American Medical Association
Council on Pharmacy &
Chemistry

annual
(A) REPRINT OF THE REPORTS

OF THE

COUNCIL ON PHARMACY AND CHEMISTRY

OF THE

AMERICAN MEDICAL ASSOCIATION

WITH THE

COMMENTS THAT APPEARED IN
THE JOURNAL DURING 1909

1909

PREFACE

The reports of the Council on Pharmacy and Chemistry of the American Medical Association have appeared from time to time in more or less complete form in *The Journal of the American Medical Association.* The more technical and scientific parts of the reports, however, in many cases, both from lack of space and because of their technical nature, have been abstracted or entirely omitted from the published reports. Believing that these scientific investigations should be available to scientists in general, especially to chemists, pharmacologists, etc., interested in medicine, this volume, containing the complete reports of the Council for 1909, as well as the comments which appeared at the time of publication, has been prepared.

Press of
American Medical Association
Five Hundred and Thirty-five Dearborn Avenue
1910

CONTENTS

Reports of the Council on Pharmacy and Chemistry

ADVERTISED CLAIMS FOR COLLARGOL

(From The Journal A. M. A., March 13, 1909.)

The attention of the Council on Pharmacy and Chemistry has been called repeatedly to the extreme and extravagant claims made for collargol, a product which the Council has accepted. The following are examples of such claims and appear in the advertising matter distributed by Schering & Glatz, the American agents for the preparation:

"COLLARGOLUM

"Is a powerful and harmless systemic antiseptic in the most varied medical and surgical infections. It checks beginning sepses and often effects brilliant recoveries in desperate ones. Recent investigations show that with its direct bactericide energy it exerts a marked electrolytic [*] and leucocytogenetic action, and thus greatly aids the natural protective forces of the body.

"Used topically, by mouth, rectally, intravenously or by inunction, Collargolum forestalls the development of sepsis from accidental or operative wounds or child-birth, arrests beginning medical and surgical infections, and often achieves brilliant recoveries in apparently hopeless cases."

Since these and similar claims were considered extravagant and unwarranted, a motion was adopted to rescind the approval of collargol and to publish the reasons therefor. Later, this action was reconsidered in part, and in place of it, it was moved that the matter be referred to a committee of three—a surgeon, a pharmacologist and an internist—to be composed of men not members of the Council. Dr. J. T. Bottomley, Boston, Dr. C. W. Edmunds, Ann Arbor, and Dr. David L. Edsall, Philadelphia, were appointed and accepted the position.

Schering & Glatz, having been advised of the appointment of this committee, objected and requested that Dr. S. Solis Cohen, Philadelphia, Dr. Reid Hunt, Washington, D. C., and Dr. Roswell Park, Buffalo, N. Y., be added to the committee. This request the Council agreed to and these gentlemen were

* See footnote page 11 of this book.

asked to serve. Drs. Cohen and Hunt accepted the position, while Dr. Rosweil Park declined to serve. Accordingly, the committee was constituted as follows: Dr. Edsall, chairman; Dr. Edmunds, Dr. Bottomley, Dr. S. Solis Cohen and Dr. Hunt. It should be noted that while the members of the committee selected by the Council were non-members of the Council, Dr. Edsall was later appointed a member by the board of trustees.

Two reports have been submitted by the committee, a majority report signed by Drs. Bottomley, Edmunds, Edsall and Hunt, and a minority report signed by Dr. Cohen. Both reports agree on the point at issue, viz., that the advertising matter issued by Schering & Glatz is misleading, both through exaggeration and misquotation.

It was moved that both reports be accepted and published, and that the thanks of the Council be extended to the members of the committee. The motion having been adopted, the reports of the committee were sent to Schering & Glatz, who replied, and their reply was submitted to the committee. The committee reported to the Council recommending minor changes in the report. The Council then voted to adopt the report as amended and directed publication. In accordance with this action, the majority and minority reports of the committee are published in this issue.

W. A. Puckner, Secretary.

COLLARGOL (CREDÉ'S COLLOIDAL SILVER)

Reports of the Committee Appointed to Consider the Claims Made Regarding Its Effects

(From The Journal A. M. A., March 13, 1909.)

MAJORITY REPORT OF THE COMMITTEE

TO THE COUNCIL ON PHARMACY AND CHEMISTRY:

Gentlemen:—The attention of the Council was repeatedly called to certain claims made by the firm of Schering & Glatz for the substance collargolum. These claims were of a most unusual character. If true, they would place the substance in the front rank of therapeutic agents; if unfounded, they would constitute a most reprehensible abuse of the confidence of the medical profession. In view of the importance of the matter, the Council wished to proceed with especial thoroughness. It was decided, therefore, to appoint a committee to consider the question whether exaggerated statements are contained in the pamphlets on collargol that have been distributed by the above-mentioned firm, the agents of the prep-

aration in this country. The undersigned, being four of the five members of the committee thus appointed, beg to submit the following report:

We have been delayed in finishing the report, because it was necessary to give considerable time to it, and, with our other duties, it was impossible to accomplish sooner the amount of work that seemed desirable. Any necessary delay, however, appeared wholly justified by the fact that the question is of very considerable importance, not alone in connection with the substance under consideration, but also because entirely similar conditions prevail with a large number of proprietary preparations, domestic as well as foreign, regarding which extremely optimistic claims are made. Any report such as this may exercise an important influence on similar investigations that are likely to appear desirable in the future.

THE IMPORTANCE OF THE QUESTION

It is manifest to any one acquainted with the situation that the very question that we are asked to settle with regard to a particular proprietary substance is one of extreme importance in its relation to many such substances; for in no way has more harm been done to legitimate methods of advertising articles of this kind, and in no way, likewise, have physicians and their patients been more improperly dealt with, than by advertisements that make apparently well-founded claims, which prove to be more or less completely erroneous, misleading, and often essentially fraudulent, if opportunity is secured to investigate their accuracy. Such practices deserve the severest censure whenever they exist.

At the present time this is, of course, particularly the case with claims regarding the pharmacologic effects and the therapeutic value of proprietary substances; for it is very easy to make assertions about these matters that are extremely difficult to disprove, even though they are grossly exaggerated or actually false, unless serious attention and much time are given in each instance to an investigation of the basis of the claims. This makes it all the more desirable, however, that, so far as possible, all claims that are very exceptional, such as those made for collargol, should be carefully investigated, and that, if any exaggerations or misstatements are found, these should be handled with great openness. Otherwise much harm will continue to be done to the public, who ultimately pay the money cost of these preparations, and whose health, and even life, suffers when anything is used for therapeutic purposes with an exaggerated impression of its value, more effectual treatment being thereby often excluded. Constant

injustice will also be done to the medical profession, because of the deception practiced on it, and to reliable manufacturers, because they must struggle against unfair methods. It is notorious that such practices are employed by otherwise honorable firms, merely because they are so prevalent; but this is all the more reason why we should wish warmly to welcome every opportunity to aid those who adopt proper methods of advertising and keep within the bounds of exact truth, and to distinguish their methods from those that tend to deceive.

CONCLUSIONS BASED ON STUDY OF LITERATURE

The committee has thought it desirable, in this instance, to confine itself, so far as possible, to a critical study of the literature to which the agents of the preparation themselves refer in their advertising matter, going beyond this only in case it should be necessary in order to confirm or disprove questionable claims; for we must repeat that the question before the committee concerned merely the truthfulness of the advertising matter. We were not instructed to prove, to disprove or to define any supposed or actual intrinsic merits of the substance; we were not called on to decide whether the claims made were possible, but merely whether they were based on adequate evidence. Our task, therefore, consisted clearly in the critical examination of the evidence submitted by the agents. We have found it possible to confine ourselves entirely to the literature referred to in Schering & Glatz's pamphlets and to a few references obtained directly from these articles. We have made no actual special search of the literature beyond this, and we have secured no verbal opinions and have ourselves conducted no experiments, and have rigorously excluded the personal clinic experience of the signers of this report, because any conclusions derived from such sources might be thought to depend on the opinion of persons biased for or against the preparation.

Some experiments were conducted for us to test one point, namely, the influence of the preparation on the actual toxicity of bacterial toxins. This appeared to be necessary, since no definite evidence was offered on this point. All the evidence that we have used is, therefore, already in print and, consequently, available to any one in the same form as that in which we have used it, in case any one desires to determine the correctness of what we have to say—excepting only the experiments mentioned, and these are given in the course of this report.

In reaching our conclusions as to the claims set forth in the pamphlets we have read critically more than 100 articles

selected from the list of over 300 references in the pamphlets; those which we have read comprising all the evidence offered regarding its pharmacologic effects and all the clinical reports on general infections contributed by clinicians whose professional positions or general standing are such as to make their opinions, whether favorable or unfavorable, of undeniable value. We have also read all other articles by any authors regarding its use in general infections, so far as they were available to us, if particular stress had been laid in the pamphlets on their contributions. The opinions that we shall give are based on the information gained in the way indicated.

THE DISPUTED CLAIMS

Let us now consider the points at issue. The claims to which the Council on Pharmacy took exception and desired to have investigated are essentially comprised in the following statement which appeared in pamphlet that is marked "B," as sent to the committee:

"Collargolum, Soluble Metallic (Collodial) Silver, is a powerful and harmless systemic antiseptic in the most varied medical and surgical infections. It checks beginning sepses and often effects brilliant recoveries in desperate ones. Recent investigations show that with its direct bactericide energy it exerts a marked electrolytic [*] and leucocytogenetic action, and thus greatly aids the natural protective forces of the body. In severe infections, collargolum should be injected intravenously or per rectum; but in mild cases, inunctions of Unguentum Credé, 15 per cent. Collargolum Ointment, are indicated. Collargolum and Unguentum Credé should be employed freely as soon as septic symptoms appear. Their prophylactic use is especially advantageous in puerperal cases."

In the pamphlet which appeared in the autumn of 1907, and which was sent to the committee as further evidence of the correctness of the statements, the following appears on the front page:

"Communications from foremost clinics and clinicians of Europe and America demonstrate to certitude that—

"Used prophylactically, it is an almost unfailing safeguard against sepsis from accidental or operative wounds or child-birth;

"Administered early, it usually arrests incipient medical and surgical infections, or renders their course briefer and milder;

"Even when employed only as a last resort it sometimes achieves brilliant recoveries in desperate, apparently hopeless cases.

"Whether exhibited intravenously, intramuscularly, rectally by inunction or locally, Collargolum is entirely harmless. Hence it

* When action was first taken Messrs. Schering & Glatz asserted that the Council misquoted one claim and said: "We never asserted that Collargolum possessed a marked 'electrolytic' action." When referred to their own pamphlets for verification, they replied that the word "electrolytic" is "a typographical error for electrocatalytic." Later Schering & Glatz say: "Our friends state that in speaking of the actions of Collargolum the word 'electrocatalytic' should be modified to read 'catalytic.' . . ."

should be used freely as soon as possible after the appearance of septic symptoms. Delay or timidity in the administration of the remedy endanger the success."

In a pamphlet entitled "New Therapeutic Agents," distributed in October, 1908, claims identical with these last quoted are made, and also the following:

"These therapeutic powers are explained by its catalytic action, which destroys toxins, bacteria and diseased cells by the phagocytic reaction which it occasions and by its inhibitory influence upon microorganic growth—effects demonstrated by laboratory studies."

Manifestly the claims made in these statements are very remarkable. There is no other drug known that has any widely credited effect on general infections with staphylococci, streptococci, the pneumococcus, typhoid bacillus, tubercle bacillus, anthrax bacillus, and the host of others of the most common forms of infections which are mentioned in these pamphlets as having been cured by collargol. Infections with some of the higher forms of bacteria (actinomyces, pathogenic yeasts, etc.) appear to be at times favorably influenced by drugs, chiefly the iodids. With several parasitic infections (malaria, syphilis, and perhaps some trypanosome infections) we have special specific drugs for each disease.

Such, in brief, have been our very limited resources in regard to infectious diseases and their treatment with drugs. With the great majority, and this includes most of the common infections, we have had no therapeutic measures of any kind that could rationally be considered to exercise any noteworthy direct control over the infection itself—we have, rather, been confined to measures that help the patient by increasing his resistance and to those that antagonize dangerous symptoms. If the claims regarding collargol are correct, we have in it for the first time a drug that will prevent nearly any bacterial infection if used prophylactically (especially puerperal infections, but these may be due to a great variety of bacteria). It is also said to check existing infections, if used early, and often produces recovery in desperate cases. No distinction is made against any variety of infection—it acts "in the most varied medical and surgical infections."

If this is true, the drug is a tremendous boon to humanity; if not true, these claims are cruelly misleading. No drug on the market that has a reliable standing has made for it claims so far-reaching as these. The very importance of these claims demands that they should not be advanced without evidence that will withstand critical examination and that is at least reasonably convincing and fairly free from contradiction—at any rate among those writers whose opinions are justly looked up to.

TWO KINDS OF ACCEPTABLE EVIDENCE

The burden of furnishing this evidence rests clearly with those who make such unusual claims. It is, of course, not our province to present new evidence for or against the drug, but to examine that submitted. Two kinds of evidence we may be prepared to find convincing: First, careful experimental demonstration that a preparation has properties that justify the expectation that it will produce the effects claimed, this to be followed by a reasonable amount of clinical demonstration that it does produce these effects in the sick human being; second, an overwhelming mass of clinical evidence that, whatever the pharmacologic action, the substance does produce the effects that are claimed. Both these forms of evidence together would be most satisfactory, but the latter alone will do, if the facts are unassailable, for we have repeatedly learned to recognize valuable effects from drugs empirically, and without being able to demonstrate clearly their manner of action.

THE EXPERIMENTAL EVIDENCE

In order, however, that the first method be convincing of such striking effects, the experiments must be extensive and the results must be very positive, and creditable investigators must not be seriously at variance with each other in their facts and conclusions. In order that clinical results shall be dependable, they must be very numerous, and the opinions must be reasonably near to unanimity, and, far more than this, they must be contributed by trained observers, and must show evidence of accurate and critical observation. Without these united characteristics, mere numbers of reports or observations count for nothing, for we well know in how many instances wonderful results have been thought to have been obtained from therapeutic measures that more or less rapidly fell into utter disrepute. Every one, we think, will agree with the conditions we have laid down. We state them here only to indicate frankly the attitude with which we approached the consideration of the testimony.

As to the pharmacologic properties claimed for the drug, those properties, as well as the clinical effects, are most systematically described in the pamphlet issued in 1907 and marked by you "C," and since this pamphlet in its context or in the bibliography covers nearly the whole matter we may devote our attention chiefly to the statements made in it. When any pamphlet is referred to henceforward we shall mean this pamphlet, unless otherwise stated. When references are made to individual investigators to substantiate the claims made we shall, of course, need to discuss the work of

these authors from a critical standpoint and comment on it with customary scientific frankness.

COLLARGOL IN THE BLOOD STREAM

In the beginning of the description of the pharmacologic properties, on page 4, it is stated:

"After intravenous injection, collargolum circulates in the bloodstream only a short time; two hours afterward, it is already deposited in the liver, lungs, heart, spleen, intestines and kidneys. After eight to ten hours it is present in the blood only in traces," etc.

No authority is given for the statement that any remains in the blood eight to ten hours after its injection. Cohn (who is repeatedly quoted by the writer of the collargol pamphlet in other connections) states directly that he could find none in the blood after forty-five minutes. The statement in the pamphlet might easily convey the impression that collargol circulates in the blood for eight to ten hours in effective quantity. This is evidently not the opinion of the agents, for, in a typewritten sheet sent to the committee by Schering & Glatz, it is argued that Brunner's results in experiments with collargol, in which the substance was injected after the infection of animals, are incomplete, because "after *an hour* (italics ours) collargol has disappeared from the blood." It is, of course, a matter of great clinical moment whether collargol is effective after one hour or for more than ten hours. The ambiguity is, therefore, very regrettable, though we are ready to believe that no misstatement was intended.

No evidence is given in the pamphlet as to the condition in which collargolum circulates—a matter of very serious importance, it would seem, for all its peculiar combination of harmlessness and great potency against infections is referred to its colloidal nature, and, unless it circulates in colloidal form, this which is emphasized as the only essentially valuable characteristic that it is recommended as having is lost. In your correspondence with Schering & Glatz which you sent to the committee, you inquired about this matter, and they answered that it was a difficult matter to determine, and that they had referred the question to the manufacturers of the substance, the Chemische Fabrik v. Heyden. Later, in their letter of Oct. 24, 1907, having heard from the manufacturers, Schering & Glatz state:

"That collargolum circulates in the body as collodial silver is shown by Hocheisen's findings, who found that it had precipitated on endocarditic ulcerations in the form of bluish-black particles. Moreover, if collargol were changed in the body to ordinary silver, or to silver salts, the large doses which are usually employed would inevitably occasion argyria—an effect which has never been seen

from it. Hamburger (*Arch. f. physiol. Med.*, 1906, Nos. 2 and 3, pp. 83-97) says that the fact that collodial silver remains as such in the blood is due to the presence of other colloids, i. e., albumin."

This is certainly not evidence. Hocheisen's observations mean merely that it had precipitated out in some form. Whether this was colloidal silver at the time of its precipitation or shortly before is not determined by his observations. Indeed, he made no attempt to settle this point. The lack of argyria means nothing definite as to the actual form in which the drug circulates, and Hamburger merely expresses an opinion on the basis of analogies with experiments "in glass"—he did not actually investigate the question, and it should be noted also that Hamburger speaks here simply of "colloidal silver," and that in the sentence immediately preceding the portion quoted speaks of how much longer electrolytically prepared colloidal silver remains in the blood than does that which is chemically prepared (collargolum is chemically prepared). We have, in fact, been unable to find any definite evidence as to the form, colloidal or other, in which it circulates, but we might direct attention to the fact that van Waveren (*Weekbl. voor Geneesk.*, No. 10, 1905) is said, in an abstract of his article, to have reached the conclusion, after experimental work, that it is quickly transformed into silver-salts in the blood. The original of his article we were unable to consult. We would also direct attention to the fact that Bamberger, whose paper is referred to favorably in another connection in the pamphlet, states (and this is not quoted in the pamphlet) that it precipitated out after injection, and we must look on collargol as providing in the blood, not a solution, but a large number of actual particles of silver, and he considers that whatever effects are obtained by it are due chiefly to the leucocytosis that these numerous foreign bodies set up. The claim, then, that collargol circulates as such in the blood is not supported by evidence, and any statement that it has been proved that it does so circulate is directly misleading.

ABSORPTION OF COLLARGOL ENEMATA

Further down on page 4 of the pamphlet it is stated that Henri and Gompel, and Loebl, have demonstrated that collargol is absorbed when administered as an enema. Here there is, in the one case, an unjustifiable assumption, and in the other painfully weak evidence. Henri and Gompel, according to the reference given, did not work with collargolum at all, so far as is stated. They use, on the contrary, colloidal silver, electrolytically prepared. This may be the same as collargolum, or it may not; but it is a noteworthy fact that

a number of Henri and Gompel's countrymen consider that the effects of the two are different, and actually describe differences that they have observed in the two substances or in their therapeutic or experimental effects. Until conclusive evidence has been produced to show that they are identical, we have no right to assume that the results of experiments done with the one may be accepted as applying to the other, any more than we have a right to assume that many other substances that appear superficially to be alike have the same actual properties until so proved.

Loebl's work is so far from offering satisfactory evidence that it scarcely deserves discussion. His evidence is comprised in the following observations. He administered per rectum in several cases in which death was sure to occur. We quote from the translation of his article in pamphlet "D":

"Histologic examination of the rectum in the one case, as that of the spleen, liver, kidneys and rectum in the other, showed *no* opaque granules [italics ours] of metallic deposit in either the stained or the unstained specimens. Only the unstained sections of the rectal mucosa in the former case showed the epithelial layer clouded and looking as if it had been dusted over with something; *but it was uncertain whether this was due to absorption or to post-mortem imbibition* [italics ours], as the last injection was administered only a few hours before death. In the spring of 1903, however, in a case of erysipelas that died a few days after the last collargolum injection, high magnification showed isolated black granules in the epithelium of the glomeruli *which were probably* [sic! italics ours] precipitated silver."

We doubt whether any one would be convinced from these observations that collargolum enemata are absorbed!

IS IT ABSORBED BY GASTRIC OR INTESTINAL MUCOSÆ?

It is also said that abundant experimental proof exists of the fact that collargolum is absorbed by the skin, by the subcutaneous and muscular tissues, and by the gastric and intestinal mucosæ. There is some evidence that it is absorbed by the skin and by the subcutaneous and muscular tissues, though Schering & Glatz omit to state here the highly important fact that many of the warmest advocates of the use of the substance insist that its subcutaneous use is impracticable, because of the danger of causing severe local reaction. We have been unable to discover any definite experimental evidence that it is absorbed by the gastric and intestinal mucosæ, though it is stated to be abundant. The closest that we have come to finding evidence is their statement from the October, 1907, pamphlet, p. 4:

"When collargolum is given per os it may be that it is precipitated by the free acid of the gastric secretion, though Beyer thinks not. Even if it is precipitated, however, it again goes into solution when the acids are neutralized by the alkaline intestinal juices."

Who, however, has presented any direct evidence that it actually is absorbed? Who has shown that after being attacked, not only by the hydrochloric acid of the stomach contents, but also by all the other substances in the digestive tract, it is still colloidal silver when it comes to the point of being absorbed, even if it does go into solution again in the intestinal contents? Most drugs, when given by mouth, are absorbed in a different form from that in which they are administered, and we certainly can not assume, without evidence, that this particular drug is an exception. With most drugs the changes that occur are of no consequence, but in this instance we must remember that the original form is of paramount importance in its supposed action. Furthermore, the fact is repeatedly stated in articles referred to in Schering & Glatz's advertising matter, that colloidal silver, *because of its colloidal character, does not pass animal membranes*, contradicts their other contention that it passes the gastric or intestinal mucous membrane in colloidal form, and it is only in colloidal form that special virtues are claimed for it. Nevertheless, this drug is positively recommended for oral and rectal administration in dangerous diseases. The statement, then, that there is abundant experimental evidence of the absorption of collarogolum as such from the alimentary canal is not only misleading but totally unjustifiable.

NOT EXCRETED IN THE URINE

Also it is stated (p. 4) that Baginsky, Buberl and Kunz-Krause have shown the presence of collargolum "in the renal excretion," thus indicating that it is partly excreted in the urine. The facts are, however, that Lange, who worked under Kunz-Krause's direction (this is the article to which the pamphlet refers, Kunz-Krause apparently having done no work on it himself) found it *absent* from the urine, and distinctly so states, and this fact is referred to in several instances by authors whom Schering & Glatz quote in this connection. It may, indeed, be seen in print in their other pamphlet that you have marked "D," in the matter that they quote on page 7: ". . . or, perhaps, as Lange holds, the metal is not excreted in the urine." Buberl states clearly that in three of the four cases in which he found it in the urine there was pyuria, and he considers its presence accidental and due merely to the fact that the leucocytes of the pus had carried some into the urine with them—not that it was excreted by the kidney. Baginsky, so far as we can determine from studying the reference given, made no observations at all on its excretion. This is clearly a direct inversion of the results

of one of these authors, a misrepresentation of the second, and pure fiction in regard to the other. These misstatements can scarcely be excused as "justifiable optimism."

EXPERIMENTAL RESULTS IN ANIMALS

Under the heading, "Modes of Action" (p. 4, *et seq.*) the fact is admitted that experiments on animals have not given concurrent results, but this is accounted for as follows:

> "Some of the experimenters have chosen a mode of infecting the animals which is far more brusque than occurs clinically; they have injected intravenously highly virulent bacterial cultures. Moreover, a negative result was to be expected in all cases in which the injection of Collargolum was made before or simultaneously with the injection of the infective material, as eight or ten hours after Collargolum is injected only traces of it remain in the blood. Experimenters who gave the Collargolum injections only when the animals showed signs of severe infection have saved them (Beyer, Pinto). Ernst Cohn's unfavorable report is criticised by Bamberger (Senator's Polyclinic) because Cohn injected the Collargolum before the infective material. Thus the infection reached the blood at a time when a large portion of the leucocytes was busied with the silver particles and the organism was robbed of an important element of protection. In one case, in which Cohn waited until the animal was violently ill, it at least outlived the control."

A critical reading of the papers referred to in this paragraph illustrates this matter from a wholly different standpoint, however. In one or two points the statement quoted above can be looked on only as a misleading mutilation of the work of Cohn, which, in actual fact, is both the most extensive and the most careful work that has been done on this part of the subject. This author carried out experiments on nearly thirty animals. He controlled his cultures carefully, to see that they were actually capable of producing infection. He injected collargol before infecting the animals in some cases, but in numerous instances he injected it after they had been infected. He also infected animals otherwise than by the so-called "brusque" method of injection. In a series of animals he rubbed streptococci into the skin and produced erysipelas, and these animals he treated as follows: One was injected with collargol before infecting it. Of the others, one was not treated at all and was used as a control, while of the remaining two, one, after it became ill, was given collargolum intravenously, the other, after it became ill, was given collargol by injection. It is a somewhat suggestive fact that in this group of animals the control was the last one to die.

Beyer, whose results are repeatedly quoted in contravention of Cohn's, did experiments, so far as one can determine from the report referred to, on no more than three animals. He used no methods to determine how virulent his cultures were,

so far as he states (he merely *says* that they were virulent), so that we have no means of determining whether his results were due merely to his having not produced an infection of any severity; the number of observations also is too small to be of any value as against the numerous negative results of more careful studies.

Pinto's paper we have been unable to read, but other authors who abstract it refer to Pinto as having done what is objected to in the work of Brunner and Cohn—namely, that he injected collargolum as a prophylactic. He is approved of because he seemed to get good results. Evidently the judgment of the writer of the pamphlet is governed more by commercial considerations than by scientific consistency. Even if the bias in such a case be unconscious, it is none the less misleading.

To turn back, however, to the criticisms of Cohn's results. In the first place, he did not, as is essentially stated, infect animals only by intravenous injections. We have already mentioned that he used other methods also. Further, Cohn's results are criticized in the pamphlet, as are Brunner's experiments in a separate sheet that was sent to the committee, because these authors injected collargolum before or simultaneously with the introduction of infectious material. This is a direct and clearly intentional misrepresentation of Cohn's work, for, as we have noted, he in many instances introduced the infectious material soon after the collargolum. He did it in most instances only ten to fifteen minutes afterward, to be sure, but this is just what Schering & Glatz apparently demand, when they insist that collargolum should not be injected much before the infective material, lest the collargolum disappear before the infective material reaches the blood, for, they say, collargolum disappears from the blood stream within an hour. Certainly ten or fifteen minutes after the infectious agents have been injected into the blood stream these agents and the collargolum ought to meet if collargolum is injected at this time. Furthermore, when Cohn used collargolum before he infected the animals, it was only ten or fifteen minutes before, and Brunner in some of his experiments used it only ten minutes to half an hour before he infected the animals. If within this short period collargolum had escaped entirely from the blood stream, it requires pretty nice judgment to determine whether it does, as is claimed, circulate in the blood stream at all.

COHN'S WORK NOT DISCREDITED

But the most objectionable feature of the paragraph in question is this: Bamberger's criticism of Cohn, which is

quoted above, when examined in the original, proves to be very weak and specious, and was apparently prompted by the fact that, unless he could discredit Cohn's results, his own work would have seemed wholly worthless. Bamberger, however, is truthful, in that, in connection with the criticism quoted above, he puts in the qualifying clause, in parenthesis, "This applies, however, only to the experiments with staphylococcus," thus intimating that there were other experiments to which his criticism did not apply. When Cohn's work is looked at carefully, this intimation appears important and pathetically weakens Bamberger's criticism, for the work with the staphylococcus is really only a small fraction of what Cohn did.

When Bamberger's criticism is translated into this pamphlet, however, the qualifying phrase quoted above has disappeared, and it is now in such form that it reads as if the criticism applied to the whole of Cohn's results and destroyed his conclusions. It implies that Cohn had in but one instance injected collargolum after injecting the animals; while, as a matter of fact, as we have stated, he did this many times. This is an injustice to Bamberger and misrepresents what he said, and it is somewhat worse than a misrepresentation of Cohn. Toward him and toward those who read the pamphlet, it is the opposite of what scientific men call honesty.

ITS PROPHYLACTIC VALUE

There is a further aspect of this criticism that is applied to the work of both Cohn and Brunner, though, as we have said, wholly unjustly to Cohn—the criticism, namely, that when collargolum is injected before infecting animals the results are valueless. Whatever the actual effects on infections may be, this criticism carries the critic himself into perilous channels, for this reason: We are told that collargolum is a prophylactic against infections. A prophylactic is, of course, usually given before the disease occurs; hence, before the infection occurs. On the other hand, we are told here that injecting the collargolum even ten minutes before the animals were infected resulted in the infection reaching the blood "at a time when a large portion of the leucocytes was busied with the silver particles, and the organism was robbed of an important element of protection." This would certainly be a strange and unfortunate sort of prophylactic. In other words, we are told in one place that collargol is an efficient and harmless prophylactic; but when an investigator has tried to use it for this purpose the idea is stamped as absurd. Such inconsistency is reprehensible from the moral as well as from the scientific standpoint.

Finally, regarding this matter, we would also direct attention to the fact that Trommsdorf, who did experiments on twelve animals and who did give his injections not only directly after infecting them, but also six to thirty-six hours afterward, had results that, he states, were absolutely negative. His paper is indexed under the literature of the pamphlet, but is not discussed in this connection. Also Baldoni, whose paper is indexed but not discussed, is said by several writers, whose articles are quoted, to have done animal experiments with unfavorable results. His original article was not available to us. It would appear, then, that this question has been attacked from all sides and that the great majority of the experiments have been negative. Indeed, all the investigations that show intrinsic evidence of having been performed with due care are decisively negative. The implied claim that pharmacologic experiments have been, on the whole, favorable is, therefore, entirely misleading.

