ANNUAL REPRINT OF THE REPORTS

OF THE

COUNCIL ON PHARMACY AND CHEMISTRY

OF THE

AMERICAN MEDICAL ASSOCIATION

FOR 1921

WITH THE

COMMENTS THAT HAVE APPEARED
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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 1921. 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

AGARIC ACID 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.

For nearly forty years, agaric acid or related preparations have been recommended for the control of night sweats in tuberculosis. There has, therefore, been ample opportunity to test this relatively simple action and to compare the effectiveness of agaric acid with other measures used for this purpose. A review of some of the standard textbooks on therapeutics and on tuberculosis shows that agaric acid has not proved to be a useful drug for this purpose. In a number of books, it is said that it is effective but that it must often be combined with opium on account of a tendency to produce diarrhea. It is too irritating to be used in subcutaneous injections. In these respects, it is inferior to atropin; and the latter seems equally, or more, effective in controlling the sweating. Hare[1] states that in his experience agaric acid does not control the night sweats. The drug is not mentioned in the discussions on the treatment of night sweats written by L. Brown (Osler's System of Medicine), by Krause (Nelson's Loose Leaf System), and by H. M. King (Forchheimer's Therapeusis). Examination of the Index Medicus for the years 1910-1919, inclusive, shows only one article indexed under this title. This was an experimental study by Fred Ransom,[2] in which the pharmacologic evidence was rather against agaric acid's being analogous to atropin in its action.

In consideration of the preceding, the Council voted to omit agaric acid from New and Nonofficial Remedies. As a matter of record, the description of agaric acid which appears in New and Nonofficial Remedies, 1921, was referred to the Council Reports and follows herewith:

AGARIC ACID.—Acidum Agaricum.—Acidum Agaricinicum.—Agaricinum.—A tribasic acid, $C_{19}H_{36}OH(COOH)_3 + 1\frac{1}{2}H_2O$, derived from *Polyporus officinalis,* Fries (Order *Hymenomycetes;* fam. *Polyporeae*) a fungus growing on the European larch and other species of larch.

NOTE.—The substance commonly sold as agaricin is an impure alcoholic extract.

1. Hare, H. A.: A Textbook of Practical Therapeutics, Ed. 17, Philadelphia, Lea & Febiger, 1918, p. 75.
2. Ransom, Fred: J. Pharm. & Exper. Therap. **10:** 169 (Sept.) 1917.

Actions and Uses.—Agaric acid is a local irritant and in large doses produces vomiting and purging, and death through central paralysis. It paralyzes the peripheral nerves of the sweat glands, arresting the secretion of sweat. It is used to arrest colliquative sweats. The experience of most clinicians is favorable, but some report that they were unable to obtain any favorable effects. The action appears in a few hours and is not lasting. Agaric acid is one-twentieth as active as atropine and does not influence other secretions.

Dosage.—The maximal single dose of agaric acid should not exceed 0.03 Gm. (½ grain) and the total daily dose should not exceed 0.1 Gm. (1½ grains). Owing to its irritant action it cannot be given hypodermically.

Agaric acid occurs as an odorless, tasteless, glistening microcrystalline powder, which melts at from 141.5 to 142 C. When heated to a high temperature it is volatilized in the form of a white pungent vapor. Agaric acid is slightly soluble in cold water; when heated with from 50 to 100 parts of water it becomes gelatinous and finally dissolves to a weakly acid solution, which possesses the characteristic property of foaming strongly when shaken. The addition of acids to hot aqueous solutions of agaric acid causes white flocculent precipitate, but a tannic acid solution (1: 100) produces neither coloration nor turbidity. With alkalis agaric acid forms water-soluble salts. Agaric acid is slightly soluble in ether, chloroform, carbon disulphide and in 130 parts 90 per cent. alcohol. It is soluble in hot acetic acid, acetic ether, oil of turpentine, and in about 10 parts of alcohol.

If to a mixture of about 0.2 Gm. of agaric acid with 3 Cc. of water 2 drops of alcoholic alphanaphthol solution (1.8) are added and then gradually 5 Cc. of concentrated sulphuric acid added the mixture should not take on a marked blue-violet color. If 0.1 Gm. agaric acid be boiled with 10 Cc. dilute sulphuric acid a turbid solution results, from which on standing on a water-bath oily drops separate, which crystallize on cooling. If 0.1 Gm. agaric acid be incinerated, it should leave no weighable residue.

ATOPHAN OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report explaining why Atophan has been omitted from New and Nonofficial Remedies. Schering and Glatz, Inc., the firm which markets this brand of cinchophen in the United States, has refused to place either the U. S. Pharmacopeial name, "Phenylcinchoninic acid (Acidum Phenylcinchoninicum)" or the N. N. R. name, "Cinchophen," on the label and in advertising, so as to make the identity of the product clear to physicians. Furthermore, the product is sold under therapeutic claims which the Council holds to be exaggerated and unwarranted.

W. A. Puckner, Secretary.

COMMERCIAL HISTORY OF CINCHOPHEN

The substance, 2-phenyl-quinolin-4-carboxylic acid, was described by Doebner and Giesecke in 1887 (*Ann. d. Chem.* [Liebig's] **242**:291). The therapeutic properties of this compound were described by Nicolaier and Dohrn, in 1908 (*Deutsch. Arch. f. klin. Med.* **93**:331). Subsequently the product was placed on the market and extensively advertised by the Chemische Fabrik auf Actien (vorm. E. Schering), Berlin, Germany. This firm also took out a patent in the United States on its production, and, in 1911, secured a U. S. trademark on the name "Atophan." In 1912, Atophan was passed on by the Council and admitted to New and Nonofficial Remedies.

When the government of the United States took charge of German-owned patents during the World War, the Federal Trade Commission, and later the Chemical Foundation, Inc., issued licenses to American firms whereby these were authorized to manufacture the compound. In the meantime, Schering and Glatz, Inc., who had been the United States representatives for the Chemische Fabrik auf Actien, also undertook to supply the drug, but did not obtain a license from the boards in charge of German patents. Also, this firm secured, in 1919, a trademark of the word "Atophan," apparently after the German-owned trademark had been canceled.

The drug "Atophan" was admitted to the U. S. Pharmacopeia as "Phenylcinchoninic Acid (Acidum Phenylcinchoninicum)." As this name proved too cumbersome, the Council on Pharmacy and Chemistry coined the abbreviated name "Cinchophen" for it, and this name is now used by all the firms which are marketing the product in the United States, with the exception of Schering and Glatz, Inc., who use the term "Atophan," first owned by the Chemische Fabrik auf Actien.

ATOPHAN, A BRAND OF CINCHOPHEN

Because of the confusion which is bound to arise from giving various names to one drug, the Council selects a common name and provides standards of identity, purity and strength for any drug which, by reason of the absence or lapse of patent rights or for other reasons, is open to manufacture by more than one firm. The Council, then, will accept such article only if it is marketed under the title adopted for New and Nonofficial Remedies. The rules provide, however, that when the Council adopts a common name for an article that has been admitted under another name, such article will be retained in New and Nonofficial Remedies under the older name if the Council name is given prominence on the label and in the circulars and advertisements, in order to avoid confusion. Accordingly, when the

period of acceptance for Atophan in New and Nonofficial Remedies was about to expire, Schering and Glatz were notified that Atophan could be retained in that publication only on condition that the name, "Cinchophen," or else the pharmacopeial name, "Phenylcinchoninic Acid (Acidum Phenylcinchoninicum)" be placed on the label and used in the circulars and advertisements.

UNWARRANTED THERAPEUTIC CLAIMS FOR ATOPHAN

At the time the Council asked Schering and Glatz to adopt cinchophen or phenylcinchonic acid as a synonym for Atophan, the firm was also requested to omit from future advertising a number of therapeutic claims to which the Council was obliged to take exception. Schering and Glatz refused the first request and made no definite promise with regard to the second. The Council, therefore, directed the omission of Atophan from New and Nonofficial Remedies, 1921.

The advertising to which the Council took exception does not appear to be distributed at present. A pamphlet has been sent out, however, which is equally objectionable. It contains unwarranted therapeutic claims and suggests that Atophan be used in conditions in which it is not indicated. For instance:

"No longer the vague, hypothetical, 'test-tube demonstrated' principle of uric acid elimination by solution, but a definite, scientifically and clinically established, physiologic stimulation of the uric acid excretion. Performed innocuously and controllable to a nicety by dosage and by urine and blood tests."

The "innocuousness" of Atophan has not been proved; on the other hand there is evidence that it is not innocuous, as the recent investigations of Hanzlik and Scott and their collaborators (Cinchophen, Neocinchophen and Novaspirin in Rheumatic Fever, *J. A. M. A.* **76**:1728 [June 18] 1921) show that it may injure the kidney.

The circular also contains the following:

"No longer, hit and miss relief of pain at the expense of the heart, the intestines, the kidneys and the nervous system, but the promptest and most reliable analgesic, anti-inflammatory and decongestive action so far known, with notable freedom from heart-depressant, renal irritant, constipating and cumulative toxic by-effects. No contra-indications, except chronic nephritis and the presence of kidney concretions."

This is misleading. The drug depresses the circulation, injures the kidney and produces symptoms of salicylism or "toxicity." It is *not* the promptest and most reliable analgesic; morphin is superior and salicylate is just as efficient. The phrase "decongestive action" is vague. Treatment of pulmonary congestion from phosgene, and congestion of the

conjunctiva in mustard oil chemosis of cats, with large doses of Atophan was ineffective; in fact, it proved distinctly harmful. This was shown by such workers as Laqueur and Magnus, and Heubner and Gildemeister (*Ztschr. f. d. ges. exper. Med.* **13**:200, 1921). It is incorrect to ascribe "decongestive" or "anticongestive" action in the true sense to Atophan (cinchophen). The principal assets of the salicylate-cinchophen class of drugs in the treatment of rheumatism and gout are their analgesic and antipyretic qualities.

The claim is made:

"In Rheumatic and Gouty Disorders, whether of the well known muscular and arthritic type, or their Eye, Ear, Nose and Throat manifestations."

The suggestion that Atophan is indicated in "their Eye, Ear, Nose and Throat manifestations" is a vague generalization without definite meaning, but nevertheless calculated to impress physicians and promote the sale of Atophan for common and minor ailments. Rhinitis and sore throat are, of course, self-limited conditions which require chiefly good habits, personal and general hygiene as prophylactic measure, and simple hot baths with rest, instead of medication, for symptomatic relief. When it comes to ear and eye conditions, Atophan certainly would do no good in otitis media, panophthalmitis, choroiditis, retinitis, etc.

The administration of Atophan is proposed "In Migrains, Hemicrania, Eye-strain, etc., often vaguely grouped as 'Headaches.'" Eye-strain and headaches are vague symptoms often arising from numerous causes that require no medication, but rather good habits, hygiene and similar corrective measures. There is always the possibility of habituation from the use of drugs for such common and vague symptoms, resulting eventually in more harm than good to the patient.

The use of Atophan is proposed "In Influenza (Grippe) for the ready alleviation of the respiratory congestion, pain and stiffness of limbs and back." Probably the entire claim is without warrant, since influenza is a self-limited disease. Atophan might relieve pain in the joints, reduce the fever, etc., but at the same time it would tend to impair the functional efficiency of the heart, which may be impaired already by the disease. Cardiac failure is one of the causes of death in influenza. The recommendation for "alleviating respiratory congestion" is certainly without warrant, since in actual trial in pulmonary congestion by Magnus et al., Atophan was found to be deleterious and not beneficial. Phosgenized cats are probably as good a test object for the alleged decongestive action of Atophan as anything could be, since, according to Underhill and Ringer (*J. A. M. A.* **75**:1531,

1920) the pathologic physiology of the circulation and respiration in phosgene poisoning and influenza are nearly identical.

Further, Atophan is recommended "In Pyorrhea alveolaris as a systemic support to local and specific measures." Atophan is not indicated here. Pyorrhea requires local medication, if anything at all. It could exert no local beneficial effects in this condition; indeed, the employment of Atophan might lead to irritation. Good dental treatment is more essential than medication.

Finally, Schering and Glatz advise Atophan "In Eczema, Pruritus and similar irritant and itching Skin Diseases with lowered blood alkalinity." The assumption that blood alkalinity is lowered in irritant and itching disease is unsupported by evidence in medical literature and the recommendation is incorrect and misleading. Neither does Atophan alter the reaction of the blood. Amelioration in these capricious conditions occurs without medication so that any relief that might be obtained could not be attributed to Atophan. The entire paragraph is misleading and will undoubtedly tend to extend the use of Atophan in conditions for which it is not suited.

BISMON 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.

Bismon has been retained for several years because there was no evidence for the opinion expressed by members of the Council that the preparation did not have the properties claimed for it. Now, however, Dr. Henry G. Barbour has made a research of the literature for evidence of the therapeutic value of colloidal bismuth preparations and his report justified the deletion of Bismon. It is recommended that Bismon be omitted and that the following statement of this action be adopted:

Bismon is a colloidal bismuth oxid. It is claimed that Bismon has the actions of other preparations of bismuth, but that, on account of its "solubility" in water (property of forming colloidal suspensions), it is more rapidly distributed over the mucous membrane of the gastro-intestinal tract.

Bismon was admitted to New and Nonofficial Remedies in 1911, and the therapeutic claims then advanced for it are now made.

The therapeutic value of Bismon having been questioned, inquiry was made in April, 1920, of the Kalle Color & Chemical Co., Inc., the American distributors of the product, to

determine whether there was any other evidence for the value of Bismon than that submitted previously. The firm was notified that the information was desired to determine the continued eligibility of Bismon for New and Nonofficial Remedies. It was explained that the claims made for Bismon had been admitted because they were not improbable, but that the Council was inclined to question them now, particularly since, during the years that Bismon has been marketed, no confirmatory evidence has accumulated.

No evidence for the value of Bismon was received from the Kalle Color & Chemical Co., Inc., nor has any been received from the firm which has taken over this business, the Color Service Corporation.

On the other hand, Dr. Henry G. Barbour, professor of pharmacology, Yale University, who, at the request of the Council, examined recent literature, reported that an investigation of the publication for the last ten years revealed no evidence of the therapeutic efficacy of colloidal bismuth salts.

In consideration of the fact that during the years that Bismon has been on the market, no supporting evidence for its claimed properties appears to have accumulated and because of the improbability that it will exercise the protecting and soothing effects of the established insoluble bismuth compounds, the Council directed the omission of Bismon from New and Nonofficial Remedies on the ground that the claims for its therapeutic value are unproved and therefore unwarranted (Rule 6).

BOROTETRAMINE ("BORO") NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Feb. 19, 1921, p. 538

The Council has authorized publication of the following report which declares Borotetramine (Takamine Laboratories, New York) inadmissible to New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

"Borotetramine" and "Boro" are names applied by the Takamine Laboratories to hexamethylenamin diborate. It is a molecular combination of hexamethylenamin and boric acid which is readily split into its components. The borates of hexamethylenamin have been known for some time. In 1907, the Atkiengesellschaft für Anilinfabrik took out a patent in Germany (D. R. P. No. 188,815) covering the preparation of the monoborate, the diborate and the triborate of hexamethylenamin. The triborate has been used in medicine under the name "Borovertin."

According to an explanatory letter from the Takamine Laboratories, Borotetramine is not intended as a means of administering hexamethylenamin and boric acid but as a means of rendering the urine acid. The firm, however, has failed to submit any evidence that the oral administration of Borotetramine materially changes the true reaction of the urine. In any case the effect cannot be greater than that of the boric acid contained in Borotetramine. Boric acid has been tried in gonorrhea, but seems to have been abandoned by modern clinicians.

The manufacturer claims that the greater solubility of Borotetramine renders it more efficient than the ingredients taken separately. Such an increased solubility, however, is of no moment, first because the compound is broken up in the stomach into its components, and second, because the solubility of boric acid is quite sufficient to insure its solution in the alimentary tract, especially in the intestine. Furthermore, Borotetramine must separate into its components before it can act; hence the administration of a compound presents no distinct advantage over a simple mixture of the components.

The Council holds that Borotetramine is a superfluous, and therefore useless, article, and hence not eligible for inclusion in New and Nonofficial Remedies.

BUTYN

Preliminary Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Dec. 10, 1921, p. 1891

Butyn is the name applied by The Abbott Laboratories, Chicago, to a new local anesthetic, proposed for use in place of cocain in surface anesthesia in the eye and for anesthesia of other mucous membranes. The Abbott Laboratories have presented Butyn for inclusion in New and Nonofficial Remedies.

Butyn is a definite chemical of nonsecret composition. Pharmacologic studies indicate that the drug is of therapeutic value. So far this value has, however, not been confirmed by adequate clinical trials; and for this reason, the Council has postponed the acceptance of the drug for New and Nonofficial Remedies. For the information of those who may wish to put Butyn to clinical trial and with the desire to make such trials of value, the Council has authorized publication of the following statement. W. A. Puckner, Secretary.

Butyn is para-aminobenzoyl-gammadinormalbutylaminopropanol sulphate. It is a white, hygroscopic solid, very soluble in water.

In the accompanying table the efficiency and toxicity of Butyn, with that of procain and cocain, are compared.

On the normal human eye, a 0.5 per cent. solution of Butyn is less efficient than a 1 per cent. solution of phenacin (holocain), but more efficient than a 1 per cent. solution of cocain or a 1 per cent. solution of eucain. Butyn solutions are nonirritant.

When injected hypodermically into albino rats, the toxicity of Butyn is two and one-half times that of cocain; but the fatal dose of Butyn (injected intravenously into cats) is about equal to that of cocain. Sublethal doses are more dangerous than those of cocain.

The pharmacologic investigation indicated that Butyn may take the place of cocain, in whole or in part, for surface anesthesia of mucous membranes; that it may be superior for this purpose, and especially for use in the eye, to other synthetic anesthetics, for the reason that it can be used in materially lower concentrations (presumably because of more prompt absorption). On the other hand, it does not appear promising for injection or spinal anesthesia, since its toxicity is materially greater than that of procain. Reports from a small number of physicians, favorable to the use of Butyn in eye work, have been submitted to the Council. However, these do not contain adequate details on which independent judgment may be based, nor do they state whether or not suitable control experiments were made.

COMPARATIVE EFFICIENCY AND TOXICITY OF BUTYN, PROCAIN AND COCAIN

	Cocain	Procain	Butyn
Efficiency on motor nerves	1	1	8
Efficiency on sensory nerve trunks	1	½	2
Efficiency on rabbit's cornea	1	⅕	1
Efficiency on frog's skin	1	⅛	2
Intradermal wheal test	1	...	2
Toxicity for perfused turtle heart	1	½	1

To those who wish to put this drug to experimental clinical trial, the Council suggests that these trials take the form of comparing Butyn, cocain and phenacain (holocain), by alternating the use of these drugs in successive cases in certain groups. The following scheme is suggested for these experiments:

Foreign body in the cornea.
Corneal anesthesia for tonometry.
Operative anesthesia of cornea and conjunctiva.
Anesthesia of cornea and conjunctiva for removal of sutures.
Anesthesia of lids for opening a hordeolum and curetting a chalazion.
Anesthesia of lachrymal points and tear passages for dilatation, etc.
Anesthesia of cornea against pain of erosions.

