c.	5 c.c.
Chlorlyptus, pleural (Exp. 15)	5 c.c.	2.5 c.c.
Eucalyptus oil, peritoneal (Exp. 16)	2.5 c.c.	No data
Eucalyptus oil, pleural (Exp. 16)	1.25 c.c.	No data
Dichloramin-T, peritoneal (Exp. 16)	1.25 c.c.	No data

The *comparative toxicity* in the various series is therefore approximately as follows:

	Chlorlyptus	:	Eucalyptus
Referee, rats, hypodermic	1/5	:	1
Rivas guinea-pig, peritoneal	1/3	:	1
Rivas guinea-pig, pleural	1/4	:	1

Evidently, the toxicity of chlorlyptus is about one-fourth of that of eucalyptus oil. The difference is considerable, but

not fundamental. Moreover, the symptoms of chlorlyptus resemble the characteristics of eucalyptus oil.

According to the tabulation of Barker and Rowntree,[1] the mean fatal dose of eucalytus oil for man, in the twenty-nine clinical cases reported in the literature, is about 20 c.c. If the toxicity ratio of the two substances were the same as for the rat experiments (a rather hazardous assumption), the fatal dose of chlorlyptus for man would be about 80 c.c.

IRRITATION

Rivas's Experiment 14 shows that chlorlyptus gives very definite irritation, apparently similar to that produced in Experiment 16 by eucalyptus oil in one-fourth the dose.

Incidentally, the referee may add from personal experience that the "chlorlyptus oil, 5 per cent. CI" is markedly irritating in the nostrils, although marked "non-irritating" on the label.

II. APPENDIX: SPECIAL REPORTS

A. COMPARISON OF CHLORLYPTUS WITH CHLORINATED EUCALYPTOL

From the Chemical Laboratory of the American Medical Association

According to the label, "Chlorlyptus" is a "Synthatized Chlorinated Oil of Eucalyptos, with Acid Reaction, containing approximately 30 per cent. Chlorine and possesses excellent Germicidal Properties, when made under our special process." It is manufactured by the Weeks Chemical Company, Philadelphia, Pa. This product was submitted to the Council on Pharmacy and Chemistry by the manufacturers, and in turn the Laboratory was asked to examine it with the idea of comparing it with the nonproprietary brands of "chlorinated eucalyptol" (used as a solvent for dichloramine-T; see New and Nonofficial Remedies, 1919, p. 70). In the submission, certain tests were described, most of which were followed. Among the statements given under the chemical properties of chlorlyptus are:

"On distillation, chlorlyptus begins to boil at about 100° C. The temperature rises as the distillation continues, accompanied by the

1. Barker and Rowntree (Bull. Johns Hopkins Hospital **29**: 215, 221 [Oct.] 1918) obtained the following results with eucalyptus oil:
Cat, hypodermic; survived 3 c.c. per kg.: killed by 5.5 c.c. per kg.
Cat, intraperitoneal: killed by 5 c.c. per kg.
Dog, hypodermic: survived 1.3 c.c. per kg.
They quote from Browning that the following doses, c.c. per kilogram, are not fatal: frogs, 0.5; rabbits, 1 to 5; guinea-pigs, 1.

decomposition of the chlorlyptus and the evolution of hydrochloric acid and chlorine."

"When brought into contact with water, chlorlyptus undergoes a process of hydrolysis . . ."

Notwithstanding the foregoing, the statement is made on the label that chlorlyptus "is a Stable Compound, not affected by heat, light or water."

The following comparisons of chlorlyptus, chlorinated eucalyptol-Abbott and chlorinated eucalyptol-Squibb were made:

Chlorlyptus is a viscous, dark brown liquid, with an acrid odor and having a specific gravity of 1.2098. Chlorinated eucalyptol-Abbott is a mobile, light yellow liquid, with a eucalyptus odor, having a specific gravity of 0.9317. Chlorinated eucalyptol-Squibb is a mobile, colorless liquid, and its specific gravity is 0.9303.

An alcoholic solution of silver nitrate added to an alcoholic solution of chlorlyptus yields a heavy precipitate of silver chloride. In the case of the Abbott chlorinated eucalyptol a slight turbidity is caused by this test; the Squibb product shows no reaction.

A 10 per cent. solution of potassium iodide is overlaid with an equal volume of chlorlyptus. Iodine is slowly liberated, being noticeable in one-half hour. With chlorinated eucalyptol-Abbott, a trace of free iodine is discernible after four hours, while with chlorinated eucalyptol-Squibb there is no free iodine present. When the respective products are shaken with an alcoholic solution of potassium iodide, no iodine is immediately liberated, thus showing the absence of "active chlorine" (difference from the hypochlorite derivatives).

When chlorlyptus is dissolved in concentrated sulphuric acid, some blackening occurs and the odor of hydrogen chloride is very noticeable. Both the Abbott and Squibb brands of chlorinated eucalyptol give a reddish mixture, with no percipitable evolution of hydrogen chloride, and still retain the characteristic eucalyptol odor.

On heating, chlorlyptus decomposes and begins to boil at from 103 to 105 C. Then a higher fraction comes over at 178 C. The distillate has a sharp odor, is acid, and frees very little iodine from potassium iodide. Chlorinated eucalyptol-Abbott does not seem to decompose. Some gaseous substance is given off at 80 C., but the liquid distils at 173 C. The distillate has no acid odor, is neutral, and liberates no iodine from potassium iodide. (In both cases the distillation was not carried to completion, approximately only about half of the volume being distilled over.)

The addition of chlorlyptus to a mixture of 10 per cent. potassium iodide, 10 per cent. potassium iodate solution, brings about the liberation of iodine, increasing perceptibly on standing. This shows that the hydrogen chloride is gradually split off, and in time will cause a solution having a

considerable degree of acidity. When this test is carried out on chlorinated eucalyptol-Abbott, a small amount of iodine is liberated in a few minutes but does not increase, showing a slight initial acidity without further hydrolysis. Chlorinated eucalyptol-Squibb yields no free iodine after standing three hours.

When the chlorine content of chlorlyptus is determined according to the method of Carius, the amount is found to be 29.6 per cent. (The manufacturers give a method of determining chlorine by Hunter's fusion method. It is believed that in this method hydrogen chloride may be lost,

PRELIMINARY TESTS ON CHLORLYPTUS AND CHLORINATED EUCALYPTOL

	Chlorlyptus	Chlorinated Eucalyptol-Abbott	Chlorinated Eucalyptol-Squibb
Odor	Acrid	Like eucalyptus	Like eucalyptus
Density and color	Dark brown; viscous, heavier than water	Light yellow; mobile; lighter than water	Colorless; mobile; lighter than water
$AgNO_3$ added to alcoholic solution	Heavy ppt.	Slight turbidity	Clear
Equal parts with KI solution	Gives free iodin slowly, noticeable in ½ hour	Gives free iodin in 4 hours; not much	No free iodin in 4 hours
Equal parts with 10% KI 10% KIO_3 solution	Much iodin immediately	Small amount of free iodin in few numbers; does not noticeably increase	No free iodin in 3 hours
Equal parts with conc. H_2SO_4	Some blackening; odor of HCl	Reddish mixture; no HCl; eucalyptol odor	Same
Alcohol KI	No iodin liberated	Same	Same as Abbott product
Heating	Decomposes and boils at 103-105 C.; then higher fraction comes over at 178 C.; distillate has sharp odor, is acid, but frees very little I_2 from KI; distillation not completed	Apparently does not decompose; some gas given off when T=80; the liquid distilled at 173 C.; the distillate did not have much odor; no HCl gas detected; no I_2 from KI; distillate was neutral (distillation not completed)	

and this opinion is substantiated by the firm's statement, "Chlorlyptus analyzed in this manner shows approximately 25 per cent. of chlorine.") The chlorine content of chlorinated eucalyptol-Abbott is found to be 0.67 per cent., and that of the Squibb brand to be 0.62 per cent. (about one-fiftieth as much as in chlorlyptus).

To sum up: Chlorlyptus differs from chlorinated eucalyptol in odor, color, density, in reaction to silver nitrate, potassium iodide, sulphuric acid and the aqueous solution of

potassium iodate and potassium iodide. The distillation of the two products occurs differently. Chlorlyptus contains nearly 30 per cent. of chlorine, which is approximately fifty times as much as in chlorinated eucalyptol. Thus it appears to have considerable chlorine in the negative form (Cl^-) which may be relatively easily split off as hydrogen chloride.

B. THE PERSISTENCE OF THE ACID

Reaction of Chlorlyptus in the Body

BY THE REFEREE

This "chlorinated ozonized eucalyptus oil" is distinctly acid to litmus paper. It is claimed that further quantities of acid are liberated on contact with water. This is credited with producing a continuous acid reaction on the surface of tissues to which the oil may be applied; and this in turn is stated to be antiseptic or germicidal.

This theoretical speculation does not take into account the large quantity of reserve alkali in the body by which it combats attempts to alter its normal reaction. It is therefore not convincing, unless it is supported by direct evidence.

In the absence of such data on the part of the promoters of the preparation, experiments were made to determine whether the oil preserves its acid reaction in contact with mucous and serous membranes. The answers were clearly in the negative.

In the mouth, the reaction becomes neutral within ten or fifteen minutes; in the pleura and peritoneum within half an hour, and probably in much shorter periods.

More detailed data follow:

SERIES A: BEHAVIOR IN THE MOUTH; HOMO

EXPERIMENT.—Chlorlyptus and to less extent Chlorlyptus Oil, are acid to litmus. They are applied:

(*a*) Drop to litmus paper and this to gums.

(*b*) Several drops directly to tongue.

(*c*) Same to gums.

The reaction to litmus paper is tried from time to time.

RESULTS.—(*a*) Applied to gums on litmus paper:

Chlorlyptus: Red color becomes gradually feebler and does not spread on the paper.

Chlorlyptus Oil: Turns blue in a few minutes.

	Acetic Acid	Chlorlyptus
Tongue,	a drop of 5 per cent: still slightly acid to litmus after ten minutes; taste almost gone in two minutes	Neutral between five and ten minutes
Gums,	a few drops between cheeks and gums: Five per cent. still strongly acid in twelve minues; distinctly acid in seventeen minutes. One per cent. still strongly acid in twenty-one minutes	Neutral between ten and fifteen minutes

CHLORLYPTUS: REACTION (LITMUS PAPER) ON CONTACT WITH TISSUE

Serial No.	Animal	When Injected	Quantity C.c.	Time of Death	Blue Litmus	Symptoms or Toxicity
1	Rat	Pleura	1	½ hour	Remains blue	None; killed; pleura not congested; lung spec. = 21; slight congestion
2	Rat	Pleura	Less than 1	1 hour	Remains blue	Negative
3	Rat	Pleura	1	23 min.	Remains blue	Almost at once bad gasping respiration and died in 23 m.; heart distend.; possibly injection penetrated lung
		Peritoneum	1	23 min.	Turns red	
4	Rabbit	Pleura	1	.....	.....	Died overnight
5	Dog	Pleura	1	¼ hour	Remains blue 20 m. p. m.	
		Peritoneum	1	¼ hour	Remains blue 20 m. p. m.	
6	Dog	Pleura	1	3 min.	Remains blue 45 m. p. m.	
		Peritoneum	1	3 min.	Remains blue 45 m. p. m.	
7	Dog	Pleura	1	20 min.	Remains blue 20 m. p. m.	
		Peritoneum	1	20 min.	Remains blue 20 m. p. m.	