To go further in quest of the pharmacologic action of collargol: The pamphlet states (p. 5) that "it has no such bactericide effect as the silver salts," and that if it had, "it would then be destructive of cells as well," and hence dangerous. We can pass this over as not offering any explanation of its action. The pamphlet, however, does dwell on its bactericidal action in various connections, and particularly refers to the work that shows that in certain concentrations it restrains the growth of bacteria. Beyer, among others, has especially insisted on the importance of this. We would note in regard to this matter the remarks made by Mann in discussing Beyer's paper (these remarks are not referred to in the pamphlet, though Beyer's paper is referred to repeatedly). Mann says that if Beyer would compare the amounts of colloidal silver necessary to control bacterial processes in the laboratory with the amounts that are used, for instance, in horses, for the purpose of controlling bacterial growth in them, he (Mann) thought that it would appear that in the latter instance something closely approaching homeopathy was being used. There is certainly no evidence that collargol, in the concentration and during the time in which it could exist in the circulation, has any bactericidal action. Statements intended to convey the impression that it has such an action are unquestionably misleading.

ITS ACTION ON THE LEUCOCYTES

Much stress is laid on the fact that collargol produces a transitory leucocytosis. There are differences of opinion on this point also, but the general evidence seems to be in favor of the occurrence of this leucocytosis. We would, however,

point out that, as several of the authors referred to in the pamphlet remark, and as is well known, a similar leucocytosis is produced by many drugs. Most of these drugs are not supposed to have the slightest influence on infections, and not one of them is credited with an influence at all like that claimed for collargolum. We may, indeed, state quite positively that at the present day the occurrence of a leucocytosis after the use of a drug is not known to have the slightest definite significance regarding its effects on a general infection; only a few enthusiasts still think otherwise. Hence this effect of collargolum, on which tremendous stress is laid in the pamphlet, cannot be considered important. The effect after injection into the spinal canal in meningitis is a different matter. There it produces a local outpouring of leucocytes which may be useful; but, as Widal and Ramond, who did this, remark, the leucocytosis was due to the presence of particles of silver, and they clearly intimate that the effect was not specific in any sense, and that any other inert insoluble substance would have done the same thing.

Finally, we are told, in heavy-faced type, that:

"By reason of its collodial nature, it has vigorous catalytic powers, which induce or enhance in the organism the process of oxidizing bacterial toxins, changing these to inert compounds."

The evidence for this is said to be that Schade has shown that:

"The electrocatalytic properties of metals, more especially in their collodial form, may be developed in the living body. They facilitate the interchange of oxygen and hydrogen in the animal tissue fluids, and effect a quick and energetic increase of oxidation in the organism. It is readily conceivable that this may rapidly deprive ptomaines and similar bodies of their poisonous character, as atmospheric oxygen does."

We need not devote much attention to this last remark, because it is stated here merely that "it is conceivable," not that Schade has shown it—and Schade actually has not shown it. It is conceivable, but it is not to be accepted until evidence has been offered to support it. All the direct evidence given is that furnished by Hamburger, who investigated the effect of collargolum on the hemolytic action of staphylococcus toxin, Neisser and Wechsberg having stated that the hemolytic properties of the latter provide a reliable test of the activity of the toxin. (The following figures are taken from Pamphlet "B.") Hamburger found that ¼ c.c. of a 1 per cent. solution of collargolum added to 1 c.c. of staphylotoxin serum prevented hemolysis; and from this he decided that it destroys the toxin. He found, however, that it increased hemolysis when ¼ c.c. of a less than 1 per cent. solution of collargolum

was used in 2 c.c. of staphylotoxin serum, and the same was true of still weaker concentrations. Does this mean that in these lesser concentrations it increases the activity of the toxin? We do not know, and are not told; but it would rather appear to do this, and certainly did not have a favorable effect.

REDUCTIO AD ABSURDUM

Let us grant that in the higher concentrations it has the influence desired on the staphylotoxin, and perhaps on other toxins, the figures given would, in relation to a human being, mean this: The concentration of (dry) collargolum, when ¼ c.c. of a 1 per cent. solution is added to 1 c.c. of other fluid (in the instance under discussion the fluid was staphylotoxin serum) is 0.2 per cent. Lesser concentrations than this increase hemolysis, according to Hamburger. Hence, to accomplish any good in the blood stream, and in order to avoid doing harm, we need at least a 0.2 per cent. concentration of collargolum in the blood. It has long been said that the amount of blood in the body is about one-thirteenth of the body weight, but more recent studies indicate that this is a little high. In order to be on the safe side, let us make it as little as one-twentieth of the body weight. With the usual so-called average man, who is commonly said to weigh about 70 kg., there would then be about 3.5 kg. of blood or 3,500 gm.; 0.2 per cent. of this amount of blood is 7 gm. That is, we should need 7 gm. of dry collargolum at each dose in order to keep up to the amount that Hamburger's figures demand if we are to do good. The preparation has been used for intravenous purposes most largely in a 2 per cent. or weaker solutions, until in the last few years, when it has been possible to use a 5 per cent. solution with the new collargolum. With the 2 per cent. solution we should need at least 350 c.c. to get the proper concentration in the blood; with the 5 per cent. solution the minimum dose should be 140 c.c.

The amount recommended and actually used, however, has ordinarily been less than 5 c.c.; only occasionally has the use of larger doses been reported, and never, so far as we know, more than 20 c.c. at a dose. Hence, if we follow Hamburger, the use of this preparation against bacterial toxins has not done any good, and, if anything, it would appear, indeed, to have done harm.

In any case the sole basis for the remarkable claim that collargol "has vigorous catalytic powers which induce or enhance in the organism the process of oxidizing bacterial toxins" are these experiments of Hamburger and Hekma, and a little consideration shows that they are totally irrelevant.

The experiments were performed *in vitro* and have no bearing on what may occur "in the organism;" they simply show that a toxin (the hemolysin of staphylococci) which so far as is known has little or no pathologic significance is probably destroyed under conditions which do not obtain in the organism.[1] To build such far-reaching deductions on such a slender base of facts is certainly gross exaggeration, if, indeed, harsher terms would not be more accurately descriptive. The claim that experiment has proved that collargol in the body oxidizes bacterial toxins to inert compounds either is dishonest or, at best, shows an uncontrolled imagination which would totally unfit its author for drawing any scientific conclusions.

Some emphasis, further, is laid in the pamphlet on Robin's studies of the effects of colloidal metals on metabolism. In regard to these, we would say again that Robin has done nothing with collargolum, so far as he states; but, on the contrary, he seems to have worked exclusively with metals that were obtained by the electrolytic method, and chiefly with gold, according to the references given. As we have said in another connection, results obtained with colloidal silver prepared electrolytically cannot by any means be considered to be results obtained with chemically prepared colloidal silver, namely, collargolum, and certainly the latter cannot properly be compared with colloidal gold. Suppose, however, that this could be done; Robin's work is, in the first place, subject to the criticism that, contrary to the first rule in such investigations, it was carried out, so far as is stated, without control of the diet. Aside from this, however, if they mean anything, his results as recorded, indicate chiefly that there was increased tissue destruction; and this, in infectious diseases,

1. Dr. J. F. Anderson, assistant director of the Hygienic Laboratory, Washington, D. C., performed, at the request of a member of the committee, several series of experiments on guinea-pigs to determine whether collargol has any destructive action either *in vitro* or *in vivo* on a toxin of real importance and one whose toxicity can be determined with accuracy, viz., diphtheria toxin. The treatment of a minimum lethal dose of this toxin with solutions of collargol up to 0.5 per cent. for 2 hours had not the slightest effect on the toxicity; nor did the injection of 1 c.c. of 0.1 per cent. collargol directly into the hearts of guinea-pigs (250 gm.) delay in the least the death of animals which received a single minimum lethal dose of the toxin. We disclaim the intention of attributing to these results a wider significance than they possess. They merely prove that collargol has no action on one of the most important and experimentally most decisive toxins. At the same time they emphasize the fact that we are not at all justified in presupposing that collargol has a general destructive action on all toxins, or even on most; or, indeed, on any toxin. If it has such action it must be definitely demonstrated with each individual toxin before claims such as the foregoing can be honestly justified; and, as we have seen, no adequate evidence on this point has ever been submitted.

is one of the things that we particularly try to prevent. The mere fact that a substance appears to have some sort of effect on metabolism is by no means direct evidence that it has a favorable effect.

This comprises all the matter of importance relating to the pharmacology of collargolum, so far as it is discussed in the advertising pamphlets and so far as we have been able to determine through other sources. It is apparent that this is wholly insufficient to establish or to aid seriously in establishing the very remarkable claims made regarding its effects and value. It seems to us, further, that while in some instances the statements made in the pamphlet are dependent merely on acceptance of insufficiently justified conclusions of the authors quoted, in other instances the statements made are directly the contrary of what the authors themselves have put into print, or they are palpable misrepresentations of the authors. Substantial experimental proof that collargolum has any of the pharmacologic actions claimed for it in these pamphlets is lacking, and this is evidence that the statements made regarding its pharmacologic effects are gross exaggerations. The misrepresentations are, however, to fair-minded persons, even more damaging evidence of the unreliability of the claims made. Whatever differences of opinion may exist as to the clinical significance of pharmacologic effects, everyone must agree that when pharmacologic claims are advanced they must be based on sound evidence. Still more important, they must not be contrary to the evidence, and, most important of all from the standpoint of common honesty, the statements made must fairly present the statements and conclusions of any investigators who are quoted. False claims are equally detrimental to the profession and to the public, whether the responsibility be referred to the house making the claims, to some subordinate, or to a vicious custom.

THE CLINICAL EVIDENCE

. It appears to us, then, that we have already sufficient evidence of conflict with the rules of the Council, which do not permit false, misleading or exaggerated statements. Let us, however, consider whether, putting aside the question as to the pharmacologic effects of the substance, there is clinical evidence of an amount and character sufficient to justify the statements regarding its clinical action.

As we have already indicated, we can not accept the standards regarding such evidence that Messrs. Schering & Glatz apparently adhere to. In their letter to you of Sept. 13, 1907, they say:

"The claims made for collargolum are perfectly justified; they are not in the least 'at variance with the current scientific conceptions of the subject,' but, to the contrary, are substantiated by an enormous literature, as you will see on perusal of the pamphlets on collargolum which we sent you some time ago, and of which we mail you another set under separate cover. Few remedies have a stronger array of testimony in their behalf. We ourselves have record of more than 300 publications, and there are doubtless numerous reports which we have never seen, particularly in French journals."

METHOD OF DETERMINING VALUE

This clearly indicates that if the number of contributions regarding a substance is large, the value of the substance is thereby established. We must very frankly state that we do not agree with this. The number of observations must be large if clinical or other studies are to furnish reliable evidence; but beyond this, and still more important than this, the studies must be made by persons who show evidence of competence, and they must have been done with accuracy and care; and in using the literature to decide a question, adverse statements must be considered with as much open-mindedness as are those that are favorable. If any other course is pursued, multiplication of so-called "evidence" is merely multiplication of error. When any drug has been extensively advertised and very optimistic claims have been made regarding it, large numbers of favorable reports may always be found, whether the drug is valuable or not. If the favorable reports alone are considered and no attention is paid to the reliability or to any unfavorable reports, it would be extremely easy with any drug to reach the conclusion that it is of the utmost value.

Considering the fact that we confined ourselves almost entirely to the literature to which the promoters of this drug themselves refer, it would seem highly probable that we have examined reports that are in larger proportion favorable to it that would have been the case had we searched also for articles to which Messrs. Schering & Glatz do not refer. It should be remembered, however, that our task was not to decide whether the drug has *any* value; if that question could be decided at all it would be only by a consideration of all available literature. What we needed to do was to determine whether it approaches reasonably near to the value set on it in the advertisements under consideration. This we have been able to do by keeping within the limits indicated.

GENERAL RESULTS OF EXAMINING LITERATURE

It is clearly impossible for us to make reference here in detail to all the literature that we have gone over. It will

suffice to take up a number of points in the pamphlet and quote a sufficient number of references to show that these points are not substantiated. These references will indicate that there is no *overwhelming* evidence that the substance is "a powerful and harmless systemic antiseptic in the most varied medical and surgical infections," or in any infection; that, on the contrary, when we consult the articles of men of recognized ability and judgment, we find that a very large proportion of them are extremely guarded in their conclusions. We find that, after extensive use of it, many of them decide that collargolum is practically valueless. Furthermore, in articles in which it is warmly recommended as a systemic antiseptic we find often intrinsic evidence that the author is clearly an unreliable enthusiast or that he presents no noteworthy evidence to substantiate his opinion; while in some instances the statements made regarding the benign effects of the preparation are accompanied by others that show such deficient or erroneous conceptions of anatomy, physiology, pathology or other fundamental medical knowledge that we should involuntarily distrust the conclusions reached by the author regarding any medical question.

CONFLICTING TESTIMONY

In addition to this, without searching outside Schering & Glatz's list but merely in looking over the articles referred to in the pamphlet, we have had our attention directed to a number of articles or discussions that directly contradict and give positive evidence against statements made in the phamphlet. Although these articles are quite as available as those that they quote, and the authors of the phamphlets must have been familiar with them, they are suppressed, and the extreme statements made are still permitted to stand. We find, indeed, direct contradiction of some statements in the pamphlet in articles from which they themselves quote, but these unfavorable statements are usually suppressed and the articles are used only in some other connection.

We find instances, likewise, in which statements attributed to an author in society reports (and such reports are generally unauthorized) are used in furtherance of the claims made, while when the original article itself is consulted the author's actual views are found to be much less favorable or actually unfavorable. This clearly misrepresents the author's real views in a way that is entirely unjustifiable.

DISTORTED REPORTS

Furthermore, and much more objectionable than any of the things that we have thus far mentioned, there are repeated

instances in which portions of articles are suppressed in such a way as to make carefully guarded and, at most, only mildly favorable statements appear laudatory to a grossly exaggerated degree; and there are instances in which words are introduced into author's sentences in order to make them more emphatic; and, finally, obsolete views of authors, that they have since corrected in later articles, are given as their present opinions.

Such methods are clearly the opposite of a fair presentation of the subject. The reader of such statements will be deceived in precise proportion to the faith that he has put in the fairness and honesty of the presentation. The higher the standing of the firm that descends to such practice the more serious the offense, the graver the abuse of confidence, and the more positive the harm done. The explanation that the offense is a common practice does not by any means lessen this harm. The principle of "caveat emptor" has no place in science, nor can it be considered laudable, when the lives of human beings may be the price.

Having found these evidences of exaggerated, false and misleading statements in regard to the clinical side of the question, as well as the pharmacologic, we feel that we have answered your question. We will, however, refer to a series of articles that exemplify the points we have made. We will take these points up, not in order, but collectively, since in repeated instances one article illustrates several of our points and we wish for brevity's sake to avoid an unnecessary amount of quoting.

It is stated on page 8 that "Locally collargolum is a *certain*, simple, *universally applicable* surgical antiseptic for the prevention and treatment of sepsis" (italic ours). Hocheisen, however, who is quite extensively quoted in two other connections but not in this, states that during two years, when he was acting as an assistant to Landerer, he used collargol in surgical cases, injecting it under the skin and into the veins, and also applying it in powder form and as an ointment in septic wounds in infected amputation stumps, in general septic conditions, in peritonitis, in severe phlegmons, in puerperal infections and in tuberculosis. He states: "I could, however, not say that I have seen even one single result that could not have been secured quite as well by the other customary surgical or general treatment that was used." He thinks the intravenous use may have some useful effects on general surgical sepsis. His opinion regarding its local use is, however, clearly positively unfavorable, after a large experience.

ITS USE IN SEPTICEMIA

The drug is particularly recommended for various forms of septicemia and pyemia, erysipelas, and especially in puerperal infections, etc. Let us see what is actually said by some of the persons referred to regardng its use in these conditions: On page 13 it is stated that Professor Tillmanns "says that he has often seen surprisingly good results from the internal administration, injection or inunction of collargolum in phlegmons, lymphangitis, general septic infections, etc." This provides examples of three very objectionable things. The facts are as follows: The reference given is to Tillmanns' "Allegemeine Chirurgie." In the seventh edition of this work, published ten years ago, Professor Tillmanns said Credé recommends this metallic silver, internally, by inunction or by intravenous administration, in the treatment of phlegmonous lymphangitis, general septic infections, in scarlet fever, diphtheria, etc. He then immediately said "no conclusion can yet be reached in regard to the internal antiseptic action of the silver in general infections. I have repeatedly seen surprisingly good results, in other cases it could not be determined that there was any effect." As to later editions of his work, we cannot find that there was any eighth edition of the "Allgemeine Chirurgie," though there was one of the "Specielle Chirurgie." In the ninth and tenth editions, however, published in 1904 and 1907, respectively, he says what was noted above as to Credé's recommendations and then alters his previous statement by eliminating any personal opinion whatever and simply says that in human cases and in animals some authors have described good results, while with others the results have been negative. That is, in one short sentence the author of the pamphlet has introduced three very objectionable methods of misleading his readers, methods which are very commonly used in such advertisements.

1. He has used an obsolete edition of the author's work that contained a clause (which the author had deliberately removed from later editions) because this clause could be dressed up into more laudatory form than any in the later editions. This suppression of an author's recent opinion because an earlier one seems more favorable we shall mention in another connection in a still more objectionable form.

2. What Tillmanns said ten years ago as to his own opinion is combined with what he said as to Credé's recommendation of the substance, and it is all referred to Tillmanns.

3. A single clause that even in the original (in the ten years' old edition) is guarded in such a way as to make it a most indifferent opinion as to the actual value of the sub-

stance is taken out from the context and put into the advertisement in such a form that the author appears to be an enthusiastic advocate of collargol. By using this method almost anything except violent condemnation of a drug, could be turned into warm praise. It is the more reprehensible because it is one of the commonest ways of misleading readers of advertisements.

Finally, we would note that while the advertisement reads as if Professor Tillmanns had come out with a warmly favorable discussion devoted to collargol, we actually find that all the matter that we have referred to is merely a mention of the substance in fine print, after he has mentioned twenty-five other substances which have been recommended by various authors as substitutes for the usual antiseptics; and when, immediately afterward, he takes up the question as to which of the numerous antiseptics that have been recommended is the most effectual and suitable, he does not even mention collargol, and in discussing the prevention and treatment of septicemia he again does not mention it, but does say "A substance that is an effectual remedy for general septic infection does not exist."

ITS VALUE IN PUERPERAL INFECTIONS

In relation to puerperal infections, let us take up several of the first references given under this heading (p. 13), which are said to attest the effectiveness of the substance in these conditions. The article mentioned as coming from Chrobak's clinic is by Buberl. It is quoted specifically in certain other connections and, as we have already shown, it is falsely quoted in connection with excretion through the urine, but the following statements are not quoted: He says that the reports regarding the clinical effects of collargol are partly positive and partly negative, a guarded expression being given by exactly those authors who have the largest amount of material at hand; and he then refers to Fehling, v. Herff, Küstner, Leopold, Osterloh, and v. Rosthorn as being examples of this latter class. Buberl's own work indicated to him that it appeared at times to exert a favorable influence on the course of puerperal fever, but that it is to be considered a specific against sepsis seems, from his experience, to be altogether too enthusiastic a statement.

Döderlein, referred to also, says, on page 43 of his book, simply that it has been recommended that metallic silver be used in impregnating ligatures. Later, on page 161, he says, in discussing the after-treatment of infected wounds: "Here silver in colloidal form and silver salts, used in intravenous infusion or in inunctions, have been recommended by Credé.

The experimental basis of this Credé silver treatment is, however, but slight, for no results that are free from criticism have been obtained in animal experiments; though it might be said regarding these observations that perhaps bacteria of too high a virulence have been used for injection, and because of this even an increased power of the blood to check their growth was insufficient. Clinical reports, both with intravenous and intradermal use, have not been unfavorable. We have ourselves very frequently used the inunction treatment without being able to reach any conclusion regarding it. Unequivocal results that strike the eye at once I have never seen."

As to Fehling, the reference is to a society report, in which it is merely stated that he had good results from the use of collargol. When the actual article by Fehling is looked up[2]—an article to which reference is not given in the index of literature in the pamphlet—it is found that he states that the substance had no bad effect, but the results were very variable. Sometimes the temperature and pulse fell; they generally improved; but there was no definite permanent fall of the temperature after the injections. As to whether any cures were due to its use, he says that he feels extremely guarded. A number of patients died and a number got well. Possibly the bad issue was sometimes postponed. Further clinical studies should be made to determine its value, but he thought it worth while at that time to continue testing it.

Harrison is correctly quoted as saying: "If one does not use collargol in those severe forms of infection, one has not done one's duty." This extremely pronounced view does not apper to us to be based on much experience. In the references given Harrison reports, so far as we can see, only two—or, at most, three—cases, one of these being from the notes of a hospital resident physician. In one of these it appears that collargolum was unable to prevent the advance of the general sepsis and the formation of an extensive local abscess and arthritis, and the condition improved only after the abscess had been opened and drained. Nevertheless, collargolum is lauded because the abscess cleared up with great rapidity after having been opened.

Osterloh, who is not referred to in the advertising matter of Schering & Glatz, though repeatedly mentioned in articles that they do quote, says[3] that he had already shown the uselessness of the ointment in severe sepsis, and then describes some cases in which he used intravenous injections with apparently

2. München. med. Wchnschr., 1903, p. 1409.
3. Wchnschr., 1902, No. 21, p. 896.

favorable influence on the temperature but no influence in controlling the disease. Three patients died and the others recovered only after the silver treatment had been stopped and other suitable surgical treatment had been instituted.

COLLARGOL IN ARTICULAR RHEUMATISM

Witthauer is very favorably referred to in some typewritten sheets[4] sent to the committee by Schering & Glatz. He had previously reported in a laudatory way in regard to the use of the substance in puerperal pyemia, and states that he has recently used it in articular rheumatism. He describes a series of cases in which he thinks the results were very good; but he makes the naive statements that if a case does not improve under the use of this substance, one may decide that either it is gout or a mixed form of arthritis, or that there was some complication present that prevented the action of the collargolum. He states that there were cases that he does not report in which "collargolum did not work so promptly and so strikingly, because mixed infections were certainly present, and new complications persistently appeared." Evidently this author modifies his diagnosis directly in accordance with the effects of collargolum, which makes his conclusions more than a little unreliable. In connection with its supposed action in pneumonia it is interesting to note that Witthauer supports his contention that it acts *in the right kind of rheumatism* by showing that in a case that it did not help the patient developed pneumonia while it was being used. He considers the pneumonia responsible for its lack of influence on the rheumatism. He also says that true streptococcic articular rheumatism may be successfully treated with collargolum, and may even be diagnosed through the collargolum treatment, because the latter is always effectual in this condition. This is rather too much of a discovery. There has been no determination as yet that articular rheumatism is definitely a streptococcic disease. To make a diagnosis of a condition by a therapeutic test before the existence of this condition is known to be a fact is surely a remarkable feat.

In the same number of the same journal, however (this is not mentioned by the promoters of the drug), Jung, writing from the Frauenklinik in Greifswald, after speaking of various measures used in the treatment of puerperal sepsis and mentioning antistreptococcic serum encouragingly, says: "The experiences with Argentum colloidale Credé in puerperal sepsis have been less favorable. In regard to this substance also there are a great number of favorable, but likewise some unfa-

4. Med. Klinik, 1907, No. 42.

vorable, reports, and in our experience in Greifswald it has not proved satisfactory. We have, as have many other observers, repeatedly seen high access of fever and severe chill appear first after its use." After describing the disadvantages attending on its intravenous use, he says: "These difficulties make the procedure seem but little suited to the use of the practitioner, and, furthermore, as already noted, we have not had any favorable results to record. The percutaneous use of collargol, which was earlier practiced, has proved to be entirely without effect and is indeed very generally discarded."

Lenhartz, who wrote on sepsis in Nothnagel's "Specielle Pathologie u. Therapie," and whose authoritative article is repeatedly referred to by others who are quoted in the pamphlet, though not given in the list of literature in the pamphlet, states: "Whether colloidal silver, recommended by Credé, promises any permanent cures I hold also to be very doubtful. However, it appears in the dose ordinarily used to be harmless. Wenckebach considers that after intravenous injections of 12 to 15 mg. of the silver in 1 per cent. solution good results were seen. For myself, after many personal experiences, I cannot confirm this favorable action." Again, in speaking of its use in puerperal sepsis, he says: "We ourselves have seen nothing worthy of comment as a result of its use."

ITS UNTOWARD EFFECT

The opinion that it causes no dangerous effects is not shared by everyone. Rittershaus[5] is correctly referred to in the pamphlet as describing such good results in erysipelas that he thinks it must be looked on as having a directly healing influence in this condition; but no space is given to another article by Rittershaus, written a year later (the authors of the pamphlet are evidently familiar with this article, because they index it in their list of the literature), in which Rittershaus says that, after further experience and further consideration, he would note that he has repeatedly had periphlebitic infiltrations and abscess formation as the result of intravenous injections, and has repeatedly seen severe cyanosis and dyspnea immediately after its use, which *probably indicated embolus of the lung.* He also frankly notes that his more mature opinion is that the effects in erysipelas and pyemia are by no means so valuable as they at first seemed to be. While it appeared to have an influence in some cases on the temperature, general condition and local disease, he believes that it is impossible to attribute much effect to it because of the great variability of the ordinary clinical picture of such

5. Therap. der Gegenw., 1904, p. 305.

conditions, and he frankly states that, contrary to his previously expressed opinion, he thinks that up to the present no specific against erysipelatous conditions has been found. As to general septic processes, he would repeat the statement made in his previous paper, that no permanent results were obtained from the use of collargolum in these conditions.

Hocheisen is quoted most extensively in connection with its use in puerperal conditions. We would note one point as regards the quotation from this author; the first sentence as given in the pamphlet is: "Collargolum is an invaluable aid in suitable cases." A correct translation of Hocheisen's words here is: "Collargolum is an aid in suitable cases." Again there appears to have been a spontaneous generation of a word, which we can scarcely consider justified even for advertising purposes, since this is a direct quotation, in quotation marks.

Bonnaire and Jeannin,[6] who are considered by Schering & Glatz to have given an entirely convincing contribution concerning its effect in puerperal sepsis, make twice a statement that appears to us to be in strong conflict with the attitude of the pamphlet, in that they say that the only active way of using the substance is intravenously. They then give a series of cases in which they used it, in 46 of which the patients actually had some disturbance of temperature, etc., after childbirth. In 3 of these the result was unknown; 10 patients died and 33 recovored. There is no evidence that many of these patients had actual septicemia or pyemia, however, and the authors themselves, while favoring its use, say that one should abandon the chimerical hope that we possess a therapeutic agent that is able to stop an infection that is in full evolution; and they state that even if collargol simply aids in gaining time, through its influence on the general condition, but permits an infected woman to traverse the period of danger, stimulating the reaction of the organism in a favorable way, providing periods of freedom from fever "which depresses the patient, takes away appetite, disturbs sleep and produces headache and causes delirium, it must still logically be accorded a large share in a happy outcome." Its effects are only transitory, and the dose must be frequently repeated, if the drug is to be of any value. Now all this may be true or it may not, but it does not sound to us like the description of a specific against puerperal or other infections. It is indeed a rather vaguely cautious statement, and it would appear that since his first paper which is referred to in the pamphlet Bonnaire has become more guarded in his views as to the efficacy of the drug.

6. L'Obstetrique, April, 1908.

ITS USE IN CEREBROSPINAL MENINGITIS

Under "cerebrospinal meningitis" the pamphlet refers to a considerable series of authors; but it is somewhat illuminating to find that the whole number of cases reported by these men is extremely small, several mentioning only one case in which collargol was used. In most instances the diagnosis was not established by any reliable means. We would contrast two statements that we think are illuminating. One is the following, which we quote from the pamphlet marked "B," p. 20, where an article by Bjorkman is given in extenso. The quotation opens in this way:

"In my own experience I have met with great success in meningitis from the combined treatment with silver inunctions (Credé) and antiseptic packs on the skull. In some instances the suppuration took an outlet through the nose and ears. . . ."

If this really occurred, as the result of the use of collargol or anything else, we should have profound confidence in its activity, indeed we should stand in awe of it; but we are inclined to hold in mind the statement of Dr. Jacobi, who says, in an article from which the pamphlet quotes (though this statement itself is not quoted) that in cerebrospinal fever collargolum had no action.

We would also note that, though Dr. Jacobi is repeatedly referred to as expressing a hopeful view regarding the use of collargolum, the pamphlet entirely suppresses the guarded statements with which he surrounds the hopeful statements. In speaking of Credé's silver preparations, he makes these remarks: "His followers are sometimes more enthusiastic than he is himself, though his own convictions approach sometimes a fervor of fanaticism." "The careful practitioner, who has seen many rockets to rise like stars and descend like sticks, will do well (to judge from what I have seen myself) to try the colloidal silver for what it is worth. We have all been looking for a soluble antiseptic which would kill cocci and toxins without harming the tissues. In this drug we are promised such a material. We are not bound to accept the dicta of enthusiasts, bent on writing an article which will carry their names through the ephemeral literature of a brief half year." In the other article referred to in the pamphlet, in speaking of these and other substances, Dr. Jacobi says: "I mention them without claiming prophetic gifts. They may be highly valuable, though whoever looks for a panacea is always mistaken."

It is, perhaps, natural that Schering & Glatz should have omitted also the following quotation from Forchheimer.[7] The

7. Cleveland Med. Jour., January, 1902.

article is, however, referred to by them. In speaking of the use of collargolum, he says that he began with a prejudice against it "on account of the fact that so distinguished a man as Credé had surrendered to commercialism." Dr. Forchheimer, at the end, gets only so far as to say that he does not unreservedly advise the use of this ointment but considers it worthy of a trial in so severe a condition as septicopyemia.

COLLARGOL IN ENDOCARDITIS AND INFLUENZA

In regard to endocarditis, the name most distinguished among those mentioned in connection with cardiac conditions is that of Wenckebach. The rest of the world, perhaps, will be inclined to think that he is overenthusiastic in his title, "An Effective Treatment in Septic Endocarditis," when we find that he has treated a large series of cases, and says that two, he thinks, are convincing and describes these, but that the other cases he will not mention because they are less convincing! One at least of the two that he describes certainly ran a course that has many times been seen when no supposedly antiseptic treatment was being used in this disease.