In these experiments, the following observations should be recorded:

Anesthesia:
- Onset
- Depth
- Penetration
- Duration

Side Actions:
- Irritation—Immediate
  Late
- Pupil diameter
- Vascularity
- Drying
- Other side actions
- Effects on intra-ocular pressure, normal and in glaucoma, when practical.

Toxic Systemic Effects, if any.

If the anesthetic is to be used in fields other than the eye, corresponding schemes for clinical observations could easily be devised.

CREO FERRUM NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

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

Creo Ferrum is a product in the form of capsules marketed by The Gross Drug Company, Inc., New York. The following "formula" is furnished the medical profession:

Iron in the form of fresh carbonate	5 per cent.
Iodine, nonirritant and fully protected	3 per cent.
Creosote prepared by our special method to assure keeping qualities and to prevent gastric disturbances	26 per cent.
Eucalyptol	q. s.
Calcium, Magnesium, Sodium	35 per cent.
Aromatics and excipient, q. s.	100 per cent.

and Tinct. Nux Vomica, 2½ mins. to capsule.

In the information furnished the Council it was stated: "The product is a mixture of the various ingredients, the salts of Calcium, Magnesium and Sodium being used to protect the more active ingredients Iron, Iodin, and Creosote. The chief ingredient, Creosote, is prepared by our special method and is a compound of Creosote and Magnesia."

No information is furnished as to the form in which the iodine is present, nor with regard to the salts of calcium and sodium that are claimed to be present. Further the amount

of the mixture contained in a capsule is not declared. Hence the composition of Creo Ferrum is essentially secret.

According to the label on the trade package of Creo Ferrum: "This invaluable Reconstructive Tonic is indicated in Chronic Bronchitis, Bronchial Asthma, Persistent Cough and all debilitated conditions that lead to Tuberculosis and other wasting diseases." This claim is an invitation to prescribe Creo Ferrum without consideration of the indications for the constituents. It also constitutes an indirect advertisement to the public. Creo Ferrum is inadmissible to New and Nonofficial Remedies because it is an irrational "shotgun" mixture of essentially secret composition which is exploited to the medical profession—and indirectly to the public—by means of therapeutic claims that are unwarranted. The presentation of a mixture such as this is an insult to modern medical practice.

CROUSTILS NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

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

"Croustils" are marketed by Laporte and Gauthier, Somerset, Manitoba (Charles Horstmann, Clifton, N. J., United States agent), as "A Dietary Bread Adapted to Several Diseases." Three forms are offered: Simple Croustils No. 1 (oaten bread), Dechloridised and Lactosed Croustils No. 2 and Glutenised Croustils No. 3.

THE MANUFACTURER'S CLAIMS

From an advertising pamphlet, we learn:

> The European and more particularly the French medical authorities have for a long time prescribed the use of dietary bread adapted to several diseases. They have recommended its use as being one of the most important factors of their cures. HENCE SPECIAL FORMULAS FOR THE MANUFACTURE OF BREAD ADAPTED TO SPECIAL DISEASES.
>
> "Croustils," owing to a particular process of handling and cooking, may be kept for years without losing their flavor or quality. This is an immense advantage over all forms of similar bread.

Simple Croustils No. 1 (oaten bread). The following "formula" for this product was furnished the Council by Laporte and Gauthier: "Wheat flour 55, Oat flour 6, Powder Milkstok 4, Pure Lard 3, Molasses 0.5, Salt 0.5, Fleischmann Yeast 0.5, Water 29.5. Total when mixed 100."

The trade package of this product contains these recommendations, which constitute an indirect advertisement to the public: "Specially recommended by all doctors for the

use of dyspeptics, those suffering from stomach troubles" and ". . . for all stomach, intestine and liver troubles."

In the advertising pamphlet, under Simple Croustils, it is asserted: "It has been demonstrated that most Stomach Diseases are due to the indigestibility of ordinary bread, either when it is taken in too large quantities or when the stomach is in such a condition as to disagree with it." It is asserted that "Croustils are obviating these objections, owing to the inclusion of new elements in their composition, and also to the particular process of handling and cooking." Finally, it is announced that "the large alimentary potential of Croustils makes of them really concentrated bread, very light to the weakest stomach and to the most delicate and diseased intestines."

Dechloridised and Lactosed Croustils. For this product the following "formula" was furnished: "Wheat flour 60, Oat flour 6, Powder Milkstock 4, Pure Lard 3, Molasses 0.5, Salt none, Fleischmann Yeast 0.5, Water 26, Total when mixed 100."

The trade package of this product bears the recommendation: "Dietetic bread for albuminuria and all cardiac affections," and the assertion that it is "recommended by all doctors for patients suffering from albuminuria and heart trouble."

In the pamphlet it is stated that Dechloridised and Lactosed Croustils are "loaves made without salt and contain 5 grammes of lactose which makes them eminently diuretic, and they are consequently prescribed in cases of cardiac trouble or of albuminuria."

Glutenised Croustils No. 3. For these the "formula" furnished was "Gluten pure 20, Wheat flour 43, Oat flour 3, Pure Lard 3, Salt 0.5, Fleischmann Yeast 0.5, Water 30, Total when mixed 100."

On the trade package of this product, it is stated that "Glutenised Croustils are specially recommended by all doctors for diabetic patients."

In the pamphlet it is claimed that Glutenised Croustils afford "all the advantages of a glutenized bread without any of its defects," and it is stated that they "possess all the chemical and therapeutic qualities of the ordinary gluten bread."

THE COUNCIL'S STATEMENT

The Council examined the information furnished by Laporte and Gauthier for their Croustils and sent the following statement to the firm:

1. It is not clear whether the formulas furnished in your letter represent the composition of the dough from which the "Croustils" are made or the composition of the finished product. If the former, the content of carbohydrate, protein, etc., of the finished products should be furnished. The composition of the "powdered milkstok" used in each of the formulas and of the "gluten (pure)" used in the third should be furnished.

2. The trade packages are in conflict with Rule 4. Before the products can receive favorable consideration, the following conflict must be removed:

> Croustils No. 1: "Specially recommended by all doctors for the use of dyspeptics and those suffering from stomach troubles . . . for all stomach, intestine and liver troubles."
>
> Croustils No. 2: ". . . for albuminuria and all cardiac affections . . . recommended by all doctors for patients suffering from albuminuria and heart trouble."
>
> Croustils No. 3: "Glutenised Croustils are especially recommended by all doctors for diabetic patients."

3. The claim is made that Croustils may be kept for years and that this is "an immense advantage over all forms of similar bread." Unless evidence is furnished to show that Croustils keep better than other products on the market, this claim cannot be accepted.

4. Croustils No. 1 (oaten bread): In view of the small content of oatmeal, the term "oaten bread" is misleading and unwarranted. The claim that "it has been demonstrated that most stomach diseases are due to the indigestibility of ordinary bread" is without warrant. Unwarranted also appears the claim that these Croustils are a "concentrated bread" which is "very light to the weakest stomach and to the most delicate and diseased intestine."

5. Dechloridised and Lactosed Croustils: While the submitted formula makes no mention of lactose, it is stated in the circular that they are "loaves made without salt and contain 5 Gm. of lactose which makes them eminently diuretic." This discrepancy in the statement of composition requires explanation. Also the claim that the addition of 5 Gm. of lactose per loaf makes them "eminently diuretic" requires proof.

Glutenised Croustils No. 3: While, as stated under 1, information in regard to composition is required, this product evidently contains much starch. Hence the circular should be revised to bring this out and to indicate the restricted indication for their use.

The Council postponed the further consideration of the Croustil products to await the firm's reply. In the meantime, an analysis was made of the submitted products by E. M. Bailey, Ph.D., of the Connecticut Agricultural Experiment Station with the following results:

ANALYSIS OF CROUSTILS

	Croustils Simple	Croustils Dechloridised	Croustils Glutenised
	Gm.	Gm.	Gm.
Net weight	374	414	686
	Per cent.	Per cent.	Per cent.
Moisture	7.62	7.55	7.88
Ash	1.67	1.25	1.50
Nitrogen	(2.74)	(2.66)	(4.84)
Protein (N x 6.25)	17.13	16.63	30.25
Fiber	0.38	0.44	0.46
Nitrogen-free extract:			
Starch	60.36	54.45	44.55
Total sugars as dextrose	5.68	10.30	5.36
Other N-free extracts	3.75	3.32	3.29
Fat	3.41	6.06	6.71

CROUSTILS INADMISSIBLE TO N. N. R.

Eight months after the Council's statement had been sent to Laporte and Gauthier, the requested information had not been received, nor was the Council advised that any of the claims objected to had been revised; therefore, the Council declared Simple Croustils No. 1 (Oaten Bread), Dechloridized and Lactosed Croustils No. 2 and Glutenised Croustils No. 3 inadmissible to New and Nonofficial Remedies because: (1) The statements relative to their composition are indefinite; (2) the therapeutic claims advanced for them are exaggerated and unwarranted (Rule 6), and (3) the recommendations which appear on the trade packages are prone to lead the public to use them illadvisedly for the treatment of serious diseases.

DIGIFOLIN-CIBA NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., April 2, 1921, p. 952

The Council has authorized the publication of the following report, declaring Digifolin-Ciba inadmissible to New and Nonofficial Remedies. W. A. PUCKNER, Secretary.

Digifolin-Ciba is a product of the Society of Chemical Industry of Basle, Switzerland. It is marketed in the United States by the Ciba Company, Inc., 91 Barclay Street, New York City. It is claimed that Digifolin-Ciba is "a preparation of digitalis leaves that have been freed from their useless and harmful principles such as Digitonin (saponin), coloring and inert matter, etc., but which does contain all the really valuable, therapeutically active constituents of the leaves, namely; digitoxin and digitalein in their natural proportions." There is no evidence that digifolin contains all of the glucosides of digitalis as they exist in the leaf, and it is extremely improbable that this is the case because one cannot remove saponin without altering the other active principles of digitalis.

The Ciba Company send out the following statements relating to Digifolin:

"'Concerning Digifolin-Ciba, A New Preparation of Digitalis,' by C. Hartung, M.D., Ph.D. Extracts from the work 'Ueber Digifolin, Ein Neues Digitalis-Praeparat' in the *Munich Medical Weekly*, No. 36, page 1944, 1912."

"'Digitoxin Contents of Digifolin-Ciba,' by C. Hartung, M.D., Ph.D., Basle, Switzerland. Reprints from the *Pharmaceutical Post*, 1913. No. 34, page 357. No. 40, page 431."

"'Pharmacological Tests of Digitalis,' by M. J. Chevalier Chef Des Travaux Pratiques de Pharmacologie et Matiere Medicale, Faculte De Medecine De Paris. Report Presented to the Societe de Therapeutique at their Meeting, May 28, 1913."

In the reprint "Concerning Digifolin, 'Ciba,'" Hartung lays stress on the presence of harmful and inert substances present in the leaf and galenical preparations, with the direct or implied statement that digifolin has an advantage in that these are absent from it. This is misleading. It is true that Boehm, whom Hartung cites, found saponin to be irritating; but Boehm states that it required 100 mg. per kilogram of body weight to induce vomiting after its oral administration. Furthermore, saponin is present in traces only in infusion of digitalis, so that the therapeutic dose contains a wholly negligible amount of it.

The following statement occurs in "Pharmacological Tests of Digitalis," by M. J. Chevalier:

"Hartung's Digifolin merits our attention, especially because it seems to possess all the pharmacodynamic properties of galenic preparations of digitalis without showing any of their disadvantages."

This claim scarcely needs comment, since it is well established that the chief "disadvantages" of digitalis are inherent in the principles which produce the desired effects of digitalis and may be avoided to a large extent by a carefully regulated dosage of any digitalis preparation. In short, the advertising for Digifolin asserts that this digitalis preparation has all the advantages of digitalis itself, but none of its disadvantages. This claim has been refuted so frequently that manufacturers must be aware that it is untenable. Further, the claims now made for Digifolin are essentially those made nearly four years ago, at which time the attention of the American agent was called to their unwarranted character.

The Council declared Digifolin-Ciba inadmissible to New and Nonofficial Remedies because the therapeutic claims advanced for it are misleading and unwarranted.

DIGITOL AND SO-CALLED FAT-FREE TINCTURES OF DIGITALIS

Report of the Council on Pharmacy and Chemistry

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

Digitol was introduced by the H. K. Mulford Company with the claim that being "fat-free" it was, therefore, less likely to produce gastric disturbance than was the official tincture of digitalis; and that it was of more uniform activity than the official tincture of that time, inasmuch as digitol was standardized while the official tincture was not. Since at the time that Digitol was introduced there was some evidence to indicate

that the nauseant action of tincture of digitalis was due to fat, believed to be present in the leaf, and assumed to be present in the tincture, Digitol was admitted to N. N. R. Subsequently the Pharmacopeia adopted a method of assaying tincture of digitalis biologically.

Later investigations have shown that tincture of digitalis (as well as other digitalis bodies) causes nausea and vomiting mainly, if not exclusively, through its action on the medulla. It has been shown, further, that the "fat" extracted from digitalis by means of petroleum ether, the solvent commonly employed for the purpose, is not especially nauseant, and it is a matter of simple demonstration that the official tincture of digitalis contains no more than traces of fat, since it is freely miscible with water with not more than slight opalescence. The mistaken view that tincture of digitalis contains fat probably arose from the fact that when a tincture of the leaf is made with strong alcohol, somewhat more of the water-insoluble material will be removed than when it is made with a diluted alcohol, as the Pharmacopeia directs.

Eggleston and Hatcher (*J. Pharmacol. & Exper. Therap.* **4**:113, 1912) compared the emetic activity of Digitol (which they referred to merely as "a fat-free tincture") and various other digitalis preparations with that of digitalis and found no essential differences in their relative emetic and cardiac activities. Following these findings the Mulford Company abandoned the claim that Digitol is less prone than the official tincture of digitalis to cause nausea, and Digitol was retained in N. N. R., because it is a standardized tincture of digitalis.

The Council has been requested to admit another so-called "fat-free" tincture of digitalis to N. N. R., and this has lead to a consideration of the status of these preparations anew. The Council has concluded that the use of the term "fat-free tincture of digitalis' is essentially misleading in that it implies that the preparation so termed is different from the official tincture of digitalis. In fact, no essential difference in action results from the removal of the "fat" from digitalis before making a tincture from the leaf.

In view of the promise of the Mulford Company to cease stressing the claim that Digitol is "fat-free," the Council has decided to retain Digitol in N. N. R., because it was introduced at a time when the official tincture was not standardized, and was, therefore, a distinct advance. Since the Pharmacopeia now provides a method for the biologic assay of tincture of digitalis, Digitol is merely a brand of tincture of digitalis. Compliance with the Food and Drugs Act of June 30, 1906, requires that a statement shall be made showing that Digitol differs from the official tincture in that the

so-called fat has been removed from the leaf before the tincture is made.

The Council announces at this time that any manufacturer who had introduced a so-called "fat-free" tincture of digitalis under any suitable name indicative of its character before the facts regarding the nauseant action of digitalis were published shall receive the same consideration from the Council with reference to the preparation that is now accorded to Digitol. On the other hand, the Council cannot admit that a manufacturer who has introduced a so-called "fat-free" tincture of digitalis after the true nature of this substance became known is entitled to similar consideration, and no such preparation can be admitted to N. N. R.

DIPHTHERIA ANTITOXIN CONCENTRATED AND GLYCERINATED VACCINE VIRUS (NATIONAL VACCINE AND ANTITOXIN INSTITUTE) OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council was informed that the license for the interstate sale of these preparations which is required by the federal law, "An act to regulate the sale of viruses, serums, toxins and analogous products in the District of Columbia, to regulate interstate traffic in said articles and for other purposes," had been cancelled by the U. S. Treasury Department on recommendation of the U. S. Public Health Service. The Council gives no recognition to a biologic product unless its interstate sale has been authorized by the federal authorities. For this reason, it directed the omission of the above named preparations from New and Nonofficial Remedies.

ETHYLENE DIAMINES 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.

The Council directed omission of the article Ethylene Amines and Derivatives and of the description of ethylene diamine, because the preparations of this type appear to have gone out of use. No brand of ethylene diamine stands accepted at the present time, and the two products referred to in the article have been omitted: Piperazine, because it was shown not to be of therapeutic value, and Argentamine, because it was off the market.

The Council directed that, as a matter of record, the article which appears in New and Nonofficial Remedies, 1921, be referred to the Council Reports:

ETHYLENE AMINES AND DERIVATIVES

Several derivatives of ethylene diamine or 1, 2-diamino ethane, $H_2N.CH_2.CH_2.NH_2$ are used in medicine.

A more complex product, diethylene diamine, piperazine, may be looked on as a condensation derivative of the first and may be obtained from it in small amount by direct heating of its hydrochloride. From this substance, a considerable number of derivatives have been obtained, several of which have been introduced into medicine.

The medical applications of these two drugs in medicine depend on their solvent action on tissues and certain products of metabolism. They both form solutions in water which are strongly alkaline without being very caustic or corrosive.

Ethylene diamine is a constituent of argentamin, a solution containing 10 per cent. of silver nitrate. The ethylene diamine is claimed to render the silver salt less irritant and more penetrating.

Ethylene Diamine Preparations

ETHYLENE DIAMINE. — Æthylendiamin. — Æthylene Diamine. — Ethane Diamine. — *a. b.* Diamino-Ethane. — $CH_2(NH_2).CH_2(NH_2)$.—1,2-diamino-ethane.

Actions and Uses.—Ethylene diamine is said to be non-corrosive and useful as an albumin solvent for the solution of false membranes in diphtheria and similar affections of the mucous membranes. It is presented for use in the form of kresamine (which see).

Ethylene diamine is prepared by heating 1,2-dibrom-ethane, ethylene bromide, with an excess of alcoholic ammonia, for twelve hours at 100 C., removing the ammonium bromide formed by infiltration, evaporating the filtrate to dryness, distilling the residue with potassium hydroxide, and collecting the fraction distilling between 115 and 130 C. and bringing the liquid by successive purifications to a constant boiling point at 117 C.

It is a clear, colorless, thick liquid, having a specific gravity of 0.87, boiling at 117 C., without decomposition, having a strong alkaline reaction, an ammoniacal odor and a caustic taste. It is freely soluble in water and may be mixed with cresols, but is not miscible with benzene (benzol) or ether. It dissolves albumin, even when boiled, very readily.

Since it is a strong base, its incompatibilities are about the same as those of sodium hydroxide.

FORMIC ACID OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The general article in New and Nonofficial Remedies on Formic Acid and Compounds makes it clear that there is no rational basis for the internal use of formic acid and its salts, the formates, and that the external use of formic acid as an irritant has no special advantage over the effects produced by other volatile acids.

The only formic acid compound now described in New and Nonofficial Remedies is formic acid itself. The term of acceptance having expired for the brand admitted to New and Nonofficial Remedies, the Council directed the omission of formic acid and accepted brand, because: (1) the external use of formic acid as an irritant has been generally abandoned, and (2) its inclusion for the purpose of providing standards is not necessary for the reason that these are provided by the inclusion of this drug in the National Formulary. As a matter of record, the general article on Formic Acid and Compounds and the description of formic acid which appear in New and Nonofficial Remedies, 1921, were referred to the Council Reports, and appear herewith:

FORMIC ACID AND COMPOUNDS

The actions of formic acid resemble those of acetic acid, but formic acid is more volatile, more irritant and more antiseptic. Formic acid and the formates are much more resistant to oxidation in the body than acetic acid and the acetates, and the formates are therefore excreted to a large extent as such in the urine. These have an irritant action on the kidneys and urinary tract, and are diuretic. Large doses cause methemoglobinemia, but the toxicity is rather low. Formic acid and the formates have no effect on the general circulation or on the motor system, as has been claimed. They have been lauded in a great variety of disorders, but there is no good evidence that their internal use produces any benefits other than psychic. The external use of formic acid as a counterirritant is rational, but it possesses no special advantage over other volatile acids.