(*b*) Dropped on *tongue:*

Chlorlyptus: Acid taste at once. Does not increase, but on contrary, becomes less.

Litmus applied after ten minutes: not acid.

Litmus applied after five minutes: distinctly acid.

(*c*) Dropped on inside of *cheek:*

Chlorlyptus, ⅓ c.c.: After six minutes, litmus very red.

After ten minutes, faintly red.

After fifteen minutes, blue.

Chlorlyptus Oil, 1 c.c.:

After three minutes, faintly red.

After eight minutes, neutral.

CONCLUSIONS.—On contact with living tissues, the acid of chlorlyptus is rapidly neutralized and absorbed.

The surface is neutral within ten or fifteen minutes.

It is therefore very improbable that the acidity is effectively antiseptic.

A comparison of chlorlyptus with dilute acetic acid shows that the chlorlyptus does not maintain the acidity even as well as 1 per cent. acetic acid.

SERIES B: SEROUS MEMBRANES

In these experiments, 1 c.c. of chlorlyptus was injected into the pleura or peritoneum. After a stated time, the animal was killed, and the reaction of the pleural or peritoneal surface was tested with blue litmus paper. The results are shown in the table.

C. TOXICITY EXPERIMENTS

By the Referee

TECHNIC

White rats were injected hypodermically with chlorlyptus or with eucalyptus oil, diluted with olive oil in the ratio of 1:4. The larger doses were divided between two or more sites of injection.

DETAILED PROTOCOLS

Hypodermic injections in white rats. Drugs diluted with 3 parts of olive oil. Doses are given as cubic centimeters of pure drug per kilogram of rat.

A. EUCALYPTUS SERIES

EXPERIMENT 1.—*1.25 c.c.;* injected VII.9.19: Active; walks about. No depression at any time. VII.10, 19. Appears normal.

EXPERIMENT 2.—*2.5 c.c.;* injected VI.30.19: Quiet—not very depressed, reflexes good (six hours).

VII.1.19—Active—reflexes good, eats moderately.

VII.2.19—Animal acts normal—eats moderately, reflexes good; active (a. m.). Later in day, depressed.

VII.4.19—Died during night of VII.3.19.

EXPERIMENT 3.—*3.75 c.c.;* injected VI.24.19: Quiet; depressed; pain reflex diminished. Animal lay on ventral surface, not supported by legs. Will get on to feet very sluggishly if turned on side (twenty-four hours). Does not eat.

VI.26.19—Depressed slightly; pain reflex present.

VI.27.19—Fairly active; eats a little.

VI.28.19—Depressed.

Died during night of VI.29.19 (three days).

EXPERIMENT 4. *5 c.c.;* injected VI.24.19: Quiet; markedly depressed (one hour). Does not get on feet when turned on side; ataxia well marked. Slight watery secretion in eyes. Reflexes diminished. Does not eat (twenty-four hours).

VI.26.19. Heart slowed and arrhythmic. Animal lies on side. Unable to walk; markedly depressed.

VI.27.19. Lies on side; does not eat. Died during night of VI.27.19 (three days).

EXPERIMENT 5.—*6.25 c.c.;* injected VI.24.19: Quiet; very markedly depressed. Heart and respiration greatly slowed. Lies on side; tears in eyes; does not eat (twenty-four hours).

VI.25.19. Temperature subnormal; cold to touch; tail stiffened and straight.

Died during night of VI.25.19 (one and one-half days).

Postmortem: Lungs congested. Liver pale in color. Spleen very dark red. Kidneys normal. Other organs normal.

B. CHLORLYPTUS EXPERIMENTS

EXPERIMENT 1.—*1.56 c.c.;* injected VI.24.19: Rather restless for an hour. Active during next four hours and following twenty-four. Eats well, reflexes good. Acts normal on VII.1.19 and since VI.26.19.

EXPERIMENT 2.—*3.75 c.c.;* injected VI.24.19: More quiet; active during next twenty-four hours. Reflex all right. Eats well; normal VII.1.19, since VI.26.19.

EXPERIMENT 3.—*5 c.c.;* injected VI.24.19: Quiet; defecation in four hours. Rather quiet for six hours. Eats well. Reflexes good; normal VII.1.19, since VI.26.19.

EXPERIMENT 4.—*6.25 c.c.;* injected VI.24.19: Quiet and breathing labored in four hours; active after twenty-four hours. Eats well. Somewhat depressed on VI.26.19; pain reflex present. On VI.26.19, eats well and fairly active. Active and eats, VI.26.27.19. Appears normal, VII.1.19.

EXPERIMENT 5.—*8.75 c.c.;* injected VI.30.19: Rather quiet during next two hours. Morning of VII.1.19, lies on stomach; quiet; does not eat very much. Pain reflexes good. VII.2.19, still depressed; does not eat. Appears normal, VII.3.19.

EXPERIMENT 6.—*12.5 c.c.;* injected VI.25.19: Quiet, but reflexes good; more quiet and depressed after several hours. Some loss of oil from wound. Died night of VI.25.19 (one day). Tail stiff. Temperature low.

Postmortem: Lungs markedly congested. Spleen and liver dark red. One kidney congested. Other viscera normal.

EXPERIMENT 7.—*12.5 c.c.;* injected VII.9.19: Quiet for one-half hour; 1.5 hours twitching of muscles of whole body, lies on side, ataxia present. Died night of VII.9.19 (one day).

EXPERIMENT 8.—*18.75 c.c.;* injected VI.25.19: Quiet; reflexes good (three hours). Some oss of oil. Depressed and turns on side (six hours). Died night of VI.25.19 (one day).

Postmortem: Lungs congested. Spleen and liver very dark red. Right kidney much darker red. Viscera normal.

D. REPORT OF DR. D. RIVAS

The following are the results of experiments conducted by me, during the past four months, on the germicidal action of chlorlyptus (chlorinated oil of eucalyptus, principal constituent $C_{10}H_{17}OCl_2$) in vitro and in vivo, and comparison also with carbolic acid, oil of eucalyptus and dichloramine in test for irritation and toxicity.

Germicidal Action.—Based on the results obtained, chlorlyptus when used in a 5 per cent. paraffin oil solution was found to be a mild germicidal against typhoid B, streptococcus and staphylococcus when these organisms were suspended in ordinary bouillon culture or sterile salt solutions.

The germicidal action was found stronger when these micro-organisms were suspended in a sterile oily or lipoid substance, such as olive oil The results of these experiments were not constant, owing probably to the imperfect suspension of the bacteria. Thus, while in some of the experiments chlorlyptus in 1 per cent. oil solution destroyed these micro-organisms, in other cases the same strength solution failed to give same result in same time.

The increased germicidal action of chlorlyptus on bacterial suspensions in olive oil may be accounted for by the fact that chlorlyptus is soluble in olive oil and not an admixture, as in the case of paraffin oil.

Chlorlyptus is not a coagulant, as are germicides of the phenol or hypochlorite types, and the germicidal action is therefore not strictly comparable.

The germicidal action of chlorlyptus oil solution, on pathogenic bacteria, on streptococcus and staphylococcus, suspended in pus, was found to be stronger than when these micro-organisms were suspended in ordinary bouillon culture or sterile salt solution. In one of the experiments, similar results were obtained when these micro-organisms were suspended in olive oil, chlorlyptus showing marked germicidal action.

Irritation and Toxicity.—The irritating action was found to be relatively mild in tests on laboratory animals. Thus, from 0.5 to 1 c.c. of chlorlyptus in paraffin oil 5 per cent. solution, injected into peritoneal or pleural cavities of guinea-pigs weighing 400 gm. was found to be without any appreciable disturbance in the health of the animal, and in some cases the injection of as much as 2 c.c. did not kill the animal.

Therapeutic Action.—Guinea-pigs were inoculated with purulent material containing streptococcus, staphylococcus and *B. coli* in peritoneal and pleural cavities respectively, and after six hours 1 c.c. of chlorlyptus 5 per cent. in paraffin oil solution was injected. Other infected animals were similarly treated twenty-four hours after inoculation, and another series forty-eight hours after inoculation. In some of these cases the animals died from shock; but in a clearly defined series in which the injection of 1 c.c. of the chlorlyptus solution was made in the peritoneum of the guinea-pigs twenty-four hours after the inoculation, the animals lived. The

control animal, inoculated with the purulent material and not treated with chlorlyptus oil solution, died.

In consideration that the injection of chlorlyptus oil solution [sic, referee] were made [? referee] in the peritoneal cavity; this substance is apt to affect the vital organs in the abdominal cavity. It is my belief that in case of wall abscess of chronic inflammation, by limiting the action of chlorlyptus to the infected area, preventing at the same time the infection of the vital organs, chlorlyptus, because of its non-irritating quality, can be used effectively as an antiseptic.

CONCLUSIONS

1. Chlorlyptus is a mild and relatively nonirritating antiseptic of marked action on pus and suppuration.

2. When bacteria were suspended in olive oil or in pus, chlorlyptus showed marked germicidal action.

3. Chlorlyptus can be injected into the peritoneum or the pleural cavities of guinea-pigs in the proportion of 1 c.c. per 400 gm. of body weight without detriment to the animal.

4. Chlorlyptus in 5 per cent. oil solution (taking Clause 3 as comparison) can perhaps be injected in man as an antiseptic agent when there is a walled-in abscess in the peritoneum or pleural cavity where there is drainage, in the proportion of 0.5 to 1 c.c. per pound of body weight with good result.

REPORT ON THE GERMICIDAL ACTION OF CHLORLYPTUS ON PATHOGENIC BACTERA IN VITRO AND IN VIVO

EXPERIMENT 1.—*The germicidal action of eucalyptus oil.*—Typhoid bacillus was destroyed in less than five minutes when exposed to the action of a 5 per cent. suspension of oil of eucalyptus. The exposure for four hours in a 5 per cent. suspension of chlorlyptus in paraffin oil was without effect on typhoid bacillus. It requires an exposure of two to four hours in a 10 per cent. suspension of chlorlyptus in paraffin oil to destroy typhoid bacillus.