Under influenza, reference is given to an article by Afanasjeff, who is stated to believe that collargolum has a specific effect on influenza infection, and his article is given in full in one of the pamphlets. One case is the evidence offered by him to prove that we have a specific. Rommel likewise is quoted as showing the profound influence of the substance in influenza, measles and other conditions. He actually describes only one case (that one is erysipelas), and then makes vague general statements about other conditions, and in a most laudatory way recommends the drug in almost all kinds of conditions; but he does not *offer any evidence* as to the correctness of his views.

ITS USE IN GENERAL MEDICAL CONDITIONS

It is stated in some typewritten matter sent to the committee by the agents, under the heading "In Medicine" (referring to its use in medical conditions): "The most exhaustive investigations are those of Professor Netter[8] on the very large material in the Hospital Trousseau of Paris." "Exhaustive investigations" seems a somewhat liberal term when we find that in the last of these two references Professor Netter gives as his most important experience the following: Nine cases of pneumonia, 9 of typhoid fever, 14 of bronchopneumonia of all kinds, and 4 of scarlet fever, together with 37 cases of diphtheria; and the effects in typhoid fever that he describes are

8. Bull. et mém. Soc. méd. Hôp., Paris, Dec. 18, 1902, Jan. 22, 1903.

not made more convincing by the fact that, while he does not mention this himself, he finds it necessary to use in the second paper the same chart that he used on page 1111 in the preceding paper to demonstrate its influence on the temperature in typhoid fever. Moutard-Martin, in discussing Netter's first paper (a fact, again, that is not quoted in the pamphlet), said that the effects described by Netter are not at all convincing of the value of collargolum; they are certainly often seen without its use, even the effects supposedly shown in the twice-used typhoid chart. Professor Netter's enthusiasm incidentally goes far beyond even the indications outlined in the pamphlet. He believes that he has used the substance with most beneficial results in gastrointestinal conditions and a variety of nervous disorders, including neurasthenia, hysteria, central nervous scleroses, epilepsy, etc. Indeed, according to him, collargolum would very narrowly escape being a panacea, for there are few pathologic conditions that would not be cured by it if we follow his view.

We would also note, in regard to another important disease, that Baginsky, whose article is, as we have said, incorrectly quoted in another connection, says (a fact that is not quoted) that he treated with collargolum thirteen patiens with severe scarlet fever and ten died. The non-fatal cases were not very malignant, and he considers it probable that recovery would have resulted under a simple dietetic treatment. He also notes that collargolum did not prevent complications in any of these cases, one developing otitis media, another nephritis, and the other an infection of the face. He reaches the final conclusion that "the attempt, then, to influence scarlet fever favorably with Credé's ointment failed in every way." This statement from so distinguished an authority is certainly sufficient to offset the general statements, without specific details, that are quoted from others.

COLLARGOL IN DIGESTIVE DISORDERS

In connection with the digestive disorders of children, it is stated in the pamphlet that Professor Schlossmann "advises 1 per cent. collargolum in sweetened milk when an intestinal antiseptic is needed." Since Schlossmann's name carries weight, we looked this point up. We find that what he actually says is: "A critical decision whether any improvement was due to the medicament or to the rational diet that was, of course, instituted is extremely difficult; but I think that I may recommend colloidal silver to those colleagues who have the slightest faith in the use of intestinal antiseptics, because, while it has decided antiseptic properties, it is entirely non-

poisonous." In other words, if one believes at all in the use of intestinal antiseptics (and Schlossmann does not say that he does, but rather intimates that he does not), one may try colloidal silver, because it is not likely to do any harm when given by mouth. This is certainly a different expression of opinion from that indicated by the statement made in the pamphlet.

It appears, however, unnecessary to multiply these references further. In relation to the clinical side of the question, matters seem to stand much as they do in relation to the pharmacologic evidence. There are, of course, many favorable expressions of opinion from clinicians; but there are many guarded or unfavorable opinions, some of which we have quoted. It is, as we have said, a matter of history that nearly any drug that has been widely advertised has had many enthusiastic advocates for a time, whatever its actual value. As to this drug, most of the authoritative writers whose articles we have seen have, at best, a guarded, and not infrequently an unfavorable, opinion. Many who have written in recent years (and this includes a number of those who are mentioned by Schering & Glatz as having presented some of the best evidence of the value of the drug), if they express an opinion on this point, consider collargolum nearly or wholly valueless unless used intravenously; and we repeatedly find the statement from those of widest experience that the effects of its intravenous use are negative or, at best, doubtful.

In spite of this, the remarkable claims mentioned in the beginning are made in the most recent pamphlets as if they were beyond question, and all modes of administration are recommended except the subcutaneous. The latter is excluded only because of the likelihood of its producing local trouble.

Collargolum is also emphatically said to be harmless, whereas severe chills and marked rises of temperature after its use are mentioned by numerous authors. Such results certainly cannot be said to be harmless. A number of writers mention severe infiltrations, and even abscess formation, from its intravenous use; and still more disquieting effects are described, notably by Rittershaus, who reports, in a number of cases, symptoms that indicated so alarming a condition as pulmonary embolism. Similar cases are mentioned by other authors.

CONCLUSION

We have presented sufficient evidence that there are gross exaggerations in the statements that were quoted in the beginning of this report, from the covers of the most recent pamphlets. In addition, we have shown instances of directly false and also of very misleading statements. These latter facts,

even more than the exaggerations, have made us feel it incumbent on us to make a frankly adverse report. Until these practices have been entirely abandoned collargol appears to us to lie beyond the pale of scientific inquiry, for the latter, which is the searhc for truth, cannot thrive in an atmosphere of falsehood or even unfairness. The question whether the substance itself has any intrinsic merit cannot be approached at all scientifically until it is approached in the spirit of truth, frankness and fairness. The manufacturers and those who profess faith in the remedy should, more than any others, be interested in removing it from its present false position.

TYPICAL PROPRIETARY EXAGGERATION

In concluding, we wish to emphasize the fact that these remarks do not apply solely to collargol or to Schering & Glatz. All that we have said really illustrates conditions that, unfortunately, are all too common. The cry that this is a "common practice" is frequently made in extenuation. In our opinion, this is all the more reason why such practices should be exposed and condemned whenever and wherever they are found. So long as they prevail the claims advanced in all advertising matter must be considered with the greatest caution, if not with skepticism.

There are, however, two lamentable facts that are especially illustrated in the present instance. The first of these is that a large array of literature, quotations and references are misused to obscure the very views that the authors of advertising pamphlets pretend to present. It is, for instance, directly claimed by Schering & Glatz in their correspondence that the "over 300 references" mentioned in the pamphlet *substantiate the claims* made for collargol. As we have seen, this is very far from being the case, and in many instances they do directly the contrary. This, as well as the other misrepresentations and misquotations, implies a confident belief—unhappily too well justified—that most doctors are either too busy or too impressionable to verify such quotations by actually reading the original sources. Even a fairly ambitious inquirer would be effectively deterred by the seemingly hopeless task of reading 350 articles. The use of the names of widely known authors further serves to quiet any doubts of the reader and deter him from making a more accurate investigation of these claims, for most men would look on it as inconceivable that any one should have the presumption to misrepresent the actual views of such authors. The average physician has considerable confidence in the better pharmaceutical houses, and the abuse of this confidence is a serious matter—most serious

of all to the pharmaceutical interests; indeed, on their part it would appear to be nothing less than suicidal.

We again disclaim the intention of singling out the firm of Schering & Glatz for criticism, though our present duty is confined to their pamphlets. On the contrary, we would urge that it is advisable and, indeed, necessary that in all instances in which remarkable claims are made the original sources on which these are based be carefully examined, whatever the substance may be and whatever firm makes the claims. We would, indeed, hold it to be an important duty of the Council to undertake such investigations in connection with any product that has been provisionally accepted, as well as with those that may be submitted in the future. The exposure of such practices, when they exist, is to the common benefit of all. We should consider that whoever has good reason to believe that such misrepresentations exist in connection with any substance can give material assistance by transmitting his information to the Council; and we would also hold that any person is remiss in the duties that he owes to the profession and to the public if he does not take such action and permits these practices to go on without doing his part to check them.

The other unfortunate fact is that while it would in some ways be very helpful if physicians could openly express their opinions in print in regard to proprietary articles in order that the good might be sifted from the useless or harmful, it is clearly very dangerous for anyone to attempt this now, for no matter how free from commercial interest in the product that he is discussing he may appear to be, anyone is always in danger of having his views, and even his very words, distorted, misconstrued, suppressed, or added to, in ways that will fit the purposes of subsequent advertisements of the drug. We thoroughly agree as to the desirability of the impartial scientific investigation of promising drugs; but we are convinced that the practices to which we have just referred are the main, if not the sole obstacles to such investigation.

We have gone into the task that you set us to a greater extent than its individual importance warranted, because as we investigated it more extensively it constantly appeared to point more clearly to an important moral that is not yet sufficiently appreciated: Advertisements of proprietary articles are usually *not even intended* to present scientific facts but, rather, the biased views or wishes of the owners.

Respectfully submitted,

J. T. Bottomley, Reid Hunt.
C. W. Edmunds. David L. Edsall, Chairman.

MINORITY REPORT OF THE COMMITTEE.

TO THE COUNCIL ON PHARMACY AND CHEMISTRY.

Gentlemen:—The question presented to the committee I understand to be the following:

"Does the advertising matter in relation to collargolum submitted by Messrs. Schering & Glatz contain exaggerations or misquotations of such character that the Council should require their withdrawal before approving the product?"

As to this, I find, in substantial agreement with the majority of the committee, that the advertising matter of Messrs. Schering & Glatz is misleading, both through exaggeration and through misquotation. It makes a number of positive assertions concerning the pharmacologic and therapeutic properties of collargolum for which conclusive evidence is lacking, and modifies the opinions of some of the authors cited, by addition as well as by omission.

The practice thus illustrated—a practice which, unfortunately, is widespread among the manufacturers of controlled medicinal preparations, including some which have been accepted by the Council—even when fairly attributable to carelessness, rather than to evil intention, is not to be condoned. On this point I have no difference of opinion with the majority of the committee.

Physicians, pharmacists, and especially the editors and proprietors of medical and pharmaceutical journals, are not, however, without a large measure of responsibility for the inception and development of this evil, and in assuming the attitude of judge or prosecutor, the American Medical Association must not lose sight of its former position as culprit. It is to be hoped that the increase of knowledge, no less than the stricter enforcement of ethical codes by medical and pharmaceutical societies, will bring about amendment among professional men. As to pharmaceutical manufacturers and distributors otherwise of good repute—such, for example, as the offenders in this particular instance—may we not expect that the censorship of the Council on Pharmacy and Chemistry and the pressure of public opinion will direct their attention to the matter so strongly that, not in mere obedience to these extraneous influences, but because of their own recognition of their very grave responsibilities, scientific and moral, they will hereafter exercise the necessary care in the preparation and supervision of their advertising?

On the contradictions in the advertising matter I lay less stress than do my colleaguse, being mindful of the contradictions that would be evident did we assemble the reports, experimental and clinical, by recognized authorities, concerning some of the oldest and most important remedial agents.

On some of the other questions incidentally raised in the report of the majority of the committee, and with much of its criticism and comment on individual observers, I reluctantly find it necessary to express dissent.

This dissent is not based on a personal prepossession arising from clinical observation of good results from the use of colloidal silver—for I agree with the majority of the committee that in an investigation of this kind personal views should be set aside. I look, perhaps, from a different viewpoint on the experimental and clinical evidence submitted. As, however, these matters have no immediate bearing on the particular question submitted, and some aspects of the discussion would lead us far afield, I do not wish to take the time or space necessary to particularize. It is sufficient that I agree with the main conclusion, even though I cannot adopt all of the reasoning of my colleagues or endorse all the views incidentally implied or set forth in their report.

PHARMACOLOGIC ACTION

In regard to the immediate matter before us, a further word is necessary. It is possible that the ordinary reader might infer from the majority findings that colloidal silver is devoid of pharmacologic action and of therapeutic value. It is true that the report does not say this, and I have no reason to believe that the majority of the committee wishes to imply it; yet to avoid misunderstanding I must enter on this point an explicit disclaimer. My own finding is that the pharmacologic action of colloidal silver is undetermined, and that while a number of ingenious conjectures have been made, with more or less plausibility, and even probability, the experimental evidence is not as yet sufficient to warrant any positive conclusion. This opinion applies as well to the experiments conducted by Dr. Anderson on diphtheria toxin as to those of Hamburger and others criticised by the majority of the committee; that is to say, Dr. Anderson's result demonstrates that under the conditions and to the extent of the experiment, collargolum is without neutralizing or destructive power on diphtheria toxin; but it would require a larger number of experiments, of many kinds, under varying conditions, and with different forms of toxin, to warrant either a general negative as to all infections, or a positive assertion as to any. On the other hand, I cannot consider the fact of the absorption of the drug from the gastroenteric tract at all doubtful, though the form or manner in which absorption takes place is not yet established; neither is the usual increase of peripheral leucocytes doubtful, though the significance of this fact remains to be determined.

THERAPEUTIC VALUE

In regard to the clinical reports, I agree with the majority of the committee that very many of them are lacking in those exact details of observation which alone permit a reader to draw conclusions as to the correctness of the diagnosis and the true influence of the remedy. This does not, however, of itself warrant us in casting suspicion on the honesty or the competency of the observers or in disputing the correctness of the statements made. It simply leaves the matter unproved. All

clinicians are aware that certain conclusions impressed on them from observation of the progress of individual cases cannot be so set forth, even in the most detailed and exact reports, as to convince others. And this will continue to be so while therapeutics remain an art rather than an exact science. Furthermore, as the majority of the committee truly points out, highly colored and optimistic—even absurd—reports are apt to be published concerning all drugs. This has occurred and will continue to occur in relation to the well established remedies of the Pharmacopeia, as well as concerning the newer legitimate remedies, and the nostrums and frauds, old and new. It is, however, as illogical to draw unfavorable conclusions from reports of this character as it would be to base favorable opinions on them. Cheiron, the wise centaur, is as fabulous as the contest of Athene and Poseidon; but the horse is, nevertheless, a very useful animal. All that can be done with reports which are lacking in exactitude and sufficiency of detail, whether from unknown writers or writers of authority, is to set them aside. We have, then, to consider such reports as may be sufficiently precise to permit analysis and conclusion and such generalizing expressions of opinion as may, from one reason or another, be of sufficient weight to arrest attention. Without specifying, I find that among the reports and opinions submitted in relation to collargolum, there is a sufficient weight of trustworthy evidence to indicate for it—a limited field of established usefulness, and beyond this the possibility of a larger field needing accurate survey. In the very general way in which medical literature at present employs the term "indication," it is justifiable to say that the drug is "indicated" under certain conditions, which can be derived from a study of its genuine literature, and which it is not the province of this report to point out.

I should like to add a few lines concerning a larger question suggested by the present inquiry: It is to be regretted that as yet no satisfactory method has been devised by which the manufacturers of controlled preparations may enter into an arrangement with observers of competence and scientific standing for the prosecution, experimentally and clinically, of the exact researches necessary to establish the pharmacology and the therapeutic advantages and disadvantages of their products. The fact that a preparation is controlled removes it, as a rule, from the field of general scientific endeavor in which investigators may be moved to labor for the advancement of knowledge; while under present conditions, observers of the character indicated are, for the most part, unwilling to undertake such observations as a matter of professional employment. If, however, an analytical chemist may properly be employed and paid for work in the line of his profession, there is no reason why a pharmacologist should not accept similar engagaments. If the chemist or the pharmacologist is expected to make an imperfect or untruthful report, then the bargain is, of course, dishonest; but if the chemist or pharmacologist is, as here

assumed, employed simply to ascertain and report the facts, the employment is an honorable one and to be commended.

I need not here recall the arguments I have repeatedly made against the policy of "control" or monopolistic "proprietorship" in the agents of materia medica. So long, however, as it continues to exist under the laws of the United States, the situation which it creates must be recognized. Either through the medium of some special public association, or through the medium of the Council, there should be brought about a condition which will permit manufacturers to employ experts for the determination of the pharmacologic and therapeutic actions of their preparations, without loss of professional standing by the clinicians or experimenters who may accept such employment.

In the case of collargolum, it is my opinion that, while the investigations hitherto conducted have not been sufficient to establish the claims made by the proprietors of the drug, or to decide either positively or negatively as to its possession of the properties which have been conjecturally ascribed to it, a more extended investigation, taking up in a systematic manner the various points necessary for such determination, is desirable. Until such an investigation has been conducted and concluded, the matter must remain in doubt, and the advertising matter of the proprietors should discriminate, as it certainly does not now discriminate, between probability and certainty, conjecture and demonstration, plausibility and proof.

In regard to one portion of the report of the majority of the committee I must register a specific dissent. I am not willing to put impute to improper motives the inclusion in the advertising bibliography of references to reports and observations unfavorable to the drug. That such reports and observations are not "featured" by the advertisers—an omission in which these promoters are, unfortunately, not unique—is simply an additional illustration of the evils inevitably resulting from the present system of private control of medicinal agents. The inclusion of the references in the published lists of papers is to be commended rather than condemned, but would have been more commendable had the advertisers indicated the character of the reports. Respectfully submitted,

SOLOMON SOLIS COHEN.

COLLARGOL

Schering & Glatz's Reply to the Report of the Council and the Rejoinder Thereto

(From The Journal A. M. A., July 10, 1909.)

REPORT OF THE COUNCIL ON PHARMACY AND CHEMISTRY

The letter of Schering & Glatz which is printed below is a reply to the Council's report on collargol published in THE JOURNAL, March 13, 1909. The letter having been submitted to the Council it was voted that it should be referred to the

committee which prepared the collargol report with the request that it report to the Council whether or not the letter is pertinent and should be published in THE JOURNAL. The letter of Schering & Glatz having been transmitted, the committee recommend to the Council that the letter be published, also the rejoinder which appears below. This recommendation was adopted and in accordance therewith the matter is published. W. A. PUCKNER, Secretary.

SCHERING AND GLATZ'S LETTER TO THE COUNCIL

Sirs:—We are glad to learn that your Chairman has, on further consideration, decided to submit to you, with our request for publication, our reply to the articles on collargol in THE JOURNAL, March 13, 1909. We shall here answer only the most important points raised by your committee.

COLLARGOL IN THE BLOOD STREAM

Kunz-Krause and Lange (*Therap. Monatsh.*, 1900, No. 10) by means of a method they specially evolved for the purpose, demonstrated collargol in the blood after 195 minutes. Beyer (*München. med. Wchnschr.*, 1902, No. 8) found traces of it in the blood after eight to ten hours. Our statement that collargol disappears from the blood within an hour did not mean that its disappearance was absolute within that time.

Hocheisen did find that collargol circulates in the blood as colloidal silver; he said (*Med. Klin.*, 1907, No. 33, case 27):

"Autopsy showed: endometritis gangrenosa, septic degeneration of the spleen, liver and kidneys; in spleen and kidneys septic infarcts. Recent ulcerative endocarditis of the aorta. Findings: on aortic valves, below the nodull, deposits of black and grayish-black coloration, or grayish-yellow, matted round structures. Microscopically these deposits proved to be crowded fields of streptococcus cultures mixed with small, bluish-black, irregularly formed scales and granules, *which were nothing else than collargol.*"

Van Waveren merely demonstrated the admitted fact that collargol is preciptated when added to a salt solution; but this is incompetent, since blood is no mere salt solution, over 7 per cent. albumen being present in the blood. Hamburger (*Arch. f. physik. Med.*, 1906, Nos. 2-3) refers to "colloid silver or collargol which has lately been recommended in bacteremias" and asks:

"How is it possible that it remains in colloidal state in the blood stream, when the blood contains so much salt and when—as already stated—salts precipitate colloids? This is due to the presence of other colloids, namely albumen."

Hamburger says, incidentally, that collargol solutions are less stable than Bredig's silver; but this referred to the old collargol. The collargol now supplied has added to it, in the course of manufacture, a little albumen, so that its solutions are very stable.

Klimmer (*Ztschr. f. Thiermedizin*, 1900, No. 8) said:

"If we did not add a substance to protect colloid silver from change by salt and hydrochloric acid, it would be precipitated by the salts of the blood and other animal fluids, and thereby virtually deprived of effectiveness."

His *in vitro* tests showed that gum acacia and albumen materially retard change of colloid silver by sodium chlorid, hydrochloric acid, lactic acid and trypsin. He also gave collargol *per os*, together with gum acacia and albumen, to a dog, and recovered 50 per cent. of the colloidal silver in the dog's feces.

If collargol were changed to salts in the body, it would be fatal in the enormous doses in which it is used. Cohn says:

"When such enormous doses do not cause the least disease phenomena, this proves with certainty that colloidal silver has no toxic effect on the organism. This behavior is all the more strange because, as is well known, metallic silver and its common salts (for instance silver nitrate) are exceedingly grave poisons which even in minimal doses can destroy that organism soon after introduction."

ABSORPTION OF COLLARGOL

The committee says:

"The fact that is repeatedly stated in articles referred to in Schering & Glatz's advertising matter, that colloidal silver, *because of its colloidal character does not pass animal membranes*, contradicts the other contention that it passes the gastric or intestinal mucous membranes in colloidal form."

There is no contradiction whatever between the two facts referred to. It is an elemental law of physiology that the mucosæ absorb *by the activity of the epithelial cells* rather than by diffusion and endosmosis. Loebl did establish the fact that collargol enemata are absorbed. He says literally (*Therap. d. Gegenw.*, April, 1904):

"The collargol enema is almost entirely absorbed, for a cleansing enema given twelve hours later brings only a slightly blackish fluid."

Seidell (*Deutsch. med. Wchnschr.*, July 20, 1908) says the Roentgen rays show how rapidly a collargol enema is absorbed.

"Thus in the case of a 15 year old girl, who received, after a cleansing clyster and a salt irrigation, an enema of 2 gm. collargol in 100 gm. water, Roentgenograms were taken at first hourly and then every two hours until ten hours after the enema. It was very clearly visible how the silver shadow changed. Most of the enema is absorbed in the first hour, the rest almost entirely in the second hour. An aqueous irrigation after eight to ten hours is returned almost clear or but slightly brownish."

NOT EXCRETED IN THE URINE

The data which we gave on this point in our October, 1907, pamphlet, were presented only for the sake of completeness, since it is of not the least practical importance or significance if collargol is excreted in the urine or not. We acknowledge that an error was made in stating that Lange found silver in the urine after administering collargol. He found it in the kidneys, not in the urine. It is also true that in Buberl's patients the presence of silver in the urines may be explained on

the ground that the respective patients had pyuria. By an error the finding of collargol in the urine was ascribed to Baginsky instead of to Bamberger.

EXPERIMENTAL RESULTS IN ANIMALS

The experiments of Cohn, Brunner and Trommsdorf have been aptly criticised by Dr. Frank P. Vale, Washington, D. C., in a paper entitled "Clinical and Experimental Experience with Colloidal Silver and a Virulent Streptococcus" (read before the Medical Society of the District of Columbia; *Am. Jour. Med. Sc.*, November, 1906). He said:

"It will be observed that in these experiments, with the exception of two intraperitoneal inoculations, the infective organism was thrown directly into the circulation in relatively overwhelming numbers. This method of inoculation in no way simulates the manner of acquiring disease through the ordinary channels of infection, when the invading organism gains access to the circulation late in the course of the disease or frequently not at all. In experiments with the streptococcus, however, three in number, Cohn inoculated the scarified ear of a dog with a loopful of the culture, followed by an intravenous injection of colloid silver, about 0.1 gm. per kilo of animal body weight, and in each instance the control lived longer.

"But in these last mentioned experiments, the silver was injected at the time of inoculation. Now the leucocytosis following the administration of colloid silver, which is at its height at the end of 24 hours, plays the important, but as yet imperfectly understood part in its action. It has been shown in efforts at prevention of sepsis through hyperleucocytosis induced by the injection of nuclein, pepton and other substances, that to obtain favorable results it is necessary that the inoculation be made at the height of the induced leucocytosis."

Dr. Vale inoculated twenty rabbits subcutaneously twenty-four hours after injecting colloid silver, when the average leucocytosis was 12,000, due chiefly to an increase in polynuclear cells. After the intraperitoneal infection the leucocytosis was of about the same intensity, but due chiefly to an increase in lymphocytes, as if the entire army of polynuclear phagocytes had responded to the call in the peritoneal cavity.

"In no case was a local reaction from the subcutaneous inoculation with the streptococcus entirely prevented, but with the largest dose of 0.5 gm. per kilo of animal weight, the inflammatory process was transitory and in marked contrast to that in the control."

As stated in our pamphlet, animal experimentation done under conditions that closely simulate those of a clinical infection, invariably has given favorable results. This is shown by the reports of numerous veterinary surgeons.

ITS PROPHYLACTIC VALUE

There is an obvious difference between administering collargol topically for the prevention of a local sepsis in an accidental or operative wound, and its use by injection into the veins. There is, therefore, no contradiction between the claim of prophylactic action for collargol and the objection to its simultaneous administration with infective material in animal experimentation.

ITS ACTION ON LEUCOCYTES

While we have not asserted that the leucocytogenetic effect of collargol is its sole explanation of its virtues, we do not, on the other hand, believe warranted the committee's assumption that the leucocytosis is of no significance whatever.

ITS CATALYTIC ACTION

The committee's "*reductio ad absurdum* argument," applied to Hamburger's findings, is based on wholly incorrect premises, Hamburger says literally:

"It is apparent from this that argentum colloidale has hastened the oxidation of the hemolytic toxins. The quantity of collargol was very small; 0.00000058 gram atoms of silver proved effective even in 2 c.c. toxic serum."

This number of gram atoms silver is equal to 0.000063 grams of silver. In a liter of toxic serum there must therefore be present, to get an effect, 0.0315 grams silver = to 0.035 collargol. Since in an intravenous injection 0.1 to 0.3 gram collargol are injected each time, Hamburger's tests demonstrate that collargol, in the quantity in which it is introduced in the blood, can hasten oxidation of bacterial toxins. The committee erroneously ascribes to Hamburger the statement that "lesser concentrations increase hemolysis." What he says is that the less collargol is added the more rapid is hemolysis.

In duplicating Hamburger's test, at the instance of the committee, Dr. Anderson has overlooked a vital step: He has failed to conduct oxygen through the solution of diphtheria toxin to which he added collargol. His bad results were therefore inevitable, but, of course, prove nothing.

Robin's work was done with electrolytically prepared colloid silver, but his results were corroborative of those obtained by other observers in demonstrating the catalytic action of colloid silver, and were therefore perfectly applicable to collargol, which is nothing else than colloid silver.

H. Fueth (University Gynecology Clinic at Leipsic) said in the *Centralbl. f. Gynœcologie*, September, 1906):

"Colloid silver acts as a catalysator, i. e., it hastens the decomposition of H_2O_2 under formation of nascent oxygen, without itself undergoing any change."

THE CLINICAL EVIDENCE

The committee concedes that the clinical evidence is extensive, but implies that it is not competent. In disproof of this we call attention to the standing of some of the physicians who have written favorably about collargol: Professor Roswell Park, Buffalo, in "Principles and Practice of Modern Surgery," 1907. Prof. B. K. Rachford, Cincinnati, in *Am. Jour. Med. Sc.*, January, 1909. Prof. F. Forchheimer, Cincinnati, in "Prophylaxis and Treatment of Internal Diseases," 1908. Prof. Norbert Ortner, Vienna, in "Treatment of Internal Diseases," 1908. Professor Plehn, in *Deutsch. med. Wchnschr.*, Dec. 24,

1908. Prof. E. C. Dudley, in "Principles and Practice of Gynecology," 1908. Dr. F. Kreissl, in "Urogenital Therapeutics," 1908. Dr. L. S. Pilcher, in "*Ann. Surg.*," January, 1907.

Surely this is competent authority. We do not understand that the committee impugns the competency of these distinguished members of the profession. The only question which remains, therefore, is to see if our claims are warranted by the tenor of this the clinical testimony. Our claims are:

1. Used prophylactically, collargol is an almost unfailing safeguard against sepsis from accidental or operative wounds or childbirth.

2. Administered early it usually arrests incipient medical or surgical infections or renders their course briefer and milder.

3. Even when employed only as a last resort, it sometimes achieves brilliant recoveries in desperate, apparently hopeless cases.

The third claim being the one most open to scepticism, its substantiation will justify the others. We refer to the publication from Bumm's clinic, which shows a clear reduction of the puerperal mortality under collargol. One of the members of the committee, Prof. Solis Cohen, has seen "two recoveries from malignant endocarditis and numerous recoveries from other grave infections" as the result of energetic employment of it intravenously and per rectum. Dr. George T. Harrien says: "I have saved cases with it that I could not have saved without it. The collargol literature, so far as we know, comprises close to 500 reports. Now, assuming that 30 of these are unfavorable, you are confronted with the conclusions of 470 observers. There is thus an overwhelming preponderance of favorable evidence. And absolute unanimity exists with hardly any remedy of the materia medica.

OUR PRESENTATION OF THE TESTIMONY

The committee alleges that we quoted from an early edition of Tillmann's "Allegemeine Chirurgie," because he there expressed himself more favorably than he did in later editions. Tillmann said:

In his 7th (1889) Edition:	In his 10th (1907) Edition:
Mehrfach sah ich ueberraschend guenstige Wirkungen, in anderen Faellen war klein Erfolg zu konstantieren.	Das Verfahren hat sich mehrfach beim Menschen bewaehrt, in anderen Faellen war es erfolglos.
(Frequently I saw astonishingly favorable effects, in other cases no success was determinable.)	(The method has frequently proved successful in man, in other cases it was without result.)

If any difference is appreciable, it is rather in favor of collargol, since in the later edition Tillmann generalizes the favorable conclusion which he originally based only on his own observations. Moreover he devotes more space in the later

edition to collargol, citing Netter, von Baracz and others. We certainly would have quoted the 1907 edition in preference to the 1899, if we had been aware of its existence, which we were not. We can not search the medical archives of the world from year to year in order to make sure that an author has not published later writings containing slight alterations of his original phraseology. The library of the New York Academy of Medicine does not possess the eighth and ninth editions of Tillmann's book, and we do not even know if the tenth edition (1907) was obtainable at the time our October 1907, pamphlet was compiled.