FORMIC ACID.—Acidum Formicum.—A liquid containing from 24 to 26 per cent. of anhydrous formic acid (HCOOH).

Actions and Uses.—See preceding general article, Formic Acid and Compounds.

Dosage.—Internally, from 1 to 20 drops of the 25 per cent. acid, largely diluted; or from 0.1 to 0.25 Gm. (1½ to 4 grains) of sodium formate. Externally, usually in a solution containing 1 per cent. of the absolute acid in alcohol or diluted alcohol.

Formic acid is a clear, colorless liquid possessing a sharp acid odor and taste. It has a specific gravity of from 1.058 to 1.061.

With lead acetate, formic acid produces a white crystalline precipitate. On warming with silver nitrate a gray turbidity and with mercuric chloride a white turbidity is produced. A solution (1 : 10) after the addition of a few drops of nitric acid should yield no precipitate with silver nitrate or barium chloride; and after neutralizing, with ammonia water, calcium chloride or hydrogen sulphide, should produce no precipitate. If 1 Cc. formic acid is mixed with 5 Cc. water and 1.5 Gm. yellow mercuric oxide warmed on the water-bath with agitation until evolution of gas ceases, the mixture, when filtered, will yield a filtrate which should not react acid to litmus (acetic acid). If 5 to 6 Cc. formic acid be titrated with normal alkali, the alkali consumed should indicate the presence of not less than 24 nor more than 26 per cent. anhydrous formic acid. Each cubic centimeter of normal alkali is equivalent to 0.046 Gm. anhydrous formic acid (HCOOH). The titrated solution should yield no empyreumatic or sharp odor.

FRUTOSEN NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

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

The following statement of the composition of Frutosen was furnished the Council: "Senna pods 22,650 gm., benz. ac. 110 gm., sugar 22,650 gm., oils 40 c.c., glycerin 11,325 gm., water q. s. 63,250 c.c. No alcohol. . . . The ingredients are mixed with the fluid extract of the pods."

From this statement it would appear that Frutosen is a glycerin-water extract of senna pods, preserved with benzoic acid and flavored with essential oils.

Senna pods are said to have an action similar to that of senna (leaves) but to be less potent. The drug is not recognized in the U. S. Pharmacopeia, is not described in the National Formulary, nor has it been deemed worthy of description in New and Nonofficial Remedies; hence no standards for the control of the drugs are provided and the uniformity of its strength or the strength of preparations made from it may be questioned.

Frutosen is inadmissible to New and Nonofficial Remedies because: (1) It is made from a drug which is not standardized in the U. S. Pharmacopeia, National Formulary or New and Nonofficial Remedies; hence the composition of Frutosen must be considered indefinite (Rule 1). (2) According to the label, Frutosen is "a natural vegetable laxative for the relief of constipation." This constitutes an indirect advertisement to the public (Rule 4). (3) The name is not descriptive of the pharmaceutic preparation that it designates, that is, it does not declare that Frutosen is a preparation of senna pods (Rule 8).

HEXALET 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.

Hexamethylenamin sulphosalicylate—a salt of hexamethylenamin and sulphosalicylic acid—was introduced as Hexal by J. D. Riedel, Aktiengesellschaft, Berlin, Germany. In the United States the name was changed to Hexalet on account of trademark complications. It is marketed here by Riedel & Co., Brooklyn.

It is claimed that Hexalet is dissociated into its constituents in the body, and therefore acts as a urinary antiseptic. It is also claimed that it has an astringent action on the urinary passages; thus the following statement was admitted to New and Nonofficial Remedies: "But little is known about the effects of sulphosalicylic acid; but as the free acid precipitates proteins, it is claimed that it produces an astringent action on the urinary passages, and would thus be of value in inflammatory conditions of the bladder and urethra."

To check the validity of the claimed astringency, for which no evidence had been presented by the manufacturer or the agent, P. J. Hanzlik, then associate professor of pharmacology at Western Reserve University School of Medicine, now professor of pharmacology at Leland Stanford Junior University School of Medicine, was asked to investigate the possibility of astringent effects being produced by Hexalet under the condition which exists in the urinary tract.

The problem was relatively simple, for the claims of astringency are based on the assumption of protein precipitation by the sulphosalicylic acid component of Hexalet. The report of Dr. Hanzlik, which follows, shows conclusively that Hexalet is not astringent, that its therapeutic properties are solely those of its hexamethylenamin component and that it is in fact distinctly inferior to hexamethylenamin itself.

This investigation makes it clear that Hexalet is in conflict with the rules that govern the inclusion of articles in New and Nonofficial Remedies, (1) in that the therapeutic claims that are made for it are erroneous and (2) in that it is an unimportant and undesirable modification of an established article, namely, hexamethylenamin. Accordingly, the Council voted to omit Hexalet from New and Nonofficial Remedies after submission of this decision and of Dr. Hanzlik's report to the interested parties.

The Council's findings were sent to Riedel & Co., Brooklyn, in November, 1920. The firm requested delay so that the report might be considered by the owners. After more than six months, no reply had been received; hence the Council directed omission of Hexalet from New and Nonofficial Remedies and authorized publication of this report.

Referee's Report

The object of the experiments reported herewith was to test the claims of the manufacturer that Hexalet[1] acts as an astringent on the urinary passages.

The composition of Hexalet is said to be hexamethylenamin sulfosalicylic acid. It is a dry, white crystalline product, possessing a strong acid taste, and it is freely soluble in water. The addition of phloroglucin in alkali to a 1 per cent. solution of Hexalet gives a red color, indicating the presence of free formaldehyde. This, of course, is due to the acidity of the solution, which decomposes the hexamethylenamin component of Hexalet. This means that Hexalet is not absorbed entirely as such; that is, the quantity of hexamethylenamin available for absorption is less than that indicated by its content in Hexalet, while the quantity of absorbable sulfosalicylate remains the same. Ferric salts give the characteristic pink to violet color of the salicyl radical with Hexalet, owing to the sulfosalicylic acid component.

METHODS OF PROCEDURE

It is alleged that the astringent qualities of Hexalet are due to its sulfosalicylic acid component. This would depend on the well known qualities of sulfosalicylic acid to precipitate protein; and for this the liberation of free acid, that is, free sulfosalicylic acid, is necessary. Therefore, experiments were made to detect the presence of free sulfosalicylic acid in urine after the administration of Hexalet by mouth and to observe the protein precipitating power of the urine in cases in which Hexalet had been administered. Observations were also made to determine the power of mixtures of Hexalet and "buffer" solutions of different degrees of acidity (i. e., hydrogen ion concentrations) to precipitate protein. This would give some idea of the degree of acidity in urine necessary to produce protein precipitation and, therefore, would indicate whether astringent action is possible in the bladder. The various technics that were used will be described in the following sections.

1. The sample used in this test was labeled Hexal, of German manufacture. Hexal is the name used abroad.

PROTEIN PRECIPITATING POWER OF HEXALET BUFFER MIXTURES OF DIFFERENT DEGREES OF ACIDITY

This was tested by observing the precipitation of 0.5 per cent. egg albumin in water by mixtures of equal parts of 1 per cent. Hexalet and buffer solutons representing different hydrogen ion concentrations, ranging from $p_H = 2.02$ to $p_H = 8.4$. To 1 Cc. of the filtered egg albumin solution in a small test tube was added 1 Cc. of the Hexalet-buffer mixture, so that the final concentration of egg albumin was 0.5 per cent., and that of Hexalet, 0.25 per cent. This concentration of egg albumin gave a strong white precipitate with 0.25 per cent. sulfosalicylic acid and also with 0.25 per cent. Hexalet. Strongly acid "buffer" mixtures, i. e., p_H values of 2.02, 3.01, 4.49 and 5.2, also precipitated the egg albumin solution, not those of p_H values of 5.9 and higher. That is, weakly acid ($p_H = 5.9$ to 6.9) and alkaline "buffers" (p_H 7.1 up to 8.4) did not precipitate egg albumin. Accordingly, this method could only be of value in fulfilling its object if Hexalet should precipitate egg albumin in "buffer" solutions of lower acidity than $p_H = 4.49$ to 5.2. This was actually found to be the case as indicated by the results in Table 1.

The results reported in Table 1 show that Hexalet can precipitate protein in degrees of acidity lower than the highest degree of acidity that has been observed in urine. In other words, astringent qualities from Hexalet might be expected in the bladder, provided the excretion of Hexalet in the urine and the acidity of the urine are high enough. An idea of the excretion would require quantitative estimation of Hexalet, or at least sulfosalicylic acid, in urine. In the absence of suitable methods for this, it will suffice for the purposes of this report to give evidence as to the excretion of free sulfosalicylic acid in the urine, for if sulfosalicylic acid is absent, the claims for the astringent action of Hexalet in urine lose considerable support.

INGESTION EXPERIMENTS

Excretion of Free Sulfosalicylic Acid in Urine.—Hexal was administered to two subjects, and the urine was collected at the end of one hour, two hours and four hours. Since free sulfosalicylic acid is rather readily soluble in ether, 15 Cc. of each of the urinary samples was taken with 10 Cc. of ether, and the ethereal extracts were tested with ferric

alum for the presence of salicyl. A positive salicyl test would indicate the presence of free sulfosalicylic acid in the urine. The results obtained are presented in the accompanying protocols. Unfortunately, the true acidity (hydrogen ion concentration) of the urines, which were acid to litmus, was not ascertained. However, in the absence of salicyl in the ethereal extracts of all the urines, it is concluded that the acidity of these was not sufficient to liberate free sulfosalicylic acid from the sulfosalicylate in the urine. After acidifying and shaking with ether, the ethereal extracts of all urines gave positive salicyl tests, showing conclusively that sulfosalicylic acid was excreted in combined form. Such urines would hardly be expected to exhibit astringent action from the precipitation of protein. Nevertheless, tests were made in this direction; and the results, which are entirely negative, are presented in the next section.

Protein Precipitating Power of Urines after Administration of Hexalet.—The filtered urines from the two subjects who took Hexalet, as indicated in the accompanying protocols, were added directly to 1 per cent. egg albumin solution and precipitation was looked for. However, all of the samples were negative in this respect, exhibiting not even the slightest cloudiness. On the other hand, the addition of a little free sulfosalicylic acid to the urine at once caused precipitation of the egg albumin. This, of course, agrees with the results and conclusions of the previous section, namely, that in the absence of free sulfosalicylic acid, precipitation of protein cannot occur and astringent action on the urinary passages need not be expected. The absence of free sulfosalicylic acid, as shown by ether extraction, and the consequent failure to form precipitates with the urine could not be ascribed to the removal of the sulfosalicylic acid by the proteins of the urinary passages; for the experiments show that there is abundant combined sulfosalicylate from which the free acid would be regenerated were the conditions in the urine favorable to the liberation of sulfosalicylic acid. The essential criterion for this is a high degree of acidity (at least $p_H =$ 6.4 to 5.6), which was not attained in these urines.

PROTOCOLS

SUBJECT E. took 2 gm. of Hexalet by mouth. The urine was collected at the end of one hour, two hours and five hours after administration Tests were applied for the presence of hexamethylenamin (bromine water), free formaldehyde (phloroglucin test), salicyl (ferric alum) and free sulfosalicylic acid (shaking urine direct with ether and applying ferric alum to residue from ethereal extract). Reaction to litmus and albumin precipitating power of the urine were also noted.

TABLE 1.—PRECIPITATION OF EGG ALBUMIN MIXTURES OF HEXALET AND BUFFER SOLUTIONS *

p_H of Hexalet-Buffer Mixture	Final p_H of Hexalet-Buffer-Albumin Mixture	Precipitation of Albumin †
8.2	7.2	—
7.2	7.0	—
7.0	6.6	—
6.6	6.4	+ faint trace; almost doubtful
6.23	5.6	+ small precipitate
5.9	4.5 (approx.)	+
5.2	...	+ strong precipitate
5.9 buffer alone		—
5.2 buffer alone		+
0.25 per cent., Hexalet alone		+ strong precipitate
0.25 per cent., sulfosalicylic acid alone		+ strong precipitate

* The final concentration of egg albumin was 0.25 per cent. and that of Hexalet 0.25 per cent.

* The following indicators were used: Methyl red for p_H = 4.4 to 6.0, rosolic acid for p_H = 6.0 to 6.4 and phenolsulphonephthalein for p_H = 6.4 to 8.4.

† In this column, the minus sign indicates negative and plus sign positive.

TABLE 2.—RESULTS *

Specimen of Urine	Reaction to Litmus	Hexamethylenamine†	Free Formaldehyde†	Free Sulphosalicylic Acid (Direct ether extraction)†	Salicylates with HCl Testing with Ether Therefore Combined Salicyl†	Power to Precipitate Egg Albumin‡	Remarks
1-1 hr.	Acid	+	+	—	+	None	
2-2 hr.	Alkaline	+	—	—	+	None	Urine cloudy
3-3 hr.	Acid	+	+ st.	—	+	None	

* Control: Sulfosalicylic acid added to urine precipitated the egg albumin solution.

† In these columns, the plus sign indicates present and the minus sign absent.

‡ Urine stood one day before examination.

SUBJECT I. took 2 Gm. of Hexalet by mouth. Urine was collected at the end of one hour, two hours and four hours. The same tests were applied as on Subject E.

TABLE 3.—RESULTS *

Specimen of Urine	Reaction to Litmus	Hexamethylenamine†	Free Formaldehyde	Free Sulphosalicylic Acid†	Salicyl After Acidifying with HCl and Extraction with Ether†	Power to Precipitate Egg Albumin
1-1 hr.	Acid	+	+ trace	—	+	None
2-2 hr.	Acid, slight	+	+ slight	—	+	None
3-5 hr.	Acid	+	+ slight	—	+	None

* Urine was examined immediately after collection.

† In these columns, the plus sign indicates present and the minus sign absent.

CONCLUSIONS

1. Hexalet dissolves readily in water, with a strong acid reaction and liberation of free formaldehyde.

2. Accordingly, Hexalet is not entirely absorbed as such. Much less hexamethylenamin is excreted than is indicated by its content in Hexalet, while the sulfosalicylic portion is probably excreted unchanged.

3. Mixtures of Hexalet with buffer solutions of different degrees of acidity (H-ion concentration) require an acidity of $p_H = 5.6$ to $p_H = 6.4$ to precipitate protein (egg albumin).

4. Hence, precipitation of protein, resulting in astringent action on the urinary passages, might be expected in urines containing Hexalet and possessing a fairly high degree of acidity though somewhat less than the highest acidity that has been encountered ($p_H = 4.5$).

5. However, after the administration of 2 gm. of Hexalet each, to two different subjects, the urines did not precipitate egg albumin and did not contain any demonstrable free sulfosalicylic acid, although they were acid to litmus and contained free formaldehyde and combined salicylate.

6. Apparently, therefore, the sulfosalicylic acid portion of Hexalet is excreted as a salt (sodium, etc.) and the acidity of these urines was not high enough to liberate the free sulfosalicylic acid which is necessary for the precipitation of protein.

7. The claims for the astringent action of Hexalet on the urinary passages made by the manufacturers are not supported by the results of this investigation. Hexalet is not only probably entirely worthless as an astringent, but also less efficient than hexamethylenamin in corresponding doses as an antiseptic for the urinary passages.

P. J. HANZLIK, M.D.

HISTAMINE HYDROCHLORIDE, SILK PEPTONE, SULPHANILIC ACID, UREASE, AGGLUTINATING SERUMS FOR THE IDENTIFICATION OF BACTERIA, WIDAL'S TEST FOR TYPHOID FEVER AND COMPLEMENT FIXATION REACTION FOR SYPHILIS NOT DESCRIBED IN N. N. R.

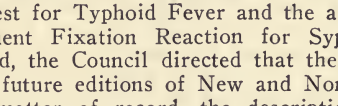
Report of the Council on Pharmacy and Chemistry

The Council has decided that those reagents used outside the body which are now in New and Nonofficial Remedies be omitted when their period of acceptance expires.

The three-year term of acceptance having expired for Histamine Hydrochloride, for Silk Peptone and the accepted brand, for Sulphanilic Acid and the accepted brand, for Urease and the accepted brands, for Agglutinating Serums for the Identification of Bacteria and the accepted brands, for Widal's test for Typhoid Fever and the accepted brands and Complement Fixation Reaction for Syphilis and the accepted brand, the Council directed that these products be omitted from future editions of New and Nonofficial Remedies. As a matter of record, the descriptions have been referred to the Council Reports and appear below.

W. A. PUCKNER, Secretary.

HISTAMINE HYDROCHLORIDE.—



The hydrochloride of the base beta-iminazolylethylamine (histamine). Histamine is closely related to histidine, from which it differs in that one molecule of carbon dioxide has been eliminated.

Actions and Uses.—Histamine hydrochloride has a powerful contractile action on certain muscular fibers and a strong vasoconstrictor action. The available evidence does not warrant a recommendation for its therapeutic use, but it is a valuable reagent for the standardization of pituitary and similar preparations.

Histamine was first prepared synthetically from iminazolylpropionic acid by Windaus and Vogt in 1907 (*Berl. d. deutsch. chem. Gesellsch.*, **40**: 3691, 1907); it was then prepared by bacterial putrefaction of histidine in 1910 by Ackermann (*Ztschr. physiol. Chem.*, **10**: 504, 1910) and isolated from ergot in 1910 simultaneously by Kutscher (*Zentralbl. f. Physiol.* **24**: 163) and Barger and Dale (*Pharm. J.* June 4, 1910, p. 710; June 18, 1911, p. 757).

Histamine hydrochloride melts at 240 C. (Corr.).

When picric acid is added to an aqueous 1 per cent. solution of histamine hydrochloride, histamine picrate is precipitated promptly; the precipitate should melt at 234 C. (Corr.). Any impurity present in the histamine hydrochloride will prevent or at least very much retard, the precipitation of this picrate.

If a 1: 1,000 solution of histamine hydrochloride is made alkaline with sodium hydroxide and a solution of diazobenzosulphonic acid (Pauly's reagent) made alkaline with sodium hydroxide be added, a cherry red color appears.

If a 1: 1,000 solution of histamine hydrochloride is mixed with an excess of bromine water, then boiled until the bromine is evaporated and sodium hydroxide added to the solution, a black discoloration occurs.

SILK PEPTONE.—Peptonum Sericum.—A preparation of peptone derived from silk and standardized to a nearly uniform optical rotary power.

Actions, Uses and Dosage.—Silk peptone is not employed therapeutically. It is used for the detection of peptolytic ferments either by changes in optical activity or by the precipitation of tyrosin. It is also valuable as an addition to culture mediums for the differentiation of bacteria.

For use, silk peptone is dissolved in water, or in testing stomach conditions it may be dissolved in the filtered contents. The solutions must be clear and entirely neutral; if acid, they must be neutralized with sodium bicarbonate or magnesium oxide. If it is desired to keep a solution for some time, it should be covered with a layer of toluene.