EXPERIMENT 2.—*Bacilliary action of chlorlyptus on the growth of pathogenic bacteria.*—Typhoid and anthrax bacilli were selected for the experiment. Two series of five tubes each were made. The culture medium used was nutrient bouillon. Chlorlyptus was added in the following proportions: Tube 1, 1: 10; Tube 2, 1: 100; Tube 3, 1: 1,000; Tube 4, 1: 10,000, and Tube 5, 1: 100,000. One series was inoculated with typhoid bacillus. All tubes were incubated for three days at 37 C.

Chlorlyptus inhibited the growth of typhoid bacillus when added to the bouillon in the proportions of 1: 10. The growth of anthrax bacillus was inhibited by chlorlyptus when it was added in the proportions of 1: 10, 1: 100 and 1: 1,000, as shown in the accompanying table. [The table was not submitted.—ED.] In one instance the growth was markedly inhibited by chlorlyptus when added in the proportion of 1:10,000.

EXPERIMENT 3.—*Germicidal action of chlorlyptus on typhoid bacillus.*—Bouillon cultures of typhoid bacillus forty-eight hours old, and a suspension of forty-eight-hour agar cultures of typhoid bacillus in sterile salt solution were used for the experiment. Chlorlyptus was added in the proportion of 1: 1,000; 1: 1,500; 1: 100; 2 per cent.; 3 per cent.; 4 per cent.; 5 per cent. and 10 per cent., respectively.

Inoculations were made in trypsinized peptone bouillon after the addition of chlorlyptus at different intervals, namely: at once, after five minutes, after ten minutes, after fifteen minutes, after thirty minutes, after one hour and after two hours, and tubes incubated at 37 C. for forty-eight hours.

Result: Growth was shown in all tubes except those in which chlorlyptus was added in the proportion of 10 per cent. and after the action of the antiseptic for two hours or longer.

EXPERIMENT 4.—*Inhibitory action of chlorlyptus in the growth of typhoid bacillus.*—Chlorlyptus was added to sterile bouillon in the proportion of 1: 100, 1: 1,000, 1: 10,000 and 1: 100,000, and incubated for forty-eight hours at 37 C. to eliminate any possible contamination of the bouillon during the manipulations. All tubes were found sterile and inoculated with typhoid bacillus.

Result: All tubes were found sterile again after being inoculated with typhoid bacillus and incubated at 37 C. for forty-eight hours, which shows chlorlyptus inhibited and the growth of typhoid bacillus in bouillon when this antiseptic was added in the proportions of 1: 100 to 1: 100,000.

Remarks: In another experiment made, chlorlyptus showed a weaker inhibitory action on the growth of typhoid bacillus.

EXPERIMENT 5.—*Germicidal action of carbolic acid.*—The technic was the same as that outlined in Experiment 1, except that carbolic acid was used instead of chlorlyptus.

Result: Carbolic acid showed a distinct germicidal action on typhoid bacillus in the proportions of 1 per cent. in ten minutes.

EXPERIMENT 6.—*Action of nitrogen gas on the growth of typhoid bacillus in bouillon and nutrient agar when chlorlyptus was added to this culture medium.*—Chlorlyptus was added to the bouillon in the proportions of 1: 100, 1: 1,000, 1: 10,000 and 1: 100,000, as outlined in Experiment 2; also to agar kept melted at 45 C. Tubes were inoculated with typhoid bacillus; plates were made of the inoculated agar tubes; all plates and tubes were incubated at 37 C. for forty-eight hours in an atmosphere of nitrogen gas.

Duplicate experiments were made with cultures of typhoid bacillus as above in bouillon and agar plates containing the same amount of chlorlyptus and incubated at 37 C. in ordinary atmosphere as control.

Result: Nitrogen gas did not show any appreciable increase of the germicidal action of typhoid bacillus when grown in medium containing chlorlyptus. Growth was about the same in cultures supplied with nitrogen gas as in those growing in ordinary atmosphere.

EXPERIMENT 7.—*Germicidal action of chlorlyptus on pyogenic bacteria suspended in an oily medium.*—Experiment with streptococcus: Cultures of streptococcus in blood agar three days old were suspended in olive oil (sterile), and chlorlyptus was added in the proportions of 1, 5 and 10 per cent. and inoculated in trypsinized bouillon at different intervals, namely: at once, after five minutes, after ten minutes, after fifteen minutes, after thirty minutes, and after one hour. Tubes were incubated at 37 C. for forty-eight hours.

Result: All tubes remained sterile. The germicidal action of chlorlyptus on streptococcus suspended in oil was almost at once and with certainty after five minutes when added in the proportion of 1, 5 and 10 per cent.

EXPERIMENT 8.—*Germicidal action of chlorlyptus on staphylococcus, suspended in sterile olive oil.*—The technic employed was the same as in Experiment 5, except that a culture of staphylococcus was used.

Result: All tubes remained sterile. The germicidal action of chlorlyptus was almost at once in the proportions of 1, 5 and 10 per cent.

Remarks: By repeating this experiment the result showed some variations. The discrepancy was probably due to an imperfect suspension of the micro-organism in the oil.

EXPERIMENT 9.—*Germicidal action of carbonic acid on streptococcus suspended in olive oil.*—The technic employed was the same as in Experiment 5, except that carbolic acid was used instead of chlorlyptus.

Result: The germicidal action of carbolic acid of streptococcus suspended in olive oil was almost at once in the proportions of 1, 5 and 10.

EXPERIMENT 10.—*Germicidal action of chlorlyptus on staphylococcus.*—The technic employed was the same as in Experiment 6 except that the carbolic acid was used instead of chlorlyptus.

Result: The germicidal action of carbolic acid on staphylococcus suspended in olive oil was almost at once, in proportions of 1, 5 and 10 per cent.

EXPERIMENT 11.—*Germicidal action of chlorlyptus on pyrogenic bacteria suspended in pus.*—Chlorlyptus was added to sterile pus in the proportions of 1, 5 and 10 per cent., and then inoculated with staphylococcus and cultures were made in bouillon at once, after five minutes, after ten minutes, after fifteen minutes, after thirty minutes, after one hour and after two hours, respectively, and tubes incubated for forty-eight hours at 37 C.

Result: Growth was shown in all tubes except those inoculated from tubes which chlorlyptus was added in the proportions of 10 per cent. after one hour.

EXPERIMENT 12.—*Germicidal action of chlorlyptus on staphylococcus suspended in sterile human blood serum.*—Staphylococcus culture in agar forty-eight hours old was suspended in sterile human blood serum, and to the suspension chlorlyptus 5 per cent. in paraffin oil was added in the proportions of 1, 5 and 10 per cent. Inoculations were made at intervals, at once, after five minutes, after ten minutes, after fifteen minutes and after one hour in trypsinized bouillon. Tubes were incubated at 37 C. for forty-eight hours.

Result: Chlorlyptus showed inhibitory action on the growth of staphylococcus in the strength of 10 per cent., but did not produce complete sterilization. Similar results were shown with the 5 per cent., and in the 1 per cent. chlorlyptus did not show any inhibitory action at all.

EXPERIMENT 13.—*Germicidal action of carbolic acid on staphylococcus suspended in human blood serum (sterile).*—The technic employed was the same as in Experiment 10 except that carbolic acid was used instead of chlorlyptus.

Result: Carbolic acid produced a complete sterilization in the strength of 10 per cent. almost at once, and with certainty after five minutes. Similar results were produced with the 5 per cent. The 1 per cent. carbolic acid did not show any appreciable germicidal action on staphylococcus.

EXPERIMENT 14.—*Toxic and irritant action of chlorlyptus.*—Six normal guinea-pigs were used for the experiment. Guinea-Pig 1 was injected peritoneally with 1 c.c. of chlorlyptus, Guinae-Pig 2 with 2 c.c. of chlorlyptus, Guinea-Pig 3 with 3 c.c. of chlorlyptus, Guinea-Pig 4 with 4 c.c. and Guinea-Pig 5 with 5 c.c. 5 per cent. respectively. Guinea-Pig 6 was used as a control and not injected.

Result: Guinea-Pigs 1 and 2 did not show any appreciable disturbance. Guinea-Pig 3 was sick for four days, after which it gradually recovered but it became sick again after one week and died ten days after the injection. Guinea-Pig 4 died over night.

Guinea-Pig 5 died six hours after injection. Guinea-Pig 5 was injected at 11:30 with 5 c.c. chlorlyptus. Ten minutes after the injection it was lying relaxed, respiration and heart normal, conjunctive reflex present. One hour after the injection the animal seemed to present symptoms resembling those of narcosis: respiration and heart were normal. After four hours there was no change in the condition of the guinea-pig except that the respiration was irregular. Five and a half hours after it showed prostration with irregular respiration and heart action. Six hours after injection the animal was dead.

Autopsy: The peritoneum showed a congestion and a fibrinous exudation, amount of liquid increased, some part of which was probably chlorlyptus unabsorbed. Spleen about normal, liver congested, kidney about normal, suprarenal glands about normal, lungs normal, pleural cavity obtained no exudation, heart soft, flabby and congested.

EXPERIMENT 15.—*Toxic and irritant action of chlorlyptus when injected into the pleural cavity.*—Six normal guinea-pigs used for the experiment. Chlorlyptus was injected in the pleural cavity as follows: Guinea-Pig 1, 0.5 c.c.; Guinea-Pig 2, 1 c.c.; Guinea-Pig 3, 2 c.c.; Guinea-Pig 4, 3 c.c., and Guinea-Pig 5, 4 c.c. Guinea-Pig 6 was used as a control.

Result: Guinea-Pigs 1 and 2 recovered about four hours after injection. Guinea-Pig 3 died three days after and Guinea-Pigs 4 and 5 four and two hours after, respectively.

Conclusions: Guinea-pigs weighing on the average of 400 gm. may be injected peritoneally with one or two c.c. or intrapleurally with 0.5 to 1 c.c. of chlorlyptus without having fatal results from the injection.

EXPERIMENT 16.—*Toxic and irritant action of eucalyptus oil.*—Three normal guinea-pigs were used for the experiment. Guinea-Pig 1 was injected with 1 c.c. of oil of eucalyptus in the peritoneum, and Guinea-Pig 2 with 0.5 c.c. in the pleural cavity. Guinea-Pig 3 was used as a control.

Result: Guinea-Pig 1 died about three hours after the injection, and Guinea-Pig 2 about two hours after the injection.

Autopsy: Both guinea-pigs showed marked congestion and a moderate degree of exudate in the peritoneum.

EXPERIMENT 17.—*Toxic and virulent action of eucalyptus.*—Three normal guinea-pigs were selected for the experiment, as in Experiment 16. The injection was made in the pleural cavity. Guinea-Pig 1 was injected with 0.5 c.c. and Guinea-Pig 2 with 1 c.c. of eucalyptus oil.

Result: Guinea-Pig 1 died the following day, and Guinea-Pig 2 one hour after the injection.