The committee points out that in reproducing Hocheisen's favorable report we left out a part of the introduction, in which he said that collargol was used by him in Landerer's clinic without his seeing any result that could not have been secured quite as well with the customary surgical or general treatment. But it was necessary to omit practically the entire introduction, including a great deal of favorable matter, as we had to sacrifice everything excepting the essence of his report in order to make a 3,000-word abstract of the 15,000-word original.

This procedure must be followed in compiling literature. If we reproduced the publication in extenso the printer's bill would be many times as great, and the physician would be quite discouraged at the very outset by the task of wading through pages of unimportant prefatory remarks and explanations, repetitions, literature reviews, etc. We are convinced of the value of collargol—else we would not introduce it—and we present the material evidence in a manner which renders it available to the busy physician. Since it is impossible to acquaint the physician with all of it, since we can in fact acquaint him with only a small part or with none at all, we must use discretion in selecting that for which we request his consideration. We certainly do not thrust before him material which we consider valueless, but chose only what we consider of real importance.

Therefore, we are obliged to omit many publications, favorable as well as adverse, which seem relatively less important. Thus the committee finds fault with us for not reproducing the report of Baginsky. But he used unguentum Credé in "scarlatinal affections of the gravest form" and "the inunctions were not instituted at the beginning of the disease but only after several days." Now we do not claim that unguentum Credé cures scarlatinal affections of the gravest form in which it is used belatedly; in our October, 1907, pamphlet, we say (p. 7):

"Unguentum Credé is inuncted as a prophylactic of puerperal sepsis and in the treatment of *mild* general septicotoxic processes."

In "severe and desperate infections" we recommend collargol intravenously. Nor do we claim that even collargol intraven-

ously cures every case. The claim is that it sometimes cures desperate cases.

Therefore, what object could have been served by reproducing Baginsky's report. We warn against the very thing which he has done.

Referring to Jeannin and Bonnaire's paper, it is not correct that "there is no evidence that the patients had actual septicemia or pyemia." These authors say:

"Collargol treatment was instituted by us only in severe, recalcitrant and general infections, or such as tended to become so. We never used it in merely benign or local infections. . . . The intravenous injections were made only after the failure of the ordinary treatment such as intrauterine irrigations, digitalis, curettage and lavage. Our statistics should therefore be compared only with the most severe form—parenchymatous metritis, septicemia, pyemia."

They conclude:

"Collargol is a method frequently effective against generalized puerperal infections or those tending to become so."

The committee thinks we intentionally withheld Osterloh's report in the *Deutsch. med. Wchnschr.*, 1902, No. 21, wherein the author expresses himself with some reserve regarding collargol. But we also did not reproduce Osterloh's later and much more favorable report (Jahresber. d. Gesellsch. f. Naturu. Heilkunde, 1904). The following is a literal translation of an abstract thereof in the *Centralbl. f. Gynakologie*, 1906, No. 15:

"After an exhaustive compilation of the casuistic literature the author relates a case which he himself observed. This consisted of a puerperal fever in a primipara (an insane subject), after manual removal of the placenta. Thrombosed vessels in both parametria, daily chills. Treatment consisted of four intravenous injections of 7 to 8 c.c. of a 1 per cent. collargol solution, in bi-daily intervals, and of 12 enemata with 50 c.c. of 1 per cent solution in average intervals of 2 days. After 5 days no more chills. The effect of collargol was favorable on cessation of chills and in improvement of the general condition. The author considers Collargol treatment especially indicated in general puerperal sepsis without localization."

Döderlein also expressed himself distinctly favorable in the *Ztschr. f. acrztl. Fortbildung*, 1907.

The committee says that we mistranslated one of Hocheisen's sentences thus: "Collargol is an invaluable aid in the treatment of puerperal sepsis," and says that the sentence should read: "Collargol is an aid in the treatment of puerperal sepsis." Hocheisen (p. 893 of the Med. Klinik) uses the word "wertvolles," which, however, would have been better rendered as "valuable."

The committee objects to our quotation from Schlossmann's paper that "he advised 1 per cent. collargol solution in sweetened milk when an intestinal antiseptic is needed." The committee seeks to draw from his paper the inference that he is not really in favor of intestinal antiseptics, but recommends collargol as a placebo to those who are foolish enough to be-

lieve in intestinal antisepsis. This assumption is not warranted, as shown by the ending of Schlossmann's paper:

"For infectious diseases of the mucous membranes, above all for ophthalmoblennorrhea neonatorum and cholecystitis, there is no other remedy (than collargol) which so intensively and rapidly leads the disease process to cure."

The committee asserts that Rittershaus reported by-effects from collargol. Rittershaus's by-effects (infiltration, embolism) were, however, not due to collargol, but to his wrong technic in administering the injections; he allowed the solution to escape into the tissues, instead of injecting into the vein, and permitted air to get into the syringe.

The committee's majority report charges that we sought to give the impression that all the reports cited in the "Bibliography" (October, 1907, pamphlet) are favorable. This is disproved by the fact that we distinctly say that Ernst Cohn's report was unfavorable and give immediately after his name the number referring to his report in the bibliography.

COMMITTEE'S CRITICISMS OF AUTHORS

The committee criticises the report of Harrison, Witthauer, Afanassjeff, Wenckebach and Netter. We need hardly take it upon ourselves to defend these authors, and merely call attention to the fact that one of Wenckebach's sentences is misinterpreted by the committee. Witthauer's observations are confirmed by those of Riebold, Plehn and others. Netter's total experience consists of many hundred cases—not of 73 cases, as the committee erroneously states. *Vide* our bibliography in the October, 1907, pamphlet.

CONCLUSIONS

We are quite ready to admit the occurrence of mistakes in our literature; but these mistakes were all trifling, unintentional, without the least importance. Errors are prone to creep into printed matter, despite every possible care, and all that can be done is to guard against their repetition when we learn of them. The committee's report contains quite a number of very important errors. We therefore regret the fact that the report was arrived at by a method of excluding defence. Having shown the unsoundness of its premises, we believe that it will collapse under the weight of its error and unjustness.

Respectfully,

SCHERING & GLATZ.

THE COMMITTEE'S REJOINDER TO SCHERING AND GLATZ'S LETTER

In reply to the Council's inquiry as to our recommendation concerning the response of Schering & Glatz to our report on Collargol, we would say that we recommend that it be published. We would state, however, that after reading it very carefully, we can not find therein any reason for altering our

previous conclusions; nor can we find any evidence that we have dealt unjustly with Schering & Glatz, or misinterpreted or otherwise misused any of the testimony that they submitted in support of their claims.

On the contrary, we find in their reply direct admission of a number of false statements that we pointed out; and further they tacitly admit numerous other objectionable things that we emphasized, such as the exaggerated presentation of authors' views, the suppression of portions of sentences and of portions of reports, and the like—all of which they evade answering, except instances that we shall mention. Indeed, they openly state that they choose for their advertising pamphlets only the matter that they "consider of real importance"—a statement that is much illuminated by the fact that the matter left out in the instance that they are discussing, as well as in various other instances, was exceedingly damaging to their claims concerning collargol.

We find, further, that in their reply they make use of the same methods that we condemned most severely in our report. Carefully comparing our original report and Schering & Glatz's reply will show that they have misquoted what we said as to Bonnaire and Jeannin and Netter in a minor way, but in a manner that appears to be intended to discredit our report. Further, in their reply—and especially in a pamphlet recently sent broadcast throughout the country—they present a most excellent illustration of a practice that we condemned with especial severity; namely, the mutilation of statements of authors through subtraction, addition, and rearrangement of words and sentences in such a manner as to make the statements appear stronger than they were, giving them in quotation marks, as if they had been taken without alteration from the authors. It is somewhat remarkable that they should have employed this practice in attempting to discredit the one instance in which they now claim that we falsely accused them of having done exactly this thing. This, again, seems to be clearly done in the belief that the precise facts will not be looked up. The particulars of this matter are as follows:

Schering & Glatz stated that we were wrong in charging that they had inserted the word "invaluable" in a sentence that they quoted from Hocheisen, and insisted that he used the word "werthvolles," which means "valuable." It would be difficult to understand their reply, were it not for the somewhat more extended reply that they have scattered through the mails. The latter clears up the legerdemain. The sen-

tence in the original pamphlet, and the one that we criticised in our report, was: "Collargolum is an invaluable aid in suitable cases." The sentence they now use is: "Collargol is an invaluable aid in cases of puerperal sepsis." This latter sentence is made up as follows: Near the top of one page of Hocheisen's paper from which they quote occurs the following statement: "Hence, Collargol is no specific, but is an aid in suitable cases." Near the bottom of the same page, after having stated a variety of types of cases in which it is not suitable, Hocheisen says: "Used according to these principles, Collargol injections constitute a valuable measure in cases of puerperal sepsis." Hence, it becomes quite clear that the sentence with which we are now presented in running form and in quotation marks is made up, in its first part, from the top of the page, and in its last part, from the bottom of the page, the word "valuable" having been changed into the word "invaluable," and transposed in position in the attempt to justify what we originally criticized.

We were really very gentle with this point in the original report. Any one who cares to read the extract from Hocheisen in Pamphlet C and compare it precisely with the original will see that Schering & Glatz actually, in Pamphlet C, have not only done what we said, but have eliminated a number of things that Hocheisen said, though the extract is given in running form and in quotation marks: and the things that are eliminated are almost all such as to guard and restrict his statements concerning the use of the substance.

Our original criticism concerning this matter was precisely correct. As to their other statements concerning the clinical evidence, we can not go extensively into this matter. We feel that it is quite sufficient to refer any one back to the details of the original report, merely directing them to note carefully in the reply as contrasted with our report the interpretation of authors in a way that appears entirely unjustifiable and particularly the evasions of the main points at issue in such matters as the quotation from Tillmanns. As to such new evidence as that referred to Osterloh, we would note here, again, that their quotation is from an unauthorized abstract; and that in the entire paper by Osterloh, which they do not seem to have consulted, but which we have, the conclusions are more cautious and guarded than those that are presented in this abstract.

The most important portions of their reply, since they relate in part to actual work, are those concerning the pharmacological evidence As to the form in which Collargol circulates, we referred to precisely the words which they now

quote from Hocheisen, when we said that he had offered no evidence. In regard to this and the other evidence that is offered concerning this point, we would say that it is perfectly palpable to any one that none of this is evidence as to the condition in which Collargol is found in the body. The most recent testimony concerning this point (and, indeed, so far as we know, the only testimony that has some appearance of soundness) is that found in the recent study by Luzzato, who agrees with the statement of Schering & Glatz that Collargol rapidly disappears from the blood-stream and is quickly found in the organs; but states that it is found there chiefly AS METALLIC SILVER, AND NOT AS COLLARGOL. This paper had escaped our attention when we made the report, and it seems still to have escaped the attention of Schering & Glatz.

As to absorption, the work of Loebl and Seidel, to which Schering & Glatz refer, we were familiar with. It is scarcely necessary to say that it is ridiculous to attempt to reach any conclusion regarding scientific matters by such gross methods. In regard to this point, also, Luzzato has some clarifying information. He states that, given per os or by enema, Collargol is either not absorbed at all or is absorbed in extremely slight amount; and he says that this is due to the fact that it is readily precipitated out as metallic silver.

As to the experimental results in infected animals, Cohn, Brunner, and Trommsdorff have, as we noted in the report, given Collargol just before, coincidently with, immediately after, and many hours after the infection; and Cohn even let some of his animals become actually ill with streptococcus skin infections before using the substance. All the results, as we stated in our report, were negative. In this section of the reply, it plainly is admitted that all of these experiments were unfavorable; but now, in criticising them, Schering & Glatz shift their ground. In the original pamphlet, Cohn was severely condemned because he gave his injections of Collargol before the infective material; and it was stated that in such a case the leukocytes would be too busy taking care of the silver to be able to attack the infection. In the new evidence now presented, we are told that the injection should be given twenty-four hours before the infection is set up, when the leukocytosis is at its height. It appears quite true that this is the only chance for success that is left; but, in the first place, these two statements are the opposite of each other and, in the second place, such results would not appear very valuable practically, because it is somewhat difficult to use a treatment before the patient gets sick. In the third

place, the practice now recommended is obviously prophylaxis; and yet, in the next section we are told that the committee's criticisms of the claims that Schering & Glatz make for Collargol as a prophylactic were very foolish, because there is a difference between giving it topically and giving it by injection—all of which can only be interpreted to mean that it works as a prophylactic when used topically, but not when given intravenously. Clearly, also, the reply at this point states, through quotation, that the important part of the action of Collargol is the leukocytosis which it sets up; and it is directly compared to nuclein and other substances that produce leukocytosis. This must mean that the supposed direct bactericidal, catalytic, and other effects described are unimportant; for such direct effects could not be dependent on a leukocytosis.

On the other hand, in the next section Schering & Glatz state that the leukocytosis is not the sole explanation of its action; and, in reply to our perfectly correct statement that the leukocytosis can not be considered to be of any definite significance in regard to its effect on a general infection, they merely say mildly that they do not agree with this. We would say, Mr. Chairman, that we consider it a little ridiculous for serious-minded persons to play this game of hide-and-seek any further. We have now been told by Schering & Glatz:

1. Collargol must not be given before the infective material, or the resistance of the organism will be lowered by obstructing the activities of the leukocytes.

2. It must be given before the infection.

3. One must, on the other hand, wait until the animal is actually sick.

4. One must, however, not give the animal a very severe infection.

5. The most important effect is the leukocytosis following its use.

6. The leukocytosis is only a fraction of its effects.

7. It has "direct bactericide energy." (Cover of Pamphlet B.)

8. "We do not claim that Collargol kills bacteria, but that it hinders their growth."

9. It is a prophylactic, when injected.

10. It is not a prophylactic, when injected.

11. It acts like nuclein.

12. On the contrary, it has some mysterious activity, all its own, etc., etc.

Let us again point out, on leaving this section, that Cohn's work is once more misrepresented, as will be seen by comparing the statements as given in the reply with the correct statements in our report.

As to their comment on our interpretation of Hamburger's work, we would say that if these new figures are given correctly, we have done Hamburger some injustice. We can not, however, see that we have done the slightest injustice to Schering & Glatz, for, as we stated in the report, we took the figures that we used and the statement that lesser concentrations increase hemolysis, from their own pamphlet (the one marked B by you), and not from Hamburger's own articles, as the latter were not available to us. The figures and statements that we used are precisely correct as given in the Schering & Glatz pamphlet. Perhaps they will now argue that, after our other criticisms of their pamphlets, it was very unwise of us to have put faith in any figures in them. But the actual figures are not the point at issue, as we noted in our report, and since we have no contention with Hamburger, but only with Schering & Glatz's use of his work we do not need to refer to his original articles.

Every one knows that colloidal silver and various other colloidal substances, as well as a host of other substances, may act as catalysers *in vitro*. The matter for consideration is not the amount necessary to produce this effect *in vitro*, but whether any such effect can be shown to occur in the organism. The assumption that it does occur is entirely unjustified, unless there be evidence in favor of it, and particularly when there is evidence against it. Robin's studies of metabolism, we have already discussed. We would further say that his results might quite as readily be called toxic as catalytic; and in our present knowledge of things, they might more suitably be called toxic. The only work with which we are familiar that bears directly on this point and that was carried out under conditions clearly simulating those met with in the diseased organism are the experiments of Dr. Anderson, in which he injected both diphtheria toxin and Collargol into the circulation of living animals. The Collargol caused no lessening of the toxicity of the diphtheria toxin. These experiments Schering & Glatz skilfully avoid mentioning, and merely insist scornfully that Dr. Anderson's other experiments (*in vitro*) were faulty, in that he did not conduct a stream of oxygen through his mixture of toxin—and Collargol —solutions. We may leave it to the judgment of others whether such a procedure would really make such experiments more convincing or less so, as an imitation of the con-

ditions that exist in the living organisms; but whatever may be said about this point, Schering & Glatz can scarcely demand that in his experiments *in vivo* Dr. Anderson should have conducted a stream of oxygen into the hearts of his guinea-pigs when he injected diphtheria-toxin and Collargol.

The truth of this whole matter seems to be that there is no direct evidence in favor of this interesting hypothesis of Hamburger, while there is some evidence against it; and there is no more reason for building sweeping therapeutic assertions on it than there would be for saying that because colloidal platinum will, *in vitro*, act catalytically in hastening the transformation of alcohol into acetic acid, we might optimistically treat acute alcoholic intoxication by the use of colloidal platinum. If we could transform the alcohol into acetic acid, it would, of course, be easy then to use alkalies to neutralize the acetic acid, and thus make the alcohol wholly innocuous.

One further point: Schering & Glatz charge that we said quite improperly that Rittershaus and others have produced dangerous symptoms with Collargol (signs of embolism of the lungs, etc.), and they state that these results were all due to faulty technic. This is hardly worth while replying to, for it is manifestly merely an entirely unjustified interpretation of the bad results we referred to; but in regard to untoward effects of drugs, experimental results in animals have illuminated many questions, and seemed to have illuminated this one somewhat brilliantly. The animal to which Schering & Glatz refer as having been studied chemically by Lange died three hours and a quarter after an injection of Collargol, nothing else having been done to it, so far as the protocol shows. Furthermore, Luzzato states that when injected into the veins Collargol produces lesions of the lungs "with extreme readiness"; and Foa and Agazzotti who also have recently made an extensive study of the effects of colloidal silver preparations, say that Collargol in small doses produces fever, phosphaturia and slight albuminuria, while large doses produce marked phosphaturia and a very severe nephritis with casts and hematuria, which, in a short time, leads to the death of the animal. In order to avoid misunderstanding we would say that the two articles last referred to we have seen only in abstract, but the abstracts were not the wholly unauthorized kind that we criticized Schering & Glatz for using, but were written by the authors themselves. In consequence of these and the other very disquieting reports we have referred to we must emphasize our previous statement that the claim that Collargol is harmless when administered in any manner is far from justified.

COLLARGOL

(From The Journal A. M. A., December 18, 1909.)

The following recommendation was submitted to the Council:

A letter from Dr. S. Solis Cohen to the Editor of THE JOURNAL has been transmitted to the Council. In this letter Dr. Cohen states that his communication to the chairman of the collargol commission should have been published with the Council's rejoinder to Schering & Glatz's reply, which appeared in THE JOURNAL, July 10, 1909. In view of Dr. Cohen's request, it is recommended that publication of his letter of dissent to the majority's findings be authorized.

The recommendation having been adopted, the letter of Dr. S. Solis Cohen is here published.

W. A. PUCKNER, Secretary.

PHILADELPHIA, May 3, 1909.

DR. W. A. PUCKNER, Chicago, Ill.

My Dear Dr. Puckner:—I have received your letter of April 30, enclosing copy of Schering & Glatz's report and of Dr. Edsall's explanatory note.

I still feel that the committee made a mistake in not permitting Messrs. Schering & Glatz to be heard before deciding on a report, although this error was in a measure corrected by submitting to them the proposed report and receiving their written comment on it before publication.

The explanatory note involves reaffirmation of a number of points of fact, theory and attitude concerning which I differed with the majority of the committee, and I am therefore unable to give it my unreserved approval. As an instance of what I believe to be hypercriticism on the part of the committee, I would cite that portion of the explanatory note relating to the Hocheisen quotation. The fact remains that Hocheisen used the word "wertvolles," and Schering & Glatz admit that they should have translated it "valuable" instead of "invaluable." The committee shows that what Hocheisen really said was: "Hence collargol is no specific, but is an aid in suitable cases," and that further on, after having described types of unsuitable cases, he adds: "Used according to these principles, collargol injections constitute a valuable measure in cases of puerperal sepsis." Messrs. Schering & Glatz now condense this into: "Collargol is a valuable aid in cases of puerperal sepsis."

It seems to me that both Messrs. Schering & Glatz and the committee are in part at fault. That is to say, Messrs. Schering & Glatz should quote exactly what an author says, with his limitations and in his exact language. They are not justified in leaving out the limiting phrase, "Used according to these principles;" they are not justified in leaving out

the limiting phrase, "no specific." On the other hand, it must be admitted that the opinion of the author in this particular instance has been substantially represented in the revised phrase, and that to magnify the importance of the incident is to leave the judicial attitude and approach that of the prosecutor.

My own opinion remains as before, that Messrs. Schering & Glatz claim too much, and that the majority of the committee doubts too much; that collargol is worthy of admittance to the list of recognized nonofficial remedies, and that Messrs. Schering & Glatz should be required to revise their advertising matter in such a way as to give the exact words of every author cited; and that all the limitations and qualifications which an author throws around his opinion should be quoted. On the other hand, they are perfectly justified in quoting experiments and conclusions, clinical observations and recommendations. of investigators and of clinicians who may have formed a favorable opinion concerning the drug or who may have established to their own satisfaction any chemical, clinical or pharmacologic fact concerning it. The evidence being submitted, the reader can draw his own conclusions as to its trustworthiness and authority. It would be manifestly unfair to set up for advertising matter a standard which is not required of text-books, namely, infallibility in observation and logic.

To avoid misunderstanding, however, I would, in conclusion, emphasize again my agreement with the majority of the committee that quotations must be exact, *verbatim et literatim*, and that statements of the results of experimental observations must be made in such a way as to convey the exact facts, and not in so partial a manner that, however innocently, they may mislead readers not familiar with the details of laboratory work.

It is time to stop bandying words in this matter, and come to an agreement and conclusion honorable to all concerned and worthy of the issue. SOLOMON SOLIS COHEN.

CERTAIN PRODUCTS OF THE ORGANIC CHEMICAL MANUFACTURING COMPANY

(Reprinted with Additions from The Journal A. M. A., May 8, 1909.)

An investigation by Dr. Torald Sollmann appeared as a report of the Council in THE JOURNAL, Sept. 5, 1908, p. 818, under the title, "Formaldehyd Derivatives; Their Fate and Action in the Body, Together with Observations on Some Other Urinary, Intestinal and Wound Antiseptics." In this paper Dr. Sollmann showed that the claims made by the Organic Chemical Manufacturing Company for certain of its

products were incorrect. The accuracy of Sollmann's findings was denied by the Organic Chemical Manufacturing Company, who issued a pamphlet in which appeared a report by Messrs. Sadtler & Son, challenging Sollmann's results, and which pamphlet was endorsed by Dr. Henry Beates, Jr.

In accordance with its regular procedure, the Council appointed a referee with instructions to investigate the matter and report to the Council. The referee submitted to the Council letters from Messrs. Sadtler & Son, Dr. Henry Beates, Jr., and Dr. Torald Sollmann, together with his own investigations and his report on them. The report of the referee and the letters of Messrs. Sadtler & Son, Dr. Henry Beates, Jr., and Dr. Torald Sollmann follow.[1]

W. A. PUCKNER, Secretary.

REFEREE'S REPORT

The referee appointed to review the action of the Council on Pharmacy and Chemistry in refusing recognition to certain products of the Organic Chemical Manufacturing Company, submits the following report:

The action of the Council was based on Professor Sollmann's investigations of the products in question, the report of which was submitted to the Council and published in THE JOURNAL of the American Medical Association, Sept. 5, 1908.

In a printed pamphlet dated Sept. 15, 1908, the Organic Chemical Mfg. Co. claims to prove not only that Professor Sollmann's report is grossly erroneous and misleading, but that it is also unfair and dishonest. The last four pages of the pamphlet consist of a report from Samuel P. Sadtler & Son,[2] a Philadelphia firm of analytical and consulting chemists, in which Dr. Sollmann's most damaging statements concerning the so-called formasal products of the Organic Chemical Mfg. Co. are contradicted and severely criticized. As the report of this firm contains the only evidence brought out against the validity of Dr. Sollmann's conclusions concerning the products of that company, it is chiefly the substance of that report which now constitutes the points at issue.

The extravagant claims and the accusations and insinuations of the pamphlet itself to which is attached the name of S. Lewis Summers, the president of the concern, need not engage the attention of the referee nor the attention of any member of the Council, including Dr. Sollmann, until it has been determined whether Dr. Sollmann's report to the Council

1. The referee's report appeared in *The Journal A. M. A.*, for May 8, 1909, p. 1511.
2. These four pages are reproduced on pages 100, 101, 102 and 103.

or the report of Samuel P. Sadtler & Son to the Organic Chemical Mfg. Co. is in accordance with the facts.

Henry Beates, Jr., president of the Pennsylvania State Medical Examining Board, seems to have experienced no difficulty in reaching the conclusion that the attack of the Organic Chemical Mfg. Co. on the Council on Pharmacy and Chemistry, and especially on Dr. Sollmann, is abundantly justified by the facts. His endorsement of the report of Sadtler & Son is printed in heavy type on the first page of the pamphlet issued by the Organic Chemical Mfg. Co.

In reply to the referee's inquiry of Dr. Beates as to why and how he came to lend his name in support of the literature issued by that company, a long communication[3] was received setting forth the remarkable merits of the products manufactured by the Organic Chemical Mfg. Co. Dr. Beates further gives the personnel of what he calls a "committee" which he appointed, and together with whom he visited the establishment where the products are made.

[We learn that the gentlemen referred to by Dr. Beates as composing the "committee," state that it is a misunderstanding as to there having been a committee; that they merely made a visit to the plant by invitation, looked at it and went away; that while interested in what they saw they made no statement other than one of courteous interest.—ED.]

The substance of the conclusions, as stated by Dr. Beates, was that "the committee had every reason to feel convinced that true active chemical compounds were being manufactured."

So far as the Council on Pharmacy and Chemistry is concerned, it is manifestly unnecessary for the referee to make any comments on these conclusions. As this report may be published, however, the referee wishes to take this occasion to make a few elementary comments. The essential claim made for the products of the Organic Chemical Mfg. Co. is the same as that made for many other proprietary preparations, namely, that they are chemical compounds made by chemical combination of therapeutically valuable ingredients which are again set free and develop their valuable properties just where they can do the most good in side the human organism. Such plausible claims appeal of course to the laity and to physicians as well, and are extensively exploited by manufacturers of all kinds of worthless products as well as by manufacturers of products which may have some merit. Even physicians do not seem generally to know that because,

3. Bates' letter appears on pages 72 to 79.

say formaldehyd, or iodin, or salicylic acid, is used in the preparation of a compound it does not at all follow that such ingredients are easily obtainable from it. Because sugar contains the formaldehyd group and salt contains the element chlorin, it does not follow that sugar and salt will set free these active chemicals within the body. It is clear that all kinds of frauds can enter into such claims for the liberation of active ingredients. The ingredients may or may not be there; if there, they may or may not be there in chemical combination, and if there in chemical combination they may or may not be set free by any agency at the command of the animal body.

The conclusion of Dr. Beates' "committee" that they saw true chemical compounds being manufactured may be all right. There certainly is no reason for denying it, for no one, so far as the referee knows, has denied that at least some of the products of the Organic Chemical Mfg. Co. are more or less pure chemical compounds. It is manifest that Dr. Beates' private "committee" has contributed nothing that is of any use to the referee.

In other parts of his letter Dr. Beates offers sundry pieces of evidence showing that the "formasal products" break up within the human body. This evidence consists of statements which he has borrowed directly from the literature of the Organic Chemical Mfg. Co., or from the report of Sadtler & Son. His statements are therefore either worthless or superfluous, for the evidence submitted by Sadtler & Son does not improve on passing through the editorship of Dr. Beates or of Dr. Summers, and when writing that letter to the referee Dr. Beates knew that the evidence of Sadtler & Son was being investigated by the referee at the request of the Council on Pharmacy and Chemistry.

Finally, as to Dr. Beates' clinical results achieved by means of the formasal products: These may or may not be able to stand close investigation and repetition. Whether they do or not is not important at the present juncture. The chief basis on which the products of the Organic Chemical Mfg. Co. were refused recognition was that unwarranted — because unproved—statements were made concerning their "gradual cleavage in the human body" and repetitions of such claims by the president of the Pennsylvania State Board of Examiners cannot be accepted as a substitute for evidence as to the truth of such statements.

So far as the referee can judge from his letter, Dr. Beates has confused his hostility to various persons, including some members of the Council on Pharmacy and Chemistry, with his

belief in the products of the Organic Chemical Mfg. Co. In no other way can the referee explain his dark hints as to politics, conspiracies, persecutions and bribery, or his unqualified approval of the slanderous pamphlet issued by the manufacturer of the "formasal" products, or his failure to recognize that loose and irrelevant suggestions of fraud could not do the "formasal" products any good in the eyes of any competent referee.

The "formasal" products were refused recognition by the Council because its first referee, Dr. Sollmann, found that the manufacturer had not proved the claim that these substances break up into their respective constituents within the human organism. Dr. Sollmann tried to verify the statements of the manufacturer, but obtained results which made it seem very clear that the manufacturer could not have even seriously attempted to prove that the formasal products yield appreciable quantities of formaldehyd or salicylic acid, or other active decomposition product within the body.

On receiving information of the action of the Council and a copy of Dr. Sollmann's report, the president of the Organic Chemical Mfg. Co. began, evidently, for the first time, to bestir himself in the direction of attempting to demonstrate the truth of his proclamations concerning the behavior of the formasal products within the human organism. To repeat his own words: "The report sent us as being that of Torald Sollmann is dishonest and within ninety days we shall prove its incorrectness beyond a question of a doubt." As a result of this remarkable decision, we have the report of Samuel P. Sadtler & Son to the Organic Chemical Mfg. Co. of Sept. 10, 1908.

According to this report Sadtler & Son seem indeed to have found no difficulty in proving the essential point which the manufacturer wanted them to prove and which he should have proved before submitting the formasal products to the Council on Pharmacy and Chemistry, namely, their decomposition into formaldehyd and salicylic acid within the human body. Sadtler & Son write: "Proving this dissociation we have found to furnish no difficulties other than is necessitated by a more detailed analysis of the urine of people taking these remedies in prescribed doses."

The detailed urine analyses to which Sadtler & Son refer are described as follows:

"Sample sent by Dr. ——— from patient (P. D.) taking 140 grains of ur-a-sol per day.