1. *To Test for Peptolytic Ferments in the Tissues.*—A small piece of the organ to be examined is introduced into a solution of silk peptone (25 per cent.), covered with a little toluene, and placed in the incubator. After a short time, if peptolytic ferments are present, a more or less abundant separation of tyrosin crystals takes place. In a similar way, liquids may be tested for peptolytic ferments by mixing the clear filtrates with the silk peptone solution.

2. *To Examine Stomach Contents for Peptolytic Ferments.*—Five Cc. of the stomach contents should be neutralized with magnesium oxide and filtered. To the filtrate 0.2 Gm. of silk peptone is added. The mixture is incubated and examined at intervals of thirty minutes for a possible separation of crystals (tyrosin). If this occurs, the presence of peptolytic ferments may be assumed; to confirm this assumption, a test for tyrosin should be aplied.

3. *The Optical Method.*—The material to be examined should receive the proper preliminary treatment, mixed with a solution of silk peptone and placed in a polarimeter tube, covered with some toluene, and the optical rotation immediately determined. This is repeated at intervals of several hours for about two days, the mixture being placed meanwhile in the incubator. If a change in optical rotation occurs, while the control solution retains the original degree of rotation, the presence of peptolytic ferments may be assumed.

Silk peptone is prepared from silk waste as follows: The material is dried at 100 C. for forty-eight hours and then treated with from 3 to 5 times its weight of 70 per cent. sulphuric acid and allowed to stand for four days. It is then diluted with ten times its volume of water cooled by ice. The sulphuric acid is neutralized with barium hydroxide and filtered through charcoal. The residue on the filter is repeatedly stirred with warm water (25 C.) and decanted, or it may be washed thoroughly with boiling water. The filtrates are concentrated at a temperature not above 40 C. The thick liquid, which must be free from barium and sulphuric acid, is poured with constant stirring into absolute alcohol, which precipitates the silk peptone. Care must be taken that the alcohol is renewed at intervals so as to maintain the proper strength for precipitation. The yield with careful technic amounts to from 20 to 30 per cent. of the product used.

Silk peptone is a white or yellowish powder, easily soluble in water, but not hygroscopic. The aqueous solution has a slight acid or amphoteric reaction. Its concentrated solutions are practically colorless and thus adapted for use in optical methods. It also possesses a high content of tyrosin.

Seiden Peptone-Roche (Silk Peptone).—A nonproprietary brand complying with the standards for silk peptone.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York).

SULPHANILIC ACID.—Acidum Sulphanilicum.—$1:4 = C_6H_4(NH_2)(HSO_3)+2H_2O$. — Para-amino-benzene-sulphonic acid.

Uses and Dosage.—The most important use of sulphanilic acid is in Ehrlich's diazo-reaction for typhoid urines.

Twenty-five Gm. of colorless aniline are gradually added to 75 Gm. of concentrated sulphuric acid in a 250-Cc. flask and the mixture warmed to from 180 to 190 Cc., under agitation, for about three hours, or until a drop of the mixture dropped into a solution of potassium hydroxide no longer gives indication of the presence of aniline. At the end of the reaction, the mixture is poured into 500 Cc. of cold water which precipitates the sulphanilic acid as a grayish crystalline powder; it is treated with animal charcoal and recrystallized from hot water (Hager I, p. 116).

Sulphanilic acid occurs as colorless crystals, slightly soluble in water, and insoluble in alcohol and ether. It is decomposed at from 280 to 300 C. It effloresces in air. It is soluble in 182 parts of water at 0 C., and in 166 parts of water at 10 C. It is not altered by boiling alkali, but fusion with alkali decomposes it, yielding aniline. Chromic acid mixtures oxidize it to chinon. Permanganate oxidizes it to azo-benzene-sulphonic acid and an excess of this reagent to carbon dioxide, sulphuric acid, ammonia and oxalic acid.

The cold saturated solution is not altered by hydrogen sulphide or barium chloride, but boiling with alkali should not produce a visible change. One Gm. of the powdered acid treated with 3 Cc. of stannous chloric solution should not be darkened. It should leave no residue on ignition.

Sulphanilic Acid-Merck.—A nonproprietary brand complying with the standards for sulphanilic acid.

Merck & Co., New York, distributors.

UREASE.—Urease is a urealytic enzyme found in certain beans, fungi and micro-organisms.

Actions and Uses.—In the presence of water, urease converts urea into ammonium carbonate, thus: $(NH_2)_2CO + 2H_2O = (NH_4)_2CO_3$. It is employed in the determination of the amount of urea in the urine, blood and other body fluids.

Dosage.—For the estimation of urea in the urine, two methods are used, with various modifications: 1. A measured amount of urine is treated with urease, and after a specified time the ammonia produced is drawn into volumetric acid by means of an air current, and the residual acid determined by titration ("Absolute Method," D. D. Van Slyke. *J. Biol. Chem.* **16**:125, 1913-1914). 2. The alkalinity of a portion of urine, treated with urease, is determined with volumetric hydrochloric acid (methyl orange being used as an indicator). This figure is corrected for the acidity or alkalinity of an equal volume of the same urine, determined with the same reagents. The corrected figure represents the ammonium carbonate formed by the conversion of the urea present (Marshall: *J. Biol. Chem.* **14**:283, 1913).

The amount of urea in blood is determined by treating as in Method 1, the blood having been mixed as soon as drawn with potassium citrate, to prevent clotting.

Arlco-Urease.—A standardized preparation of the urealytic enzyme obtained from the jack bean, *Canavalia ensiformis.*

Actions, Uses and Dosage.—See preceding general article, Urease.

Manufactured by the Arlington Chemical Co., Yonkers, N. Y. No U. S. patent. U. S. trademark applied for.

In the preparation of arlco-urease, jack bean meal is treated with water and the aqueous extract filtered. The solution so obtained is precipitated by pouring into acetone, the precipitate washed and dried by desiccation over dehydrants. The dried precipitate is finely ground and standardized by methods reported by Van Slyke and Cullen. (*Proc. Soc. Exper. Biol. and Med.,* Dec. 17, 1913.)

Arlco-urease is a fine, white powder, freely soluble in water, forming an opalescent solution.

If 0.1 Gm. of arlco-urease is dissolved in 1 Cc. of water and the solution added to 5 Cc. of a 1 per cent. solution of pure urea, the mixture should hydrolyze 0.0168 Gm. of urea in fifteen minutes at 25 C. or in correspondingly less time as the temperature approaches 50 C. as a maximum.

Urease-Dunning-H. W. & D.—A standardized preparation of the urealytic enzymes obtained from the jack bean.

Actions, Uses and Dosage.—See preceding general article, Urease. Urease-Dunning is supplied in the form of tablets only (see below).

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

Urease-Dunning Tablets-H., W. & D.—Each tablet contains 0.025 Gm. of urease-Dunning.

Urease-Dunning is a fine, almost white powder with little taste or odor; it is soluble in slightly alkaline water. It is practically free of the water-soluble proteins, which are precipitated by hydrochloric acid, and of proteins that are insoluble in water. Aqueous solutions deteriorate after standing a few days.

Urease-Dunning may be assayed as follows: To 5 Cc. of a 2 per cent. solution of urea, in water previously heated to from 38 to 40 C. add 25 Mg. of urease-Dunning (one tablet), and keep the mixture at the temperature stated for one hour; then add 0.05 Cc. of methyl orange test solution, and titrate with tenth-normal hydrochloric acid. From 20 to 25 Cc. should be required to neutralize it, equivalent to from 60 to 75 Mg. of urea.

Urease-Squibb.—Jack bean urease.—A standardized preparation of the urealytic enzyme obtained from the jack bean, *Canavalia ensiformis.*

Actions, Uses and Dosage.—See preceding general article, Urease. Urease-Squibb is supplied in the form of powder and tablets.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Urease-Squibb Tablets, 0.1 Gm.—Each tablets contains 0.1 Gm. of urease-Squibb.

An aqueous extract of the jack bean is filtered, the clear filtrate reduced to dryness, the dry powder extracted with absolute alcohol, acetone and ether, dried, and the dry powder mixed with monopotassium sulphate and dipotassium phosphate in proportion to produce the maximum hydrolytic action and stability of the enzyme.

It is a fine, white, practically odorless and tasteless powder, which dissolves readily in cold water, forming an almost clear solution.

If 0.1 Gm. of urease-Squibb in 1 Cc. of water be added to 5 Cc. of phosphate-urea mixture (according to the "absolute method") and digested at 20 C. for fifteen minutes, it will decompose sufficient urea to liberate from 100 to 150 Cc. of fiftieth-normal ammonia by aeration.

AGGLUTINATING SERUMS FOR THE IDENTIFICATION OF BACTERIA.—These serums are prepared by immunizing an animal with a proved strain of the specific organism until the serum yields a high content of specific agglutinins (see under Serums). The animal is then bled, the serum collected, and sometimes dried for better preservation.

For use of dried serum, a weighed portion of the powder is dissolved and the solution added to a suspension of a pure culture of the organism in question in physiologic sodium chloride solution so as to make a dilution of the known strength. After from one to twenty-four hours' incubation, clumping of the organism, which may be observed by the naked eye or under the microscope, is evidence that it is the same as the one used for the preparation of the serum.

Usually a series of tubes is prepared containing different dilutions of the serum, and the highest dilution which shows definite clumping is taken as the agglutinating titer of the serum with respect to the organism in question. Control tubes, containing only the saline suspension or saline suspension with normal horse serum, should be used to ensure that the organisms do not clump spontaneously. Other tubes, containing the serum in its given agglutinating titer and a suspension of an undoubted strain of the organism from which the serum was made, should be used to ensure the potency of the serum under the conditions of the experiment. Correct interpretation of agglutination phenomena requires considerable bacteriologic training.

H. K. Mulford Company, Philadelphia.

Cholera Agglutinating Serum.—The dried blood serum of horses which has been injected with killed cultures of the cholera vibrio. It is intended for the diagnosis of cholera by the agglutination of suspected cholera vibriones.

For use the serum is dissolved in salt solution so as to make a definite dilution, commonly 1: 100. A drop of this is mixed with the suspected culture and the mixture is observed under the microscope for evidences of agglutination.

Agglutinating Serum for the Identification of Bacillus Paratyphosus A.—Marketed in sealed ampules each containing 1 Gm. of the dried serum having the agglutinating titer 1: 20,000. Intended for use by the macroscopic method, the reading being taken after twenty-four hours.

Agglutinating Serum for the Identification of Bacillus Paratyphosus B.—Marketed in sealed ampules each containing 1 Gm. of the dried serum having the agglutinating titer 1: 50,000. Intended for use by the macroscopic method, the reading being taken after twenty-four hours.

Agglutinating Serum for the Identification of Bacillus Typhosus.—Marketed in sealed ampules each containing 1 Gm. of the dried serum having the agglutinating titer 1: 24,000. Intended for use by the macroscopic method, the reading being taken after twenty-four hours.

WIDAL'S TEST FOR TYPHOID FEVER.—This most important test depends, also, on agglutination; but the problem is reversed. The serum is unknown and the bacteria are known typhoid bacilli. The following two modifications allow the use of killed bacilli, so as to make it practically a bedside test in lieu of more exact laboratory determinations.

Bass Modification of the Widal Test.—The agglutination is observed on a glass slide with the naked eye.

H. K. Mulford Company, Philadelphia.

Bass Test for Typhoid Fever.—The outfit consists of the following items: (*a*) suspension or emulsion of killed typhoid bacilla, each cubic centimeter containing approximately 10 billion killed bacilli: (*b*) glass slide on which to mix the emulsion with suspected blood; (*c*) slide with dried smear of infected blood, this slide is to be afterward used for mixing the emulsion and suspected blood on Slide B; (*d*) needle for pricking ear or finger to obtain suspected blood from the patient; (*e*) pipet for dropping typhoid emulsion and water on slide, previous to mixing with suspected blood.

Borden's Modification of the Widal Test.—In this test the serum of the blood is mixed with salt solution and then with a suspension of killed typhoid bacilli, so as to bring the dilution up to 1 to 50. The positive reaction is determined by noting that the clumps of bacilli sink to the bottom of the test tube and leave a limpid, clear fluid above a small, white flocculent mass of agglutinated bacilli.

H. K. Mulford Company, Philadelphia.

Mulford's Widal Test Outfit (Widal Reaction for Serodiagnosis of Typhoid Fever).—The outfit consists of the following items, all packed in a box containing fixed test tube rack: (*a*) 30 cubic centimeter stock bottle of suspension or emulsion of killed typhoid bacilli; (*b*) 30 cubic centimeter stock bottle of physiological solution of sodium chloride, containing 1 per cent. of phenol; (*c*) 10 cubic centimeter dropping flask for salt solution; (*d*) 10 cubic centimeter dropping flask for typhoid suspension; (*e*) six graduated test tubes; (*f*) one graduated pipet; (*g*) twelve small capillary bulbs or tubes to collect blood serum and (*h*) one needle.

COMPLEMENT FIXATION REACTION FOR SYPHILIS.—This test depends on the presence in the blood serum of syphilitics of some immunity product, which, in the presence of an "antigen," combines with the "complement" which is present in all fresh blood, so that the "complement" is not available for a further immunity reaction.

This further immunity reaction, which is used to test the absence of uncombined or "unfixed" complement in the mixture with syphilitic blood or its presence in case the mixture has been made with nonsyphilitic blood, is the hemolytic reaction, which is performed as follows:

If an animal, such as a rabbit, be immunized by injection of human red blood cells, its serum will contain an "amboceptor" which, in the presence of "complement," will dissolve human blood cells in a test tube. This is called an antihuman hemolytic system. If sheep cells were used for immunization we should have an antisheep hemolytic system. The original Wassermann reaction for syphilis (a modification of the Bordet-Gengou complement fixation technic) used an antisheep hemolytic system and fetal syphilitic liver extract as antigen. The Noguchi modification uses an antihuman hemolytic system, and a lipoid extract from the heart muscle, not necessarily syphilitic. Fresh guinea-pig serum is used as complement in both cases, and tests are necessary to determine the units of complement and of amboceptor necessary barely to cause the hemolysis of a definite amount of suspension of washed blood corpuscles. Further tests of the antigen must be made to show that it will not inhibit hemolysis in itself, but will do so in the presence of known syphilitic serum. The test proper is made by incubating complement, antigen, and a fixed amount of the suspected serum for one hour; then the amboceptor and the washed corpuscles of the hemolytic system are added, and the whole is incubated again. A positive test will be indicated by absence of

hemolysis, the red corpuscles having settled to the bottom and the fluid being colorless above them. Proper controls must be set up.

It is thus seen that the reaction is a complicated one, being really a series of reactions between at least five substances, successive bodies being introduced to test for the presence or absence of others. Evidently even more skill in technic and in interpretation is required than with agglutination reactions.

Noguchi Modification of the Wassermann Test.—The Noguchi test for syphilis is a modification and simplification of the Wassermann test and involves the use of antihuman amboceptor, a solution of "antigen" and "complement," the latter to be obtained from the blood of a guinea-pig.

Amboceptor.—This is obtained by injecting washed human blood corpuscles (erythrocytes) into rabbits, at intervals of from five to seven days, over a period of five or six weeks. Ten days are allowed to elapse before the last injection. The rabbits are then bled and the serum collected. Filter paper is now saturated with this serum and allowed to dry. The paper is cut in strips and set aside until wanted for use. In this form, amboceptor will keep for a considerable length of time.

Amboceptor paper is standardized by measuring its specific activity. The measurement of specific activity consists in finding the amount of amboceptor necessary to cause hemolysis in 1 Cc. of suspended human red corpuscles, one drop of blood in 4 Cc. of physiological solution of sodium chloride with 0.02 Cc. of fresh guinea-pig serum. This is incubated at a temperature of 37 C. for one hour. The quantity of paper necessary to cause hemolysis under these conditions is known as one unit. In the syphilis test two units are used.

Antigen.—This is made by rubbing liver or heart tissue with sand and extracting with absolute alcohol. Macerate 10 Gm. of tissue in 100 Cc. of alcohol for one week at 37 C., shaking the container every day. Filter until clear. Evaporate the filtrate. Dissolve the resulting extract in ether. Pour this solution into a large quantity of acetone. The acetone precipitates certain lipoid substances which are then collected and redissolved in methyl alcohol, in ratio of 3 per cent. This constitutes the antigen solution. For use mix 1 part of this with 9 parts, 0.9 per cent. sodium chloride solution. This dilution should not cause hemolysis in an amount of 0.4 Cc., and 0.4 Cc. should not inhibit hemolysis.

H. K. Mulford Company, Philadelphia.

Serodiagnosis of Syphilis (Noguchi System).—The test consists of amboceptor paper and antigen in a package, accompanied with full directions for use.

KAL-PHENO TOOTH PASTE AND KAL-PHENO TOOTH POWDER

Report of the Council on Pharmacy and Chemistry

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

Kal-Pheno Tooth Paste and Kal-Pheno Tooth Powder were considered at the request of the Kal-Pheno Chemical Co. and because, in addition to the claims ordinarily advanced for dentifrices, they were claimed to possess medicinal qualities.

The following incomplete statement of composition appears in an advertising booklet:

Kal-Pheno Paste contains 37% Chlorate of Potash, and the Powder contains 22%.

FORMULA

Chlorate of Potash 37%, phenolated 1/10 of 1%.
Mentholated Magnesium Carbonate.
Calcium Carbonate, Benzoinated.
Oil of Eucalyptus.
Oil of Gaultheria.
Oleum Myrtii.
Hydronaphthol and
Our wonderful anti-fermentative element,
MENTHO-FORMO-THYMOLATE.

The label on the tube of the paste sent to the Council bore the declaration that the product contained 37 per cent. of potassium chlorate, which agrees with the foregoing. The carton in which this tube was enclosed, however, declared the paste to contain 40 per cent. In addition to the information quoted above from the booklet, the label of the tooth powder states that the amount of "mentholated carbonate of magnesia" is 14 per cent.

In the information sent the Council, it is declared that the vehicle used to prepare the paste is glycerin. Here, it is also asserted that Mentho-Formo-Thymolate is a powder "derived from the use of Menthol-Thymol with 1/10 of 1% Formaldehyde reduced by addition of alcohol," none of which, it is said elsewhere, remains in the finished product, "which under heat with use of a rapidly revolving machine is reduced to a solid white substance from which the essential ingredient of each material has been changed, and when ground, results in a new compound on which we have been granted letters patented by U. S. government for a new composition of matter. This powder is present in Kal-Pheno to the extent of less than 1/50 of 1%. . . ." No information was furnished the Council in regard to the composition of Mentho-Formo-Thymolate. In the United States

Patent 1107389 which appears to have been issued for this dentifrice, it is stated that the "reaction product of menthol and thymol with formalin or formaldehyde, which may be and is preferably produced in a porcelain pulverizing machine by uniting crystal methol (substantially 70%), formalin (substantially ½ of 1%) and thymol (substantially 29½%)." The ingredients are mixed and manipulated; and in the end, a powder is obtained, but, so the patent states, it is not known "to what extent and in what manner these various ingredients . . . unite or combine."