EXPERIMENT 18.—*Toxic and irritant action of dichloramin-T, 0.5 per cent. in chlorcozane.*—One guinea-pig was used for each experiment. It was injected with 0.5 c.c. and Guinea-Pig 2 with 1 c.c. of dichloramin-T peritoneally.

Result: Both animals became restless immediately after the injection, and died twelve hours after of acute hemorrhagic peritonitis.

EXPERIMENT 19.—*Effect of chlorlyptus on staphylococcus suspended in salt solution and one of that solution injected into the peritoneum of the guinea-pig.*—Three guinea-pigs were used for the experiment. Guinea-Pig 1 was injected with 0.5 c.c. of staphylococcus suspension as control. Guinea-Pig 2 was given the same, and immediately after received 1 c.c. of chlorlyptus. Guinea-Pig 3 was injected with the same amount, and chlorlyptus was injected twenty-four hours after injection.

Results: Guinea-Pig 1 was sick and weak with loss of appetite for some days, but gradually recovered. Guinea-Pig 2 died over night.

Autopsy: There was a large amount of exudate in the peritoneal cavity, irritation of the intestine, and other signs of acute inflammation. A moderate degree of congestion; spleen not enlarged; liver showed cloudy swelling and fibrinous exudate; lungs and heart about normal except for a moderate degree of congestion but no exudate. Guinea-Pig 3 was sick for some days, but recovered gradually one week after.

EXPERIMENT 20.—*Effect of chlorlyptus in vivo on staphylococcus.*—The experiment was conducted in the same way as in Experiment 17, but 2 c.c. were used instead of 1 c.c.

Result: Guinea-Pig 1 was injected with 2 c.c. staphylococcus suspension and died over night. Autopsy showed that the animal died of acute peritonitis. The peritoneum showed some fibrinous exudate and mesenteric vessels. Guinea-Pig 2 was injected with 2 c.c. of staphylococcus, and eighteen hours after was injected with 1 c.c. of chlorlyptus. The animal died two weeks after injection. Guinea-Pig 3 was injected with 2 c.c. staphylococcus suspension, and twenty-four hours after with 1 c.c. of chlorlyptus. The Guinea-Pig died ten days after. Autopssy revealed bronchopneumonia of the left lung and acute miliary abscess in the liver.

SPIROCIDE NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Jan. 22, 1921, p. 259

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

"Spirocide" (The Spirocide Corporation of New York) is advertised as a new and successful treatment of syphilis by fumigation and inhalation. According to the information presented to the Council, Spirocide is a mechanical mixture of metallic mercury 25 per cent., copper sulphate 25 per cent., cypress cones 20 per cent., henna 20 per cent., nut gall 5 per cent., and dried pomegranate 5 per cent. It is supplied in the form of greenish-gray tablets weighing about 10 gm. each, and containing, therefore, about 2.5 gm. (about 38 grains) of mercury. It is sold in packages of six tablets.

The following directions for its use are contained in a pamphlet recently distributed:

"Spirocide is administered by means of fumigation and inhalation. The patient is disrobed to the waist and placed in a light chair, preferably with arms. A pastil or tablet of Spirocide is placed on a small plate, or open receptacle, after being ignited by holding in a gas or alcohol flame for a minute or so until it begins to smoulder. The plate with the burning Spirocide is then placed on the floor between the patient's feet or just under the chair. A small shelf or platform between the lower rounds of the chair is an excellent location for the plate containing the burning mass. When all is in position a sheet should be thrown over the patient and arranged to enclose the whole. The patient should breathe naturally and inhale the vapor, which will rise and fill the canopy surrounding him. The treatment will require 15 to 30 minutes, or until the Spirocide is burned up. The patient may complain at first of a slight choking sensation, and there may be some tendency to cough. This can be removed by raising the sheet long enough to let in a little clear air. The eyes should be closed or lightly bandaged to avoid smarting."

Experiments conducted in the A. M. A. Chemical Laboratory show that Spirocide, when ignited, burns slowly with consequent volatilization of mercury. The several organic constituents serve as fuel and the copper sulphate possibly acts as a regulator of the combustion. During the burning process the cypress cones, henna, etc., are consumed but most, if not all, the copper remains behind, the mercury only being vaporized. It is asserted in the advertising pamphlet that Spirocide is indicated in all stages of syphilis, primary, secondary and tertiary, and in all its complications or sequelae. In these varying conditions one tablet daily or every other day is recommended until six treatments have been taken, though it is stated that "occasionally, depending on the severity or the duration of the disease, it may be wise to give nine treatments, the last three at intervals of two, three or more days."

Some of the results which it is claimed are obtained with Spirocide are:

"At the completion of this course of treatment with Spirocide, all signs or evidences of syphilis are removed, and in ten days to three months all Wassermann tests prove negative. Any further treatments than the original course of fumigations are rarely needed. Wassermann's will be found uniformly negative after a period which, according to the patient, may vary from ten days to three months. These results have been obtained in cases in which Salvarsan and kindred preparations have been employed without the slightest benefit."

In a letter to the Council the "scientific observer" of the Spirocide Corporation declared:

"We do not claim that the vaporization method is new. We do claim, however, that this combination of mercury produces more rapid volatilization, certain absorption and undoubted effect than any form of mercury administered by any method known to science without the usual danger. That this is so we are willing to prove by comparison with other methods both by ourselves and many observers scattered over the United States. . . ."

To determine the validity of the claims made for Spirocide, the Corporation was asked to present the evidence which it offered. In reply, the corporation's "scientific observer," Dr. J. Lewengood, submitted 83 case reports from a number of different observers, including those from military hospitals and a state institution, and also a reprint of an article published by him in the *New York Medical Journal*, Feb. 21, 1920, wherein were reported eight cases which received "Spirocide Treatment." In no case were controls with other methods of mercury administration carried out.

This material the Council sent to two recognized syphilographers for an opinion. One of the consultants reported that of the 83 cases, 20 dealt with patients who had also received arsphenamin medication and, therefore, these 20

cases could not be considered as evidence concerning the value of Spirocide. As to the remaining cases, he found on the whole that the history and data furnished were far from sufficient to warrant the claims made. In many of the cases emphasis was laid on the Wassermann test, as though this test were the only thing to be considered in a case of syphilis. He pointed out that in one case the reaction changed from negative to strongly positive after six treatments and that in several cases the phenomena reported cannot be explained by anything else than a desire to get a negative blood test. For example, one case had Spirocide treatment and a Wassermann, 1 plus, 55 days after; the author then reports that 19 days later the reaction had become negative and, therefore, the change must be due to Spirocide. In several of the cases reported it is even questionable if the patients were syphilitic. The consultant concluded that the evidence submitted by the Spirocide Corporation failed to prove the claims made for Spirocide. He pointed out on the other hand that patients readily become salivated from the use of Spirocide, often after 8 to 10 treatments.

The second consultant replied that in his opinion the claim that Spirocide produces more "undoubted effect than any form of mercury administered by any method known to science without the usual danger," was not substantiated. He believed that it was not as effective as some other methods, that the dosage is not as exact and that, therefore, it is not as free from danger when the drug is pushed.

The Council's two consultants were also asked whether or not, in their opinion, the administration of mercury by inhalation is a method which the Council should endorse to the extent of recognizing a preparation based on this principle. This same inquiry was also sent to the members of the editorial board of the *Archives of Dermatology and Syphilology*. Five replies were received. One advised a thorough study of the different methods of administering mercury by inhalation. The other four were opposed to such recognition on the ground that as the dosage is not exact the effects, therefore, are not certain.

In consideration of the opinions expressed by its consultants, the Council declared Spirocide inadmissible to New and Nonofficial Remedies because (1) the claims made for it are unproved and unwarranted, (2) the routine use of an inexact method for the administration of mercury is detrimental to sound therapy and (3) the name is not descriptive of its composition, thus failing to remind the physician who uses these pastils that he is administering metallic mercury.

HELMITOL OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Jan. 22, 1921, p. 260

Helmitol is hexamethylenamin methylencitrate. It was introduced with the claim that it was superior to hexamethylenamin—which acts in acid fluids only—in that it is equally efficient whether the urine is alkaline or acid.

In 1918 The Bayer Company, which then marketed the product in the United States, was notified that the Council questioned the claims made for Helmitol and desired evidence to substantiate them. In 1919 the same notification was sent the Winthrop Chemical Company, which in the meantime had secured control of the product. Pending the submission of evidence, the Council continued the acceptance of Helmitol for New and Nonofficial Remedies with the statement that the actions and uses of hexamethylenamin anhydromethylencitrate were those of hexamethylenamin.

W. A. PUCKNER, Secretary.

The following report on Helmitol was made by the referee in charge of hexamethylenamin compounds and preparations, adopted by the Council and sent the Winthrop Chemical Company:

"Helmitol is a compound of anhydromethylencitric acid and hexamethylenamin. It was introduced with the claim that it would be antiseptic even in alkaline urine. The Council did not entirely trust the evidence, but continued to list Helmitol in N. N. R., merely as a salt of hexamethylenamin, until satisfactory data should become available. These have now been furnished by Hanzlik (*Journal of Urology* **4**:145) who has shown that:

"1. The alkalinity required to split off formaldehyd from anhydromethylencitric acid is greater than exists in the urine, even in advanced ammoniacal fermentation.

"2. Even if any formaldehyd were liberated in ammoniacal fermentation, it would at once become inactive by combining with ammonia.

"3. Urine after the administration of anhydromethylencitric acid actually putrefies readily.

"4. Less than 5 per cent. of the anhydromethylencitric radicle reaches the urine, the remainder being destroyed in the body.

"The only reason for the existence of Helmitol was this claim of antiseptic action in alkaline and putrefying urines. Since this has been disproved, there remains no reason for retaining Helmitol in N. N. R.; on the contrary, its retention would only tend to continue the fallacy on which it was based.

"It is, therefore, recommended that Helmitol be no longer listed with New and Nonofficial Remedies, and that this report be published, after the usual submission to the manufacturers."

In accordance with the recommendations of the report, the Council has directed the omission of Helmitol from New and Nonofficial Remedies and has authorized the publication of this report.

AQUAZONE (OXYGEN WATER)

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Aquazone is stated by the Aquazone Laboratories, Inc., Los Angeles, Calif., to be a supersaturated solution of oxygen in water carrying approximately five and one-half times as much dissolved oxygen as ordinary water.

In a booklet advertising the product the following statement appears bearing on the therapeutic use of Aquazone:

> "In view of the recognized fact that many toxins and bacteria are oxidized by the presence of oxygen, the value of employing excess dissolved oxygen in the treatment of various diseases will readily suggest itself to the medical mind."

The booklet suggests that Aquazone is of value in the treatment of influenza, pneumonia, typhoid, Bright's disease and kindred disorders. It is also stated therein that in the treatment of fevers it lowers the temperature and that the administration of 3 bottles of Aquazone (about 618 Cc. or 21 fluidounces representing 23 Cc. or 0.033 gm.—1½ grain—of oxygen) is of value for "preventive and tonic purposes."