"Day's sample was 1,030 c.c. This was made slightly alkaline with sodium carbonate and extracted with ether to remove neutral substances. After making acid with hydrochloric acid.

"Ether extract, 0.5170 grams (7.50 grains).

"This sublimed in needle crystals gave a strong $FeCl_3$ test and had the melting point of salicylic acid.

"The residue was then boiled with caustic soda solution and any possible basic principles extracted with ether and discarded. The residue was then made acid with hydrochloric acid and extracted again with ether.

"Second acid ether extract, 0.4664 grams (7.0 grains).

"This responded to the same test when the sublimed needles were taken."

It will be seen that Sadtler & Son have endeavored to distinguish between the undecomposed methylene-di-salicylic acid of the ur-a-sol and the free salicylic acid which should be present in the urine if the disalicylic acid is decomposed in passing through the organism. They purified the ether extract by subliming it and found that the product so obtained gave the ferric chlorid reaction as well as the melting point of salicylic acid.

These tests they fortified by showing that the solubility of salicylic and methylene-di-salicylic acid in benzol are very different and may be used as a means for distinguishing between the two.

If these tests of Sadtler & Son could be accepted as proving this crucial point, the decomposition of methylene-di-salicylic acid, there would be little need for further discussion. The referee would then move for a reconsideration of the Council's action on the formasal products. Unfortunately, the tests as described above by Sadtler & Son have no value and seem to represent only an extremely uncritical piece of commercial work. As this statement is a rather severe criticism of the work of Sadtler & Son, and since the essential point of the whole controversy is involved in it, it will be necessary to go into this matter in some detail. The referee will, however, be correspondingly brief when discussing the less consequential points raised by Sadtler & Son.

As evidence bearing on the subject, the referee has a communication from Sollmann[4] describing a repetition of the experiments described by Sadtler & Son. This communication from Sollmann the referee forwarded to Sadtler & Son in order to give them every opportunity to prove their point. Sadtler & Son availed themselves of this opportunity, and so far as Sollmann is concerned, they are therefore having the last word.

Sollmann's subject took in a day 10 gm. ur-a-sol, and he obtained from the corresponding acidified urine 0.47 gm. of ether extract.. This residue gave the ferric chlorid reaction, but it showed neither the solubility nor the melting point of salicylic acid.

4. Dr. Sollmann's communication appears on pages 79 to 91.

In these tests Sollmann omitted one point: he did not test the melting point of the sublimed urinary residue, as Sadtler & Son had done. Sollmann gives an excellent reason for not following Sadtler & Son in this respect. He found the pure methylene-di-salicylic acid breaks up and yields salicylic acid when heated until a sublimate is obtained.

In this manner Sollmann proves as definitely as any referee would be likely to require that the findings of Sadtler & Son, as described in their report to the Organic Chemical Mfg. Co., are "based on false premises."

It was a matter of considerable interest to the referee to see what Sadtler & Son could say to this damaging fact brought out by Sollmann.

In their communication[5] to the referee is found the following paragraph:

"Sollmann's criticism of the testing sublimates obtained by strong heating is quite just. We only did this once, and while the practice was indefensible on theoretical grounds we believe we only fell into it because an ether extract showed such a mass of low temperature sublimated needle-like crystals that it did not take a temperature that would break up methylene-di-salicylic acid. We certainly would not have tried such, as we have been familiar with this acid for five or six years, as we had tested this acid for Dr. Summers about that long ago."

Sadtler & Son are to be given credit for having thus frankly admitted a blunder of fundamental importance in the point at issue. In their remaining discussion on "the presence of salicylic acid in urine," Sadtler & Son "hedge" and explain and shift the ground with some dexterity, but they fail to "make good" on the essential point. Take this paragraph:

"We would not expect to have it so decomposed as to give a sublimate of salicylic, as we had devised a test for the analysis of acetyl-methylene-di-salicylic acid in which the salicylic acid is obtained by heating with fused caustic potash to 250 C., and we found that it had to be heated well up to that temperature to complete the elimination of the formaldehyd residue. This test we have reported to the Organic Chemical Co., but not as yet published. In this case it merely tends to show that methylene-di-salicylic acid does not break up with any great ease when heated."

The stability of the salt of an acid in hot caustic potash has no particular bearing on the stability of the free acid. Sadtler & Son might as well have tried to prove that carbonic acid or chloric acid is stable because potassium carbonate and potassium chlorate can withstand considerable heat.

On another page we find the following paragraph which evidently is intended to prove that it is permissible to use the sublimates in determining whether the urine contains salicylic or methylene-di-salicylic acid:

---

5. The communication from Sadtler & Son to the referee appears on pages 91 to 100.

"The four printed pages of our report appearing in Dr. Summer's pamphlet did not contain all the points that we observed in making our tests. One of them is that in the test we here described and in several other analyses of urine from people taking Ur-a-sol we found to take place, what we have only noticed with very easily sublimable compounds, such as salicylic and benzoic acids, namely, that as ether was driven off from an extraction, the walls of the flask were covered with crystals. In one case we tested these crystals as to melting point and found them to be salicylic acid. We know from having evaporated etherial solution of methylene-di-salicylic acid that it does not sublime at such low temperatures. We have also found that by heating both acids, viz., salicylic and methylene-di-salicylic, in flasks in an oil bath that salicylic acid sublimes very noticeably at considerably below 100 C., while methylene-di-salicylic acid did not sublime at all at temperatures to which we heated the bath, which happened to be 170 C."

Why Sadtler & Son should insist on using the subliming process in the treatment of their ether extracts after Sollmann has shown how elusive it proved in this case and in their own hands—that they have not attempted to explain. Sollmann has, of course, had no opportunity to reply to the statements contained in the above paragraph.

It may be added that the "experience" of Sadtler & Son as to sublimates deposited on the flasks when urinary ether extracts are evaporated does not agree with that of the referee, who has frequently seen such sublimates obtained from urines where there was no occasion to look for salicylic acid. As a matter of fact, the referee obtained it from his own urine after taking ur-a-sol just as he has often obtained it before when not taking ur-a-sol. Sadtler & Son, in the above paragraph, say that they once tested such a sublimate from a ur-a-sol urine as to its melting point and found it to be salicylic acid. But the melting point of such an unpurified sublimate has little if any value, and Sadtler & Son say nothing about the ferric chlorid reaction of those particular crystals. The referee did apply this reaction to his sublimate and was thus able to exclude salicylic acid. The reaction was entirely negative.

To quote again from Sadtler & Son's communication to the referee:

"As to what Sollmann says of the quantitative separation of methylene-di-salicylic acid from salicylic: It will be noticed that Sollmann only speaks of extracting with ether in the way we spoke of on page 13. A very important part of what we did was briefly described, chiefly on page 14, as follows: 'The residue was then boiled with caustic soda solution and any possible basic principles extracted with ether and discarded. The residue was then made acid with hydrochloric acid and extracted again with ether.'

" 'Second acid ether extract, 0.4664 grams (7.0 grains).'

" 'This responded to the same test when the sublimed needles were taken.'

"It was this second extraction, after we had gotten out all the acid principles the first time, that we obtained by boiling with alkali. We have not been able to ascertain just what the compound is which is soluble in water but insoluble in ether until boiled with caustic soda and then gives rise to salicylic acid (or, if this is objected to, to bodies closely resembling salicylic acid). It is not methylene-di-salicylic acid, as that would have been easily extracted

with ether. We believe it to be salicyl-uric acid, for various reasons, and, if it is, it demonstrates the work of the drug, as it is claimed to be a uric acid solvent. This, however, is not our concern, as in the present paper we are only desirous of substantiating our tests as reported to the Organic Chemical Co. The fact remains that each time we have carried out this test, we have apparently found more salicylic acid in this combination. Dr. Sollmann does not refer to this at all, and if he admitted it we believe he would have to admit the action of the preparation, as the salicylic acid which is supposed to come from the methylene compound is supposed to be therapeutically active and just such a combination as we have found would be expected."

Here Sadtler & Son have a point against Sollmann. The latter did not go beyond the ether extraction in the acidified urine. On the other hand, there was no apparent reason why any such procedure should be adopted. And as is seen from the above paragraphs, Sadtler & Son do not now, on the basis of the last two extractions, claim the presence of free salicylic acid in the urine. They are now discussing some unknown "compound," which, on boiling with alkalies, gives rise "to bodies closely resembling salicylic acid." The unproved and improbable hypothesis as to "salicyl-uric-acid" may furnish Sadtler & Son with an interesting topic for further investigation, but has nothing to do with the practical point at issue. The referee, passing judgment on the basis for the Council's decisions concerning the formasal products, could fairly have left out of consideration the new turn which Sadtler & Son introduce in the shape of this salicyl-uric acid compound. He decided, however, to determine for himself how much basis Sadtler & Son had for advancing such a hypothesis and he regrets to say that here again he failed to find any evidence worthy of serious consideration.

It is clear that in order to demonstrate the presence of any salicylic acid compound in the ur-a-sol urines which is soluble in ether only after being decomposed by boiling alkalies one must be sure that he has first extracted all the methylene-di-salicylic acid which the ur-a-sol urines admittedly do contain, before he boils the remainder with alkali. This Sadtler & Son did not do. They simply assumed that any methylene-di-salicylic acid present "would have been easily extracted with ether." This assumption is unwarranted. It is also inexcusable since by means of the ferric chlorid reaction one can determine with very little work when the ether extracts no longer take up any more substance giving the characteristic color reaction.[6]

Working with 200 c.c. of acidified ur-a-sol urine the referee found that it took seven extractions. Sadtler & Son worked

6. To test the ether solution it is only necessary to pour some of it in a test tube containing a little *very* dilute ferric chlorid solution and shake. The aqueous solution assumes a color proportionate to the amount of methylene-di-salicylic acid in the ether.

with fully four times as large a volume and made no check as to when the extraction was finished.

The conclusion is clear. The new evidence introduced by Sadtler & Son is worthless. When acidified ur-a-sol urine is thoroughly extracted with ether, subsequent boiling with alkali sets free no weighable salicylic acid. Sadtler & Son, it will be noted, obtained almost half a gram. The referee obtained perhaps a few tenths of a milligram, i. e., barely enough for one rather faint color reaction. Incidentally it may be remarked that the uric acid fell out in perfectly typical fashion from the ur-a-sol urine after the addition of hydrochloric acid. The referee's ur-a-sol urine was obtained by taking 8.5 gm. of ur-a-sol in the caurse of about ten hours.[7] *The urine obtained in the course of twenty-four hours was very rich in methylene-di-salicylic acid or unchanged ur-a-sol but contained at most only traces of salicylic acid.* This essential point the referee has proved in the following manner:

Ur-a-sol is almost completely insoluble in dilute hydrochloric acid; salicylic acid is soluble. Consequently by merely adding enough hydrochloric acid to the urine to make a 1 per cent. solution the expected phenomenon happens, a precipitate comes down at once. This precipitate is very soluble in ether, is very little soluble in benzol and gives the ferric chlorid reaction.

The acidified urine was kept at 5 C. over night and filtered. To the filtrate was added sodi hydrate equivalent to the previously added hydrochloric acid. The filtered urine so obtained gave only an exceedingly faint reaction with ferric chlorid. To be specific it gave less of a color than the original urine diluted forty times. As the filtrate represented urine diluted with one volume of liquid this observation proves that less than one-twentieth of the substance giving the color reaction with ferric chlorid is left in the filtrate. It is certain, therefore, that less than 5 per cent. of the product in the urine could be salicylic acid. How much, if any, of this 5 per cent. actually is salicylic acid is of course immaterial.

---

7. Having myself taken this quantity of ur-a-sol, I feel justified in saying something concerning the taste of the stuff, although this is a point that hardly deserves the discussion it has received in the appended communications. The taste of a drug to a healthy person who takes it as an experiment is apt to be very different from the taste to a person who is sick and who believes or hopes that the drug will cure him. To me the stuff called ur-a-sol was very disagreeable, and I had the taste of it in my mouth the entire day. Only once did it have any nauseating effect. That, again, is, however, largely a matter of personal idiosyncrasy.

It will be noted that Prof. Sadtler now admits a more pronounced salicylic taste (p. 12). It is rather curious that he should have obtained this impression from less than a gram, but not from a "pinch" of the product which has such a slight solubility as ura-sol.

In the light of this positive demonstration that the substance which gives the ferric chlorid reaction in ur-a-sol urines is not salicylic acid it is useless to make this report unnecessarily long by going into detailed refutals of the several smaller points raised in the report of Sadtler & Son. In Dr. Sollmann's report to the referee will be found adequate replies to every point.

The referee will, therefore, only very breifly touch on a few points. (1) As to the solubility of salicylic acid and methylene-di-salicylic acid in benzol. The fact that Sadtler obtained a positive color reaction with his "one minute" benzol extract of the urinary ether extract proves not that the substance consisted of salicylic acid, but that the reaction is also obtained with ur-a-sol. The referee obtained a positive reaction with ur-a-sol when he followed Sadtler's directions. The reaction is, however, much weaker with ur-a-sol or with the urinary extracts than with salicylic acid. Incidentally, it may be said that Sadtler's procedure is more complicated than is necessary and correspondingly less reliable. The use of alcohol can advantageously be omitted. If ur-a-sol be shaken one minute with benzol and a little of the filtered benzol is poured directly into a very dilute ferric chlorid solution and shaken a very decided color reaction is obtained in the aqueous solution. Why diminish the reaction by the addition of alcohol?

(2) The Organic Chemical Mfg. Co. has made all the capital it could out of Professor Sadtler's accusation that Dr. Sollmann had erroneously quoted Fränkel as to the behavior of methylene-di-salicylic acid in the human organism. Fränkel has settled this point in favor of Sollmann.

(3) The question as to formaldehyd liberation when the formasal products are treated with various reagents (water, acids and alkali), has lost its significance since we now know that no salicylic acid is split off when the products pass through the human organism. To quote from the original report of Sadtler & Son: "If salicylic acid is found so abundantly in the urine when acetyl-methylene-di-salicylic acid (ur-a-sol) is taken, it is evident that a corresponding amount of formaldehyd was liberated." That no formaldehyd is liberated is now equally evident from the demonstrated absence of salicylic acid from the urine.

The referee has gone over the tests made by Sollmann and by Sadtler & Son (except the phenyl hydrazin test which it seemed not worth while to take up) as to the liberation of formaldehyd by ur-a-sol, sodiformasal, iodomuth and guaialin. In view of the sensitiveness of these color tests it is entirely

losing sight of the essential point at issue to dispute as to which test is more sensitive or more reliable. If formaldehyd were split off there would be no trouble about getting abundant tests and all results short of most decided positive ones are really negative in so far as any practical point of view is concerned. As a matter of fact, however, none of the products split off any formaldehyd when treated with water, hot or cold, or with dilute acid or alkali. Sollmann's original report is therefore correct and the findings of Sadtler & Son are erroneous.

Sollmann's later tests as reported to the referee give traces or "fair traces" by the Jorissen test when by Sollmann's original test they were entirely negative and by Sadtler's tests distinctly positive. Sollmann's faint reactions as reported to me are due, in the opinion of the referee, to the fact that he reversed the order of adding his reagents. What Sadtler's "distinct" or "strong" tests are due to, the referee does not know. When properly made the Jorissen test gives entirely negative results.

As to the tests used by Sadtler & Son and involving the use of concentrated sulphuric acid the referee entirely agrees with Sollmann who says that such tests are not adapted to prove that formation of formaldehyd under the influence of water or very dilute acids and alkalies. Sadtler's reply to this criticism of Sollmann is rather disingenuous: "How Dr. Sollmann can read into my description of my tests the idea that any of the substances in solid form were put into strong sulphuric acid I do not see, and yet that is what he is apparently talking about."

No, that is not what Sollmann is talking about. Placing "the substance to be investigated in contact with concentrated sulphuric acid" does not imply that the substance must be added in solid form. It also covers the conditions of Sadtler's experiments of adding the solution of a substance to be investigated in contact with concentrated sulphuric acid.

(4) For the sake of completeness the referee ought perhaps to explain the findings of Dr. Latham Clarke, whose report the Organic Chemical Mfg. Co. has quoted so ostentatiously in behalf of their contention that the taking of ur-a-sol gives rise to salicylic acid in the urine. Dr. Clarke was engaged by that company for the purpose of working out a practical method of manufacture of a certain product. On the last day of his engagement in the shop of that company Dr. Clarke was asked to test a "ur-a-sol" urine for salicylic acid. He did so and obtained positive results. The method consisted of passing compressed steam over the dried urine residue and

testing the solution so obtained by means of ferric chlorid. No attempt was made to determine whether methylene-disalicylic acid would not also go over with steam. *The test was therefore, of course, not conclusive and Dr. Clarke authorizes the referee to say that he is no longer willing to stand for the validity of the test and further that he very much regrets that his name was ever connected with it.*

(5) As to the antiseptic properties of ur-a-sol, Sadtler & Son sent the referee a small sample of ur-a-sol urine which gave a fair ferric chlorid reaction. Twelve hours after this urine was received it began to grow cloudy and in the course of two or three days a considerable deposit had formed. The usual decomposition resulting in the formation of ammonium carbonate and a characteristic odor did not set in. The referee's own ur-a-sol urine behaved in the same manner, while a sample to which he added a little chloroform remained clear. Essentially similar results were obtained by adding ur-a-sol directly to a fresh sample of urine.

(6) Finally it should be said that the letter to the Organic Chemical Mfg. Co. from the secretary of the Council on Pharmacy and Chemistry with regard to the rejection of its products might have been more full in which case it undoubtedly would also have been more accurate. The brevity and the inaccuracy of the letter was, however, more than compensated for by the fact that the company also received the full report of the referee. The pamphlet published by the company indicates that the author of it understood very well the import of the details contained in Sollmann's report, yet chose for advertising purposes to confuse the contents of a mere routine letter with the well considered statements of the referee, Dr. Sollmann.

The referee does not recommend reconsideration of the Council's action on the products of the Organic Chemical Mfg. Co.

LETTER OF DR. HENRY BEATES, JR., TO THE REFEREE

PHILADELPHIA, Dec. 31, 1908.

Replying to your favor of the 23d ult., in which you as "referee" make inquiry as to whether I had any statement or explanation to make as to how or why I had come to lend my name to the support of the literature contained in the pamphlet published by the Organic Chemical Mfg. Co., which was issued as an explanation and for the purpose of elucidating certain facts concerned with a report which was approved and caused to be published by the Council on Pharmacy and Chemistry of the American Medical Association, in which products of this company were adversely criticized, I beg

leave to state that long before this controversy arose, and before I knew where and by whom these remedies were manufactured, reputable physicians of wide experience directed my attention to the products under consideration. There can be no question but that the recommendations by these skilled therapeutists as to the efficiency of these remedies were solely the consequence of their profound interest in the alleviation of the afflicted, and the welfare of suffering humanity; and that they were and are above the suspicion of ever having had any commercial interest whatsoever with manufacturers of medicines, it seems superfluous to state.

I found from their use, as with all reliable medicines, when properly administered for the class of disease for which they are indicated, that there were invariably secured, pronounced and well-defined beneficial effects. It was during my employment of them that attention was directed to the said report, which was so contrary to the facts of extended and prolonged clinical tests, as to convince me that some grave error had been committed. From what I learned, I was induced to make an especial investigation into the glaring discrepancy existing between clinical facts and the adverse report. I will later refer to a committee[8] which I previously requested to form and, with me, investigate the laboratory of the company in question, if permitted to do so, but with the distinct understanding that the names of the gentlemen forming the committee, as well as its conclusions, should not be utilized for the business purposes of the concern. The company, I may here remark, has faithfully observed this agreement, notwithstanding the fact that the conclusions of the committee were very favorable to it.

Thus I set about to acquaint myself with data, whether for or against the company's answer or the Council's report, before allowing my name to be used in connection with the literature of that pamphlet. Not unmindful of the fact that an error made by a judicial body, composed of men of reputation, and enjoying the confidence and esteem of the profession, and especially because of the eminence of their positions, we find that too frequently error is blindly accepted as truth by that large percentage of unthinking followers, who regard the fiat of authority as infallible; and also of the fact that one instituting inquiry and daring to suggest error is naturally subjected to the criticism of being disloyal, I assumed the attitude I have, because I believed it a duty to do so, even though personal interest might be jeopardized. The belief should not be entertained that the eminent are infallible, and that their conclusions should not be subjected to analysis before being accepted as true and final. It is the disregard of this fundamental principle which so frequently results in the perpetuity of error, until its disastrous consequences force unbiased study and investigations.

8. Previously referred to in the referee's report, page 61.

As an advocate of the purposes and work of the Council, and because of the very interest I have in its reliability and integrity, I feel it a duty to make every effort possible to induce a questionable conclusion to be revised, and if an error be discovered, to have it corrected, in justice to right action and scientific accuracy.

Efforts were made to induce the Council to revise its action, but seemingly without avail. Why does not the Council grant hearings in such instances and offer opportunity for explanation and demonstration, pro and con?

The pamphlet in question, replying to the report, sets forth certain facts, as yet not disproved, which prove unreliability. Thus, at the bottom of page 5 and top of page 6, it shows that the statement: "Since the claims of the formasal compounds are based entirely on the assumption of the action of formaldehyd within the body" is not proved to be incorrect, but that the statement is absolutely unwarranted. The same is also a fact with the remainder of this quoted sentence: "Which claims were proved unwarranted by the report." Examination of the report proves that the statement was not proved at all. The critic's own admission, as the report certainly asserts, affirms that he was unable to distinguish between salicylic acid and methylene-di-salicylic acid in the urine, and that he did not know how to look for evidence to warrant such a statement. Again, Dr. Sollmann's letter of October 20, to you, contains the following admission that he did not prove it, namely: "None of this amounts to a final proof that these products are not decomposed in the body; and I have with care avoided any statement to this effect. I have held, however, that the company have failed to substantiate their claim and this, therefore, was unwarranted." Is it not a great error to condemn products before having obtained the proof? Is this fact to be denied, even if the company does not explain?

If there was any question as to the duty of having loaned my name to the literature of that pamphlet; if there was any question as to error and a consequent unreliability of the report; if there was any question as to the carelessness and haphazard conclusion emasculating the reliability of that report; this admission of Dr. Sollmann, that he did not have the proof and that he with care avoided any direct responsible statement to this effect, removes all question of doubt, and completely justifies the use of my name to the literature of that pamphlet, published in behalf of the cause of justice, and the efficiency of the medical profession in its relationship with the highest interests of fellow man.

Many medicines effect certain results in the living body, which chemical analysis fails to explain. To mention this for emphasis, not only because the reports of skilled therapeutists of extended experience, as well as the results of my own practice, unquestionably demonstrate that these remedies

not only produce definite and positive results; but that competent chemical analysis explains many reasons why these results are to be largely anticipated from their administration, when adequate doses are employed.

These compounds, which are not pharmaceuticals, are so encapsulated by chemical condensation that they undergo gradual cleavage in the human body, and by the even supply, as it were, of their active component parts, doubtless exert their full therapeutic vaule within the living body, without unduly disturbing the stomach, depressing the heart's action, or impairing the physiologic integrity of the blood; results which frequently follow the use of other salicylic and formaldehyd compounds, when given in adequate doses.

It is not here necessary to cite in detail the history of cases if many of my patients suffering with rheumatism and forms of eczema, symptomatic of the so-called uric acid diathesis, of cases of articular rheumatism, involving the smaller points, who taking ur-a-sol in from sixty to ninety grains a day for several months, now possess hands and feet that any one examining them would not know had ever been afflicted in the manner described; of other cases simulating rheumatism resulting from gonorrheal infection, who had been taking twenty grains of ur-a-sol in powder form, from four to six times daily, with well defined and excellent results; and this without any of the circulatory depression and cyanosis which is so frequently seen with other salicylic acid compounds. For years I have used this remedy in the vesical disorders so commonly occurring in advanced prostatic hypertrophy. The renal secretion, even in the summer, remaining free from putrefaction for many days, when large doses were administered.

I have met some cases in which large doses, used repeatedly throughout the day, have been followed with some disturbance of the stomach, but nothing to compare with that which would have resulted with other salicylic acid compounds, as experience had proven. Some people do not like the taste of the remedy, but the great majority of them do not dislike it, and when it is taken into consideration that the cases in question had been taking other salicylic acid compounds, and objected to their use because of the unpleasantness, and then uncomplainingly took these, the error of the sweeping statement of the report, regarding the disagreeable taste, is proved.

With iodomuth I obtained those results which are usually ascribed to the action of iodin. I repeat, therefore, that with iodomuth splendid results can be confidently relied upon, because of the disassociation of the compound by the cells of the tissues of the living body, and the liberation of those principles which bring about the desired effects in question. In intestinal troubles, and even in tuberculous diarrhea and dysentery it is of great value. In ulcerations and in inoperable fistula, in ulcerative gummata and in a number of similar

uses, I have obtained benefit with this odorless product, far superior to those, in my hands at least, secured by the use of the other commonly employed remedies. Last evening I introduced into the deep urethra, with a urethroscope, about eight grains of iodomuth. This morning the patient awoke with pronounced iodism and came to me for relief from these phenomena. Is not this evidence of disassociation, and, what influence did the pancreatic juice exert in effecting it? Dr. Sollmann's report would lead one to understand that he possessed the secret of the process of life, and, that the power of disassociation was to be found in the action of the pancreatic fluid, and of a dead animal.

Certainly then, a report which denies the action of iodomuth on living tissues, because it is based on experiments tried with dead tissue, is open to question. To my mind, it is faulty; therefore, unreliable.

The report suggests that subnitrate of bismuth possesses virtues equal to iodomuth and can be submitted therefor. From a scientific point of view such statements are about as reliable as would be a recommendation for the substitution of coal oil for water for gratifying thirst. It lacks scientific value and is misleading. Then again, there is a reference in the report, to iodomuth being used by the critic as an urinary antiseptic. Such an indication for the use of iodomuth, I cannot find in the literature published by the company; therefore, we have another misleading statement, which is practically a deception. Effort is made by the critic to demonstrate that as a urinary antiseptic it is valueless. This criticism is based on the action of the smallest element of its composition, the formaldehyd, with a single dose only, which would yield one-third of a grain in twenty-four hours. The unreliability of such conclusions, when based on an experiment as faulty, is very apparent and needs no fire-fly in an African forest.

Guaialin, because of the effects following its use, must in some way undergo disassociation. My clinical results in bronchitis and in tuberculosis of the kidneys, unquestionably prove this statement to be true. The critic's statement that it is "probably" not absorbed, and his failure to attempt to prove it in the living body, is inexcusable, amounting in my judgement to either carelessness or ignorance, and should certainly receive the especial attention of the referee. The use of ferric chlorid reaction for salicylates, setting forth a negative report (see THE JOURNAL A. M. A., Sept. 5, 1908) which certainly could not be anything else but negative, because it does not contain any salicylic acid in composition, is another glaring defect.

Even if salicylic acid was contained, or if the ferric chlorid reaction was used for a phenol test, it would signify no more than a negative action to be found in a-s-phen which contains

46 per cent. of salicylic acid. To use this now as an explanation for a statement is a questionable expedient.

Another factor in the report, which renders it valueless, is the self-evident inadequate doses employed. Nothing more need be said concerning this defect. Its unreliability is self-evident. I ask in all justice how this report, approved by the Council on Pharmacy and Chemistry of the American Medical Association can command the confidence of the profession. when such faults are so conspicuously and glaringly prominent?

Scientific investigation demands accuracy and thoroughness, and if we are to have an auxiliary, as it were, to the Pharmacopeia on evidence like this, the effort had better be abandoned.

The admission by the critic that he did not know how to find any evidence that formaldehyd is split off from the compounds in the economy, and his making use of the quotation: "This agrees with Fränkel's statement," forces me to the conclusion that this use of "Fränkel's statement" is additional evidence of weakness. It raises the question why the quotation was used, especially when such positive and beneficial results from clinical use can be so unmistakably demonstrated. A similar quotation from the German literature in regard to another product of the Organic Chemical Mfg. Co. came to my knowledge in the earlier part of the year. (This literature gave due credit to Dr. S. Lewis Summers for the creation of the compound, and then conveyed the impression that the product was not absorbed. The average reader of it would almost certainly be given the impression that this product is not absorbed, and yet, if carefully or analytically read, it is seen that positive language making such an assertion is wanting! Why this ambiguity?) To make sure that the product was not correctly reported as to cleavage, I personally took full doses of it, without noticing any symptoms from its use, and had the twenty-four hours' renal secretion chemically analyzed by Professor Sadtler. His analysis demonstrated that the remedy in question, a-s-phen, does undergo cleavage in the living human economy, and that it sterilizes the urine as well.

In addition to this evidence, well-authenticated specimens of urine, voided by a patient suffering from typhoid fever, was forwarded to Professor Sadtler, who submitted the same for examination to a noted biologic expert, without leaving him know the purpose in view, or of any knowledge of the medicine taken. The first specimen submitted was voided prior to the commencement of the administration of a-s-phen. "Plates were made, using litmus-lactose agar, acid acid-lactose agar and gelatin. Large numbers of colonies of organisms were obtained, even with high dilutions. The most numerous of these belonged to the coli group. About 300 colonies were isolated and about 50 of them closely studied. It was found

that about half of them were *Bacillus coli* and half *Bacillus typhosus.* The presence of *B. typhosus* was confirmed by using Widal's test."

The second specimen submitted was voided by the same patient after the use of a-s-phen for four days. It "showed the presence of the same organisms, but there was a great reduction in the number of the colonies of the coli group, including those of typhoid organisms. It is difficult to state the exact amount of the reduction, but it is safe to say that it was something over 50 per cent."

"I might say, in addition, that several specimens of normal urine were used for comparison, and that the second specimen shows a pathologic condition considerably below normal."

This proves why so many clinicians who use a-s-phen at the onset of an infectious disease, like typhoid fever, report so many mild and aborted cases.