The patentee states, in the patent for this dentifrice, "I prefer to use about three parts by weight of the magnesium carbonate to one part of the reaction product of menthol and thymol with formalin or formaldehyde." As the Kal-Pheno Chemical Co. declares that its product contains less than one-fiftieth of 1 per cent. of this reaction product, the dentifrice should contain but three-fiftieths of 1 per cent. of magnesium carbonate and not 14 per cent., as declared on the tooth powder label. Evidently, also, this patent is typical of that long list of patents which several years ago caused the Council to protest against their issuance on unproved and improbable claims (Need of Patent Law Revision, J. A. M. A. **70**:115 [Jan. 12] 1918).

It is claimed that Kal-Pheno is "not merely an antiseptic but a potent germicide" which "destroys and prevents the development of harmful bacteria." The short time during which dentifrices can act efficiently, no matter how potent their germicidal constituents and the apparent composition of the powder, makes this claim highly improbable. No evidence in substantiation of it was submitted to the Council. Equally improbable and unsupported by evidence are the claims that this product will "cure" inflammations and ulcerations or that it is of value for the "treatment of abscesses and Pyorrhea."

Aside from the presence of "our wonderful antifermentative element, Mentho-Formo-Thymolate," the potassium chlorate content of Kal-Pheno is the chief "talking point" of the manufacturer. It is claimed that potassium chlorate, by virtue of being "phenolated," is acted on by the acid secretion of the mouth with consequent neutralization of this acidity. However, a concentration of acid, such as may occur in the mouth, is devoid, for all practical purposes, of any decomposing action on potassium chlorate. In addition, the magnesium carbonate and calcium carbonate in the preparation would tend to neutralize such acidity. Thus it would appear that, for the purpose for which it is present, potassium chlorate is a superfluous ingredient of Kal-Pheno, except as a talking point.

The Council finds Kal-Pheno Tooth Paste and Kal-Pheno Tooth Powder inadmissible to New and Nonofficial Remedies, because their composition is indefinite and semisecret, because unwarranted therapeutic claims are made for them and because they are needlessly complex and unscientific preparations.

SOME OF LOESER'S INTRAVENOUS SOLUTIONS

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., April 16, 1921, p. 1120

The Council has authorized the publication of the following report on "Loeser's Intravenous Solution of Hexamethylenamin," "Loeser's Intravenous Solution of Hexamethylenamin and Sodium Iodid," "Loeser's Intravenous Solution of Sodium Salicylate," "Loeser's Intravenous Solution of Salicylate and Iodid," "Loeser's Intravenous Solution of Sodium Iodid" and "Loeser's Intravenous Solution of Mercury Bichlorid," put out by the New York Intravenous Laboratory, Inc.

W. A. PUCKNER, Secretary.

The intravenous solutions of "Hexamethylenamin," "Hexamethylenamin and Sodium Iodid," "Sodium Salicylate," "Sodium Salicylate and Sodium Iodid," "Sodium Iodid" and "Mercuric Chlorid" marketed by the New York Intravenous Laboratory, Inc., are solutions of official substances sold under their official names. They would, therefore, be outside the scope of the Council were it not that special and general therapeutic claims are made for them. Such special claims, for instance, are contained in an advertisement in the *Illinois Medical Journal* for Oct. 20, 1920, which gives, under the various drugs, a list of diseases in which the drugs are said to be "indicated." The Council is unable to agree with some of these recommendations. The fundamental objection, however, is the general claim of superiority and safety of the intravenous method.

The intravenous solutions named above would naturally have little sale if such special claims were not made for them. While the claims may not be made directly, they are carried by such display phrases as: "For the progressive physician seeking improved clinical results" and "A safe practical office technique."

The Council continues to hold that intravenous medication, generally, is not as safe as oral medication, even with relatively harmless substances (a fact again illustrated by the results of Hanzlik and Karsner, *J. Pharmacol. & Exper. Ther.* **14**:379 [Jan.] 1920), and that it does not give "improved clinical results" except under rather narrowly confined cir-

cumstances, namely, if the drug undergoes decomposition in the alimentary tract, if it is not absorbed, if it causes serious direct local reaction or if time is an urgent element. Each intravenous preparation for which advantage over oral administration is claimed, directly or by implication, must be examined from these points of view.

The Council has recognized intravenous preparations which satisfied these requirements. It is evident, however, that hexamethylenamin, sodium iodid and sodium salicylate do not. When given orally, they do not undergo material decomposition in the digestive tract; they are rapidly absorbed; they cause no direct local reaction, and in the conditions in which they are used, the hour or so which is required for absorption is immaterial, especially as they are used continuously for some time. Mercuric chlorid does, indeed, produce some local irritation; but there is as yet no convincing evidence that its intravenous injection causes less injury than oral administration. More experience under controlled conditions is needed before the intravenous use of mercuric chlorid can be approved. Especially objectionable are the fixed proportion mixtures of sodium iodid with sodium salicylate and with hexamethylenamin. The dosage of all three drugs has to be adapted to individual conditions. This is impossible when giving them in fixed proportions.

The Council voted not to accept "Loeser's Intravenous Solution of Hexamethylenamin," "Loeser's Intravenous Solution of Hexamethylenamin and Sodium Iodid," "Loeser's Intravenous Solution of Sodium Salicylate," "Loeser's Intravenous Solution of Salicylate and Iodid," "Loeser's Intravenous Solution of Sodium Iodid" and "Loeser's Intravenous Solution of Mercury Bichlorid" for New and Nonofficial Remedies, because they are sold under misleading claims regarding their alleged safety and efficiency. In view of this fundamental objection the individual claims for each preparation were not passed on.

MAMMARY GLAND PREPARATIONS OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The following report explaining the omission of Mammary Gland Preparations from New and Nonofficial Remedies has been authorized for publication.

W. A. Puckner, Secretary.

Mammary gland preparations were admitted to New and Nonofficial Remedies when there was promise that they might be found to have therapeutic value.

The following statement appears in New and Nonofficial Remedies, 1921: "Mammary Gland.—The extracts of the mammary gland are said to have effect on the uterus. It is stated that they are useful in profuse menstruation of young girls and young women, and in menorrhagia occurring at the time of the menopause."

The term of acceptance for the mammary gland preparations in New and Nonofficial Remedies having expired, the referee in charge of animal organ preparations recommended in his report on the annual revision of New and Nonofficial Remedies, that, in view of the slight evidence which has accumulated during the many years of trial, these preparations and the general article on Mammary Gland be omitted from the next edition of the book.

The Council adopted the recommendation of the referee and directed the omission of Mammary Substance-Armour and Mammary Substance Tablets-Armour.

MIXED POLLEN EXTRACTS: HAY FEVER FALL POLLEN EXTRACT-MULFORD, HAY FEVER SPRING POLLEN EXTRACT-MULFORD, POLLEN ANTIGEN FALL TYPE-LEDERLE, AND POLLEN ANTIGEN SPRING TYPE-LEDERLE 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.

The treatment of a certain type of hay-fever—pollinosis—by means of extracts prepared from the pollen of plants is essentially in the experimental stage. For this reason, the pollen extract preparations now admitted to New and Nonofficial Remedies were accepted with the stipulation that the three-year period for which articles ordinarily are accepted should not apply, but that their acceptance might be terminated at the end of any year.

Among the accepted pollen extract preparations are the following, each of which represents the pollen of a number of plants:

POLLEN ANTIGEN FALL TYPE-LEDERLE (Lederle Antitoxin Laboratories).—A liquid obtained by extracting the pollen of ragweed, goldenrod, wormwood, and maize.

POLLEN ANTIGEN SPRING TYPE-LEDERLE (Lederle Antitoxin Laboratories).—A liquid obtained by extracting the pollen of timothy, redtop, June grass, orchard grass, sweet vernal grass, meadow foxtail, meadow fescue, rye and wheat.

These "mixed" pollen extracts were accepted because the manufacturers presented some evidence that it was judged warranted the employment of these mixtures.

Early in 1920, the Council appointed a special committee to determine the status of preparations used for the treatment and diagnosis of hay-fever and allied conditions. The committee consists of Karl K. Koessler, Chicago; W. T. Longcope, New York; Oscar M. Schloss, New York, and I. Chandler Walker, Boston.

This committee reported to the Council that it was unanimous in the opinion that multiple pollen extracts are unnecessary modifications of pollen extracts representing single plants and that the claims for the value of such multiple pollen extracts in the treatment of hay-fever are unwarranted, for the reason that practically all observers who have worked with pollen extracts have concluded that there are only two or three pollens which are responsible for the large majority of cases of hay-fever, namely, timothy, which is the cause of spring hay-fever in the East, and spring vernal grass and June grass which have been found to be the cause of spring hay-fever in the Middle West, and, finally, ragweed, which is the cause of autumn hay-fever. For practical purposes, therefore, in the East at least 90 per cent. of the patients may be treated by two extracts alone. Patients whose hay-fever is not caused by one or the other of these pollens may be suffering from a hay-fever produced by any one of a long series of pollens, most of which do not appear in any of the mixtures now on the market, and which, indeed, may be indigenous to certain localities. This is particularly true, in the Middle West, of the spring hay-fevers, and in the Far West, where the sagebrush and many grasses not found in the East, and not now included in the multiple extracts, may be the cause of hay-fever.

The recommendations for the use of mixed extracts, therefore, are misleading. Patients who do not respond to the extracts from timothy and ragweed will probably not respond to the mixed extracts. The specific pollen to which these patients are sensitive will have to be determined by a long series of tests, and special extracts made for their treatment.

The committee recommended that multiple pollen extracts be held inadmissible to New and Nonofficial Remedies on the ground that unwarranted therapeutic claims are made for them, and because they are unscientific and useless articles.

The Council adopted the report of the committee and directed that Hay Fever Fall Pollen Extract-Mulford, Hay Fever Spring Pollen Extract-Mulford, Pollen Antigen Fall Type-Lederle and Pollen Antigen Spring Type-Lederle be omitted from New and Nonofficial Remedies.

MON-ARSONE NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., June 18, 1921, p. 1781

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Mon-Arsone is offered by The Harmer Laboratories Co. as "a new and non-toxic arsenical for the treatment of syphilis." In the advertisements for Mon-Arsone, it has been claimed that with this drug "the toxic, corrosive and uncertain reactions attending the use of arsphenamine have been entirely eliminated" and that "it has a therapeutic value equal to arsphenamine, but extensive case reports fail to record the slightest toxic reaction following its use."

According to the manufacturers, Mon-Arsone is disodium-ethylarsonate, the sodium salt of ethylarsonic acid, derived from arsenic acid by replacement of one hydroxyl group by the ethyl group — $AsO(CH_2CH_3)(OH)_2$. Mon-Arsone is related to sodium cacodylate, which is the sodium salt of dimethyl-arsenic acid—$AsO(CH_3)_2OH$—derived from arsenic acid by replacement of two hydroxyl groups by two methyl groups. Ethylarsonic acid and its potassium salt were described by La Coste[1] more than thirty-five years ago, and the use of the sodium salt of methylarsonic acid was proposed in France some years ago. The Harmer Laboratories Co. claims originality for Mon-Arsone in that it was the first to prepare the sodium salt of ethylarsonic acid and to propose its therapeutic use.

It was reported several years ago by Castelli[2] that sodium cacodylate and the sodium salt of methyl arsenic acid were devoid of effect on experimental trypanosomiasis and spirochete infections. Careful clinical observations in this country

1. La Coste: Annalen der Chemie (Liebig's) **208**: 34.
2. Castelli, G.: Arch. f. Schiffs- u. Tropen-Hyg. **16**: 605, 1912.

by H. J. Nichols[3] and H. N. Cole[4] have demonstrated the inefficacy of sodium cacodylate in the treatment of human syphilis.

Animal experiments carried out in the U. S. Hygienic Laboratory by Voegtlin and Smith[5] show that Mon-Arsone is devoid of any practical trypanocidal action. Thus, the "therapeutic ratio" (the ratio of the minimal effective dose to the lethal dose) was about 1, that is, it was effective therapeutically only in approximately fatal doses; the therapeutic ratio for arsphenamine in similar conditions was 17, and that of neoarsphenamine, 28.

The findings that sodium dimethylarsenate (sodium cacodylate), sodium methylarsenate, and sodium ethylarsenate are devoid of any practical trypanocidal action and the conclusion that sodium cacodylate is inefficient in the treatment of human syphilis does not prove that Mon-Arsone is without effect on the disease. These findings, however, certainly demand convincing therapeutic evidence to warrant the recommmendation for the use of the drug in the treatment of syphilis—particularly because the drug is proposed as a substitute for arsphenamine, the value of which is established.

When the Council first took up the consideration of Mon-Arsone, the only evidence for the claim that it "has a therapeutic value at least equal to that of arsphenamine" consisted, with one exception, of reports from those who had experimented with the drug for The Harmer Laboratories Co., including a report by B. L. Wright, L. A. Kennell, and L. M. Hussy,[6] the latter of The Harmer Laboratories Co. These reports appeared to show that the administration of Mon-Arsone caused less reaction than arsphenamine, and that the immediate effects, judged by the clinical symptoms and the response to the Wassermann test, appeared to be good. These trials extended over too short a period of time to permit judgment as to the permanence of the results. A report by an independent observer seemed to indicate that Mon-Arsone does not have the sterilizing action on syphilitic lesions which it is usually believed arsphenamine exercises.

After examining the available evidence, the Council advised The Harmer Laboratories Co. that the claim that Mon-Arsone has a therapeutic value equal to arsphenamine appeared unwarranted; that, in the opinion of the Council, Mon-Arsone should not be used except under conditions that justify the

3. Nichols, H. J.: Salvarsan and Sodium Cacodylate, J. A. M. A. **56**: 492 (Feb. 18) 1911.
4. Cole, H. N.: A Study of Sodium Cacodylate in the Treatment of Syphilis, J. A. M. A. **67**: 2012 (Dec. 30) 1916.
5. Voegtlin, Carl, and Smith, H. W.: J. Pharmacol. and Exper. Therap. **16**: 449, 1921.
6. Wright, B. L.; Kennell, L. A., and Hussey, L. M.: M. Rec. **97**: 607 (April 10) 1920.

experimental trial of an unproved drug, and should not be used in a routine way until the permanence of its effects has been established, and, consequently, any advertising propaganda for the drug by The Harmer Laboratories Co., was to be deprecated.

In its reply The Harmer Laboratories Co. admitted that its advertising claim that Mon-Arsone was at least equal to arsphenamine therapeutically had been based on reports on fifty cases and on additional reports that were beginning to come in at that time. The Harmer Laboratories Co. submitted a list of hospitals and physicians using Mon-Arsone. A letter of inquiry sent by the Council to those who, according to the names in the list supplied by The Harmer Laboratories Co., had used Mon-Arsone, brought seven replies.

The clinical evidence contained in these replies was to the effect that Mon-Arsone had been used in the various types of syphilis and that there was a certain beneficial effect, both clinically and as shown by the Wassermann reaction. In certain instances, the Wassermann reaction changed from a four plus to a negative reaction. The reports showed that the efficacy of Mon-Arsone as compared with that of arsphenamine preparations has not been adequately studied. One physician who has used Mon-Arsone extensively reports that in many of the cases treated there seemed to be nearly as good results from the use of Mon-Arsone as are frequently obtained from the use of arsphenamine. He reports, however, that it was necessary in eleven out of one hundred cases to change from Mon-Arsone to neoarsphenamine.

In view of the fact that there is definite lack of evidence to show that Mon-Arsone is the equal of arsphenamine therapeutically, and because of the reports that in some cases it is inferior, Mon-Arsone should not be used in the treatment of syphilis generally, until its therapeutic status has been more rigidly investigated and conclusive evidence of its superiority to arsphenamine preparations obtained.

The Council voted not to admit Mon-Arsone to New and Nonofficial Remedies and reaffirmed its conclusion that the claim that Mon-Arsone has a therapeutic value equal to that of arsphenamine is premature and unwarranted; that Mon-Arsone should not be used except under conditions that justify the experimental trial of an unproved drug, and that the advertising propaganda for the drug by The Harmer Laboratories Co. is to be deprecated.

When the preceding report was sent to The Harmer Laboratories Co., the firm submitted a reply in which it was stated that:

1. In certain instances patients improved under Mon-Arsone who, previously, had not improved under arsphen-

amine, and that this should be taken to offset the report of the one hundred cases in which the use of Mon-Arsone had to be abandoned in 11 per cent. of the cases.

2. The Harmer Laboratories Company has abandoned the claim that Mon-Arsone is therapeutically equal to arsphenamine and that it now furnishes the drug to such men as care to use it simply on the basis of its special and useful characteristics.

The Council heartily endorses the recent warning against the use of untried medicaments which was issued by the U. S. Public Health Service.[7]

Since the Council's report was prepared, a report on the effects of Mon-Arsone on experimental syphilis has been published by Nichols,[8] from the Division of Laboratories, Army Medical School, which concludes:

"1. Disodium-ethylarsinate, or mon-arsone, tested on rabbits infected with syphilis shows no spirocheticidal power. The tissues are fatally poisoned as soon as, or before, the spirochetes are affected.

"2. For its practical use in syphilis, there is no such germicidal basis as exists in case of the arsphenamine group."

"NATIONAL IODINE SOLUTION" NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., June 4, 1921, p. 1592

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

"National Iodine Solution" is a proprietary sold by the National Drug Co., Philadelphia. From inquiries received by the Council on Pharmacy and Chemistry, it is evident that the product is extensively brought to the attention of physicians by means of circulars. The name implies that it is a solution of iodin, and the inference is given that it has the advantages of iodin without the disadvantages.

COMPOSITION

In view of the foregoing, the Council began an investigation of "National Iodine Solution," and in turn asked the A. M. A. Chemical Laboratory to analyze it. The chemist's report follows:

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7. J. A. M. A., June 12, 1920, p. 1654.
8. Nichols, H. J.: The Spirocheticidal Value of Disodium Ethyl Arsinate (Mon-Arsone), J. A. M. A. **76**: 1335 (May 14) 1921.

According to the label of National Iodine Solution, "each fluid ounce represents three grains Proteo-albuminoid compound of iodin (National)"; also an alcohol declaration of 7 per cent. is made. Otherwise no information is given as to the composition either of the "solution" or of "Proteo-albuminoid compound of Iodine."

Each bottle contained about 115 c.c. (nearly 4 ounces) of a yellowish solution, acid in reaction, having an odor resembling that of hamamelis (witch hazel); its specific gravity at 25 C. was 0.9860. Qualitative tests indicated the presence of zinc, alcohol, sulphate, an iodin compound (the solution gave tests which indicated a very small amount of free iodin; most of the iodin was in the form of ordinary iodid), a small amount of vegetable extractives, and traces of aluminum and potassium. If any protein was present, it was in amounts too small to be identified, though a small amount of a nitrogenous compound was present. The amount of solids in "National Iodine Solution" was equivalent to 0.72 per cent. and the amount of ash, to 0.2 per cent. Quantitative estimations yielded the following:

Alcohol (by volume)	7.0	per cent.
Zinc (Zn^{++})	0.096	per cent.
Iodin (free and combined)	0.029	per cent.
Sulphate (SO_4^{--})	0.146	per cent.
Protein (N x 6.36)	0.012	per cent.