In view of the preceding, the Aquazone Laboratories were informed that the Council desired evidence to show that the administration of Aquazone is capable of producing effects other than those which may be obtained from the administration of ordinary potable water. In particular, evidence was requested for the claims referred to above.

In reply, the Aquazone Laboratories submitted letters from twenty-nine physicians, all of Los Angeles. Without exception, the letters were non-committal. So far as can be judged, the only therapeutic test to which this preparation has been subjected by these physicians, is its use during the course of a large variety of diseases (chronic gastritis, eclampsia, pneumonia, nephritis, cystitis, neurasthenia, typhoid fever, influenza, pylo-nephritis, polycythemia, etc.) while in addition, other treatment was used. The administration of ordinary water by mouth would undoubtedly have served quite as well.

The Council declared Aquazone inadmissible to New and Nonofficial Remedies because the therapeutic claims made for it are unwarranted (Rule 6) and because its use is irrational (Rule 10) for the reason that oxygen given by stomach in this way is of little or no value.

BISMUTH AND IRON CITRATE SOLUBLE (WELLCOME BRAND) AND BISMUTH AND LITHIUM CITRATE SOLUBLE (WELLCOME BRAND) OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Bismuth and Iron Citrate Soluble (Wellcome Brand) is a "scale salt" containing bismuth citrate and ferric rendered soluble in water by the use of ammonia. Its administration is proposed by the manufacturer, Burroughs Wellcome and Co., in cases of dyspepsia accompanied by anemia.

Bismuth and Lithium Citrate Soluble (Wellcome Brand) is a "scale salt" of bismuth citrate and lithium citrate. This preparation is recommended by the manufacturers, Burroughs Wellcome and Co., as a convenient form of medication when both the effects of bismuth and lithium are desired, as in gouty dyspepsia.

In considering the question of the continued inclusion of these two preparations, the questions were raised: 1. Are soluble bismuth salts an effective and desirable method of obtaining the effects of bismuth? 2. Is it rational to administer bismuth and iron simultaneously in fixed proportion? 3. Is the small amount of citrate which is contained in bismuth and lithium citrate soluble (Wellcome Brand) of practical value in gouty conditions and is it rational to administer bismuth and lithium citrate in fixed proportions?

In view of these questions, the Council directed that the following inquiry be sent to Burroughs Wellcome and Company:

> "The Council has instructed me to inquire if you have any evidence for the therapeutic value of your products Bismuth and Iron Citrate Soluble (Wellcome Brand) and Bismuth and Lithium Citrate Soluble (Wellcome Brand), other than that which was sent to the Council at the time that these products were accepted for New and Nonofficial Remedies. This information is desired so that the continued eligibility of your product for New and Nonofficial Remedies may be determined.

"While a preparation is accepted for New and Nonofficial Remedies if it gives promise of therapeutic usefulness, the Council holds that the continued recognition of such an article should be contingent on the accumulation of definite and confirmatory evidence of therapeutic value. In determining the continued acceptability of Bismuth and Iron Citrate Soluble (Wellcome Brand) and Bismuth and Lithium Citrate Soluble (Wellcome Brand), the Council will consider the desirability of combining iron compound with bismuth compound and of the combination of bismuth citrate with lithium citrate. The Council will also consider the question of the therapeutic value of the soluble 'scale' salts of bismuth as a class.

"It is hoped that you can assist the Council in determining the value of your above named named preparations."

In reply the firm stated that there was no additional evidence for these products.

Bismuth and Iron Citrate Soluble (Wellcome Brand) and Bismuth and Lithium Citrate Soluble (Wellcome Brand) were admitted to New and Nonofficial Remedies in 1909. Were they possessed of distinct therapeutic value, this should have been demonstrated by this time. In the absence of confirmative evidence for their usefulness, the Council directs their omission from the list of New and Nonofficial Remedies on the ground that they are irrational and superfluous articles.

CAPSULES FOLIA-DIGITALIS (UPSHER SMITH) AND TINCTURE OF DIGITALIS (UPSHER SMITH)

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report which explains that Capsules Folia-Digitalis (Upsher Smith) and Tincture of Digitalis (Upsher Smith) were not accepted for New and Nonofficial Remedies because they were found to have the status of pharmacopeial articles which do not require the supervision of the Council.

W. A. PUCKNER, Secretary.

Capsules Folia-Digitalis (Upsher Smith) and Tincture of Digitalis (Upsher Smith) are advertised and sold by Upsher Smith, St. Paul, Minn., with the claim that these preparations represent digitalis of uniform potency. The ground for this claim is (1) the drug is always obtained from the same source (grown in Minnesota), the inference being that the relative proportions of the readily absorbable and the difficultly absorbable digitalis principles are more constant than with digitalis obtained from different sources, (2) the drug is collected and dried with great care, all dead leaves and leaves growing next the ground being rejected, (3) the drug contained in the capsules and the tincture is assayed bio-

logically by the Hatcher cat method. (Hatcher and Brodie: *Am. J. Pharm.* **82**:360, 1910.)

Capsules Folia-Digitalis (Upsher Smith): each capsule contains 0.065 gm. (1 grain) of Minnesota digitalis leaf, purified by winnowing and physiologically standardized by the Hatcher cat method so that the average toxic dose injected intravenously is 0.065 gm. per Kg. of cat.

Tincture of Digitalis (Upsher Smith): prepared according to the U. S. Pharmacopeia process from Minnesota digitalis leaf and physiologically standardized by the Hatcher cat method so that the average toxic dose injected intravenously is 0.65 Cc. per Kg. of cat.

The Council finds that these preparations have the status of official articles and are, therefore, not within the scope of New and Nonofficial Remedies: first, because no therapeutic claims are advanced for them other than those commonly ascribed to digitalis and second, they are marketed under official titles and consequently are under the control of the authorities charged with the enforcement of the Federal Food and Drugs Act.

COAGULEN-CIBA OMITTED FROM N. N. R

The Council has authorized publication of the following report announcing the deletion of Coagulen-Ciba from New and Nonofficial Remedies.

W. A. Puckner, Secretary.

Coagulen-Ciba, a product of the Society of Chemical Industry, Basle, Switzerland, was admitted to New and Nonofficial Remedies in 1915. It is stated to be an extract prepared from blood platelets and to contain thromboplastic substances (cytozym, thrombokinase, thrombozym) mixed with lactose. Extensive clinical reports appeared to justify its acceptance for New and Nonofficial Remedies with Fibrin Ferments and Thromboplastic substances.

In 1918 Dr. Arthur D. Hirschfelder reported to the Council that of a number of specimens of Coagulen-Ciba examined by him, failed to accelerate the coagulation time of blood.

In view of Dr. Hirschfelder's findings, the Therapeutic Research Committee of the Council invited Dr. P. J. Hanzlik to undertake an exhaustive investigation of thromboplastic substances, the Council, in the meantime, temporarily retaining Coagulen in New and Nonofficial Remedies until the investigation was completed.

The following report on the eligibility of Coagulen-Ciba was made to the Council by Dr. Hanzlik:

Object: To test the claims of thromboplastic and hemostatic activities.

Claims: Coagulen is alleged to be a "physiological styptic prepared from the natural coagulants of animal blood contained in the blood platelets. It has the characteristics of a lipoid." (If cephalin is meant it is difficult to understand why platelets should be selected in preference to other abundantly supplied organs such as brains).

"Coagulen is indicated in all cases of external and internal hemorrhage due to a deficiency of the coagulating power of the blood: epistaxis, hemophilia, hemorrhage from gastric or duodenal ulcer, melaena neonatorum, hemorrhage from the gums, the lungs, the bladder, the uterus, hemorrhage during or after operations (turbinectomy, tonsillectomy). It has also been used as a prophylactic before operations, likely to produce severe hemorrhage."

"In cases of true hemophilia one application of 5 grains of coagulen usually suffices to control the hemorrhage." "In gastric and intestinal hemorrhage the internal administration of coagulen will be found effective." "In bonegrafting, plastic surgery, dentistry and nose and throat surgery the application of a 10 per cent. solution of Coagulen will be found to be of valuable assistance in controlling hemorrhage and oozing."

"It is a non-toxic and non-irritating powder to which a certain amount of sugar has been added, with a view to ensuring its prompt solution in water or physiological sodium chloride solution."

Description: "Coagulen is a yellowish granular powder with but slight odor, a sweet taste and is readily soluble in water or a normal salt solution." The dry Coagulen obtained corresponds to the description claimed. Old specimens show the presence of dark brown particles. Coagulen is marketed in 3 forms: (1) as dry powder containing lactose, which, it is claimed, facilitates solution in water; (2) as 3 per cent. sterile solution in ampoules;[1] (3) tablets.

1. An ampoule labeled as follows: "Coagulen-Ciba, 20 c.c. in sterile solution ready for use. To be shaken. Importé de Suisse. Op. No. 968" was found to measure only 15 c.c. Another ampoule with the same label and Op. No. 9641 contained considerable sediment.

Methods of Study: The alleged thromboplastic activity was tested by the method of Howell and a modification of this method by Fenger as described in "New and Nonofficial Remedies." In the Howell method dog or cat blood is used, while beef blood at body temperature is used in Fenger's method. In other respects the methods are essentially the same. Briefly these consist of noting the acceleration of coagulation time in a mixture of equal parts of serum and the thromboplastic agent to which about an equal part of oxalate plasma is added. Under these conditions cephalin causes clotting in about 1 minute or even less as compared with 20 to 30 minutes or more of the control.

The effects were compared with freshly prepared cephalin and other thromboplastic agents, using saline (0.9 per cent. NaCl) as control. The effect of different concentrations was also studied.

The literature of the manufacturers claims that Coagulen is harmless. This was tested by making intravenous and subcutaneous injections into guinea-pigs, using saline and cephalin as controls.

Bloods of 4 different species were used, namely, cat, dog, beef and human. Dog's peptonized blood and plasma were also tried.

The 15 different tests that were made in vitro were carried out with 3 different samples of fresh dry Coagulen (from manufacturer), 2 old samples (one from Council on Pharmacy and Chemistry and one of our own), 3 fresh specimens of sterile solution in ampoules (from manufacturer), one old specimen and 4 small ampoules (Council on Pharmacy and Chemistry).

The tablets were not tested since these are made from dry Coagulen and the results would hardly be expected to show anything different.

Results: The results obtained may be briefly summarized as follows: (1) 0.1 per cent. to 5 per cent. Coagulen did not accelerate the coagulation time of blood and oxalate plasmas in the majority of tests any more than the controls of saline, while 0.1 per cent. cephalin was found to shorten the coagulation time from ⅓ to ½.

(2) There was no difference between the behavior of old and fresh specimens.