Last January certain evidence was shown me, which evidence I trust you will have the privilege of seeing. It helps in understanding some possible factors involved in the present controversy, and underlying the error which is of far more seriousness than the majority of physicians at present realize. In the halls of the meetings of the American Medical Association at Atlantic City and New Orleans four or five years ago, discussions were rife concerning this whole matter. There were those, not to be included in this present controversy, who were evidently bent on advocating products of foreign manufacture, which these in question rivaled, and in their efforts to insure patronage, they decried the remedies of home manufacture. It was that that made some of us in the profession who are governed by principles, not of ponderable character, skeptical, and disposed to carefully examine into matters of this sort, which are so contrary in theory to the facts of experience. Additional evidence strengthening this attitude was afforded by a combination in restraint of trade on the part of certain foreign manufacturers when the attempt was made to deprive the Organic Chemical Mfg. Co. from purchasing its supply of raw material, phenetidin, from which a-s-phen is manufactured; and thus if possible, by flatly refusing to sell, to prevent a competitor, large or small, from manufacturing a medicine which is superior to that of their own manufacture. This it was that caused me to form the committee previously referred to. I arranged with Dr. Summers, then a comparative stranger, to have his establishment visited. On this committee were men like Profs. Joseph P. Remington and Clement B. Lowe, and practitioners like J. Madison Taylor, and pharmacologists like Horatio C. Wood, Jr. The committee was shown every detail of manufacture in an instructive manner, by a son of Dr. Summers, a graduate of Harvard, and whose work in chemistry while there was of such character as to cause him to receive honorable mention, on his diploma, for excellency in chemistry. The

committee had every reason to feel convinced that true active chemical compounds were being manufactured.

Professor Sadtler has proved that the presence of formaldehyd can readily be detected in the formasal compounds; not only by the tests described in the literature of that pamphlet, but also by a proper application of the very same test which Dr. Sollmann stated that he used, with negative results, Professor Sadtler has done more; he has voluntarily described the technic to be observed in the problem and thus enable any one sufficiently interested to demonstrate for himself the error of the report, approved by the Council, regarding this point.

Another fact, for which I would like an explanation from the Council, is why Rule 5 was used as a basis for rejection of bis-forma-sal, when by the same rule, the Council admits such products as aspirin and phenacetin? Even if necessary to strain Rule 5 as to the validity to patent right or copyright against bis-forma-sal, it could not be applied with any degree of comparison as with the products just mentioned—except as to geographical source.

These are some of the reasons why I loaned my name to the literature of that pamphlet. A copy of a letter was sent me by Dr. Simmons, alleged to have been addressed to him from Philadelphia, which intimated the probability of my having a financial interest in the company. It was signed by the *honorable anonymous*. As this supplies a possible interpretation of my endorsement, you should see it, and my reply. I suppose it might be proper for me to stoop sufficiently to notice the letter and to deny direct or indirect commercial interest in the company whatsoever. It has always been a matter of principle with me, when able, to endeavor to correct error and avoid persecution in so doing.

I recognize the ever-impending danger threatening selfish interests which accompany a struggle for truth and justice, but only moral cowards shirk the duty taught by the Golden Rule. If I am in error, when shown so to be, no one will be more eager to acknowledge the fact.

Yours very respectfully,

HENRY BEATES, JR.

LETTERS OF DR. SOLLMANN TO THE REFEREE

LETTER 1

Oct. 20, 1908.

1. I herewith submit my side of the controversy, which has been raised by Dr. Summers, concerning my report on "Formaldehyd Derivatives." Since Dr. Summers does not adduce any facts in support of his accusation that my report was prompted by personal motives, I may be excused from discussing this part of his statements. I would add, however, that I would have been glad had his products justified a favorable report.

2. A considerable part of the protest of Dr. Summers is not against my report, but against the wording of the letter (reproduced on page 2 of the pamphlet), in which the secretary transmitted the action of the Council. This letter was indeed based on my recommendation to the Council, recorded on page 301 of Volume VII of the Council Bulletin.

My communication recites in abstract the previous reports on this product, presents the report which has since been published by direction of the Council, and ends with these words: "Since the claims of the formasal products are based entirely on the assumption of the action of formaldehyd within the body, *reform of the claims is quite inconceivable.* I therefore recommend that all the formasal products be placed in Class D" (rejected).

I willingly concede that this wording could have been made more specific; but this seemed superfluous, since the detailed reasons for rejection are given in the report (pages 27 to 29), which accompanied this recommendation, as well as the letter of the secretary. The words which I have underscored show that this sentence was intended merely to explain why I recommended absolute rejection, instead of suspended rejection. From page 28 of my public report (on which the action of the Council was based), you will perceive that I took full account of the part which Dr. Summers ascribes to the salicylic component. The classification by the secretary of iodomuth and guaialin as "formasal products" was doubtless an expedient of convenience. I have nowhere classed them in this manner, neither in any report nor in any communications to the Council.

3. Were it necessary to recapitulate the grounds for recommending the non-acceptance of these products, I would submit the following:

REASONS FOR REJECTING THE PRODUCTS OF THE ORGANIC CHEMICAL CO.

General ground: Unwarranted and misleading pharmacologic claims.

Specifically: A. The claim is made in connection with all the products that the liberation of CH_2O plays an important part in the alleged internal antiseptic action of these products. This claim was rejected.

(a) Because no evidence was adduced to show that the compounds are decomposed in the body; to the contrary, the experiments made by me indicated that these products do not liberate CH_2O under the action of reagents and ferments as active as the conditions apt to be encountered in the body; that no formaldehyd is present in the urine; that no test was submitted by the company to differentiate between methylene-di-salicylic acid and free salicylic acid. None of this amounts to a final proof that these products are not decomposed in the body; and I have with care avoided any statement to this

effect. I have held, however, that the company have failed to substantiate their claim, and this was, therefore, unwarranted. (b) Conceding the possibility that the methylene-di-salicylic acid is decomposed in the body, it does not necessarily follow that this decomposition should involve the generation of active quantities of CH_2O. The company had submitted no evidence which would support their statement; and the failure to find CH_2O in the urine and in the test-tube experiments speaks against this. The claim that the antiseptic efficiency of the salicylate component is vastly increased through the formaldehyd was therefore held unwarranted.

B. The claim is made that ur-a-sol is devoid of nauseant taste. As the sample from an original sealed package is markedly nauseating in the dose recommended by the company, this claim was held unwarranted.

C. The claim is made that these compounds of methylene-di-salicylic acid are superior in therapeutic efficiency to all other salicylic derivatives. A definite claim of this kind can only be accepted when it is supported by sufficient definite evidence. Until this has been done, the claim must be judged exaggerated. As far as urinary antiseptic power is concerned, the ur-a-sol seems inferior both to sodium salicylate and to phenyl-salicylate.

4. In the following I purpose to consider seriatim the objections made to my report by Dr. Summers and Professor Sadtler. I may be permitted to postpone my answers to the summarized accusations contained on pages 3 of the Summers' pamphlet, since these are repeated with more detail in other places.

5. The composition of the products was not verified by me, since this did not come within my scope.

6. I am next accused of employing a formaldehyd test of inferior value. Professor Sadtler, on whose authority this accusation is based, does not give his reasons for condemning the Jorissen test, beyond stating that "it is rarely used by food analysts" who deal with formaldehyd under conditions entirely different from those present. In defense I beg to submit that,

(a) According to the published data, the Jorissen test is more delicate than the phenol-sulphuric acid test employed by Sadtler.

(b) This corresponds to the facts when both tests are skillfully made and compared in actual practice.

(c) The phenol-sulphuric acid test and the salicylic acid tests employed by Sadtler are theoretically and practically unsuitable for the solution of the present problem.

In evidence of the above, I submit the following:

(a) In the literature, the delicacy of the Jorissen test is stated as 1:800,000 (Nicolaier, *Ztschr. f. klin. Med.*, 38: 364); while that of the phenol test is stated as 1:200,000 (Leffmann

and Beam, Food Analysis, 2d ed., p. 219). These statements being by different observers, working doubtless under different conditions, Mr. Hanzlik and I have compared the delicacy of the two tests, under identical conditions:

(b) The Jorissen test was made by adding to 10 c.c. of the formaldehyd solution about 5 mg. of dry phloroglucin, then 0.5 c.c. of 10 per cent. NaOH. The phenol test was made by mixing 10 c.c. of the solution with 5 drops of 1 per cent. phenol and pouring cautiously on 10 c.c. of concentrated H_2SO_4. For the salicylic test, the solution was poured on an equal volume of concentrated H_2SO_4, containing a trace of salicylic acid. Controls were made for each series. The results, referred to absolute CH_2O, were as follows:

Reaction.	Plain.	Doubtful.	Very Doubtful.
Jorissen	1:500,000	1:800,000	1:1,000,000
Phenol-sulphuric	1:250,000	1:500,000	.....
Salicyl-sulphuric	1:1,000	.....	1:100,000

I am therefore forced to the conclusion that Professor Sadtler's assumption as to the delicacy of the two tests is contrary to the facts.

(c) Any method which places the substance to be investigated in contact with concentrated sulphuric acid would *a priori*, be unsuitable to investigate the decomposition of the substance by water, dilute acids or dilute alkalies. In the following experiments the dry substance was added to the salicylic sulphuric acid to show the extent to which the sulphuric acid itself liberates CH_2O from these products.

URASOL: No change in one-half hour.
SODIFORMASAL: Positive test at once.
GUAIALIN: Very strong test at once.

It is therefore evident that the sulphuric acid tests, either phenol or salicylic, are not generally applicable when the decomposition of methylene compounds by weaker reagents is to be investigated. They could only be used with ur-a-sol, or if the conditions be so arranged that none of the original substance can enter into the test. Professor Sadtler's statement that the decomposition of sodiformasal by concentrated H_2SO_4 proves "*aqueous* dissociation," is incomprehensible to me, in view of the above facts.

7. Since the CH_2O test as employed by Sadtler does not easily admit of definite conclusions as to the decomposition of these substances by weaker reagents, it may seem superfluous to check the results which he obtained thereby. For the sake of completeness, however, I have done so, with the results shown in the table on the following page.

The reactions are so slight that it is in most cases doubtful whether the test is positive or negative. This may account for the discrepancies in the results. At all events, the decomposition, if it exists, is insignificant for practical purposes.

For instance, the quantity of CH_2O liberated from 1 gm. of ur-a-sol or sodiformasal after standing 24 hours with 1 per cent. NaOH, acidulating and distilling, cannot amount to more than 0.5 mg. or 1/200 of the CH_2 contained in the molecule.

8. Concerning the reference to my remarks on novaspirin, the manufacturers do not now, so far as I know, claim any action from the formaldehyd component. It is, therefore, immaterial in the present connection *where* it is split off.

9. Concerning the question of dosage, I employed all the products in the average single dose advised by the manufacturers. The dose of sodiformasal (1 gm.) would correspond to 0.0903 gm. or 1.38 grains of CH_2O (not 0.69 grains, as claimed by Summers). Had this formaldehyd been excreted unchanged, it would surely have given the corresponding test in the urine. As I have shown, however, CH_2O is not excreted as such, and I have not, therefore, in any place, used the absence of this substance in the urine as an argument against the decomposition of the methylene derivatives. I am therefore at a loss as to the meaning of Dr. Summers' objection in this connection to the doses used by me.

10. The quotation cited on page 28 of my report, from a pamphlet of the company, made claims for the taste of ur-a-sol which claim I find erroneous. Since the first paragraph of said pamphlet does not mention the taste, I can see no reason why I should have quoted it in that connection; the same applies to the reference to headache, etc.

11. As to the taste of ur-a-sol, I regret that I must again contradict Professor Sadtler's statement that "Ur-a-sol is practically tasteless, instead of having a nauseous taste," even if the elastic term "practically" is stretched to the utmost. This, at least, is true of the sample, which I received in the original package and a portion of which I shall transmit to you for verification. It possesses the typical "mawkish" taste of the salicylic acid, quite different from that of any of the other salicylate esters. This may be due to the impurity of the product; but my remarks apply to the article "ur-a-sol," not to the chemically pure acetyl-di-methylene-di-salicylic acid. To settle this point, I have transmitted to Professor Sadtler a 1-gram sample of the ur-a-sol, asking him to convince himself of the correctness of my statements of the taste of *this dose* (underscored in the letter). To this Professor Sadtler replied that twice placing "a pinch" of the same on the tongue, he was "unable to recognize any unpleasant taste; in fact, much of any taste of any character." May I ask you as referee to decide this question, remembering that the character of a taste depends largely on its intensity and that my statements referred to the above, ordinary dose?

12. Postponing until later the question whether formaldehyd is split off in the body, I wish to refer to their statement that they have no knowledge that this claimed formaldehyd

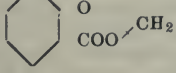
Article Used.	Test.		In Water for Few Minutes, Filtered.	In Water for Over Night, Filtered.	In 1% HCl Over Night and then Distilled.	In NaOH 1% Over Night and then Distilled.	In 1% NaOH Over Night, Acidulated and Distilled.	In Water for 24 Hours; Not Filtered.
Urasol.....	Sadtler method.	Sollmann result.	No test.....	No test.....	Doubtful trace.	Doubtful trace.	Doubtful trace.	No test.
		Sadtler result...	No test.....	Distinct test..	Distinct test...	Distinct test...	Stronger test.	
	Jorissen test.....		No test.....	Trace.....	Trace	Trace	Trace.....	No test.
Sodi-formasal.	Sadtler method	Sollmann result.	No test.....	Slight test...	No test.....	No test.....	No test.	
		Sadtler result...	No test.....	No test.....	Slight test.....	Slight test.....	Slight test.	
	Jorissen test.....		No test.....	No test.....	Fair trace.....	Fair trace.....	Fair trace.	
Guaialin ..	Sadtler method.	Sollmann result.	No test.....	No test.....	Slight trace	Trace.....	Trace.....	Strong test.
		Sadtler result...	Distinct test. ..	Strong test....	Strong test.....	Moderate test..	Moderate test.	
	Jorissen test.....		No test.....	No test.....	Doubtful trace.	No test.....	No test.....	No test.

acts as a urinary antiseptic. I am ready to believe that Dr. Summers lacks this knowledge; indeed, that is a main contention of my report. It contradicts, however, the meaning of his advertising circular, namely, "not only has the sting been removed, but there is a vast increase in the therapeutic efficiency, through the condensation with formaldehyd. Formaldehyd is the king of antiseptics. It is a most valuable urinary antiseptic. As a uric solvent it stands second only to salicylic acid. Unlike salicylic acid, it is unsafe to administer formaldehyd alone or in aqueous solution." I cannot see any meaning in these statements, except that formaldehyd is split off and acts as a urinary antiseptic.

13. As to my comments concerning the urate solvent properties of citarin, it requires rather a stretch of imagination to speak of the "quite sympathetic graciousness" of the words, "this makes me feel somewhat skeptical as to the claimed urate solvent action."

14. I can see no contradiction between my statement that "I have found no evidence that formaldehyd is split off from the formasal products," and my further statements that the company had failed to furnish tests which would distinguish between salicylic and methylene-di-salicylic acids. I shall recur to this subject presently.

15. On page 7 Dr. Summers accuses me of being "most positively misleading" in my use of a statement by Fränkel (p. 585 as correctly stated by Sadtler) that "methylene salizylsäure" does not form formaldehyd in the body. I submit that an accusation of so serious a nature should be based on definite evidence. In fact, however, it appears to be based on nothing more than Professor Sadtler's assumption that Fränkel did not mean what he said. Sadtler contends that Fränkel would have used the term "methylen-di-salizylsäure had he referred to formasal, while by "methylen salizylsäure" he would refer to a compound of the formula



This assumption seems to me wholly unwarranted, for the following reasons: Firstly, because the "di" is often omitted in German. In Roscoe and Schlorlemmer's Lehrbuch, I find

"Methylen thiocyanat" $CH_2(SCN)_2$.
"Methylen acetat" $CH_2(OC_2H_3O)_2$.

Secondly, Fränkel contrasts rather than compares the "Methylen salizylsäure" with "Methylen oxyuvitinsäure." Thirdly, a compound of the formula assumed by Professor Sadtler (if, indeed, it exists) could not properly be termed "Methylensalizylsäure," because it would not be an acid, since it does not contain any COOH radicle.

I regret that the attack by Dr. Summers forces me to express my conviction that Professor Sadtler acted hastily in reflecting on the fairness of my quotation on no better ground than the arbitrary assumption that Dr. Fränkel was careless in the use of his chemical terms. I have written to Dr. Fränkel to give him the opportunity to explain his meaning In any case, however, I think that I may protest against being criticized for assuming that an author means what he says.

16. I may now discuss the question whether or not di-methylene salicylic acid is decomposed in the body. This can only be finally decided by discovering the decomposition products, or by isolating the undecomposed substance. The fact that this substance is not materially decomposed by moderately active reagents and scarcely by ferments outside the body (as shown by the generally negative results), renders any considerable decomposition within the body very improbable. While analogy is always uncertain as an argument, this fact suffices to place the burden of the proof of such decomposition on the shoulders of those who make the claim.

As I have shown, the absence of formaldehyd from the urine cannot be used as an argument, because this substance is itself decomposed in the body. The whole direct proof must therefore hinge on the nature of the substance giving the ferric chlorid test in the urine. Is this salicylic acid or methylene-di-salicylic acid? I took the standpoint that the decomposition could not be considered as demonstrated until this point had been decided. I further considered it incumbent on those claiming such decomposition to furnish this proof.

The only facts bearing on this point, as submitted by the company, was in the form of a statement (p. 120, vol. vi, Bul.), by Dr. Latham Clark, viz.: "I have examined your urine for the purpose of determining the form of elimination of ur-a-sol from the system. From my examination I am of the opinion that the formaldehyd which was combined with the salicylic acid was split off from the same within the system. This can be substantiated by the fact that free salicylic acid was found in the urine, indicating that the salicylic acid was a decomposition product of the reaction."

It will be noted that this is merely an opinion. In order to make it subject to control and thus available as evidence, the secretary addressed a letter to Dr. Clark, as stated in my report. Again no evidence was submitted. Dr. Summers may be able to understand the reasons for this failure of Dr. Clark's to substantiate his assertion; to me, none that are creditable are apparent. The portions of the letter referring to Rule 5, which Dr. Summers considers an explanation, have no bearing whatsoever on the present controversy.

If, then, Dr. Summers knew of the method of distinguishing between the free and combined salicylic acid, which he now adduces, he has only himself to blame for not submitting it

at the proper time. He was given every opportunity. When he failed to avail himself of it, I can scarcely be blamed for concluding that he did not know of any, and that his claim was an assumption, pure and simple. I took care to avoid any statement that the decomposition was disproved. The last sentence on page 7 and again the conclusions on page 18 of my report, demonstrated that I did not consider the question finally settled. I did not consider it incumbent on me, however, to conduct lengthy researches to supply information which should have been furnished by the manufacturer; and I therefore contented myself with stating that the latter had not made good his claims.

Dr. Sadtler's report at last supplies the tests which the manufacturer should have submitted with his claim. Unless a source of error should be discovered in Dr. Sadtler's results (which I am now checking), I am ready to concede that the methylene group is split off somewhere within the body. I shall report to you on these tests as soon as they are completed. In any case, however, I still hold that evidence is lacking that it has been split off as formaldehyd. Professor Sadtler's statement to this effect appears to me a pure assumption. He adduces no evidence whatsoever. I directly deny the claim that there is any formaldehyd in the urine, as implied in the claims quoted above.

17. Dr. Summers again asserts that the urine after ur-a-sol is antiseptic, basing his claim on a result of Professor Sadtler. I do not question Professor Sadtler's results (which I am also controlling); indeed, it appears to me very probable that these large quantities might have a slight antiseptic action. I maintain, however, that this action is insignificantly small in comparison with therapeutically equal doses of hexamethylenamin, and is very much inferior to that of the ordinary salicylates.

18. As to iodomuth, it is unnecessary for me to discuss the arguments, as Dr. Summers brings no evidence to contradict any of my statements. He accuses me, however, of having taken only "a fraction of a dose." My report shows that I took 1 gm. (15.4 grains). The dose mentioned in Dr. Summers' advertising matter is 5 to 50 grains. The tests for iodid, I may incidentally remark, are more delicate than those for gallic acid.

19. As to Guaialin, Dr. Summers accuses me of "knowing next to nothing." My report shows, however, that no formaldehyd is split off by boiling with water or acid, or by distilling with alkali, or by pancreatic digestion; that the latter does not liberate guaiacol or benzoic acid; and that the compound scarcely delays pancreatic putrefaction.

20. In conclusion, I wish to remove two misapprehensions under which Professor Sadtler seems to labor:

(a) He states that my pancreatic tests showed that ur-a-sol and sodiformasal were decomposed more readily than salol. This he must base on the success of the salicylate reaction.

Unfortunately, however, the undecomposed formasal products also give this same reaction, as Professor Sadtler concedes; so that the success of this reaction proves nothing as to the formasal products. Had Professor Sadtler referred to the formaldehyd tests, on the same page, he would not have fallen into this error.

(b) He remarks "As to guaialin, we can hardly see how Dr. Sollmann could have expected to have obtained tests for salicylic acid, as it does not contain any in its decomposition." It is true that the heading on page 5 states "B. Ferric Chlorid Reaction for Salicylates." I adopted this general heading because I did not consider it necessary, especially for anyone with chemical knowledge, to be informed in detail that the same test is also applicable to the guaiacol of the guaialin.

21. Finally, I regret that I cannot comply with Professor Sadtler's formal demand to withdraw my statements as to the formaldehyd liberation question and as to the taste of ur-a-sol. On the contrary, I am constrained to reaffirm them. I also reaffirm that the claim as to the liberation of salicylic acid from ur-a-sol was unsubstantiated, but I am glad to accede that he has now furnished data which I, unsuccessfully, tried to obtain from Dr. Summers and Dr. Clarke, and which may make it possible to settle this question. On the other hand, I believe that Professor Sadtler should withdraw his charges that I used an unsuitable method of detecting formaldehyd; that I misstated the taste of ur-a-sol, and that I misquoted Fränkel. These are plain questions of fact, in regard to which there cannot honestly be two opinions.

Respectfully submitted.

TORALD SOLLMANN.

LETTER II

Nov. 4, 1908.

I herewith submit further data as to the formasal products, covering the following points:

I. The alleged misquotation from Fränkel.
II. Methods of distinguishing between salicylic and methylene-di-salicylic acid.
III. The form in which ur-a-sol is excreted in the urine.
IV. The efficiency of large doses of ur-a-sol in preventing urinary fermentation.

The experiments described in the following were performed by Mr. P. J. Hanzlik under my supervision:

I. The Alleged Misquotation from Fränkel.—According to Sadtler and Summers, I perverted Fränkel's meaning in the passage which I quoted. To settle this question I have resorted to the obvious method of applying directly to Dr. Fränkel—a course which, I may be permitted to observe, should have been taken by Professor Sadtler before the accusation was made. I append the letter received from Dr. Fränkel which reads, as translated:

"The remark in my book (p. 585 of the Argneimittel-synthese, II Ed.) refers as you *correctly* state, to methylene *di* salicylic acid. I do not know of any methylene *mono* salicylic acid, nor is such mentioned in Beilstein nor Friedlander's Patentschriften." (Italicized words were underscored in the original.)

Further comment is, I believe, unnecessary.

II. Methods of Distinguishing Between Salicylic and Methylene-di-salicylic Acid.—Sadtler mentions two methods for this purpose, namely: 1. The melting point of the sublimed crystals. 2. That salicylic acid is soluble in cold benzol, while methylene-di-salicylic acid is insoluble. The experiments on which these methods are based are not described in detail.

1. Melting Point of the Sublimed Crystals: To test the availability of the methods, we prepared some methylene-di-salicylic acid by precipitating a watery solution of sodiformasal with HCl. We attempted to crystallize this from alcohol and absolute alcohol, but with very indifferent results. Crystallization from ether was more successful. The crystals were finally washed with benzol and after drying were compared with salicylic acid, as follows:

Substance.	Melting Point. Fusion Begins.	Fusion Complete.
(a) Salicylic acid	156 C.	158 C.
(b) Methylene-di-salicylic	205	210

The two substances can, therefore, be distinguished by their melting point. Sadtler, however, applied the test, not to the substance itself, but to the sublimates. We therefore sublimed some of the purified methylene-di-salicylic acid and the sublimate showed the melting point not of the methylene-di-salicylic acid but of free salicylic acid (156 to 158 degrees). This might be due, either to impurity of our substance, or to decomposition by the heat of sublimation. The former is improbable, since any contamination by free salicylic acid would have been removed by the benzol treatment. To make certain, however, we repeated the experiment, but carrid the sublimation further, collecting the sublimate in three portions. All of these, however, showed substantially the same melting point, namely:

Fraction 1, 156-158 degrees
Fraction 2, 158-160 degrees
Fraction 3, 158-162 degrees

It is plain, therefore, that the melting point of the sublimate does not permit the distinction of salicylic and dimethylene salicylic acid, because the heat sublimation decomposes the latter, with liberation of free salicylic acid. Sadtler's conclusion, that the methylene-di-salicylic acid is excreted as free salicylic acid, is therefore based on false premises.

2. Solubility in Cold Benzol: Sadtler states that the benzol does not dissolve methylene-di-salicylic acid. This is contradicted by the following experiments: Some of our purified methylene-di-salicylic acid was left in contact with benzol for

1, 5 and 24 hours. The filtrates were shaken with a dilute solution of ferric chlorid: they gave salicylate reactions, increasing with the time of contact. The dissolved substance is not contaminating salicylic acid, for it gives the formaldehyd test with concentrated sulphuric acid. Dimethylene salicylic acid is therefore somewhat soluble in benzol, sufficiently so that the latter gives the salicylic reaction. This method cannot therefore be used qualitatively, as was done by Sadtler, and his conclusions are again based on false premises. The solubility may, however, be utilized by making the method quantitative, since the solubility of the two acids in benzol is very different. This will be described in the next section.

III. The Form in which Ur-a-sol is Excreted in the Urine.—P. J. H. took ten 1 gm. doses of ur-a-sol between 7 a. m. and 7 p. m. The twenty-four-hour urine was collected in two fractions.

A. 7 a. m.-7:30 p. m. = 530 c.c.
B. 7:30 p. m-7 a. m. = 260 c.c.

A fifth of each of these urines was used for sundry tests. The remainder (4/5) was mixed and treated by the method adopted by Sadtler. The ether residue purified by again dissolving in ether, shaking with NaOH solution, acidulating the watery layer, extracting with ether, and evaporating. The purified ethereal residue weighed 0.379 gm. This would correspond to 0.474 gm. in the twenty-four-hour urine, which coincide almost exactly with the quantity obtained by Sadtler. This ether residue gives the ferric chlorid reaction which is common to both acids. To distinguish between them, it was subjected to the following tests:

1. Solubility in benzol: A quantitative comparison was made by placing 0.1 gm. each of salicylic acid, purified methylene-di-salicylic acid and urine—ether residue, each with 25 c.c. of benzol, filtering after twenty-four hours and evaporating and weighing the residue. Result: There was dissolved of salicylic acid, 0.100 gm.; methylene-di-salicylic acid, 0.025 gm.; urine residue, 0.030 gm. The solubility of the extract corresponds therefore to that of methylene-di-salicylic acid and not to that of salicylic acid.

2. Melting point: This was determined after the benzol treatment, the part which had dissolved in benzol and the part which had remained undissolved being treated separately. The data for the pure acids are given for comparison.

Substance.	Liquefaction Starts at—	Is Complete at—
Salicylic acid	156	158
Methylene-di-salicylic acid	205	210
Urine residue dissolved in benzol	158	Quantity not sufficient.
Urine residue not dissolved in benzol.	158 to 160	210

The urine residue begins to fuse at the temperature of salicylic acid; 25 degrees higher, however (185 degrees), it

is only in a state of semifusion. Complete liquefaction occurs only at the temperature of dimethylene salicylic acid. The residue, therefore, certainly does not consist exclusively of salicylic acid; it contains methylene-di-salicylic acid.

3. PRESENCE OF METHYLENE RADICLE: If the statements of Sadtler were correct, that the compound is excreted as free salicylic acid, then the residue could not give any formaldehyd reactions. In fact, however, it gives a good characteristic pink color with the salicylic sulphuric and with the phenol-sulphuric tests. The solution in benzol does not give a certain reaction, which is not strange considering its small quantity. It must, therefore, be concluded that the compound contained in the urine after taking ur-a-sol and which reacts with ferric chlorid is not free salicylic acid, as claimed by Sadtler, but methylene-di-salicylic acid, as stated by Fränkel. The melting point indicates that it contains some free salicylic acid, but the solubility shows that this is at most a trace.

IV. The Efficiency of Large Doses of Ur-a-sol in Preventing Fermentation.—Sadtler states that the urine of his patient "was practically sterile, as it kept four days without getting turbid, and in two weeks, when it was thrown out, did not have any odor of putrefaction." Our urine contained the same average quantity of ether residue as that of Sadtler; but since the volume was less, the percentage must have been greater in our case. Of the two fractions, A contained considerably less than B. Small samples of the two fractions were kept at room temperature in unstoppered flasks, with the following results:

Room Temp.	Time of Standing.	Reaction.	Appearance.	Microorganisms.
Urine A.	1 day.	Alkaline.	Very turbid.	Numerous mobile bacteria.
Urine B.	1 day.	Alkaline.	Slightly turbid.	Mobile bacteria.
	2 days.	Alkaline.	Very turbid.	
	2 weeks.			Mould.

Bacteria evidently developed quite well, although the odor was not very pronounced. The antiseptic action of the urine is therefore quite limited, notwithstanding the large amount of drug consumed. TORALD SOLLMANN.

LETTER OF SAMUEL P. SADTLER TO THE REFEREE

PHILADELPHIA, Nov. 16, 1908.

As promised in my letter of November 9, I am presenting to you some points in answer to the criticisms which Dr. Sollmann made on my chemical tests in his communications to you under date of October 20 and November 4. My answers will be mainly with reference to two questions: (1) the formaldehyd test, and (2) the presence of salicylic acid in the urine.