These findings indicate that each hundred cubic centimeters contains about 7 c.c. of alcohol, 0.5 gm. of zinc sulphate, U. S. P. ($ZnCO_4+7H_2O$.), 0.03 gm. of iodin, 0.01 gm. of protein (calculated as such from nitrogen times the factor 6.36) and some hamamelis. Expressed in equivalent apothecary terms, each fluidounce contains essentially:

Zinc sulphate	2⅓ grains
Iodin (free and combined)	⅛ grain
Protein	1/25 grain
Alcohol	34 minims

This amount of alcohol is equivalent to about 3½ fluidrams of hamamelis water. Although the label states that each fluidounce contains three grains of "proteo-albuminoid compound of iodine," yet the sum of the protein (calculated from nitrogen content) and iodine components is equivalent to less than ⅕ grain (0.012 gm.).

"National Iodine Solution" appears to be very similar to "Gonocol (The National Drug Co., Philadelphia, Pa.)," which was analyzed by the Bureau of Chemistry of the U. S. Department of Agriculture. The bureau stated that "it [Gonocol] consisted essentially of an aqueous solution of zinc sulphate, hamamelis water, a small amount of alcohol, 0.38 grain of iodin, and 0.36 grain of protein per fluid ounce."

It is evident that "National Iodine Solution" is not a solution of free (elementary) iodin, as the name suggests; instead it appears to be a solution of zinc sulphate in hamamelis water containing less than 0.03 per cent. of combined iodin and *not more than a trace of free iodin.* "National Iodine Solution" is one more to be added to that already long list of proprietaries which make capital of the high esteem in which physicians hold iodin.

THE CLAIMS

An advertising circular sent to physicians begins:

"Dear Doctor: We beg to suggest a line of treatment while using National Iodine Solution which our many years of experience has proven to us to give the best and quickest results in the treatment of inflammation of the urethral tract . . ."

In it are given directions for the treatment of "acute gonorrhea, male," "anterior urethritis," "anterior-posterior urethritis," "ardor urinae and chordee," etc., by means of National Iodine Solution and other proprietaries of the National Drug Company's make. In fact the solution is claimed to be "Indicated in All Conditions of Urethra Accompanied by a Discharge."

COMMENT AND CONCLUSIONS

The therapeutic claims made for "National Iodine Solution" are unwarranted. Such a solution is not indicated in all conditions of the urethra, accompanied by discharge. The advise contained in the circular is equivalent to mail order treatment of gonorrhea.

It is of interest to note that an identical, or a similar, solution prepared by the National Drug Company as a treatment for gonorrhea and intended for use by the laity, by the federal authorities (Notice of Judgment No. 8150, issued Jan. 25, 1921) in that it misled and deceived the purchaser or purchasers thereof in the statements regarding the therapeutic or curative effects of the article, which false and fraudulently represent it to be indicated in all conditions of the urethra accompanied with a discharge, "whereas in truth and in fact it was not."

The Council would emphasize that if physicians give heed to advertising such as that sent out by the National Drug Company for this preparation the medical profession cannot with good grace protest against the routine treatment of venereal diseases by quacks and "patent medicine" venders.

NORMAL HORSE SERUM STERILE, GONOCOCCIC VACCINE AND ANTI-TYPHOID VACCINE IMMUNIZING (NATIONAL VACCINE AND ANTITOXIN INSTITUTE) 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.

The period for which Normal Horse Serum Sterile, Gonococcic Vaccine and Anti-Typhoid Vaccine Immunizing of the National Vaccine and Antitoxin Institute, Washington, D. C., had been accepted terminated with the close of 1921.

To aid in determining whether these products were eligible for continued inclusion in New and Nonofficial Remedies, the manufacturer was asked to send copies of the labels and circulars for these products which were now in use. This request was not complied with. Further, the Council was informed that the license for the interstate sale of these preparations, which is required by the federal law "an act to regulate the sale of viruses, serums, toxins and analogous products in the District of Columbia, to regulate interstate traffic in said articles and for other purposes," had been cancelled by the United States Treasury Department on recommendation of the United States Public Health Service.

The Council gives no recognition to a biologic product unless its interstate sale has been authorized by the federal authorities. For this reason, it directed the omission of the preparations named above from New and Nonofficial Remedies, without determining whether they were in conflict with other rules governing the recognition of articles.

NORON NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

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

Noron is the proprietary name applied by The Heron Company, New Brunswick, N. J., to a 1:1,000 solution of normal oxyquinolin sulphate in water. Normal oxyquinolin sulphate has been used in medicine for a considerable time under the name chinosol, applied to it by the patentee.

The Council declared the preparation Noron inadmissible to New and Nonofficial Remedies because its name does not meet the provisions of Rule 8, which concedes to the discoverer of a new therapeutic agent the right to name it. The Heron Company had no part in the discovery of oxyquinolin sulphate or of its therapeutic properties. On the contrary, the name is inadmissible under the clause of Rule 8, which, to guard against the confusion which results from the application of numerous proprietary names to the same article, prohibits the recognition of a proprietary name for an unoriginal product. Since oxyquinolin sulphate is fully described in the literature, the sale of the product or simple preparations of it under names other than its true name, or that under which it was introduced (Chinosol), is a detriment to the rational use of drugs.

NUCLEIN PREPARATIONS OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report which announces omission from New and Nonofficial Remedies of nuclein, nuclein compounds and preparations and the accepted brands, namely: Nucleinic Acid-Merck, Nuclein-Abbott, Nuclein Solution-Abbott, Nuclein Tablets-Abbott and Sodium Nucleinate-Merck.

W. A. PUCKNER, Secretary.

Preparations of nuclein were first described in New and Nonofficial Remedies, 1911. This action was taken because they were then used to a considerable extent and because the claims for the products which were accepted had been radically revised.

For several years past, the Council has considered the elimination from New and Nonofficial Remedies of all nuclein preparations and compounds on the ground that they had not been proved to have therapeutic value. The products now accepted were retained provisionally until the present time because no special claims were advanced for them. The following statement appears in New and Nonofficial Remedies, 1921, under Nucleins and Nucleic Acids: "Actions and Uses.—Some years ago these acids and the nucleins were intoduced as remedies in tuberculosis, and to a slight extent this use continues. It has been held that their administration increases the number of white corpuscles and in consequence becomes of value in treating infections. The evidence on which these claims are based, however, is neither clear nor convincing."

To determine whether nuclein preparations should be included in New and Nonofficial Remedies, 1922, the Council obtained the opinion of ten physicians who, it believed, were competent to render expert opinion.

None of these had considered nucleins of sufficient promise to use them in their practice.

These replies indicate that a group of representative physicians in this country have had no experience with nuclein preparations. The opinion, therefore, of a group of representative physicians from all parts of the country does not warrant the use of nuclein preparations.

Accordingly, the Council directed the omission from New and Nonofficial Remedies of the chapter devoted to nuclein preparations and rescinded the acceptance of the brands of this product now in New and Nonofficial Remedies.

OSMIUM TETROXIDE OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report explaining the omission from N. N. R. of Osmium Tetroxide and the accepted brand, Osmic Acid-Merck.

W. A. PUCKNER, Secretary.

The period having expired for which the accepted brand of Osmium Tetroxide stood accepted, a referee reported that on consultation with neurologists he had come to the conclusion that the use of Osmium Tetroxide for intraneural injection as a means of producing nerve degeneration has been generally abandoned in favor of injections of alcohol. Accordingly, the Council voted that Osmium Tetroxide and the accepted brand be omitted from N. N. R. As a matter of record the description of Osmium Tetroxide which is contained in N. N. R., 1921, appears below:

OSMIUM TETROXIDE—Osmium Tetroxidum. — Osmic Acid.—Osmium Anhydride.—OsO_4.—The anhydride of a theoretical acid obtained by the action of nitrohydrochloric acid on osmium.

Actions and Uses.—Intraneural injections are used to produce degeneration of nerves for the relief of persistent neuralgias. The treatment is best applied by injecting from 0.5 to 1 Cc. of a fresh 1 or 2 per cent. solution directly into the preferably exposed nerve. The result is sometimes immediate, but more commonly it is not complete until after one or two weeks, or it may even fail entirely. If successful, the effects may persist for several months, when it may become necessary to repeat the injection as the cure is rarely, if ever,

permanent. The local reaction is always painful, but not serious. It is not advisable, perhaps, to use osmium tetroxide in renal disease.

Osmium tetroxide occurs in the form of white or yellowish crystals which are slowly soluble in water (1: 50); it is also soluble in alcohol and ether but the solutions decompose. Osmium tetroxide melts at 40 C. and boils at about 100 C. It evaporates even at ordinary temperatures, yielding very irritating and extremely poisonous vapors, attacking the eyes and lungs. It is decomposed by contact with organic substances (Brit. Codex, 1907).

From aqueous acidified solutions of osmium tetroxide, hydrogen sulphide precipitates brown osmium sulphide, OsS_4 which is insoluble in ammonium sulphide. An aqueous solution of osmium tetroxide decolorizes indigo solution. Iodine is liberated from potassium iodide solutions by osmium tetroxide. Treated with sulphurous acid, aqueous solutions of osmium tetroxide become yellow, turning to brown and finally becoming blue; tannic acid produces a red color, becoming brown; ferric chloride and alcohol reduce osmium tetroxide to the metal osmium.

Osmic Acid-Merck. — A nonproprietary brand complying with the standards for osmium tetroxide.

Merck & Co., New York, distributors.

OXYL-IODIDE NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., July 2, 1921, p. 57

"Oxyl-Iodide" (Eli Lilly & Company) is said to be the hydroiodid of cinchophen; and the claim is made that it exerts the effects of cinchophen and of iodid. Because of inquiries which have been received, the Council decided to determine the eligibility of "Oxyl-Iodide" for New and Nonofficial Remedies. Dr. P. J. Hanzlik, formerly associate professor of pharmacology at Western Reserve University School of Medicine, now professor of pharmacology at Leland Stanford Junior University Medical School, who has made a study of the action of salicylates and cincophen, was asked to report on the therapeutic value and the rationality of "Oxyl-Iodide." His report appears below.

After considering Doctor Hanzlik's report, the Council declared "Oxyl-Iodide" inadmissible to New and Nonofficial Remedies because it is an irrational combination, marketed under claims that are unproved and consequently unwarranted.

W. A. PUCKNER, Secretary.

"Oxyl-Iodide," marketed by Eli Lilly & Company, is claimed to be the hydroiodid of phenylcinchoninic acid, containing 33 per cent. of iodin and 67 per cent. of phenylcinchoninic acid (cinchophen). Its solubility resembles that of cinchophen,

being low in water and acid mediums, and higher in the presence of alkalis. Whether "oxyl-iodide" is decomposed into its constituents in the presence of alkalis does not appear to have been determined. However, if this were the case, the intestine, after administration of "oxyl-iodide," would contain cinchophen and sodium iodid in the same forms as if these agents were administered individually so that nothing would be gained by administering "oxyl-iodide." Being, like cinchophen, practically insoluble in acid mediums, "oxyl-iodide" would have no advantage over the latter so far as gastric irritation is concerned.

DOSAGE

The dosage advised is from one to three tablets containing 3 grains (0.2 gm.) each of "oxyl-iodide." The total dosage would depend on the condition to be treated. In rheumatic fever, which requires a full therapeutic or so-called, "toxic" dose of cinchophen, about 12 to 13 gm. would be administered intensively. Since each tablet of "oxyl-iodide" contains 0.13 gm. of cinchophen, the total number of tablets of "oxyl-iodide" required would be 100, or two and one-half bottles of forty tablets each. At the same time the patient would receive 6.6 gm. of iodin (as iodid). This might be distinctly objectionable because of the production of the disagreeable symptoms of iodism in some persons, and indicates that the fixed proportion of the iodin constituent would be objectionable.

Even a smaller dosage, such as 5 gm. of cinchophen, which gives partial relief in rheumatism and similar conditions, would still require a patient to take a full bottle, or forty tablets, of "oxyl-iodide," and at the same time about 2.7 gm. of iodin would have to be ingested.

Furthermore, rheumatic fever, the arthritides, gout and related conditions in which cinchophen is indicated do not require iodid. Therefore, "oxyl-iodide" would not be the remedy of choice in these conditions, and its use would be irrational and illogical.

ACTIONS

No data on the pharmacologic actions of "oxyl-iodide" are presented in the manufacturer's literature. Presumably, the compound would exhibit the actions of its individual components, i. e., cinchophen and iodin (as iodid), though probably less efficiently, owing to its low solubility. This is also indicated by the following statements of the manufacturer: "The analgesic action of 'oxyl-iodide' is gradual. A word of caution is necessary to those who may expect immediate relief from pain." Therefore, why use "oxyl-iodide" in place of more dependable analgesics, such as salicylate or cin-

chophen. The following statements appear far-fetched: "There is a stimulation of the endocrines which is perhaps more marked in the thyroid gland, although it is probably shared by the pituitary and other glands which function in a chain-like control. . . . There is stimulation of cells with increased flow of secretion, visibly demonstrated by the nasal mucous membrane after 'oxyl-iodide' has been taken for some time. The general action on mucous membranes favors elimination of toxins and waste products."

It is probable that "oxyl-iodide" acts as a uric acid eliminant, though there is no reason to suppose that it is more effective than cinchophen alone. No data are given for this in the manufacturer's literature.

USES

Successful use of "oxyl-iodide" is claimed in brachial and sciatic neuritis, lumbago, muscular rheumatism, arthritis deformans, chronic arthritis (". . . in some instances were apparently cured"), subacute bronchitis, circumflex neuritis, traumatic orchitis, eczema and rheumatism. However, a careful reading of the protocols of seven cases, representing these conditions, gives an unfavorable impression as to the real contribution to the recovery by, or value received from, "oxyl-iodide." Summarized, the opinions as quoted by the manufacturers in support of their claims for "oxyl-iodide" are briefly as follows:

Case 1. "Of course, the case is not complete yet, but I am looking for continued betterment."

Case 2. "For two weeks past her improvement has been marvelous."

Case 3. "The joints are still enlarged and we do not hope to clear them entirely. . . ."

Case 4. "Undoubtedly, removal of the kidney had much to do with improvement."

Case 5. "I think I have gotten very good results."

Case 6. "Some apparent benefit."

Case 7. "She is practically free from pain, and the muscle and joint stiffness is now slight."

These inconclusive opinions certainly do not agree with the favorable impression which other portions of the manufacturer's literature create. If the factor of natural recovery in the conditions represented by these seven cases is given due weight, little, if anything, is left to the credit of "oxyl-iodide." Such clinical evidence as is supplied by the manufacturer indicates that the therapeutic efficiency of "oxyl-iodide" is doubtful, and not an improvement over either cinchophen or iodide.

IODISM

Iodism cannot be avoided by the use of "oxyl-iodide," for the manufacturer's literature states that "the dosage of 'oxyl-iodide' may be pushed to iodism as manifested by skin symptoms. . . . To avoid iodism there should be an occasional interruption of treatment." "Oxyl-iodide," therefore, has no advantage over ordinary sodium iodid to avoid iodism. Usually, the conditions which require cinchophen do not require the simultaneous administration of iodids, and vice versa. If administration of iodid and cinchophen together should be indicated or desirable, these can be given separately with the added advantage that the iodid can be easily reduced or withdrawn in case iodism supervenes, and the cinchophen could be continued if necessary. Since conditions do not arise frequently enough to warrant the use of iodid and cinchophen together, the existence of such a product as "oxyl-iodide" is unwarranted.

Finally, the manufacturer himself recognizes that phenylcinchoninic acid (cinchophen) can take the place of "oxyl-iodide." Under "dosage," the circular states: "A few patients may be idiosyncratic to the iodides and find they cannot take 'oxyl-iodide.' For the latter chloroxyl, the hydrochloride of phenylcinchoninic acid, is recommended." The action of the hydrochlorid of phenylcinchoninic acid does not differ, of course, from that of cinchophen. The difficulties of assigning a clear-cut, definite, therapeutic rôle to "oxyl-iodide" in order to justify its existence, alongside well-known and tried remedies are self-evident.

CONCLUSION

"Oxyl-iodide" is pharmacologically and therapeutically an illogical, irrational and unjustified substitute for cinchophen and iodids. The conditions which require the administration of cinchophen do not as a rule require the administration of iodid and vice versa. If it is desirable to secure the effects of iodid and cinchophen together, these can be more conveniently and advantageously administered as separate agents, permitting in that way a better control of their actions. This cannot be accomplished with "oxyl-iodide," in which the proportion of iodid and cinchophen are fixed. Symptoms of iodism cannot be avoided by the administration of "oxyl-iodide." The objective evidences for its actions and uses are totally lacking; and the clinical opinions concerning its therapeutic benefits in different disease conditions are inconclusive and hedging, and, if anything, contradictory to the favorable impressions which the language of the advertising matter is likely to create.

PIL. MIXED TREATMENT (CHICHESTER)

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Oct. 22, 1921, p. 1355

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

"Pil. Mixed Treatment (Chichester)" is a proprietary preparation of the Hillside Chemical Co., Newburgh, N. Y. It is sold in the form of pills, each said to contain 1/20 grain of mercuric iodid and 5 grains of potassium iodid.

In 1907 the Council examined the therapeutic claims advanced for this preparation and found that they were unwarranted, exaggerated and misleading. It found, also, many misleading statements in regard to the product itself. Furthermore, the A. M. A. Chemical Laboratory found the pills to be "short weight" in potassium iodid content.

At the time that the Council examined Pil. Mixed Treatment (Chichester), a dermatologist of recognized standing, to whom the "literature" for this product had been submitted for an opinion, made the following report:

"Assuming that this pill contains what is claimed for it, one-twentieth (1/20) of a grain of biniodid of mercury and five (5) grains of potassium iodid, it presents neither an original nor a very useful formula.

"The literature furnished by the company abounds in suggestions that the mixture, as they prepare it, represents some unusual potency which is not possessed by the ordinary mixture of these same drugs in the same proportion. These suggestions may of course be dismissed without consideration. There is nothing mysterious in a mixture of potassium iodid and biniodid of mercury and this formula is no more entitled to special consideration than any other pill or tablet of the same composition prepared by any reputable pharmaceutical firm.

"The formula of this pill, however, does not represent a good combination. It is offered for use both during the active secondary period of syphilis and for tertiary lesions. The pill does not contain enough mercury to be an efficient remedy for secondary syphilis and not enough potassium iodid to be satisfactory in the treatment of tertiary lesions. It is neither fish, flesh, fowl, nor good red herring. A patient with secondary syphilis should not be dosed all the time with potassium iodid and for the treatment of tertiary lesions he should have a very much larger quantity of potassium iodid than can be given in these pills without giving toxic doses of mercury.

"The statement that this pill 'does not impair the appetite nor disturb digestion and is well borne by patients who cannot tolerate iodids otherwise administered' is a bald claim which cannot be justified by experience. The most unsatis-

factory way of administering potassium iodid is in solid form. A patient who can stand potassium iodid in pill form, as it is furnished in this preparation, can stand it in any form in which it is ever administered.

"In short this preparation is neither agreeable nor efficient. The greatest objection to it is its inefficiency, for it is offered as an adequate preparation for the treatment of syphilis in all of its stages, whereas it is neither satisfactory for the treatment of secondary syphilis nor of tertiary lesions."