(3) No acceleration of coagulation *in vitro* was observed even with the highest concentrations tried, namely 25 and 50 per cent.

(4) Irrigations made with fresh dry coagulen in solution and sterile solution in ampoules on superficial bleeding from the foot-pads of 3 normal and peptonized dogs and local application to hemorrhages from dissected femoral arteries and bone and liver wounds of 3 dogs showed that coagulen was no more active than normal saline.

Toxicity. Subcutaneous and intravenous injections of different doses of Coagulen solutions (fresh ampoules) and dry Coagulen in solution in 8 guinea-pigs produced definite anaphylactoid symptoms with injury to the circulatory and respiratory systems as indicated by cardiac dilatation, abdominal congestion and pulmonary hemorrhages, congestion, distention and sometimes thrombi. On the other hand, the control animals injected with saline and cephalin remained practically unharmed.

Conclusions: The results obtained justify the following conclusions:

(1) Coagulen is entirely inactive as a thromboplastic and hemostatic agent.

(2) Coagulen is distinctly injurious when injected systemically.

(3) The claims of hemostatic efficiency and harmlessness for Coagulen by the manufacturer appear exaggerated and unjustified.

Recommendations: Because of its uncertain composition, the possible dangers when injected systemically, and its inactivity as a thromboplastic and hemostatic agent when tested by several different methods, Coagulen merits no recognition as a therapeutic agent for inclusion in New and Nonofficial Remedies.

The detail evidences used as the basis of this brief report concerning Coagulen will be published shortly in the *Journal of Pharmacology*,[2] together with the results with other thromboplastic agents.

2. Since the report was sent to the manufacturers, the results have been published. Hanzlik, P. J., and Weidenthal, C. M., Plasma and Blood Clotting Efficiency of Thromboplastic Agents in Vitro and their Stability, J. Pharmacol., and Exper. Therap. **14**: 157 (October) 1919; Hanzlik, P. J., Karsner, H. T., and Fetterman, J., Anaphylactoid ditions, J. Pharmacol. and Exper. Therap. **14**: 189 (Oct.) 1919; Hanzlik; P. J., Karsner, H. T., and Fetterman, F., Anaphylactoid Phenomena from Thromboplastic Agents, J. Phamacol. and Exper. Therap. **14**: 229 (Nov.) 1919.

The preceding report was sent to the American agent for the Society of Chemical Industry, Sept. 8, 1919.

In reply the American agent, Ciba Co., Inc., on March 22, 1920, sent the Council "some additional clinical reports on the use of Coagulen-Ciba in the treatment of Hemorrhages supporting our claims of the merits of Coagulen-Ciba."

The material submitted by the Ciba Co., contains no objective evidence for or against the efficiency of Coagulen-Ciba but merely opinions. As a rule these opinions are favorable

though conditional and hedging and quite unconvincing. Nothing was submitted to offset or challenge the findings of Dr. Hanzlik's report.

Since the evidence indicates that Coagulen-Ciba has little, if any, efficacy as a hemostatic, the Council directed its omission from New and Nonofficial Remedies.

COOPERATION OF THE PHARMACEUTICAL HOUSES

Report of the Council on Pharmacy and Chemistry

In reply to the suggestion made last year by President Bevan that there should be closer cooperation between the large pharmaceutical houses and the Council on Pharmacy and Chemistry, the Council submitted to the Board of Trustees of the American Medical Association the statement which appears below.

The Board of Trustees submitted the statement to the House of Delegates of the American Medical Association at the New Orleans meeting of the Association with this comment: "Evidently the problem resolves itself into this: The Council, constituted of scientific men, working without remuneration in the interest of scientific medicine and the medical profession, expects—and rightfully—the cooperation and support of the members of that profession. What is needed, therefore, is the active sympathetic cooperation of physicians; the cooperation of pharmaceutical houses will follow as a matter of course. (*J. A. M. A.*, May 1, 1920, p. 1234.)

The following is the recommendation of the Reference Committee to which the Report of the Board of Trustees was referred: "A perusal of the Trustees' Report, 'Cooperation of the Pharmaceutical Houses', is well worth the time of every member of the profession, and your committee would emphasize the statement of the Trustees: 'The Council, constituted of scientific men, working without remuneration in the interest of scientific medicine and the medical profession expects—and rightfully—the cooperation and support of the members of that profession. What is needed, therefore, is the active sympathetic cooperation of physicians; the cooperation of pharmaceutical houses will follow as a matter of course.'"

Your committee would go still further and move that a vote of thanks of the House be extended to those scientific men who have devoted so much valuable time to the welfare of the Association" (*J. A. M. A.* May 8, 1920, p. 1322).

W. A. PUCKNER, Secretary.

(From the Report of the Board of Trustees to the House of Delegates of the American Medical Association, *J. A. M. A.*, May 1, 1920, p. 1234.)

"Cooperation of the Pharmaceutical Houses: At the opening meeting of the House of Delegates last year, President Arthur Dean Bevan suggested the desirability of greater cooperation between the large pharmaceutical houses and the Council on Pharmacy and Chemistry. The need of such cooperation has been recognized by the Council from the first. In no one direction has the Council made greater effort than in its endeavor to secure the fullest cooperation of the various pharmaceutical houses. The difficulty has been, and always must be, the fundamental antagonism between objectives that are largely commercial on the one hand and purely scientific on the other. Nevertheless, the Council has always believed—and has acted on the belief—that there is a possible middle ground wherein the interests of therapeutics would not be injured but would go hand in hand with a commercial development based on enlightened self interest.

"The profits to be made by a pharmaceutical house from the sale of a staple drug—a pharmacopeial, National Formulary, or nonproprietary preparation — which enters into free competition with other drugs of the same kind, are moderate; the profits to be made from the sale of a proprietary medicine on which the manufacturer holds a monopoly are usually large—sometimes enormous. There are, broadly, two kinds of proprietary preparations advertised to physicians: One represents laborious research ending in the production of a new medicinal chemical; this product can be patented and the manufacturer can obtain a seventeen-year monopoly on its manufacture and sale. The other represents no research but comprises simple mixtures—frequently of the "shotgun" variety—of well known pharmaceuticals, or biologic products sold under trade names. As these do not represent anything new or original the manufacturer is unable to obtain a patent, but by means of the trade name he can and does obtain a perpetual monopoly. This, from a business standpoint, is more valuble than the limited monopoly granted by a patent. It is not surprising that proprietary remedies of the latter type flourish so long as physicians unthinkingly accept and prescribe them solely on the manufacturer's valuation.

"The Council has practically the undivided support of manufacturers of medicinal chemicals; that is, of proprietaries of the first mentioned type. But pharmaceutical firms which have found it profitable to promote proprietaries of the second type—"specialties," unscientific or ordinary mixtures of pharmaceuticals or biologic products sold under trade names — have not supported the Council.

"When the Council was organized, it was hoped and believed that all the large pharmaceutical houses would find it possible and desirable, if not actually more profitable, to shape their business methods so as to make their proprietary and other articles conform to those conservative standards on which the Council bases its rules, and thus render such articles acceptable for New and Nonofficial Remedies. It soon developed, however, that the methods of the pseudochemical companies, whose sales propaganda in the interest of unscientific nostrums with its attending damage to scientific medicine had led to the establishment of the Council, had found their lodgment in most of the pharmaceutical houses. It was a genuine disappointment to the Council to find that some of the large and old-established firms were not only unwilling to cooperate with the Council, but in many instances exhibited a definite antagonism to the Council's work.

"The object — and duty — of the officers of pharmaceutical houses is primarily to pay dividends to their stockholders. Through skilful advertising or the persuasiveness of "detail men," they are able to induce physicians to prescribe their controlled products, on which there

are large profits, even though such products have not only not been accepted by the Council, but, in many instances, have been disapproved. Is it any wonder that concerns which put out such products are indifferent or openly antagonistic to the work of the Council? The matter is largely one of business policy. When the medical profession as a unit will support the Council in its work, then such firms will find it good business policy to accede to Dr. Bevan's suggestion—but not before."

Evidently the problem resolves itself into this: The Council, constituted of scientific men, working without remuneration in the interest of scientific medicine and the medical profession, expects—and rightfully—the cooperation and support of the members of that profession. What is needed, therefore, is the active, sympathetic cooperation of physicians; the cooperation of pharmaceutical houses will follow as a matter of course.

ELECTRARGOL OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report which explains that Electrargol—a preparation of colloidal silver—was omitted from New and Nonofficial Remedies because unwarranted claims are made for it.

W. A. PUCKNER, Secretary.

Electrargol, manufactured by Comar & Cie, Paris, France, and distributed in the United States by E. Fougera & Co., New York, was admitted to New and Nonofficial Remedies in 1914.

An examination of the current advertising having revealed that unwarranted claims were made for Electrargol, the following report on the continuance of Electrargol in New and Nonofficial Remedies was adopted by the Council on the recommendation of the referee in charge of silver preparations, and sent E. Fougera & Co., Oct. 18, 1918.

Electrargol is an electric colloidal silver, marketed in the form of a very dilute (0.04 per cent.) solution and used mainly for injection against systemic infection; also used to some extent locally.

The label is not objectionable, except for the unexplained phrase "POUVOIR CATALYTIQUE: 25."

As advertising matter E. Fougera & Co. submited a treatise on "The Therapeutic Colloids" by the Clin Laboratories. This contains a number of statements that are misleading and exaggerated. This is all the more important because our knowledge of "therapeutical colloids" is so meager.

The following are examples:

p. 4. "We know now that organic actions and reactions are for the most part due to the formation of particular complexes between the natural colloids of the organism or between these colloids and those introduced from without. *The complexes formed under these conditions possess properties which may be manifested either by an increase of the intraorganic oxidations, by greater activity on the part of the nutritive exchanges by enhancing the functions of defense against toxins, or, lastly, by increased secretion or elimination. Henceforth the properties of antitoxins, and the functions of agglutination, digestion, etc., must be regarded as due to the reaction of the colloids* inter se.

"Artificial colloids are possessed of all the catalytic and fermentative properties presented by the natural enzymes which are also nothing more nor less than colloids."

p. 5. *"Colloidal metals are possessed of all the physico-chemical biological properties which have just been described as belonging to the colloids."*

p. 7. "Electrargol is the foremost anti-infectious product employed at the present time in therapeutics. It has been utilized in a very large number of diseases"

"Speaking generally, it may be stated that Electrargol is the remedy *par excellence* in all infectious diseases involving the pulmonary apparatus."

p. 12. "Among affections of the respiratory tract successfully treated by means of the electric colloid metals, must be mentioned influenza which was one of the earliest indications and on which numerous works have been published."

p. 20. "Cholera. First to be mentioned are the cases and researches of Dr. E. MARIOTTI. This observer published in *La Riforma Medica* the results of his observation during the cholera epidemic at Santa Maria C. V. (Italy) in July and August, 1911. In all the cases recorded by MARIOTTI the efficacy of Electrargol is most marked, it brought down the temperature to normal, regulated the intestinal functions, stimulated the organism and reestablished diuresis and, in general, disintoxicated the organism."