FORMALDEHYD TESTS

It will be remembered that Dr. Sollmann said in his original report: "Iodomuth liberates formaldehyd, most with alkali,

doubtful traces with acid, none with water. Guaialin, sodiformasal and ur-a-sol; these do not liberate formaldehyd in any reaction, even on boiling or distillation." These were the statements that I controverted and by the application of two different tests, viz., the phenol-sulphuric test and the U. S. Pharmacopeia test, in which dilute aqueous solution of formaldehyd is run into sulphuric acid containing a little salicylic acid proved to be incorrect.

Before taking up any discussion of results, a few words as to the choice of tests and the question of their applicability to the case under consideration. I did not follow Dr. Sollmann's method and use the Jorissen test, saying with regard to it: "The so-called Jorissen or phloroglucin test is not regarded by expert chemists as the most delicate or reliable of formaldehyd tests and is rarely used by food analysts in the examination for formaldehyd. We used instead the well-known phenol test, using pure phenol in 1 per cent. solution and concentrated sulphuric acid." Dr. Sollmann makes several statements in criticism of my choice and my expression of views about the tests. He says that food analysts "deal with formaldehyd under conditions entirely different from the present." In reply, I would say that his tests and my tests were carried out with dilute aqueous solutions, acidified or made alkaline, and in some cases with the distillates therefrom. These are the exact conditions under which food analysts work except in the application of those tests where milk proteids play a part in the test. I did not use any tests requiring the presence of milk to produce a reaction.

Does Dr. Sollmann know that Jorissen first proposed his test as a means of recognizing formaldehyd in milk (see Nicolaier's article quoted by Dr. Sollmann), that Jorissen is Professor of "Food Investigations" in the University of Liége in Belgium (as he can see by consulting "Minerva"), and that his original publication was in connection with "Service de Surveillance des aliments en Belgique" in 1897?

Dr. Sollmann next says that "according to the published data, the Jorissen test is more delicate than the phenol-sulphuric acid test." I am willing to grant that, if the question of dilution or solution alone is to be considered. I did not refer to that. It is not "delicate or reliable" because of the transient character of the coloration and the difficulty of distinguishing the formaldehyd-produced color from that which develops in a blank test from an alkaline phloroglucin solution alone. The best authority on this is the "Official and Provisional Methods of Analysis," published by the U. S. Department of Agriculture, Bureau of Chemistry, under the editorship of Dr. H. W. Wiley, as Bulletin No. 107, Washington, 1907. This Bulletin says (p. 185), in speaking of the phloroglucin method: "A bright red coloration (not purple) is formed at the zone of contact if formaldehyd be present. . . . The clear red color given by the use of this reagent forms quickly and in the presence of but a small amount of

formaldehyd soon fades." It is for this reason that the phloroglucin (or Jorissen) test is regarded by expert chemists (both food analysts and others) as not so reliable. The red color, when a trace of formaldehyd only is present, cannot be well distinguished from the gradual development of the purple due to the alkaline phloroglucin solution when exposed to air. On the other hand, a dilute aqueous formaldehyd solution to which a trace of phenol has been added when allowed to flow into a test tube and form a layer on pure colorless sulphuric acid will develop gradually a rose-colored contact ring which does not develop in any degree in a blank test. Hence chemists prefer it as a reliable test sufficiently delicate for most purposes.

Dr. Sollmann next says: "The phenol-sulphuric acid test and the salicylic-sulphuric test employed by Sadtler are theoretically and practically unsuitable for the solution of the present problem." I can only say to this that I fail to see the reason for such a view and believe it to be founded on a misconception of these tests. That such misconception exists in Dr. Sollmann's mind I must conclude, moreover, from his remarks in his communication of October 20 when he says: "Any method which places the substance to be investigated in contact with concentrated sulphuric acid would *a priori* be unsuitable to investigate the decomposition of the substance by water, dilute acids or dilute alkalies." And again: "It is therefore evident that the sulphuric-acid tests, either phenol or salicylic, are not generally applicable when the decomposition of methylene compounds by weaker reagents is to be investigated." How Dr. Sollmann can read into my description of my tests the idea that any of the substances in solid form were put into strong sulphuric acid I do not see, and yet that is what he is apparently talking about. I would suggest that he read carefully in some good manual, like Allen, the details for carrying out the Hehner phenol-sulphuric acid test and in the U. S. Pharmacopeia, eighth rev., p. 265, the test for formaldehyd in aqueous solution, and he will see how my tests were applied. If he will also read carefully my description of my application of the Pharmacopeial test (Summers' pamphlet, p. 15) he will see that the term "aqueous dissociation," as used by me, did not involve "decomposing sodi-formasal by concentrated sulphuric acid," as Dr. Sollmann seems to think. He will notice that the aqueous solution, which was filtered into sulphuric acid, must have undergone aqueous dissociation to furnish the formaldehyd and salicylic acid which were needed to produce with the sulphuric acid the color reaction described in the Pharmacopeia as indicating formaldehyd.

Since Dr. Sillmann has so obviously misunderstood my method of carrying out the phenol-sulphuric acid, I may be pardoned for expressing a doubt if the results of his repeating my tests which he tabulates in his communication of

October 20 are really comparable with what I had previously stated in my report.

Coming now to the repetition of my tests, I determined to try on the same solutions, (1) the phenol-sulphuric test of Hehner; (2) the phloroglucin test as prescribed by "official methods" in Bulletin 107; and (3) the phenyl-hydrazine and ferricyanid tests, now accepted by chemists generally as the most delicate of all the formaldehyd tests. For a description of this see Bulletin No. 107, p. 184. Other descriptions of the phenyl-hydrazine test and the best conditions for its application are found in the *Journal of Amer. Chem. Soc.*, 1900, p. 132, and in the "Proceedings of the New Jersey Pharmaceutical Association" for 1905, p. 70. This latter article by Charles H. Lawall, a food chemist of large experience, is the fullest and clearest and is accompanied by a table in which the comparative results of nine different formaldehyd methods are placed side by side.

The solutions to which my new set of tests were applied were prepared exactly as had been done by me in my previous report, except that the first set of aqueous extracts, where only a few minutes' contact with the solid preparation was allowed, were prepared, as was done by Dr. Sollmann, that is, brought to boiling, immediately cooled and filtered. All the others were left at room temperature over night and then distilled as stated and tested. The results of these tests are stated in tabular form on page 33.

In explanation of the statement of results, I would say "doubtful," "faint test" or "slight test," "distinct test," "positive test," and "strong test" express the relative order of the results.

I would call attention to several things that are apparent in these results: First, the phenyl-hydrazine is the most delicate, while the phloroglucin test is the least satisfactory (for reasons already stated). Second, the solutions resulting from aqueous dissociation with water alone gave results which in general were stronger for formaldehyd than when the samples were digested with acid and alkali and distilled.

The explanation of this is known to chemists who have had occasion to work with formaldehyd tests. In distillation a portion only of the formaldehyd present will come over in the distillate and a portion polymerizes to paraform and remains in the last portion in the distilling bulb (see article by Leonard & Smith, *Analyst*, 1897, p. 6).

These results, if compared with those given by me before, show some slight differences, but I believe in the main they substantiate them, and indeed, as illustrating simple formaldehyd liberation by aqueous dissociation, they are stronger. In this matter they are in harmony with the results obtained by filtering the aqueous extracts into the sulphuric acid when carrying out the U. S. P. test on Sodi-formasal and Ur-a-sol, as before described by me.

TABLE OF FORMALDEHYD TESTS.

Substance.	Test Applied.	In Water for Few Minutes.	In Water Over Night.	In Dilute Acid Over Night and Then Distilled.	In Dilute Alkali Over Night and Then Distilled.	In Dilute Alkali Over Night, Made Acid and Distilled.
Urasol.....	1. Phenol-sulphuric.	Faint test.	Distinct test.	Distinct test.	Distinct test.	Distinct test.
	2. Phloroglucin.	Faint test.	Distinct test.	Faint test.	Distinct test.	Distinct test.
	3. Phenyl-hydrazine.	Distinct test.	Positive test.	Strong test.	Strong test.	Strong test.
Iodomuth...	1. Phenol-sulphuric.	Strong test.	Positive test.	Slight test.	Slight test.	Slight test.
	2. Phloroglucin.	Strong test.	Distinct test.	Slight test.	Slight test.	Slight test.
	3. Phenyl-hydrazine.	Strong test.	Positive test.	Slight test.	Positive test.	Positive test.
Guaialin....	1. Phenol-sulphuric.	Distinct test.	Doubtful test.	Distinct test.	Distinct test.	Distinct test.
	2. Phloroglucin.	Doubtful test.	Faint test.	Distinct test.	Distinct test.	Slight test.
	3. Phenyl-hydrazine.	Strong test.	Distinct test.	Distinct test.	Distinct test.	Slight test.
Sodi-Formasal.	1. Phenol-sulphuric.	Positive test.	Distinct test.	Slight test.	Slight test.	Slight test.
	2. Phloroglucin.	Doubtful test.	Doubtful test.	Slight test.	Slight test.	Slight test.
	3. Phenyl-hydrazine.	Strong test.	Positive test.	Slight test.	Slight test.	Slight test.

THE PRESENCE OF SALICYLIC ACID IN THE URINE

The four printed pages of our report appearing in Dr. Summers' pamphlet did not contain all the points that we observed in making our tests. One of them is that in the test we here described and in several other analyses of urine from people taking ur-a-sol we found to take place, what we have only noticed with very easily sublimable compounds, such as salicylic and benzoic acids, namely, that as ether was driven off from an extraction, the walls of the flask were covered with crystals. In one case we tested these crystals as to melting point and found them to be salicylic acid. We know from having evaporated ethereal solution of methylene-di-salicylic acid that it does not sublime at such low temperatures. We have also found that by heating both acids, viz., salicylic and methylene-di-salicylic, in flasks in an oil bath that salicylic acid sublimes very noticeably at considerably below 100 C., while methylene-di-salicylic acid did not sublime at all at temperatures to which we heated the bath, which happened to be 170 C.

We would not expect to have it so decomposed as to give a sublimate of salicylic, as we had devised a test for the analysis of Acetyl-methylene-di-salicylic acid in which the salicylic acid is obtained by heating with fused caustic potash to 250 C., and we found that it had to be heated well up to that temperature to complete the elimination of the formaldehyd residue. This test we have reported to the Organic Chemical Co., but not as yet published. In this case it merely tends to show that methylene-di-salicylic acid does not break up with any great ease when heated.

As to the benzol test, the Organic Chemical Co. did not know of it until we reported it to them, and so they were not in shape to disclose it earlier. In Dr. Sollmann's second letter to you he speaks of carrying out a benzol test, but not the one we had described on page 16, and there is quite a difference between them. We said: "We found that benzol does not dissolve methylene-di-salicylic acid, while even in the cold it takes up sufficient salicylic acid to give a ferric chlorid test after filtering and adding enough alcohol to dissolve the benzol solution. The methylene-di-salicylic acid test is negative." Dr. Sollmann says: "Sadtler states that the benzol does not dissolve methylene-di-salicylic acid. This is contradicted by the following experiment: Some of our purified methylene-di-salicylic acid was left in contact with benzol for 1, 5 and 24 hours. The filtrates were shaken with a dilute solution of ferric chlorid; they gave salicylate reactions, increasing with the time of contact. The dissolved substance is not merely contaminating salicylic acid, for it gives the formaldehyd test with concentrated sulphuric acid. Di-methylene-salicylic acid is therefore somewhat soluble in benzol, sufficiently so that the latter gives the salicylic reaction. This method cannot therefore be used qualitatively, as was

done by Sadtler, and his conclusions are again based on false premises."

Our test may not have been described fully enough, but it could not be construed to be anything like the one Sollmann proposes. We do not dispute that if carried out the way he says that one would get the results he did. But our idea was to distinguish between methylene-di-salicylic and salicylic acid and not to produce such a drastic test that no difference is distinguishable. We reaffirm the result of our tests, and find on repetition of them, with control tests using the pure acids, that we get the same results.

It can be seen that if we take a few drops of the benzol solution which has had only a momentary contact with the material to be tested, and dilute it with enough alcohol to take up a few drops of aqueous ferric chlorid (as well as the benzol) that it is very different from keeping benzol in contact with the material for even one hour and then taking the whole volume of the benzol solution and shaking it with aqueous ferric chlorid. In planning our test we proceeded with caution, as we did not dare to hope that we could find a solvent for salicylic acid that the rather analogous body was absolutely insoluble in. It served our purpose, however, to find that the test we described in our report would show the difference we claimed for it. We have just repeated the test in this way: We took 0.1 gram each of salicylic acid (purified by benzol) and shook for about 1 min. with 10 c.c. of pure benzol filtered. To five drops of this solution were added 5 c.c. of 95 per cent. alcohol, shaken, and then 2 drops of neutral U. S. P. ferric chlorid test solution. We obtained tests with salicylic acid and not with methylene-di-salicylic acid. We also applied the test to urine extracts just obtained by us, as we will describe later on.

Sollmann's criticism of the testing sublimates obtained by strong heating is quite just. We only did this once, and while the practice was indefensible on theoretical grounds, we believe we only fell into it because an ether extract showed such a mass of low temperature sublimated needle-like crystals that it did not take a temperature that would break up methylene-di-salicylic acid. We certainly would not have tried such, as we have been familiar with this acid for five or six years, as we had tested this acid for Dr. Summers about that long ago.

As to what Sollmann says of the quantitative separation of methylene-di-salicylic acid from salicylic. It will be noticed that Sollmann only speaks of extracting with ether in the way we spoke of on page 13. A very important part of what we did was briefly described, chiefly on page 14, as follows. "The residue was then boiled with caustic soda solution and any possible basic principles extracted with ether and discarded. The residue was then made acid with hydrochloric acid and extracted again with ether.

Second acid ether extract, 0.4664 grams (7.0 grains).

This responded to the same test when the sublimed needles were taken."

It was this second extraction, after we had gotten out all the acid principles the first time, that we obtained by boiling with alkali. We have not been able to ascertain just what the compound is which is soluble in water, but insoluble in ether until boiled with caustic soda and then gives rise to salicylic acid (or if this is objected to, to bodies closely resembling salicylic acid). It is not methylene-di-salicylic acid, as that would have been easily extracted with ether. We believe it to be salicyl-uric acid for various reasons, and, if it is, it demonstrates the worth of the drug as it is claimed to be a uric acid solvent. This, however, is not our concern, as in the present paper we are only desirous of substantiating our tests as reported to the Organic Chemical Co. The fact remains that each time we have carried out this test, we have apparently found more salicylic acid in this combination. Dr. Sollmann does not refer to this at all and if he admitted it we believe he would have to admit the action of the preparation, as the salicylic acid which is supposed to come from the methylene compound is supposed to be therapeutically active and just such a combination as we have found would be expected.

Sollmann might as well have omitted discussing the melting point of these residues, as they are manifestly too impure. The solubilities given on page 4 of his letter are of like order, as other things than methylene-di-salicylic acid and salicylic acid are present and no approximation would be possible.

On page 5 his mention of finding evidence of the formaldehyd radicle is to the point, but not in the least to be wondered at, as it is not surprising that some unchanged compound is to be found when one takes this relatively large dose.

We have already sent you a specimen of urine that we have just been testing. One of us is probably in receptive condition for taking this material as he has been for some time troubled with uric acid and urates in his system, and has found them in the urine. This sample has remained unclouded for 36 hours and we know from experience that an ordinary urine will not remain unclouded for more than about 18 hours. This is ample confirmation of that part of our statement.

We have spoken of a benzol test on this sample of urine. We will only say briefly that we can easily obtain a salicylic acid test by a one minute contact with the residue which is slightly stirred up with a rod.

Both the first ether extract (.540 grams) and that after boiling (.1338 grams) gave a sublimate on the oil bath at 170 C. which gave the ferric chlorid test when it was treated with 10 c.c. of benzol for one minute and five drops of this clear liquid were taken and 5 c.c. of 95 per cent. alcohol added with one drop of test solution of ferric chlorid. This was

controlled, as already mentioned, by means of purified methylene-di-salicylic acid when we get no change in color whatever.

With regard to the erroneous interpretation of Fränkel's meaning, when on p. 585 of his "Arznei mittel-Synthese" he compares the action of methylene-salicylic acid in the organism with that of methylene-oxy uvitic acid or as Dr. Sollmann prefers to put it "contrasts" them, I can only bow to the author's statement, made in his letter to Dr. Sollmann, that when he said "methylene-salicylic acid" he meant methylene-di-salicylic acid. Two things misled me in forming my conclusion as to the meaning of Fränkel: First, the close comparison or contrasting of the action of "methylen-salizyl-säure" with that of "methylen-oxy uvitic-säure," while giving a structural formula for the latter, showing it to be a compound formed from one molecule of acid, and second, that when he refers later (on page 597, and in the index) to methylene-digallic acid, he gives it its correct name and does not call it methylenegallic acid. Both salicylic acid and gallic acid are monobasic phenol acids, the methylene derivatives are analogous, and if one was correctly named, I assumed the other would be and hence finding it contrasted in physiologic action with methylene-oxy uvitic acid (a one-molecule compound acid) I took what I thought to be the obvious meaning of the term as here used.

Lastly with regard to the taste of ur-a-sol, Dr. Sollmann calls attention to my having failed to take the full dose when passing upon the question of its taste. I took, instead "a pinch on my tongue." I confess to having overlooked the requirement that I take all in the paper at a dose. I had preserved the paper with the ur-a-sol sample and have just taken the balance at a dose. I recognize a more pronounced taste than before and some suggestion of salicylic acid taste, but cannot stretch my imagination to call it a nauseating taste. My son who has carried through the urine tests after taking ur-a-sol in repeated doses tells me the same thing, as to the taste, so I must say that I cannot grant this point, although I would have done so willingly, if I could be brought to believe it.

In conclusion, I would say I believe I have covered the ground of what my son and I had stated in our report to the Organic Chemical Co. and the points controverted by Dr. Sollmann in his two comunications to you. As I said to you in my letter of November 9, I am treating this as a personal matter and have put in nearly a week's work to straighten out questions of scientific fact and show the correctness of chemical tests previously given by me. I have no intention of rendering a bill for this to Dr. Summers, as a possible beneficiary of this work, nor shall I accept any money from him for it, should he offer it. I am, in fact, doing it in order that the Council of Pharmacy and Chemistry shall not make a great mistake, if I can prevent it, by making this review of the chemical tests.

I consider Dr. Sollmann's chemical tests as faulty and liable to lead to wrong conclusions. That he entirely misapprehended the meaning of my statements in some cases I have pointed out, and that he has failed to inform himself as to the best methods of testing, is equally indicated.

I was a member of the Council of Pharmacy and Chemistry for three years and willingly joined in every effort to expose frauds and am still desirous of doing so. I feel, however, that the best way to do this is to be sure that you have the facts with you before sweeping statements are made, such as appeared in Dr. Sollmann's first publication on these synthetics here discussed. They can only bring discredit on the Council in the end.

SAM'L P. SADTLER,
For Sam'l P. Sadtler & Son.

REPORT OF SAMUEL P. SADTLER & SON TO ORGANIC CHEMICAL MFG. CO.

PHILADELPHIA, Sept. 10, 1908.

In discussing the report of Dr. Torald Sollmann to the Council of Pharmacy and Chemistry, we would say that we will only take up that which bears directly or indirectly on chemistry. The report is unfortunately incomplete for the reason that so much stress is laid on the lack of evidence of dissociation of your methylene compounds. Proving this dissociation we have found to furnish no difficulties other than is necessitated by a more detailed analysis of the urine of people (for the most part patients regularly taking ur-a-sol) taking these remedies in prescribed doses. We have received three authenticated samples of urine from a reputable hospital physician. These came from as many different patients, accompanied with a letter of transmittal. We also analyzed the samples of urine from a person taking iodomuth and one from a person taking guaialin, both duly authenticated.

We have made several tests on urine from patients taking ur-a-sol in the regular course of treatment. We will detail one of these tests:

Sample sent by Dr. —— from patient (P. D.) taking 140 grains of ur-a-sol per day.

Day's sample was 1,030 c.c. This was made slightly alkaline with sodium carbonate and extracted with ether to remove neutral substances. After making acid with hydrochloric acid.

Ether extract, 0.5170 grams (7.50 grains).

This sublimed in needle crystals gave a strong Fe Cl_3 test and had the melting point of salicylic acid.

The residue was then boiled with caustic soda solution and any possible basic principles extracted with ether and discarded. The residue was then made acid with hydrochloric acid and extracted again with ether.

Second acid ether extract, 0.4664 grams (7.0 grains).

This responded to the same test when the sublimed needles were taken.

The urine, from a patient regularly taking 140 grains of ur-a-sol a day, was practically sterile; as it kept four days without getting turbid, and in two weeks, when it was thrown out, did not have any odor of putrefaction.

These analyses show conclusively that the compounds are broken up. If salicylic acid is found so abundantly in the urine where acetylmethylene-disalicylic acid was taken it is evident that a corresponding amount of formaldehyd was liberated (if not more) due to the fact that salicylic acid would not all come off in the urine in one day.

Dr. Sollmann, in the galley proof of his article furnished the Organic Chemical Mfg. Co., quotes from Fränkel's Arzneimittel Synthese, 2d edition, as follows: "Während Methylensalicylsäure im Organismus keine Formaldehyd abspaltet, sondern unverlendert im Harn erscheint." This, he says, substantiates his tests that no formaldehyd could be split off from methylendisalicylic acid compounds. A reference to Fränkel's book (page 585 and not page 293) shows that methylensalicylic acid, a compound built up from one molecule of salicylic acid condensed with formaldehyd to produce a methylene derivation, is intended and the comparison is made with methylenoxyuvitic acid, the structural formula of which follows. This is also made up of one molecule of the acid condensed to form a methylene compound. Fränkel obviously did not report methylene-di-salicylic acid, and he does not confirm Dr. Sollmann at all.

Dr. Sollmann's results bearing on formaldehyd liberation from the preparations of your company, may be summarized in his own language as follows: "Iodomuth liberates formaldehyd: Most with alkali, doubtful trace with acid, none with water. Guaialin, sodi-forma-sal and ur-a-sol: These do not liberate formaldehyd in any reaction, even on boiling or distillation."

The so-called Jorissen or phloroglucin test is not regarded by expert chemists as the most delicate or reliable of formaldehyd tests, and is rarely used by food analysts in the examination for formaldehyd. We used instead the well-known phenol test, using pure phenol in 1 per cent. solution and concentrated sulphuric acid. With these we got the following results:

Formaldehyd tests with phenol and sulphuric acid:

An amount of the sample such as would go on a knife point (about 0.05 grams) was taken with 10 c.c. of water or 1 per cent. HCl or 1 per cent. NaOH solution.

Two of the four compounds can also be tested for formaldehyd liberation very simply by the application of one of the official tests given under "Liquor Formaldehydi" in the U. S. Pharmacopeia, 8th revision, p. 265. This test reads as follows: "If to 5 c.c. of sulphuric acid in which a little salicylic

acid has been dissolved, 2 drops of solution of formaldehyd be added and the liquid very gently warmed, a permanent deep, red color should immediately appear."

This test is a very sensitive one, and the reagent (a little salicylic acid dissolved in sulphuric acid) is perfectly colorless until the formaldehyd solution is added to it.

Sodi-forma-sal, if shaken with water and the solution filtered into pure sulphuric acid, is immediately decomposed and gives the deep-red color, showing the liberation of the formaldehyd and salicylic acid under the influence of aqueous dissociation.

Bis-forma-sal, another of the preparations of your company, of analogous constitution, gives the same test, indicating the liberation of formaldehyd and salicylic acid under the influence of aqueous dissociation.

Ur-a-sol, shaken with water for some time and allowed to stand, then filtered, will also give the test when the filtrate is run into sulphuric acid, although not so strongly as the other two because of its slight solubility in water.

Ur-a-sol is practically tasteless, instead of having a nauseous taste, as stated in the report to the Council.

Article Used.	In Water for a Few Minutes.	In Water Over Night.	In Dilute Acid Over Night and Then Distilled.	In Dilute Alkali Over Night and Then Distilled.	In Dilute Alkali Over Night, Made Acid and Distilled.
Ur-a-sol	No test.	Distinct test.	Distinct test.	Distinct test.	Stronger test.
Iodomuth ...	Distinct test.	Strong test.	Moderate test.	Moderate test.	Strong test.
Guaialin	Distinct test.	Strong test.	Strong test.	Moderate test.	Moderate test.
Sodi-forma-sal.	No test.	No test.	Slight test.	Slight test.	Slight test.

These tests show conclusively that all of these four compounds referred to in Dr. Sollmann's article will liberate, under conditions chosen by him, formaldehyd, readily enough recognized by well-known accepted formaldehyd tests.

With regard to Dr. Sollmann's statement that he was unable to distinguish by chemical tests between methylene-di-salicylic acid and salicylic acid itself, we found that benzol does not dissolve methylene-di-salicylic acid, while even in the cold it takes up sufficient salicylic acid to give a ferric chlorid test after filtering and adding enough alcohol to dissolve the benzol solution. The methylene-di-salicylic acid test is negative.

The statements of his report to the Council on Pharmacy and Chemistry bearing on the formaldehyd liberation question;

his deduction that the methylene-di-salicylic acid compounds are not decomposed in passing through the system (because of his inability to distinguish between salicylic acid and methylene-di-salicylic acid); and his statements about the taste of ur-a-sol, should therefore be withdrawn, as their incorrectness is clearly shown.

As to the action of the pancreatic extracts it may be seen from Dr. Sollmann's article that two out of the three decompose ur-a-sol and sodi-formasal even better than salol, which has long been known as an intestinal antiseptic, and when the channel through the system becomes sufficiently alkaline to dissociate it into its components it breaks up readily enough. This would undoubtedly be the case with ur-a-sol and sodi-forma-sal. As to guaialin, we can hardly see how Dr. Sollmann could have expected to have obtained tests for salicylic acid, as it does not contain any in its composition.

Another thing, the laws of reversible chemical reaction would tend to prevent great dissociation of many of the compounds Dr. Sollmann used, unless the dissociation products were removed when formed, as they would be in many cases in the economy, where they can dialyze through tissues and be taken up in the blood. SAM'L P. SADTLER & SON.

GLYCOZONE

Report of the Council on Pharmacy and Chemistry, with Comments

(From The Journal A. M. A., June 5, 1909.)

A number of specimens of Glycozone purchased in the open market were examined by a sub-committee. The product was found to be a mixture of approximately 90 per cent. glycerin, 5 per cent. glyceric acid, a small amount of water and traces of undetermined matter. The absence of hydrogen peroxid or other peroxids was demonstrated.

In its report the sub-committee held that: (1) The name of the product is objectionable and misleading; (2) the statements made in regard to its composition also are misleading; (3) the claims for its therapeutic value are exaggerated and untrue. Since the objectionable statements have been given wide publicity among physicians as well as among the laity, the sub-committee recommended that attention should be called to the matter in THE JOURNAL.

The report of the sub-committee was adopted by the Council.
W. A. PUCKNER, Secretary.

COMMENTS—While the name gives the impression that ozone or some similar substance is an essential constituent of Glycozone, or else that the preparation is a compound or derivative of ozone, and while the earlier advertisements stated that Glycozone was "glycerin combined with ozone," the examination made by the Council shows that there is no basis of fact for such inferences.

In the advertisements the "chemical formula" $C_3H_6O_4 + C_3H_8O_3$ appears under the word Glycozone. From the Council's report it is apparent that $C_3H_6O_4$ stands for glyceric acid and the $C_3H_8O_3$ for glycerin, and, therefore, indicate the chief constituents of Glycozone. Few, doubtless, would recognize the first formula as being that of glyceric acid, a product practically unknown in medicine, nor would many associate glycerin with the second. The evident intent is that physicians should accept the formula as a badge of respectability.

According to the label on a trade package, Glycozone is "prepared only by Charles Marchand, chemist," and is "an absolute cure for dyspepsia, catarrh of the stomach, ulcer of the stomach, heart-burn," etc. The label further reads: "This remedy is positively harmless. By destroying the microbian element in the stomach it prevents the fermentation of food and stimulates digestion." An examination of medical literature fails to reveal any basis for these claims. While glycerin possesses some antiseptic properties, it is evident that the glycerin which constitutes 90 per cent. of this remedy is not the agent that gives the glycozone such phenomenal virtues. General literature contains nothing that would indicate that glyceric acid in any quantity, with or without glycerin, possesses these miraculous properties. If by "microbian element" is meant microbic organisms, the statement is without foundation. There is nothing in this product which possesses these bactericidal powers.

The circular which accompanied a trade package, envelopes the preparation in an air of mystery. Derivation from, or close relation to, ozone and hydrogen peroxid is vaguely hinted at, without definite assertion. Thus, the chief therapeutic properties of glycozone and hydrozone are compared as follows:

"Hydrozone instantly destroys the microbian element, leaving the tissues beneath in a healthy condition."

"Glycozone acts more slowly, but not less certain, as a stimulant to healthy granulations."

There is no similarity between the action of hydrozone, which is a hydrogen peroxid preparation, and glycozone, which consists of a mixture of glycerin and glyceric acid. The representation is false and misleading. The following statement, also, is an unwarranted exaggeration of the facts:

"As an internal medication in fermentation of food, catarrhal and inflammatory conditions of the stomach, and intestinal disorders, its action is prompt and effective, giving immediate relief to the patient."

The following is another illustration of the vague statements made: After asserting that glycozone is hygroscopic and that it will deteriorate by absorption of water unless securely

corked, it is stated that "Its healing properties increase with age." Whatever mysterious ingredient there may be present in this mixture to justify the statement that the healing properties increase with age can only be conjectured. To humbug the patient further he is advised to use only a "silver, glass or hard rubber spoon."

MIGRAININ

Report of the Council on Pharmacy and Chemistry Rescinding Acceptance of the Preparation

(*From The Journal A. M. A., June 5, 1909.*)

The Council having voted to rescind the acceptance of Migrainin and to omit it from New and Nonofficial Remedies (Appendix), directed publication of the report given below.