During the fourteen years which have elapsed since the Council's first examination of Pil. Mixed Treatment (Chichester), arsphenamin has been added to the syphilographer's armamentarium and much has been learned about syphilis and its treatment. While there exist differences of opinion as to the exact value of arsphenamin in the treatment of syphilis and there are even some who desist from the use of arsenic compounds of any kind, no syphilographer of standing countenances the routine treatment of syphilis with a fixed combination of mercuric iodid and potassium iodid. The use of Pil. Mixed Treatment (Chichester) is on a par with the use of certain "blood purifiers" which were advocated at a time when the treatment of syphilis was a baffling problem.

PRESENT DAY CLAIMS

The present advertising, which reads as if it had been written in the heyday of proprietary license, is, in effect, an invitation to treat syphilis in its various stages and manifestations with Pil. Mixed Treatment (Chichester). If heeded by those who read the advertising of the Hillside Chemical Co., it will result in much harm to the public and the profession. For this reason, the present report of the Council is published as a protest against any advertising propaganda advocating the routine treatment of a disease which requires that each case be studied carefully so that prompt and efficient measures may be applied to the various manifestations of the disease.

The following advertisement appeared recently in several medical journals:

"Medicine is an Exact Science — on Paper Only!" Every general practitioner of medicine is called upon to treat Syphilis occasionally. He cannot depend upon the use of arsenicals alone. In most cases, "mixed treatment" the giving of mercury and iodides is required to get satisfactory results. PIL MIXED TREATMENT (CHICHESTER) accurately and successfully meets the indications and assures definite action. Important advantages:

Ready solubility of mercury in combination with Potassium Iodide.

Avoidance of gastric, buccal or intestinal disturbance.

Easy administration, can be taken at any time, anywhere.

Economical, both drugs in one combination.

Accurate adjustment of dosage to each individual case.
Full physiological action — assured by purity of content.
Secrecy—patient or friends do not know nature of medicine. Pil Mixed Treatment (Chichester) has been time tested and trial proven. It needs no introduction to the thousands of physicians who prescribe or dispense it.

While the advertisement does not directly so advise, yet it is a subtle invitation to the general practitioner to use Pil. Mixed Treatment (Chichester) and thus save himself and his patient the time and inconvenience which the rational

One reason scientific medicine lags. Uncritical medical journals perpetuate—for a price—the use of nostrums.

treatment of syphilis imposes. A circular "The Treatment of Syphilis Simplified and Improved" begins:

"No therapeutic fact is more conspicuously and decisively established than that a radical cure of syphilis can be effected by the continuous administration, from the period of development, of a proper combination of mercury with iodine."

Continuing, it is admitted that mercury is the most efficacious drug in the primary and secondary stages of syphilis and iodin in the tertiary stage, but it is asserted that:

". . . it is now granted by all syphilologists that the antiluetic action of these drugs is immeasurably augmented by properly combining them, and that the best results are obtained when they are conjunctively administered throughout the entire course of the disease."

Arguing along the same lines, this circular continues:

". . . it was not until mercury and iodine in the form of Pil. Mixed Treatment (Chichester) was evolved that the marked advantages of the combined employment of these drugs in the various stages of syphilis became a scientific certainty."

Further we are asked to believe that:

"Because of the greatly increased potency of mercury and iodine when combined, as in Pil. Mixed Treatment (Chichester), the foremost syphilologists are now agreed that the employment of these drugs in such form should be enjoined as soon as the disease develops, and should be thus continued until a cure has been effected; in other words, Pil. Mixed Treatment (Chichester) should be made the sole antisyphilitic medication throughout all stages of the disease."

The circular illustrates the extent to which our knowledge of drugs may be distorted and misrepresented and the public health jeopardized in the exploitation of a proprietary medicine.

PROPRIETARY CLAIMS

In its advertising, the Hillside Chemical Company claims that Pil. Mixed Treatment (Chichester) both as to formula and method of preparation "in the incapsulated powder forms" was "brought to the notice of the profession by Dr. W. R. Chichester of New York, an eminent Syphilographer and recognized authority in the therapeutics of Syphilis." It is claimed that this pill "is perfectly soluble, tasteless, non-irritant, and therefore well adapted to a sensitive stomach." It is claimed that the pill "is always preferable to one extemporaneously prepared, which, even if identical in composition, often gives negative results."

An examination made in the chemical laboratory of the Association to determine whether the product now marketed contains the claimed amount of potassium iodide indicated that this was the case. The chemist who made this examination commented as follows on the claim that in this pill, potassium iodide is rendered tasteless, that the pill is "perfectly soluble" and that extemporaneous pills of "identical . . . composition, often give negative results."

"That the potassium iodid has been rendered tasteless is false, naturally; the pills when placed in the mouth, after removal of the coating, have the characteristic taste of alkali iodides. The claim that the pills are entirely soluble is incorrect; they contain a large amount of insoluble material, probably kaolin. The assertion that an extemporaneous compound prescription even if identical in composition with the

Chichester pill is often inert, is absurd and a reprehensible attack by suggestion of the ideal that the physician shall write his prescription to meet the individual needs of his patient and that the pharmacist shall compound the prescriptions of the physician as they are required. It should also be pointed out that while much is said about the potassium iodide in the Chichester pill being in powdered form, the pill mass is solid and very slowly soluble and the claim of being in powdered form is, if immaterial, also incorrect."

As to the asserted standing of the alleged discoverer of the formula for Pil. Mixed Treatment: Dr. William R. Chichester appears to have lived and practiced in New York since 1886 or longer, but the claim that he is an "eminent Syphilographer" seems to have originated with the exploiters of "Pil. Mixed Treatment." Search failed to show the name of W. R. Chichester among authors of textbooks of syphilis or any other branch of medicine or among authors of contemporary literature in the Index Medicus from 1907 down to the present; nor did a search of the catalogue to the Surgeon General's Library reveal W. R. Chichester as ever having published anything on syphilis or any other subject.

Pil. Mixed Treatment (Chichester) is sold under therapeutic claims which are unwarranted and misleading. The preparation well illustrates the abuses which are connected with the exploitation as proprietaries of established drugs or mixtures of established drugs.

QUASSIA COMPOUND TABLETS

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., July 9, 1921, p. 141

The Council has authorized publication of the following report, declaring that Quassia Compound Tablets (Flint, Eaton and Company) are inadmissible to New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

Quassia Compound Tablets, marketed by Flint, Eaton and Company, Decatur, Ill., according to the label on a trade package submitted to the Council, contain in each tablet:

Quassia	¾ grain
Chionanthus	1 grain
Wahoo	¾ grain
Nux Vomica	½ grain
Cascara	⅓ grain
Aloin	¼ grain
Ipecac	1/16 grain
Podophyllin	¼ grain
Gingerine	*q. s.*

In the advertising the "Cascara" of the label is replaced by the indefinite term "Cascarin" and the "Gingerine *q. s.*" by "Carminative Antigripe *q. s.*" Flint, Eaton and Company informed the Council that "Carminative Antigripe is C. P. Sodium Sulphite of which each tablet contains ¼ grain." The tablets were treated with dilute hydrochloric acid and the odor of sulphur dioxid became apparent. This shows that the company's statement to the Council, that the tablets contain a sulphite, is correct and the formula on the label is incorrect.

In the advertising for this preparation we read:

"A careful study of this formula [which formula? That on the label or that in the general advertising?—COUNCIL] will reveal the outstanding fact that, while there are several drugs employed, each ingredient is there for a purpose and all do splendid teamwork. If your patient is constipated because the stomach is not sufficiently energetic, the Quassia stimulates that organ to an increased secretion of digestive fluids and sets it to working normally. If the liver be sluggish, the Chionanthus and Wahoo prompt it to increased activity. Chionanthus has no superior for producing a sustained healthy hepatic condition. Should the bowels be slow and uncertain, the small doses of Aloin, Cascarin and Podophyllin stimulate to free peristaltic action, while the Nux Vomica sets the nervous system right. We use an effective Antigripe so that there is no griping."

It is absurd to suppose that a complex mixture of drugs in fixed proportions can have the actions claimed for Quassia Compound Tablets. As regards the claim that "Chionanthus has no superior for producing a sustained healthy hepatic condition," it was brought out in a report of the Council on "Some Unimportant Drugs" (Reports of Council on Pharmacy and Chemistry, 1912, p. 36) that the "claims for this remedy [Chionanthus] are not supported by experimental evidence and the clinical reports of its use fail to show indications of discriminating critical observation. It is not noticed by most pharmacologic authorities."

Of Wahoo (Euonymus N. F.) the "Epitome of the U. S. P. and N. F." says: *"Actions and Uses.*—Obsolete cathartic; toxic digitalis effects. *Caution:* The uncertain absorption of this drug makes its use inadvisable."

Quassia Compound Tablets (Flint, Eaton and Company) are inadmissible to New and Nonofficial Remedies because: (1) They contain drugs of unproved value; (2) their composition is needlessly complex, and, therefore irrational; (3) unwarranted therapeutic claims are made for them; (4) the name is misleading and not descriptive of their composition, and (5) the statement of their composition is indefinite and incorrect.

SAPHANOL CONCENTRATE AND SAPHANOL AROMATIC

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report which explains that Saphanol Concentrate and Saphanol Aromatic were found inadmissible to New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

Saphanol Concentrate, according to the information furnished the Council by the Saphanol Products Company, is composed of phenol, 33 per cent.; glycerin, 37 per cent.; salicylic acid, 8 per cent.; boric acid, 12 per cent.; oil of peppermint, 4 per cent.; oil of cassia, 2 per cent.; menthol, 2 per cent., and thymol, 2 per cent.

In the advertising, Saphanol Concentrate is described as "a true germicide, destroying all germs instantly, yet entirely harmless to the most delicate or inflamed tissue." Saphanol is said to be "indicated in pyorrhea alveolaris, gingivitis, sore or inflamed gums, after all extractions, in all ulcerations or pus formations in the mouth and teeth." It is stated that the preparation may be incorporated in ointments, suppositories, tooth powder, and paste, surgical dressings, surgical soaps, etc.

Saphanol Concentrate is inadmissible to New and Nonofficial Remedies because (1) No supporting evidence was furnished the Council for the highly improbable claim that it destroys all germs instantly, and yet is entirely harmless to the most delicate tissue; nor is there any evidence that in the treatment of pyorrhea, it has any advantage over other, well known and simpler adjuvants in the treatment of pyorrhea (Rules 8 and 10). (2) The name is not descriptive of composition; and thus the preparation will be used without full appreciation that it is claimed to contain 33 per cent. of phenol (carbolic acid).

Saphanol Aromatic, according to the information furnished the Council by the Saphanol Products Company, has the following composition:

Saphanol	72 minims
Alcohol (U. S. P.)	150 minims
Oil of Peppermint	19 minims
Oil of Wintergreen (synthetic)	14 minims
Oil of Cassia	19 minims
Oil of Horsemint	14 minims
Thymol	8 grains
Menthol	12 grains
Water to make 1 pint.	

NOTE.—In this formula it should be understood that the proportions of oil of peppermint, oil of cassia, menthol and thymol are given without reference to the quantities of these constituents added in the form of Saphanol Concentrate.

In the advertising, Saphanol Aromatic is described as "an Aromatic, Germicidal, Antiseptic Healing Emulsion, Pleasant to use. For Pyorrhea, Gingivitis, Sore, Bleeding, Inflamed or Pus Infected Conditions of the Mouth and Teeth."

In the instructions for the use of Saphanol Concentrate, discussed in the preceding report, it is advised that the patient use Saphanol Aromatic in conjunction with the treatment. While the primary or initial recommendation is for the use of Saphanol Aromatic as "a daily mouth wash to continue and complete the work done by the dentist," it is claimed that it is indicated in a host of other conditions. The label on the trade package contains recommendations for the use of the preparation "as a gargle for sore throat, diphtheria and tonsilitis, as a nasal douche for catarrh, influenza, hay fever, cold in the head, for . . . ulcers or inflamed conditions." It is asserted also on the trade package, that the article is "of great value for sunburn, insect stings and bites, poison ivy and water poison"; and the purchaser receives the vain promise that "it quickly removes all pimples, blackheads, and eruptions."

Saphanol Aromatic is inadmissible to New and Nonofficial Remedies because: (1) It is advertised with unwarranted therapeutic claims (Rule 6), in such a way that the public is likely to depend on it for the treatment of serious conditions which require early diagnosis and treatment (Rule 4). (2) It is a complex mixture, containing ingredients which are of no probable assistance to one another (Rule 10) and marketed under a name which is not descriptive of the composition.

SOFOS OMITTED FROM NEW AND NONOFFICIAL REMEDIES

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Sofos, marketed by the General Chemical Company, New York, N. Y., is a mixture of sodium acid phosphate and sodium bicarbonate, which, when dissolved in water, yields sodium phosphate and carbon dioxid. The proprietors advised the Council that they had decided to advertise Sofos to the public through the daily press, and, for this reason,

requested that the Council discontinue its acceptance of the product. Since the advertising of proprietary laxatives in the lay press is not considered to be in the interest of the public, and, for this reason, is held contrary to the principles which govern the inclusion of articles in New and Nonofficial Remedies, the Council has directed the omission of Sofos from New and Nonofficial Remedies.

TOXICIDE

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Oct. 8, 1921, p. 1197

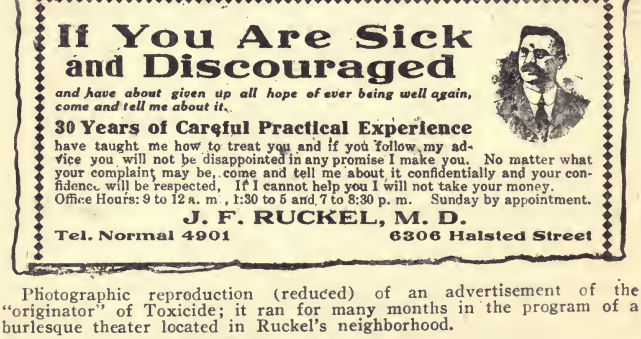
The Council has authorized the publication of the following report. W. A. PUCKNER, Secretary.

Toxicide (Toxicide Laboratories, Chicago) is alleged to be a remedy which "increases systemic resistance," is "used for immunizing against septic infections" and "is indicated in any case of septic infection, capable of inducing inflammation and pus formation, regardless of location or kind of tissue involved." The following statements bearing on the composition of the preparation are furnished by the manufacturers:

"Toxicide contains Lachesis 12X, Tarantula 6X, Psorinum (special) 15X, Silicia 6X and Excipient q. s. (the excipient is sweet milk).

"These remedies are combined in the sweet milk and put through a process of development, which produces the curative agent which we call 'Toxicide' . . .

"Put up in tablet form, sugar coated and colored red."



Photographic reproduction (reduced) of an advertisement of the "originator" of Toxicide; it ran for many months in the program of a burlesque theater located in Ruckel's neighborhood.

No information is given as to the proportions, either relative or actual, of the ingredients. Neither is any information given regarding the "process of development" to which the

mixture is subjected, nor the amount of the finished mixture which is contained in Toxicide tablets.

The Toxicide Laboratories present the following "theory":

"In combining these remedies and processing with milk, we develop a latent immunizing active principle, which usually controls the most virulently active, septic infections promptly."

There is no evidence, however, that any effort has been made to demonstrate the presence of a "latent immunizing active principle" by scientific methods of modern immunology. The following claims for the use of Toxicide appear on the label:

"Acne, boils, carbuncles, furuncles and abscesses of the most virulent types usually begin to show improvement within 4 to 12 hours after beginning administration.

"In badly infected wounds, Toxicide will check the further destruction of live tissue and should always be given for a few days before and after operations on pus cases.

"For gunshot wounds and other conditions difficult to sterilize or drain, Toxicide is the ideal remedy.

"For abscesses existing or threatened in any obscure location, the middle ear, the mastoid, the frontal or any accessory sinuses, Toxicide is of inestimable value.

"If administered early, in fractures, compound or simple, or for laceration and other injuries, inflammation, swelling, soreness and destruction of tissue will be greatly mitigated."

In support of these claims there are offered letters from physicians who have used Toxicide with good results. None of these testimonials present evidence that the reported effects were due to Toxicide. The asserted—and highly improbable—action of Toxicide could be determined only by an extensive series of carefully controlled clinical trials—and such evidence is entirely lacking. In fact, the claims appear to have no better basis than the coincidence which is stated to have led to the discovery of the "remedy"; namely, that a boil on the neck disappeared shortly after the administration of Toxicide!

The Council finds Toxicide inadmissible to New and Nonofficial Remedies because: (1) The identity and amount of the potent constituent or constituents have not been furnished; (2) the preparation is advertised indirectly to the public; (3) the name "Toxicide" is therapeutically suggestive, and (4) the therapeutic claims, being unsubstantiated by evidence, are unwarranted.

[Editorial Comment.—It seems rather preposterous that a scientific body, such as the Council on Pharmacy and Chemistry, should have to waste its time in investigating and reporting on such an obviously unscientific product as "Toxicide." So long, however, as there are physicians who will take preparations of this sort seriously, the Council feels that

it is its duty to report on such products. The problem, in fact, was well stated in a letter addressed to the editor some months ago by the secretary of a county medical society who had just received a visit from a representative of the Toxi-

TOXICIDE
The Remedy that saves Life and Limb

The principal action of Toxicide is to immunize man or beast against the toxic and irritant properties of decomposing organic matter, which it seems to do almost perfectly, even though sepsis has become well established. It also prevents inflammation, tenderness and death of bruised and lacerated tissues, whether infected or not.

If administered early in case of fractures, compound or simple, including severe bruises, lacerations or other injuries, but little inflammation, pain or swelling will develop and no infection will take place.

In case of badly infected wounds with or without sloughing, it will stop the further destruction of live tissue so quickly that you cannot believe without a demonstration. All dead matter will slough away or be absorbed but no more will die.

Many injured arms and legs that are now being sacrificed could easily be saved if **Toxicide** were administered, as it precludes all danger from infection and prevents breaking down of the bruised and lacerated tissues.

Toxicide should always be given for a few days before and after operating on pus cases. It also does much toward preventing shock and sepsis in major operations. You need not be so particular about drainage if **Toxicide** is used for the reason that the discharge will promptly lose its virulent nature besides all the live tissue will be practically immune to infection.

Toxicide has no action on the gonococci but is helpful in mixed infection where there is much pain and swelling. Has not been used for cancer but probably will be useful. Would suggest a trial.

Gunshot wounds and other conditions difficult to sterilize or drain, offer a field of great importance.

For an abscess existing or threatened in the frontal sinuses or in the ear or any other obscure or dangerous location it is of inestimable value. If **Toxicide** is administered within a reasonable time there will be no need for a mastoid operation, but if late after an operation has become necessary the opening need not be extensive for the discharge will cease very soon.

Toxicide has been used with remarkable results in hip joint disease and in tubercular conditions of the bones. In fact it is useful wherever there is a tendency to pus formation regardless of the kind of tissue involved.

If possible administer early in appendicitis, it will often prevent the necessity for an operation. In case the operation becomes necessary **Toxicide** lessens the tendency to shock and peritonitis.

Boils, pimples, carbuncles, and abscesses are controlled so promptly and positively that neither you or I would believe without seeing.

Toxicide has produced wonderfully beneficial results in puripural peritonitis, also in peritonitis from appendicitis or following abdominal operations; it also does much to prevent shock following major operations.

DOSE

One tablet every hour until improvement sets in, then gradually reduce the frequency of the dose.