In submitting this report, the Council explained that Electrargol would be omitted from New and Nonofficial Remedies unless a thorough revision of the advertising claims was made within a reasonable time.

As the reply of E. Fougera & Co. indicated that a genuine effort was being made to comply with the request of the Council for a revision of the advertising claims, the Council voted to continue Electrargol in New and Nonofficial Remedies, 1919.

A reply to the preceding report was received from Comar & Cie, Jan. 15, 1919, and reported to the Council thus:

The Council on Oct. 17, 1918, adopted the report of the referee that the advertising matter contained misleading and exaggerated statements, of which examples were given. It was directed that this report be submitted to the agents, and that Electrargol be omitted from N. N. R. unless a thorough revision of the claims be made within a reasonable time.

A reply dated Jan. 15, 1919, has been received from the French manufacturers. This discusses at considerable length the parts of advertising that were cited by the referee, and concludes with a refusal to modify these statements, with one exception.

The reply indicates that Comar & Cie made their statements in good faith—a matter that had not been discussed by the referee. Beyond this, however, their arguments are generally not convincing.

They consist largely in citing "authorities" for particular statements which are accurate enough in themselves, but to which objection was raised because of the manner in which they were used which resulted in unjustifiable deductions. In part, the arguments supported the point of view that a manufacturer is not responsible for quotations that he takes from the medical literature, but that the whole responsibility rests first on the author of the paper, and then on the reader who accepts it. As Comar & Cie put it, "It is impossible for us to admit that there is anything in this action that would deceive an instructed reader, such as a physician is a priori." The Council has on every suitable occasion emphasized that this naive attitude is as untenable as it would be for the disseminator of a slander to unload his responsibility on his informer or on his hearer. When manufacturers undertake to supply physicians with information regarding the actions and uses of their products, they thereby assume responsibility for the statements they make.

Otherwise, the most dangerous as well as the most absurd claims and statements could and would be justified under the cloak of editorial immunity.

The reply is too lengthy to be reproduced in full. It is here abstracted:

1. The report objected to the "unexplained phrase," "Pouvoir Catalytique:25." The manufacturers now explain that this number expresses the rapidity of decomposition of hydrogen dioxid under the influence of Electrargol. This clears up the statement somewhat, but is not satisfactory. Methods of standardization, to be accepted, must be explained with sufficient detail so that they can be checked by independent observers.

2. Objection was taken to quotations from the section on "Physico-Chemical and Biological Properties of the Colloids." The reply undertakes to defend these statements, one by one, and ends with the assertion that this portion of the pamphlet was not intended to have any therapeutic bearing. "Son but ne vise nullement le côté thérapeutique." It is, however, just from this standpoint that the statements are objectionable. Take, for instance, the statement that the products of the interaction of colloids ". . . *possess properties which may be manifested either by an increase of the intra-organic oxidations, . . . by enhancing the functions of defence against toxins or, lastly, by increased secre-*

tion or elimination." This is not a statement of abstract physics, but it has a definite value as a pharmacologic or therapeutic statement. Moreover, they furnish as their definite "proof" conclusions derived by Robin from the supposed effects of metallic ferments on metabolism in pneumonia.

The pamphlet goes on to explain that the phenomena of immune reactions and of fermentations are of colloidal nature. While the statements made may, in themselves, be unobjectionable, they do not furnish a sound basis for therapeutics. This, however, was the evident intent of the two succeeding paragraphs:

"It is easy to grasp the therapeutical interest that attaches to the introduction into the organism of bodies possessed of properties peculiar to themselves which, having been converted into the colloidal state, acquire a whole series of fresh properties capable of exerting a pronounced biological influence.

"Colloidal metals are possessed of all the physico-chemical and biological properties which have just been described as belonging to the colloids"

3. Passing to the direct therapeutic claims, objection was made to the statement that "Electrargol is the foremost anti-infectious product employed at the present time in therapeutics." The reply maintains that this statement is justified, but confesses that it may appear exaggerated. This exaggeration is attributed to the translator of their pamphlet, who rendered their French "L'Electrargol est le premier des médicaments anti-infectieux" into "Electrargol is the foremost anti-infectious product. . . ." The reply is open to the suspicion that it is not entirely frank. In fact, they propose to alter their *French* version to "L'Electrargol, médicament surtout anti-infectieux."

The remaining objections referred to the wide field of usefulness claimed for Electrargol. The manufacturers maintain that their statements are fully justified by the clinical reports. To the referee, the available abstracts of these reports are totally inadequate to justify the sweeping statements, for instance, that "Electrargol is the remedy *par excellence* in all infective diseases involving the pulmonary apparatus." The letter itself fails to establish further confidence when it states that in influenza "Dr. Florand (Soc. méd. des hôpitaux, 16 Oct. 1918) observed that Electrargol sometimes gave results superior to those of specific serums." Nor is confidence in the value of their therapeutic selections enhanced, when they fail to see anything amiss with the results of Mariotti in epidemic cholera, when he attributes to Electrargol the most marked efficiency in all cases: "It brought down the temperature to normal, regulated the intestinal functions, stimulated

the organism and reestablished diuresis and, in general, disintoxicated the organism."

In view of the refusal of the manufacturers to modify their claims for Electrargol, with the one exception noted, the Council directed that the preparation be omitted from N. N. R., because of unwarranted and exaggerated therapeutic claims.

FERRIC CACODYLATE OMITTED FROM NEW AND NONOFFICIAL REMEDIES

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the report which appears below, explaining the omission of ferric cacodylate, from New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

Iron cacodylate, the ferric salt of cacodylic acid, was admitted to New and Nonofficial Remedies in 1917. It is required to contain from 39.7 to 44.9 per cent. of arsenic (As).

The following statement of the action, uses and dosage of iron cacodylate appears in the 1920 edition of New and Nonofficial Remedies:

> "Actions and Uses.—Ferric Cacodylate has the properties of iron salts and of arsenic. Its use has been proposed in conditions in which the effects of iron and the mild arsenic action of cacodylates is desired.
>
> "Dosage.—from 0.015 to 0.1 Gm. (¼ to 1½ grains)."

The period for which the iron cacodylate preparations now in New and Nonofficial Remedies were accepted coming to an end with the close of 1920, the Council decided to determine if sufficient evidence for the value of ferric cacodylate has accumulated to warrant its continued recognition. The following is the report of the referee of the Committee on Therapeutics to whom the matter was assigned:

> "As far as the Referee knows, the only claim that Iron Cacodylate has as a therapeutic agent is that it forms a convenient method for the administration of Iron and Cacodylate (while there is no reason why a drug should not be given by mouth, usually intramuscularly, and apparently it has recently been given intravenously). The effects to be expected from its use are those of iron and arsenic.
>
> "Granted that iron and arsenic are valuable therapeutic agents, Iron Cacodylate is not a satisfactory preparation in which to administer these drugs for the following reasons:

"1. It would appear that Cacodylates are not the best form in which to administer arsenic. Cacodylates in therapeutic doses exert but a feeble action. Small quantities may be reduced to cacodyl $(CH_2)_4As_2$, and varying amounts to inorganic arsenic. The amount transformed to arsenic is apparently unknown and probably varies in different individuals. On these grounds alone the use of the cacodylates where an arsenic effect is desired seems dubious.

"2. The amounts of iron and cacodylates contained in the doses recommended are small when compared with the usual doses of either iron or cacodylate. The amount of iron in the Iron Cacodylate preparations is small, about .0036 gram per dose, while the preparations admitted to 'Useful Drugs' contain much larger amounts per dose recommended. The list follows:

Massa Ferri Carbonates.....	Fe per dose	.042 gm.
Pilulae Ferri Carbonates.....	"	.058 gm.
Tinctura Ferri Chloride.....	"	.022 gm.
Ferri et Ammonii Citrae.....	"	.042 gm.

"The approximate amount of arsenc in Iron Cacodylate in the commonly recommended doses varies from .012 gm. to 0.024 gm., while the amount of arsenic in Sodium Cacodylate in the recommended doses varies between .021 and ,35 gms. It would seem that a much more rational method of administration of these two drugs would be separately, in which case a better control over the dosage is possible.

"3. The Referee has been unable to secure reliable clinical evidence that Iron Cacodylate is a serviceable preparation. A search of the available literature for the past fifteen years has been made, also Drs. Edsall, Longcope, Stengel, Hoover, Phillips and Miller have been consulted. These physicians know nothing of its use.

"4. In view of the above, it appears to the Referee that Iron Cacodylate is an irrational and useless method of the administration of iron and arsenic."

The Council adopted the report of the referee and directed that iron cacodylate be omitted from the 1921 edition of New and Nonofficial Remedies.

GRANULAR EFFERVESCENT SODIUM PHOSPHATE COMPOUND (SQUIBB)

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Granular Effervescent Sodium Phosphate Compound (Squibb) contains in each drachm, 5 grains of exsiccated sodium phosphate and 1 grain each of sodium benzoate and sodium salicylate in an effervescent base consisting of sodium bicarbonate, citric acid and tartaric acid. The manufacturer stated that physicians have suggested its use as an eliminant in gout, rheumatism and other conditions connected with the uric acid diathesis. However, no evidence was submitted that this combination of drugs possesses special therapeutic merit.

The Council declared Granular Effervescent Sodium Phosphate Compound (Squibb) inadmissible to New and Nonofficial Remedies because the use of a preparation containing sodium phosphate, sodium salicylate and sodium benzoate in fixed proportion is irrational. Sodium phosphate is a useful laxative. If such an active drug as sodium salicylate is required, it should be used alone or in a combination which permits the regulation of the dosage according to the needs of the patient.

ITTIOLO OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report, announcing the omission of Ittiolo from New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

Ittiolo is an ammonium sulphoichthyolate preparation manufactured in Italy by the Societa Industrie Chimiche, and sold in the United States by Guiseppi W. Guidi, New York.

The following report was made by a referee, adopted by the Council and sent to the American agent for Ittiolo:

> "The A. M. A. Chemical Laboratory analyzed two commercial specimens of Ittiolo and found that they differed in several particulars from the New and Nonofficial Remedies' requirements for the product. For example: the New and Nonofficial Remedies' standard for Ammonium Sulphate in Ittiolo is 6.2 per cent., whereas the Laboratory findings were, respectively, 16.35 per cent., and 19.2 per cent. Again, the New and Nonofficial Remedies' standard for Sulphidic Sulphur is 0.66 per cent., while the Laboratory findings were, respectively, 3.0 and 2.56 per cent. The American agent for Ittiolo was informed of the results of the analysis of the Laboratory. He was informed, further, that the recent analyses of Ittiolo did not agree with the findings of the firm of commercial chemists, whose findings had been submitted to the Council by him and upon whose report the New and Nonofficial Remedies' standards had largely been based. In reply, the importer submitted the results of two analyses of Ittiolo, one by another commercial laboratory and the other by an Italian chemist. Both of these reports essentially confirmed the A. M. A. Laboratory findings and showed that the market product differed considerably from the standards claimed for it.
>
> It is recommended that Ittiolo be omitted from New and Nonofficial Remedies unless the American agent will, within a reasonable time, adopt standards for it, which correctly indicate its composition and will give assurance that the product will be properly controlled.

At the expiration of three months, the Council had received no assurance from the American agent that any effort was being made to standardize Ittiolo or to insure the uniformity of its composition. Accordingly, the Council directed the omission of Ittiolo from New and Nonofficial Remedies and authorized publication of its report.

LIBRADOL

Report of the Council on Pharmacy and Chemistry

The Council has authorized for publication the following report which explains why Libradol was found ineligible for New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

Libradol is manufactured by Lloyd Bros., Cincinnati. According to a circular (a "readily removable" label) which accompanies the trade package, its "uses" are: "In colds, croup and acute bronchitis. In local congestions; in lung trouble, in acute inflammations of this or any other organ, especially if pain or soreness be present. In lumbago, sciatica, or in rheumatic pains of the joints or muscles. Applied to the forehead, it induces sleep."

Libradol is offered in two forms, "Libradol Mild" for infants and supersensitive persons which is said to be "destitute of drug energy" and Libradol "Regular" which is "highly medicated," the "constituents" being "DRACONTIUM. SANGUINARIA. CEPHAELIS. MELALEUCA. LOBELIA. LAURUS. CAPSICUM. TOBACCO."

According to a circular, "The sanitary plasma Libradol" is "a homogeneous, highly medicated, and exceedingly potent compound, in plastic form," which "carries the energies of its drug constituents and the high antiseptic qualities of Laurus Camphora and Melaleuca." It is stated: "The Drug Influence of Libradol is necessarily different from that of any known single member of the Materia Medica. But yet, no mystery either in medicine or of pharmacy is claimed as a part of its composition or process of manufacture. It is a thing peculiar to itself, the result of the study of the drugs from which it is derived and compounded. These drugs may be studied at leisure by whoever cares to do so. . . ."

The following information bearing on the composition of Libradol was furnished by Lloyd Brothers in response to a request from the Council to aid in the consideration of the preparation:

> " 'Compound Lobelia Powder' has been, since 1852, official in the *American Dispensatory,* in the first edition of which (1852) its formula is given, as follows:
>
> " 'Take of Lobelia, in powder, twelve ounces; Bloodroot and Skunk Cabbage, in powder, of each, six ounces; Ipecacuanha, eight ounces; Capsicus, in powder, two ounces. Mix them.'
>
> "This preparation came increasingly into demand with the Eclectic profession, the principal use for which it was first employed (as an emetic), being finally displaced by its local application in bronchial pneumonia troubles, when sprinkled on a greased cloth and applied to the chest."

"In 1898, Dr. Finley Ellingwood petitioned Lloyd Brothers to make for him, in plasma form, ready for application, a compound carrying the ingredients of the old 'Compound Lobelia Powder,' strengthened by the addition of Melaleuca leucadendron, Laurus camphora and Nicotiana tabacum. Experiments not very encouraging in a pharmaceutical sense were made, and it was not until repeated requests had been made that a product was at last satisfactorily prepared and forwarded to Dr. Ellingwood (1900), with no thought other than that of serving him personally in his practice. This product he used and commended to his professional friends, and under his commendation it came into professional demand."

An examination of the information submitted by Lloyd Brothers showed Libradol to be in conflict with the principles and rules that govern in the acceptance of articles for New and Nonofficial Remedies as follows:

Composition (Rule 1).—The information which has been received gives little idea of the actual composition of the preparation; for example, the statement that Libradol "carries the energies of its drug constituents and the high antiseptic qualities of Laurus Camphora and Melaleuca" gives no indication as to the part or parts of the Laurus Camphora or Melaleuca employed. If the statement is correct, that Libradol "is a homogeneous, highly medicated, and exceedingly potent compound," it is essential that the several potent ingredients be stated clearly and not merely hinted at by their qualities. Other conflicts with Rule 1 might be enumerated, but the foregoing citations state the direct conflict; and this has not been removed, although an inquiry was sent to Lloyd Brothers for a statement of the amount of each potent ingredient in a given quantity of Libradol.

Indirect Advertising (Rule 4).—The recommendation for the use of Libradol in the treatment of colds, bronchitis, lumbago, sciatica and rheumatic pains, which accompanies the trade package, is prone to lead the public to depend on it in cases where definite treatment is imperative.

Unwarranted Therapeutic Claims (Rule 6).—Libradol is recommended in a great variety of conditions and is especially claimed not only to relieve pain, but to remove the cause of pain. This is explained as follows: "In the study of the physiological action of many drugs, it was found that the constituent remedies in this combination exercised a most salutary influence, not only upon the sensibility of the nerves involved, but upon the capillary circulation within the diseased area, the muscular structures therein included, and, subsequently, upon the course of the advancement of the congestive and inflammatory processes, and upon secretion, exudation, adhesion, induration, hypertrophy, suppuration and excretion."

Granting, for the sake of argument, that carefully controlled experimental clinical evidence were available to substantiate this statement with reference to a single case of pain, the statement would be misleading when considered as a general explanation of the preparation's relieving pain by removing the cause of pain when taken in connection with the conditions for which it is recommended and in which pain is even a minor symptom. Still, if pain were relieved in these cases by removing the cause, the patient would be cured of the conditions which give rise to the pain, and these include: "Acute pain in the chest; . . . acute inflammation in the chest; . . . persistent local pain; . . ." (This might be interpreted as including tuberculosis; pneumonia; cancer, and appendicitis.) "lumbago; sciatica; articular rheumatism" (gonorrheal infections?).

Name (Rule 8).—The name, derived from *Dolar* and *Liber*, suggests the claimed action of the preparation (the relief of pain) rather than the drugs said to be presented by it.

Irrational Composition (Rule 10).—It is quite possible that Libradol will relieve pain in certain instances and that the drug constituents present in Libradol "Regular" make this more effective than "Libradol Mild" which is "destitute of drug energy"; this, however, is no justification for the use by physicians of a cataplasm containing or made from skunk cabbage, bloodroot, ipecac, melaleuca (oil of cajeput?), lobelia, laurus camphora (camphor?), capsicum and tobacco. The combination is thoroughly irrational and a reminder of a past century. Further, the Council knows of no evidence to support the following claims:

"As a stimulant Capsicum has the power of neutralizing depressant remedies like Lobelia and Tobacco."

"Our association of its desirable constituents with those of Lobelia, in connection with the modifying influence of Capsicum, Melaleuca, and Laurus Camphora, permits a more free use in Libradol than would be possible were it to be employed alone."

"Capsicum, Melaleuca, and Laurus Camphora in Libradol tend to counteract the excessive relaxative and depressant effects of Lobelia."

"The great value of Melaleuca in Libradol is its quality of modifying and controlling the action of the associated energetic constituents of the drugs Tobacco and Lobelia, which reduce congestion and inflammation, but which would, unsupported, be too depressant."

Libradol is inadmissible to New and Nonofficial Remedies because its composition is complex, irrational and semi-secret, and because its name and the unwarranted therapeutic recommendations made for it will lead to its ill-advised use.

THIOSINAMINE AND THIOSINAMINE COMPOUNDS

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report, explaining the omission of thiosinamine (allyl sulphocarbamide, allylthiourea) from New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

The general article, Thiosinamine and Thiosinamine Compounds, which appears in New and Nonofficial Remedies, 1920, makes it clear that the evidence for the usefulness of thiosinamine is unsatisfactory, notwithstanding that the drug has been in use for 28 years and a proprietary preparation of it (Fibrolysin) was at one time given extensive publicity. Since this long opportunity for observation has failed to produce satisfactory proof of its value, it is improbable that the substance possesses any real usefulness. The Council, therefore directed that the description of thiosinamine and the discussion of thiosinamine and thiosinamine compounds be omitted from New and Nonofficial Remedies. As a matter of record this matter was referred to the Council Reports and appears below.

THIOSINAMINE AND THIOSINAMINE COMPOUNDS

Thiosinamine was introduced by Hebra and Unna, 1892. It has been credited with the cure of lupus and with causing the absorption of exudates, lymphatic swellings, scar tissue, etc. The administration must be continued for weeks, and combined with massage and other adjuvant measures. It is, therefore, difficult to judge whether it has any value. The clinical opinions are contradictory, and no satisfactory explanation has been offered for its reputed effect. On the whole, its value after these years of use, is not firmly established. It seems to be generally admitted that some softening of scar tissue occurs, which, however, is temporary.

Although it is usually well borne, except for the bitter taste and acid eructations, it may produce toxic systemic effects (Digestive disturbance, lassitude fever: *J. A. M. A.*, March 18, 1911, p. 835), and these may set in suddenly after it has been used for a time without toxicity. In animals, relatively small doses produce severe changes in metabolism and parenchymatous degeneration but without evidence of connective tissue changes. Larger doses impair respiration. (Tyrode: *Arch. Internat. de Pharmacod.* **19**:195, 1910.)

It is used by hypodermic injection in lupus, chronic glandular tumors, cicatrices, etc., and by the mouth in stricture, corneal opacity and chronic deafness.

Thiosinamine cannot be dissolved in water, and the alcoholic or glycerine solutions produce local irritation. Fibrolysin is a soluble compound of thiosinamine and sodium salicylate. This is practically free from the objectionable local effects.

THIOSINAMINE. — Thiosinamina. — Allyl Sulphocarbamide. — Rhodaline. — $(NH_2).CS.NHCH_2.CH : CH_2$. — Allylthiourea.

Actions and Uses.—See general article, Thiosinamine and Thiosinamine Compounds.

Dosage.—From 0.03 to 0.1 Gm. (½ to 1½ grains) in capsules or tablet triturates; in subcutaneous injections, from 0.05 to 0.2 Gm. (1 to 5 grains) in 15 per cent. alcoholic or 10 per cent. glycerinated water solution.

Thiosinamine is prepared by warming together volatile oil of mustard (chiefly allyl thiocyanate) and alcoholic solution of ammonia, collecting the crystalline product of condensation, and recrystallizing from alcohol.

It forms colorless crystals, having a slight alliaceous odor and bitter taste and melting at 74 C. It is moderately soluble in water, but is decomposed by this solvent. It is soluble in about 3 parts of alcohol and readily soluble in ether.

Thiosinamine is incompatible with water, which decomposes it, but this change is to a limited extent prevented by the presence of glycerine.

INDEX OF PROPRIETARIES, MANUFACTURERS AND AGENTS