CAUTION: When **Toxicide** has accomplished its work, discontinue, otherwise it will so thoroughly destroy all irritants that granulating and healing of the wound will be retarded. (Do not use in Syphilitic Subo before opening for it has no action on Syphilis but will retard suppuration.)

For further particulars, address

DR. J. F. RUCKEL

Phone Normal 4901 **6306 South Halsted Street, Chicago, Ill.**

Who originated the remedy sixteen years ago and has since used it in more than 1,000 cases with marvelous results.

Photographic reproduction (greatly reduced) of an advertising circular used some time ago describing the marvels (alleged) of Toxicide.

cide Laboratories and who sent to THE JOURNAL some of the advertising matter that he had received from the same source. This physician wrote:

> "I do not wish to trouble you with this kind of material, usually deposited safely in my waste paper basket, but the enclosed was handed to me today by a 'bird' who is calling on all the doctors and making strong statements. When he claimed that 'Toxicide' is being used

in the Presbyterian Hospital, Chicago, and that the Council on Pharmacy is considering it seriously, etc., etc., I wish to know whether I am missing any real good thing. If it has any real virtue, I would like to know about it, but if it has not, it seems to me that something ought to be done to head him off as some doctors are sure to fall for some of it."

The Toxicide Laboratories is, apparently, merely a trade name used by the alleged originator of "Toxicide," J. F. Ruckel, M.D. According to our records, Ruckel was born in 1860 and was graduated by the Chicago Homeopathic Medical College in 1886. He claims to have originated Toxicide about twenty years ago and to have prescribed it "in over 3,000 cases." In addition to Toxicide, the Toxicide Laboratories also put out "Dianasiac for Nymphomania and Satyriasis" and "Somnosine for Insomnia."]

UROTROPIN OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

Urotropin is a proprietary name applied to the substance which is known in chemical literature as hexamethylenetetramin and which is designated hexamethylenamine in the U. S. Pharmacopeia. The Council has authorized publication of the following report explaining that Urotropin was omitted from New and Nonofficial Remedies because Schering & Glatz, Inc. (the firm that markets this brand of hexamethylenamin in the United States), refused to place the U. S. Pharmacopeia name Hexamethylenamine (hexamethylenamina) on the label and in its advertising so as to make clear to physicians the identity of the product, and, furthermore, because it was sold under therapeutic claims which the Council held unwarranted.

W. A. PUCKNER, Secretary.

Commercial History of Hexamethylenamin

The substance which is generally referred to in chemical literature as hexamethylenetetramin, the cyclic condensation product of formaldehyd and ammonia, appears to have been described first in 1860 (Butlerow: *Ann. d. Chem.* **115:** 322, 1860). Subsequently, numerous references to the preparation, properties and constitution of the substance appeared in chemical literature.

Hexamethylenetetramin is said to have been first used for therapeutic purposes by G. Bardet, who, in 1894, reported to the Société de Thérapeutique that he believed this substance to be a uric acid solvent. At about the same period,

A. Nicolaier, who gave Bardet credit for suggesting the use of hexamethylenetetramin as a uric acid solvent, announced the discovery of its antiseptic action (*Centralbl. f. d. med. Wissensch.* **32**:897, 1894; *Deutsche med. Wchnschr.* **21**:541, 1895). Shortly thereafter as a result of Nicolaier's publication, the Chemische Fabrik auf Aktien vorm. E. Schering, Berlin, Germany, began to offer the product to the medical profession under the trademarked and non-descriptive name "Urotropine." In the United States, it was marketed by Schering and Glatz, who then were acting as American agents for the Schering works of Germany.

It soon became evident that hexamethylenetetramin was a valuable drug. As the substance was introduced at a time when new "synthetic" drugs were rapidly appearing and when unlimited and uncritical confidence was placed in them, and before the medical profession became skeptical of the claims advanced by manufacturers for their respective "discoveries," it was not long before this new drug was placed on the market by many firms, each applying its own name and often keeping the chemical character of it in the background. Some of the names which were thus applied to hexamethylenamine were Cystogen, Aminoform, Formin, Uritone, Urisol, Cystamine.

In 1907 the late Professor J. O. Schlotterbeck, then a member of the Council, protested against the confusion caused by the marketing of a given drug under different names. He stated that it was not uncommon for a physician to prescribe two or more of these identical substances in the same mixture, expecting to get the combined action of different urinary antiseptics; also, that patients had been treated first with hexamethylenamin under one name and later by the same substance under another name (THE JOURNAL, Jan. 19, 1907, p. 241).

Hexamethylenetetramin was admitted to the eighth revision of the U. S. Pharmacopeia. In part because of this official recognition and standardization and in part because the extravagant reports of its virtues had been largely discounted, physicians have in general, prescribed the drug by its pharmacopeial name, with one notable exception: Urotropin. One reason for this is that Utropin was the first proprietary brand of hexamethylenetetramin introduced; a second reason is that through the extensive and persistent advertising of the proprietary name under which the substance was introduced, it has become firmly fixed in the minds of many physicians. Another is that the product was claimed to be of greater purity than the product sold under the pharmacopeial or other name although no evidence confirmatory of this claim has ever been published. On the other hand, Daniel Base, as long ago as 1907, found that hexamethylenamin sold under its pharmacopeial name is just as pure as when sold under proprietary names. When, in 1907 urotropin was admitted to New and Nonofficial Remedies, the published description showed that it was manufactured by

the Chemische Fabrik auf Aktien vorm. E. Schering, Berlin, and that Schering and Glatz were the United States agents. In 1919, the description was revised to show that Schering and Glatz were no longer selling the German product.

While it is the general practice to omit articles that are admitted to the U. S. Pharmacopeia for the reason that their quality is guaranteed under the federal Food and Drugs Act and because pharmacopeial nonproprietary articles are rarely advertised with claims that require the Council's control, yet, in the case of Urotropin, it was retained because it was sold under a name not recognized in the pharmacopeia and because special (proprietary) claims were made for it.

Urotropin Marketed Under Unwarranted Therapeutic Claims

The period for which Urotropin stood "Accepted" expired with the close of 1921. To determine its continued eligibility for New and Nonofficial Remedies, the Council examined the labels and circular matter sent by Schering and Glatz for the purpose and also a booklet "Urotropin," subsequently sent by the firm to physicians.

It was found that the pamphlet contained a number of unwarranted statements. Particularly objectionable are the claims made for the use of Urotropin as an antiseptic in body fluids that are alkaline, such as the cerebrospinal fluid, bile, aqueous humor of the eye, saliva, the excretions caused by middle ear infection and other excretions of the nasal, bronchial, laryngeal and mucous membranes. The lack of efficacy of hexamethylenamin in alkaline secretions is generally admitted and the clinical references to the use of hexamethylenamin in the pamphlet are obsolete. In the introduction to the pamphlet, Schering and Glatz state that they are well acquainted with the scientific research work discrediting the efficiency of hexamethylenamin in nonacid mediums, but that they feel that the accumulated evidence for its efficacy in such conditions should not be "brushed aside." However, the pamphlet is not made up of quotations, but of unqualified statements. With one exception, all references to the antiseptic properties of the drug in alkaline mediums are previous to 1913, that is, before the importance of reaction of the medium was fully appreciated. To quote these earlier articles without regard to the later work, which in most eyes discredited them, constitutes in effect an exploitation of this brand of hexamethylenamin under unwarranted therapeutic claims.

Urotropin a Brand of Hexamethylenamine, U. S. P.

In consideration of the confusion which arises from the application of different names to an identical article, the rules of the Council provide that when an article which has been accepted for New and Nonofficial Remedies is admitted

to the U. S. Pharmacopeia under another name, it will be retained, provided the official name is given prominence on the label and in the advertising of such article. Neither the label nor the advertising for Urotropin gives prominence to the pharmacopeial name as a synonym nor indeed does it bring out the fact that Urotropin is a brand of hexamethylenamine, U. S. P. Schering and Glatz, Inc., was advised that Urotropin could be retained in New and Nonofficial Remedies only on condition that the objections to the therapeutic recommendations were removed and on agreement that the U. S. P. name appear on the labels and circular matter. The firm did not offer to make the product eligible for continued recognition; accordingly the Council directed the omission of Urotropin because of conflict with Rule 6 (Unwarranted Therapeutic Claims) and with Rule 8 (Objectionable Names).

VITAPHOS

Report of the Council on Pharmacy and Chemistry

Because of inquiries received, the Council has authorized the publication of the article which appears below. The Grain Chemical Company, Inc., says that it does not intend to put Vitaphos on the market.

W. A. PUCKNER, Secretary.

In 1917, the General Drug Company requested the Council to consider its preparation Vitaphos with the view of admitting it to New and Nonofficial Remedies. It was found that Vitaphos was prepared from corn (maize), that it had a composition similar to that of Phytin, a preparation found inadmissible to New and Nonofficial Remedies, and that the claims made for it were exaggerated and unwarranted. The following statement of the consideration of Vitaphos was adopted by the Council and sent to the General Drug Company:

Vitaphos is a product of The Grain Chemical Company, sold by the General Drug Company, New York. According to the specifications of a patent submitted by the General Drug Company, Vitaphos is obtained by precipitating the liquor in which corn is steeped as a preliminary step in the manufacture of corn starch. The liquor, which is acid from the presence of sulphurous acid, is rendered alkaline and the precipitate which is produced is collected and purified. This purified precipitate which contains nitrogenous matter and certain organic and inorganic phosphates, is the substance Vitaphos.

Vitaphos is not of constant composition and is not a new product. According to the patent specifications, it contains from 2 to 3 per cent. of nitrogen and 8 to 15 per cent. of phosphorus, partly in organic combination. A printed circular issued by the General Drug Company claims 15 per cent. of phosphorus, while a statement sent to the Council declares 15.6 per cent. of calcium oxide and 13.15 per cent.

of magnesium oxide. Analysis of a specimen of Vitaphos gave 2.3 per cent. of nitrogen, 12.3 per cent. of phosphorus, with more calcium and less magnesium than the submitted analysis claims. In the circular, it is stated that the phosphorus is mainly present in the form of a "double calcium and magnesium salt of inosite pentaphosphoric acid $C_6H_6(OH)(H_{2\theta}PO_4)_5$" and the published analysis conveys the impression that the salt has a constant composition.

A product apparently closely resembling Vitaphos was introduced ten years, or more, ago under the name of Phytin, the product being made from legumes mainly. The published analyses of the compounds prepared by methods similar to those used for the manufacture of Phytin show that, depending upon the method used, they differ widely in composition. The patent according to which Vitaphos is said to be made is more recent than the patent for Phytin, but it does not make a new product, nor is it likely to produce one of definite composition.

According to the advertising, Vitaphos is one of the numerous "nerve stimulants" exploited in recent years. It is claimed to be valuable because the phosphorus is in the form of an organic compound and not as an inorganic phosphate. Thus it is claimed:

> "All inorganic phosphorus, when taken internally, even in minute quantities, must be converted into organic combinations before assimilation can take place. Vitaphos, however, is readily and fully absorbed without discomforting sequelae."

These claims are without warrant. Also these:

> "Vitaphos is a marked stimulant to the nervous system and aids actively in the growth of bone. It tends to reduce tissue waste and to preserve the body.
>
> "In Vitaphos practically the entire content of phosphorus of the cereal is present, and being a plant product, it furnishes the ideal phosphorus compound, in that the phosphorus is in combination with an organic base such as is suitable for furnishing phosphorus to the delicate organization of the germinating plant."

It does not follow that because this inosite phosphate may have a certain value to the germinating plant, it has use in human growth. In the patent specifications for Vitaphos, the inventor seems to recommend the product as a yeast food.

Vitaphos is said to be of value in a long list of disorders. One half page of a circular is devoted to an enumeration of the conditions in which it is claimed to be indicated. It is asserted:

> "Vitaphos is useful in the treatment of every condition in which phosphorus is indicated . . .
>
> "The principal use of Vitaphos is as a nerve tonic."

The praises of lecithin are sung, but Vitaphos is claimed to be much better because it has more phosphorus and nitrogen.

The claims for therapeutic efficiency are not greatly different from those made in the past for other phosphorus compounds such as the hypophosphites, the glycerophosphates, lecithins, etc., which have been the subjects of Council reports (The Hypophosphite Fallacy, J. A. M. A. **67**: 760 [Sept. 2]; The Therapeutic Value of the Glycerophosphates, J. A. M. A. **67**: 1033 [Sept. 30] 1916; Lecithin Preparations Omitted from N. N. R., A. M. A. Council on Pharmacy and Chemistry Reports, 1915, p. 122).

There is no evidence to indicate that the phosphorus of Vitaphos is more readily available than in inorganic phosphates. It seems well established that these organic phosphorus compounds have no advantage from that standpoint over the simple inorganic phosphates.

Some of the claims of the Vitaphos circular read much like those advanced for Phytin, which the Council found unacceptable about two years ago (J. A. M. A., Jan. 30, 1915, p. 456). Just as it was asserted that Phytin "radically and permanently removes sexual debility" so it is claimed that "Vitaphos has a marked effect in cases of sexual exhaustion and debility, acting as a tonic and stimulant and in many instances as an effective aphrodisiac." Vitaphos and Phytin are essentially identical.

The Council declared Vitaphos inadmissible to New and Nonofficial Remedies because the therapeutic claims are exaggerated and unwarranted.

The Grain Chemical Company, the producer of Vitaphos, thereupon requested postponement of the consideration of Vitaphos in order that its clinical value might be further determined.

In 1919, Vitaphos was again presented, apparently as a product "prepared from corn and autolyzed yeast."

The following memorandum on the new Vitaphos was prepared by the referee in charge of the preparation and sent to the Grain Chemical Company by the Secretary of the Council:

In the lack of further statements regarding the make-up of Vitaphos (which according to the letter of H. A. Metz has been changed in composition from time to time, Z being the latest component to be used) the referee must assume that "Vitaphos is prepared from corn and autolyzed yeast" (Dubin: Med. Times **47**: 43 [Feb.] 1919).

The experimental evidence, conducted with pigeons fed on a diet of polished rice, merely suggests that additions of yeast preparations, either prevent the polyneurites ordinarily developed by such a diet or relieve the symptoms if they have already appeared prior to feeding yeast products. In other words, the product contains some of the so-called "antineuritic vitamine", a factor essential to prevent the onset of beriberi when certain types of inadequate diets are used. There is nothing novel about this; and corn is not essential to the preparation of "antineuritic vitamine" from yeast.

There is no demonstration that yeast or its derivatives prevent scurvy; on the contrary, the available experimental evidence is opposed to this hypothesis.

In so far as is known at present, the water-soluble vitamine in yeast is only one of the vitamine factors essential to growth. There is neither evidence nor probability for the justification of the "hope" (Dubin, p. 43) that Vitaphos will prove of value in such a broad way as is indicated by "failure on the part of the agents of metabolism, in non-pathologic conditions, to maintain proper body nourishment." There is no evidence adduced, for example, that it is antiscorbutic, or that it contains the essential vitamine factor present in butter fat.

The claims regarding the richness in nitrogen and phosphorus have long since been held as scientifically undemonstrated.

In 1920, under date of February 25, the Grain Chemical Company presented a new Vitaphos which it claimed was prepared from "corn, autolyzed yeast, and orange juice in vacuum at a low temperature, thereby assuring the presence of the vitamines in active form, since it has been amply demonstrated that under such conditions no deleterious influence is exerted on the activity of the vitamines." The product

is recommended primarily as a preparation furnishing "antineuritic, antirachitic, and antiscorbutic vitamines." In support of this contention, a paper by Dubin and Lewi on "The Preparation of a Stable Vitamine Product and Its Value in Nutrition" (*Am. J. M. Sc.* **159**:264 [Feb.] 1920) is offered. Emphasis is further placed upon the content of calcium (amounting to 10 per cent. of calcium oxide), and of phosphorus 15 per cent., in the product; and this feature is pointed out in relation to the well known need of calcium and phosphorus in the metabolism of growth.

On this latest form of Vitaphos, the referee reported:

Without entering into minute details regarding this newest Vitaphos product and the claims made for it, the referee desires to call atttention to the following points:

So far as one can judge from the very indefinite statements regarding composition, the product is largely composed of Phytin and other constituents of "corn solubles." Why such material should continue to be included in a supposedly novel therapeutic product is not clear. In fact, it is admittedly merely an incidental component of Vitaphos, although, according to the submitted "composition," it makes up a large proportion thereof. The calcium content can at best play a very insignificant rôle. For if the advised dosage of 15 grains per day (for children) is followed this would yield 0.1 gm. of calcium oxide, a quantity less than is contained in 3 ounces of cow's milk. In fact, if one examines the balance protocols of the metabolism experiments on children, in the submitted article by Dubin and Lewi, the calcium content of the Vitaphos, in comparison with that of the rest of the diet, can have played at most an insignificant part in the calcium nutrition of the children—even assuming that the Vitaphos calcium was properly utilized. As a matter of fact, the retention of calcium in the most successful infant experiments recorded was no more favorable, and in cases actually less favorable, when Vitaphos was given than in the control periods. We may, therefore, dismiss consideration of any special virtue in the calcium of 15 grains of this product, so long as cow's milk and inorganic lime salts are readily available.

There is no evidence that Vitaphos contains all *three* of the vitamines claimed for it. Neither yeast, nor orange, nor corn solubles are demonstrated to have any antirachitic potency, particularly if the latter is assumed to be represented by the fat-soluble vitamine (fat-soluble A). In support of this, the referee refers to the investigations of Hess, as well as the report of the Medical Research Committee, National Health Insurance, on the Present State of Knowledge Concerning Accessory Food Factors, Special Report Series No. 38, H. M. Stationery Office, London, 1919.

According to the submitted composition, Vitaphos would not be expected to contain fat-soluble vitamine, nor has any evidence been offered that it will cure rickets.

Inasmuch as it is admitted (in the 1920 Vitaphos communication) that "the value of Vitaphos lies largely in its vitamine content," the referee can see no advantage in the use of a complicated mixture of unknown composition with respect to the quantity of orange and yeast—the potent factors—included therein. At the present time, yeast products are available in dried form, and orange juice is almost always available as such, and can readily be dried without loss of antiscorbutic potency. In using yeast and orange juice as such the physician may know something, even if in an empiric way, about the dosage required. In the case of Vitaphos he has no facts, aside from the dosage statement

on the label, upon which to base his procedure. The referee believes that the interest of medicine will be better served, so far as the "antineuritic" and "antiscorbutic" vitamines are concerned by administration of simpler products of known characteristics until vitamines have been isolated or furnished in some more concentrated form. Recent investigations show no advantage in the use of autolyzed yeast in the preparation of its water-soluble vitamine (Osborne and Wakeman: J. Biol. Chem., 1919).

The Council adopted the report of the referee and declared Vitaphos inadmissible to New and Nonofficial Remedies for these reasons:

1. The composition of Vitaphos is indefinite (Rule 1). In spite of the "composition" furnished the Council, no real indication of the amount or the sources of the active ingredients is given. The "tentative analysis" means little from the therapeutic standpoint. How is one to judge, therefore, whether a dose is equivalent to much or little orange juice or yeast?

2. The therapeutic claims are unwarranted (Rule 6). Vitaphos cannot be an "antirachitic" in the sense of containing the fat-soluble vitamine. Its physiologic value as a source of calcium is also exaggerated.

3. Vitaphos is an unscientific mixture (Rule 10), which presents no advantage over readily available vitamine preparations.

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