W. A. PUCKNER, Secretary.

SUPPLEMENTAL REPORT ON MIGRAININ

To the Council:—Koechl & Co., American agents for Migrainin (Meister Lucius & Bruning) asserted that this preparation was a mixture of antipyrin 85 parts, caffein 9 parts and citric acid 6 parts. The experiments of F. Zernik (*Apoth.-Ztg.*, 1906, p. 686), however, showed that Migrainin consisted of antipyrin 90.88 parts, caffein 8.4 parts and citric acid 0.45 parts. When the attention of Koechl & Co. was called to this they informed the Council, on June 20, 1907, that the formula they gave was given them direct by the manufacturers abroad and that they, Koechl & Co., did not question its accuracy. They, however, offered to "write abroad and have the manufacturers confirm the formula as given." On July 23, 1907, Koechl & Co. wrote the secretary of the Council that the manufacturers had informed them that Migrainin contains 90 per cent. antipyrin and 9.1 per cent. caffein citrate. This being an acknowledgment that the former statement submitted was incorrect, the Council voted that the approval of Migrainin should be reconsidered. Examination of the product, therefore, was taken up in the Association's laboratory and an original specimen, purchased in Chicago, was found to contain moisture 0.7 per cent., antipyrin 90.93 per cent., and instead of caffein citrate 9.1 per cent., citric acid 0.51 per cent., caffein 8.53 per cent. This analysis agreed essentially with the composition of Migrainin as found by Zernik.

1. Caffein citrate is readily hydrolyzed by water, but in the dry form the existence of three caffein citrates is possible, as follows:

(1). $C_8H_{10}N_4O_2.C_6H_8O_7$ contains 50.28 per cent. caffein.

(2). $(C_8H_{10}N_4O_2)_2C_6H_8O_7$ contains 66.91 per cent. caffein.

(3). $(C_8H_{10}N_4O_2)_3C_6H_8O_7$ contains 75.18 per cent. caffein.

If the "caffein citrate" in Migrainin is present as in (1) there should, according to the statement of the manufacturer, be present 4.57 per cent. caffein; if as in (2), 6.08 per cent. caffein; if as in (3), 6.84 per cent. caffein: the quantity found is 8.53 per cent. If

the caffein citrate is present as in (1), the citric acid present should be 4.53 per cent.; if as in (2), 3.02 per cent., and if as in (3), 2.26 per cent.; the citric acid found equals 0.51 per cent. This shows that the most recent statement of the firm, viz., that Migrainin contains 9.1 per cent. caffein citrate, is incorrect, no matter what interpretation is given to the meaning of the term caffein citrate.

While the discrepancies between the statement of the firm and the facts are perhaps not great, nevertheless they show that even the formula last given is incorrect, and that the statements of Koechl & Co., while no doubt made in good faith, were in this instance unreliable.

In recent advertising matter issued by Koechl & Co., "phenozon-caffein citrate" is given as a synonym for Migrainin, one circular stating that "Migrainin is phenozon-caffein citrate," etc. In the same circular the following also appears: "In the treatment of migraine with phenacetin or antipyrin, the attack is delayed, while with Migrainin it is usually permanently stayed." This will, no doubt, lead physicians to infer that Migrainin is not a mixture of antipyrin and caffein citrate, but that it is some new compound. While the firm disclaims any intention to mislead, it does not offer to withdraw or modify this circular. It is recommended, therefore, that the approval of Migrainin be rescinded and that it be omitted from New and Nonofficial Remedies.

SALIT

Report of the Council on Pharmacy and Chemistry Rescinding Acceptance of the Preparation

(*From The Journal A. M. A., June 5, 1909.*)

The Council was advised that Salit (Heyden Chemical Works), a preparation which previously had been approved, was being advertised to the public in Germany, and that it therefore should be classed with "patent medicines" intended for popular use. The following report was presented by a sub-committee:

SUPPLEMENTAL REPORT ON SALIT

To the Council:—The secretary reported to the Council that Salit is advertised to the laity abroad, but that the manufacturer had agreed that these advertisements should not appear in those foreign papers which are shipped to this country. The Council decided that in accordance with precedent the advertising of products in foreign lay journals should be held a conflict with the rules, and it voted that the acceptance of Salit be reconsidered. It is now recommended that Salit be refused recognition, and that it be omitted from New and Nonofficial Remedies.

The report was adopted by the Council and its publication directed. W. A. PUCKNER, Secretary.

SUCCUS ALTERANS

Report of the Council on Pharmacy and Chemistry

(*From The Jornal A. M. A., June 26, 1909.*)

The following report was adopted by the Council:

It is believed that unwarranted and exaggerated therapeutic claims are made for Succus Alterans by its manufacturers, Eli Lilly & Co., Indianapolis. In view of the disastrous results which may follow, if, from the statements made, physicians should be led to rely on the product as a treatment for syphilis, it is recommended that Succus Alterans be refused recognition and that this fact be published with comments.

W. A. PUCKNER, Secretary.

COMMENT: Succus alterans is a preparation which has been put on the market for some years by Eli Lilly & Co., as a remedy for syphilis. The serious character of this disease and especially the deplorable results that ensue from its improper or insufficient treatment, should make a firm hesitate to advise any treatment for it which experience has not demonstrated to be at least as efficacious as that which is generally accepted and well proved. Succus alterans is the result of a combination of circumstances; no one person is responsible for it. It was probably the natural desire for a remedy free from the occasional injurious results of mercury that led Dr. J. Marion Sims to advocate the use of a collection of indigenous American plant drugs, sarsaparilla, stillingia, xanthoxylum, etc., which had a local reputation for the cure of syphilis. These drugs are supposed to be inert when the dried plants were used, and this gave an opportunity for the development of a nostrum. The ingredients are well known, but as their virtues are supposed to be lost in drying, the physician cannot have his druggist compound them, but must, perforce, prescribe the proprietary combination.

Those who consented to experiment with the new remedy soon found that the claims to curative properties were unfounded, but the strong commercial interests backing it have prolonged its life to the present time. Authorities on syphilis either say nothing about the preparation or mention it merely to condemn; but the proprietors of the nostrum continue to assert that it is not only practically a specific in syphilis, but now recommend it for various derangements of the blood and all sorts of skin diseases.

This being the case, what shall the wise physician do? Shall he blindly follow an authority of a past generation or shall he recognize that the claims of an interested manufacturer ought not to weigh against the consensus of his present-day confrères who have given the treatment of syphilis their

special attention? The exploitation of such a preparation is deserving of strong censure. By such methods the firm places itself on the same plane as those nostrum venders, who advertise certain antiseptic sprays and gargles as cures for epidemic meningitis and diphtheria and thereby deprive credulous victims of the curative antitoxin treatment. Succus alterans is not a new remedy on trial for its possibilities of improvement in therapeutics; it is an old mixture which has been tried and found wanting.

PAPAYANS BELL

Report of the Council on Pharmacy and Chemistry

(*From The Journal A. M. A., August 14, 1909.*)

The following report of a sub-committee was submitted to, and adopted by, the Council and its publication directed.

W. A. PUCKNER, Secretary.

Papayans (Bell) made by Bell & Co., Orangeburg, N. Y., is said to consist of the "digestive principle obtained by our own exclusive process from the fruit of *Carica papaya*, combined with willow charcoal, chemically pure sodium bicarbonate and aromatics." The following statement appears on the package: "For the treatment of dyspepsia, flatulence, nausea, vertigo, hyperacidity, palpitation and other symptoms of indigestion and the vomiting of pregnancy. Peritonitis, cholera morbus, alcoholism and seasickness." "Digests every variety of food, removes every symptom of indigestion, restores the entire digestive tract to a normal condition." The dosage is recommended as follows: "From one to three tablets before meals, or two hours after eating. In severe cases, three tablets dissolved in hot water and repeated as necessary."

A circular which accompanies the package details the therapeutic virtues of the preparation and contains what purports to be extracts from medical journals, in which Papayans is recommended.

Examination of specimens purchased in the open market showed them to contain the following ingredients: Charcoal, sodium bicarbonate, ginger, saccharin and oil of gaultheria. As the product is said to contain papain, the presence of enzymes was tested for, with the result that it was found to possess neither proteolytic nor amylolytic properties. The results of our examination are in accord with the results obtained by a member of the Council, who examined the product independently, and who writes:

"We have made some extended tests with Papayans Bell, and find that the tablets consist essentially of sodium bicarbonate and charcoal, with a little flavoring matter. We find no digesting power for starch or egg albumin. At any rate, no appreciable change follows in the albumin in three hours, and no conversion to sugar in the same time, or change of starch to a point where the iodin reaction is weakened. The product seems to be practically inert."

It is recommended that Papayans Bell be refused recognition, and that publication of this report be authorized.

COMMENT: It will be remembered that two other products of Messrs. Bell & Company have been discussed in this department: Salacetin (Bell)[1] and Sal-Codeia (Bell).[2] Salacetin was examined with several "synthetics" which all turned out to be mere acetanilid mixtures. Salacetin, advertised as "a combination, with heat, of Salicylic and Glacial Acetic Acids and Phenylamine" when examined "was found to be a mixture and to contain the following ingredients approximately in the proportion given: Acetanilid, 43; sodium bicarbonate, 21; and ammonium carbonate, 20." Sal-Codeia (Salacetin-Codein) therefore, would be the same with codein added.

Papayans (Bell) seems to be consistently fulfilling the life-history of the average nostrum. Made of well-known drugs and invested by its manufacturers—or exploiters—with virtues absurdly disproportionate to the known properties of the alleged constituents of the nostrum, the preparation was introduced to the world *via* the medical profession. With the help of thoughtless physicians, aided by a skillful and aggressive advertising campaign and augmented by the "free sample" device, the business grew and prospered. The bottles with the name and address of the compnay blown in the glass and with the varied therapeutic indications for the nostrum printed both on the label and on a circular in which the bottle is wrapped, have carried the manufacturer's message to the drug-taking public.

Apropos of this point, the recent "literature" contains what purports to be endorsements of the nostrum by medical journals. Thus there is quoted from the *New York Medical Journal*, Jan. 2, 1909, in part, the following recommendation: ". . . we venture to suggest to our readers who have not tried this remedy that they prescribe one *original sealed package* of Papayans (Bell) and that they carefully note the results from its use." [Italics ours.—ED.] Having seen an "original sealed package" we believe that we can predict the "results from its use." On any patient not mentally unbalanced, the result would be that the next dose of Papayans (Bell) he thought that he needed would be purchased from the druggist direct.

That such results are not hypothetical is evidenced by the statements of the exploiters of Papayans (Bell) that "the

1. *The Journal A. M. A.*, June 3, 1905, and July 1, 1905; reprinted in the "Propaganda for Reform in Proprietary Medicines."
2. *The Journal A. M. A.*, Nov. 4, 1905; reprinted in the "Propaganda for Reform in Proprietary Medicines."

annual sale now exceeds four hundred million tablets." Assuming this statement to be true, it would be necessary for every physician in the United States to prescribe over three thousand of these tablets every year—if they reached patients only through the physician! The company's own figures indicate that the time is about ripe to take care of this vast army of self-drugging laymen and recent circular letters seem to recognize it. The physician is notified that druggists are now furnished with Papayans (Bell) "in sealed packages of thirty and one hundred tablets." The medical man is told that the firm has "not forgotten the days when physicians' orders made our success possible" and says it is "sincerely grateful to the doctors who gave us orders in the days when we were struggling for recognition." This tacit admission of the value of the physician as an unpaid agent for nostrum houses should be given thought by those physicians who prescribe such preparations.

While, so far as we know, Bell & Co. have not yet advertised in the daily press, they are not averse to furnishing the laity with samples when requested. An Ohio physician sent us the following letter received by a young woman who had written asking for samples:

Miss X—— Y——,
Z——.

Dear Madam: As requested, we are mailing you sample of our Papayans (Bell) for Indigestion.

If a sufferer from Indigestion, we want you to give it a thorough trial as directed and note remarkable results that we believe you will get from its use.

Kindly write us if you are unable to obtain it from your local druggist, as it is stocked by nearly every good drug store in the United States. Yours truly, BELL & CO.

Evidently Bell & Co., while admitting that their financial success is largely due to the kindly, though misguided, efforts of physicians, are not going to let a little thing like loyalty to the medical profession interfere with a possible sale of their tablets.

THE L. D. JOHNS COMPANY

A discussion of the methods of Bell & Company would not be complete without reference to a concern which seems to be closely connected with it: the L. D. Johns Company, whose "only product" is a sugar-coated laxative tablet. Regarding the "sugar-coated" tablet, a visitor at the place of business of Bell & Company and the L. D. Johns Company, wrote: "These companies apparently are not in possession of any tablet coating machines and in questioning on this point stated that some of their tablets were sent out to be coated." There is a sameness regarding the claims for the laxative

tablets of the two companies that might lead one to suspect that the same individual prepared both. For instance:

CASCARANS (BELL)	DR. JOHN'S TABLETS.
"Taken as directed, it permanently removes the great majority of cases of habitual constipation."	"Taken as directed . . . permanently remove the great majority of cases of habitual constipation, torpid liver and sick headache."
" . . . a harmless vegetable preparation."	"A harmless vegetable remedy."
" . . . for the removal of pimples, yellowness and greasiness of the skin. . . ."	" . . . removes pimples, blotches, sallowness and greasiness of the skin . . ."
" . . . one tablet at night, one night and morning, or, in severe cases, one three times a day, gradually decreasing the frequency of the dose as improvement permits."	"One at night, one night and morning, or, in severe cases, one three times a day. Gradually decrease the frequency of the dose as improvement permits."

According to a leaflet sent out with samples by the L. D. Johns Company, the company is capitalized for $500,000, divided into 50,000 shares at $10.00 each; these shares are sold to those physicians who will agree "to prescribe the tablets at every suitable opportunity, to introduce them to other physicians" and "to promote their sale in every ethical way"! If the list of physicians' names and addresses which the company sends out as comprising the eastern stockholders is to be relied on, it would seem that many medical men are promoting their sale. In prescribing it is, of course, "necessary to specify 'Dr. Johns' Tablets No. XXX (*Original bottle*).'" As the name is on the bottle, it is not unbelievable that, as the company says in its prospectus, because of "our method of advertising, a large and very profitable business is being created" That the L. D. Johns Company expects to profit by the self-drugging which this method of prescribing fosters is evident:

"Physicians not stockholders in this company suffer from the continual refilling of their prescriptions and from the recommendation of the *preparation prescribed by patients* to others. [Italics ours.—ED.] Our stockholders *benefit* by the refilling of their prescriptions and by these recommendations."

Put baldly the case amounts to this: Physicians who prescribe "Dr. Johns' Tablets" not only are likely to foster self drugging, but they will reap dividends therefrom. Truly a nice business to be in!

While Bell & Company and the L. D. Johns Company are said to be entirely distinct, they are to be found at the same address at Orangeburg, New York, and as will be seen, the officers of the two companies are more or less related.

BELL & CO.		L. D. JOHN CO.
PRESIDENT - -	JOHN L. DODGE -	PRESIDENT.
SECRETARY - -	GEO. C. TENNANT	VICE-PRESIDENT.
VICE-PRESIDENT -	CHAS. B. SMITH -	SEC'Y & TREASURER.

EXPLOITING THE PROFESSION

Nostrum promoters have two simple ways of "working" the medical profession. The first—and the more profitable—is, by lavish distribution of free samples, to get physicians to prescribe the blown-in-glass "original package" with the inevitable result of large sales direct to the laity. By the second method, which is merely a modification of the first, the physician furnishes the capital for floating the nostrum and then takes his share of the resulting profits. There may not be quite as much money in the second method for the promoter, but then the risks are correspondingly less. If the firm fails, the stockholders are the losers; the promoter is not necessarily "out" anything. From a commercial standpoint, a combination of the two methods is, of course, ideal.

SERUMS AND VACCINES

Report to the Council on Pharmacy and Chemistry of the Committee on Serums and Vaccines

(From The Journal A. M. A., September 13, 1909.)

The Council having decided to consider serums and vaccines for inclusion with New and Nonofficial Remedies, it appointed a committee of the Council to consider these products and to report thereon. The committee submitted a preliminary report and recommended its publication; the recommendation was adopted and in accordance therewith the preliminary report is published below.

W. A. PUCKNER, Secretary.

REPORT OF THE COMMITTEE ON SERUMS AND VACCINES

The committee on serums and vaccines submits the report given below and recommends its publication:

If the term drug is used in the broad sense it will be admitted that the vaccines, viruses and serums constitute one of the most important groups of drugs with which the physician has to deal. Some preparations of this group are specific cures for certain diseases; others are invaluable in prophylaxis and diagnosis. The great importance of exercising some degree of governmental control over these products was recognized by the passage by Congress in 1902, of a law entitled "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." This law antedated by several years the law controlling the substances more usually called drugs.

In order that the physician may obtain information in a concise form concerning this important group of remedies, the Council on Pharmacy and Chemistry voted to include in "New and Nonofficial Remedies" a description of the preparations which may be legally sold in interstate commerce in the United States and which are not in conflict with the rules of the Council. To this end those firms which have licenses to manufacture and sell in interstate commerce remedies of this class have been invited to submit descriptions of their products to the Council. These descriptions will appear later.

It has been deemed advisable to publish at the present time a complete list of the manufacturers, both foreign and American, who have secured licenses. In order to obtain such a license it is necessary for an establishment desiring it to request the Surgeon-General of the U. S. Public Health and Marine-Hospital Service to have an inspection made of its laboratories, methods, products, etc. This inspection is made by an officer of that service, and consists in a careful examination of the stables, laboratory facilities, methods, animals, collection of the serum, standardization, and tests for potency, purity and amount of preservatives. Samples of the products from licensed manufacturers are bought on the open market and examined at frequent intervals in the Hygienic Laboratory of the Public Health and Marine-Hospital Service. The inspection of the laboratories is repeated at least once a year and if insanitary conditions are found, or if the products are not what they are claimed, the license is suspended.

Antidiphtheritic and antitetanic serums are required to conform strictly to the standards which have been established by the United States Government. There being no established standard for the various other products, they are not examined for their therapeutic value in the laboratory, but are tested for the amount of preservative and freedom from bacterial and toxic contaminations. Vaccine virus is examined particularly for its freedom from pathogenic bacteria, especially tetanus, and also for its potency. The list of manufacturers follows:

LIST OF ESTABLISHMENTS MANUFACTURING SERUMS, ETC., LICENSED PRIOR TO JULY 15, 1909

License No.	Establishment.	Products.
1	Parke, Davis & Co., Detroit, Mich.	Antidiphtheritic serum, antitetanic serum, antistreptococcic serum, antigonococcic serum, erysipelas and prodigiosus toxins (Coley), tuberculins, bacterial vaccines and vaccine virus.
2	H. K. Mulford Co., Philadelphia, Pa.	Antidiphtheritic serum, antitetanic serum, antistreptococcic serum, antipneumonic serum, antigonococcic serum, antidysenteric serum, tuberculins, bacterial vaccines and vaccine virus.
3	Dr. H. M. Alexander & Co., Marietta, Pa.	Antidiphtheritic serum, antirabic virus, vaccine virus and tuberculins.

5	Fluid Vaccine Co., Milwaukee, Wis.	Vaccine virus.
8	Cutter Analytic Laboratory, Berkeley, Cal.	Antidiphtheritic serum, antistreptococcic serum, antityphoid serum, tuberculin and vaccine virus.
9	Frederick Stearns & Co., Detroit, Mich.	Antidiphtheritic serum, streptolytic serum, pneumolytic serum.
11	Pasteur Institute of Paris, France.	Antidiphtheritic serum, antistreptococcic serum, antiplague serum, antidysenteric serum, antimeningococcic serum and serum antivenimeux.
12	Chemische Fabrik auf Actien (vorm. E. Schering), Berlin, Germany.	Antidiphtheritic serum and antistreptococcic serum.
14	Health Department of the City of New York.	Antidiphtheritic serum.
15	W. R. Hubbert Serum Laboratory, Detroit, Mich.	Antidiphtheritic serum.
16	National Vaccine and Antitoxin Institute, Washington, D. C.	Antidiphtheritic serum, antigonococcic vaccine, vaccine virus and normal horse serum.
17	Lederle Antitoxin Laboratories, New York City.	Antidiphtheritic serum, antitetanic serum, tuberculins, bacterial vaccines, vaccine virus, antistreptococcic serum, and suspension of lactic acid bacilli.
18	Burroughs, Wellcome & Co., London, England.	Antidiphtheritic serum, antistreptococcic serum, antityphoid serum, antistreptococcic vaccine, antistaphylococcic vaccine, antigonococcic vaccine and antityphoid vaccine.
19	Memorial Institute for Infectious Diseases, Chicago, Ill.	Antidiphtheritic serum.
21	Swiss Serum and Vaccine Institute, Berne, Switzerland.	Antidysenteric serum, antipneumococcic serum, antimeningococcic serum, antiplague serum, antistreptococcic serum, anticholera vaccine, antiplague vaccine, antityphoid vaccine and tuberculins.
22	Institute Bacteriologique de Lyon, Lyons, France.	Antidiphtheritic serum and normal goat serum.
24	Farbwerke, vormals, Meister Lucius & Bruning, Hoechst-on-Main, Germany.	Antidiphtheritic serum, antistreptococcic serum, antidysenteric serum and tuberculins.
25	Tuberculin Society of St. Petersburg, St. Petersburg, Russia.	Tuberculinum purum.
26	Institut de Vaccine Animale, Paris, France.	Vaccine virus.
27	Institut Pasteur de Lille, Lille, France.	Serum antivenimeux.
28	Bacteriologisches Inst. Linger, Dresden, Germany.	Pyocyanase.

WATERBURY'S METABOLIZED COD-LIVER OIL COMPOUND

Report of the Council on Pharmacy and Chemistry and Laboratory Contribution on Which It Is Based

(*From The Journal A. M. A., October 9, 1909.*)

The following report has been adopted by the Council and its publication directed.

W. A. PUCKNER, Secretary.

To the Council:—Your committee on pharmacology has read with interest the contribution from the Association's laboratory on Waterbury's Metabolized Cod-Liver Oil Compound. The report shows that misleading and false statements are made in regard to the composition of the product and also that exaggerated and unwarranted claims are made for its therapeutic value. In view of the attempt of the Waterbury Chemical Co. to create a false impression in regard to the therapeutic value of the composition of its product, it is recommended that the following report be adopted and published:

The Council believes that there is a preponderance of evidence to indicate that whatever therapeutic value cod-liver oil has, that value depends chiefly, if not entirely, on its fat (oil). In the opinion of the Council, the word cod-liver oil should not be used in connection with any preparation unless it consists to a large extent (25 per cent. or more) of cod-liver oil. Since Waterbury's Metabolized Cod-Liver Oil Compound contains no appreciable quantity of cod-liver oil, the name is incorrect and misleading, and as a cod-liver oil preparation it is believed to be wholly valueless. The Council has previously voted that Waterbury's Cod-Liver Oil Compound be refused recognition because of conflict with Rules 1 and 6.

[CONTRIBUTION FROM THE CHEMICAL LABATORY OF THE AMERICAN MEDICAL ASSOCIATION.]

Waterbury's Metabolized Cod-Liver Oil Compound

W. A. PUCKNER AND L. E. WARREN

A full-page advertisement of Waterbury's Metabolized Cod-Liver Oil Compound appeared in the *Iowa Medical Journal*, March 15, 1909, in the form of a letter purporting to give the results of an analysis of the product made for the firm by a Chicago chemist. In this letter-advertisement the chemist states at the outset that the results of his examination "are somewhat at variance with the statements made in THE JOURNAL." These statements he quotes as follows:

1. It is a clear liquid and no globules of oil are seen under the microscope. It is, therefore, not an emulsion.
2. It is of acid reaction when mixed with water and remains clear when strongly acidified. Hence it does not contain a soap, and is not a saponification of fat.
3. It mixes with water without precipitation; hence, it cannot contain more than traces of a fatty acid.

The chemist admits in his letter to the firm that his analyses verify statements 1 and 3, but regarding statement 2 he says: "I find that your preparation is acid in reaction, but when strongly acidified gives a distinct turbidity within 10 minutes and a voluminous precipitate within 1 hour. This precipitate is shown to consist of fatty acids of cod-liver oil, which are thrown down by the splitting of the soaps, on acidifying either with sulphuric or hydrochloric acid." From these results he states that to him it seems that the "preparation does not deserve the statement that it contains no soap, as there is no question whatever of the presence of cod-liver oil."

While in the letter published in this advertisement the chemist claims to have demonstrated the presence in the product of "saponified cod-liver oil" he *omits to mention the quantities* of the soap present. In the article that originally appeared in THE JOURNAL (Oct. 13, 1906), in addition to the three paragraphs quoted by the chemist, the following statements were made:

"By these simple tests a physician is easily able to demonstrate that the preparation does not contain cod-liver oil. It is therefore valueless for the purpose of nutrition for which we give the oil. More careful analysis confirms the results of these tests and shows that it contains no fat or fatty acids (except the merest traces) . . ."

At the time these statements were published in THE JOURNAL, the *St. Paul Medical Journal*, October 1906, contained an advertisement for Waterbury's Metabolized Cod-Liver Oil Compound, which contained this statement:

"The only tasteless preparation on the market which contains Cod-Liver Oil in its entirety. The metabolized product is obtained by the action of digestive ferments on pure Cod-Liver Oil."

In the *Ohio Medical Journal* of Feb. 15, 1907, there appeared in the form of an advertisement what purported to be an analysis of Waterbury's Metabolized Cod-Liver Oil Compound by Prof. C. N. Kinney of Drake University. While Professor Kinney made a quantitative analysis of the preparation the quantities were omitted from the analysis as published. A footnote added by the Waterbury Chemical Company called attention to this fact and closed as follows:

"Any physician who is not satisfied with the analysis we will be only too glad to furnish the complete analysis by our representatives."

If this weirdly constructed sentence meant anything, it meant that the complete analysis would be furnished on request. Such requests to the company, however, from various sources failed to elicit the information required nor was the "complete analysis" forthcoming. The inference to be drawn is fairly plain.

In a circular accompanying the product as sold at present, this statement occurs:

WATERBURY'S
METABOLIZED COD LIVER OIL COMPOUND
With Creosote and Guaiacol or Plain.

DOES CONTAIN COD LIVER OIL
DOES ALLAY FERMENTATION
DOES AID DIGESTION
DOES ASSIST ASSIMILATION
BUT DOES NOT DISTURB THE STOMACH

As previous examinations disclosed only the merest traces of cod-liver oil in the product while claims were made that it "represents cod-liver oil in its entirety," and in view of the fact, too, that present advertisements emphatically declare that cod-liver oil is present in the preparation as now sold, it was thought best to examine some of the preparation with especial reference to the quantities of fatty acids from cod-liver oil.

The results of the examination, the details of which are given below,[1] are briefly as follows: The total quan-

1. A trade package of Waterbury's Metabolized Cod-Liver Oil Compound was purchased in the open market and examined in the Association laboratory. The product was a pale brownish-yellow, very slightly turbid liquid, having an acid reaction and a malt-like odor. The odor was in no way suggestive of cod-liver oil or of cod-liver oil preparations. When strongly acidified with hydrochloric acid no precipitation or increase in turbidity was observable at once, as would be the case were soaps present in appreciable amounts. On standing over night the acidified solution gave a flocculent precipitate. On shaking the acidified solution with ether-chloroform mixture and evaporating the solvent, a brownish, partially crystalline residue was obtained, the greater proportion of which appeared by qualitative tests to consist of *salicylic acid*.

Ether-Chloroform-Soluble Matter: A portion was strongly acidified with hydrochloric acid and extracted with an ether-chloroform mixture. The solvent was washed with water, evaporated, the residue dried at 98 C. and weighed; 500 c.c. of the product gave 1.5222 gm. or 0.3044 gm. per 100 c.c. Attempts to separate the salicylic acid quantitatively from the fatty acids by crystallizing the former from hot water were not entirely successful.

Free Fatty Acids—Salicylic Acid: The ether-chloroform-soluble residue was treated with hot water and filtered. The residue on the filter was dissolved in warm alcohol, the solvent evaporated to dryness, the residue treated with hot water to remove salicylic acid, and filtered. The undissolved residue on the filter was dissolved in warm alcohol, filtered and the filtrate evaporated to dryness, the residue dried and weighed as free fatty acid; 500 c.c. gave 0.0362 gm. in the first separation. The first crop of salicylic acid crystals, which separated from the hot water filtrate on cooling, was filtered out, the filtrate evaporated to small bulk and allowed to crystallize a second time. The first and second crops of salicylic acid were united, dried at 60 C., and weighed; 500 c.c gave a total of 0.8421 gm. salicylic acid, or 0.1684 gm. per 100 c.c. A second yield of fatty acids was obtained from the filtrate from the salicylic acid separation by the process employed for the first, 0.0204 gm. being obtained. Total fatty acids isolated amounted to

tity of acids isolated amounted to about 0.3 per cent., and of this amount about two-thirds was *salicylic acid.* Thus it appears from the examination of the specimens bought on the open market that the preparation contains at most but 0.1 per cent. of the fatty acids from cod-liver oil, a totally insignificant quantity.

Notwithstanding the protestations by the manufacturers, in the form of published analyses and circulars, it is seen that the statement published in THE JOURNAL, Oct. 13, 1906, p. 1207, are essentially substantiated; it is further evident that the product does not deserve to be designated as a cod-liver oil preparation. To obtain a medicinal dose of cod-liver oil the patient would be compelled to swallow the contents of a bottle of this mixture, and as the product contains 11 per cent. alcohol the patient who did so would probably experience a degree of exhilaration not referable to cod-liver oil.

CELLASIN

Report of the Council on Pharmacy and Chemistry

(Reprinted with additions from The Journal A. M. A., Oct. 30, 1909)

Cellasin, a product of Mead Johnson & Co., was the subject of a report by the Council on Pharmacy and Chemistry in THE JOURNAL, Sept. 12, 1908. In this report, the Council voted that cellasin be refused recognition on account of the exaggerated chemical and therapeutic claims made for it. The manufacturers having taken issue with these findings, the Council decided to reinvestigate the product, and the matter was referred both to the original investigator (Referee A)

0.0566 gm., or 0.011 gm. per 100 c.c. This residue gave the Pettenkoffer test for bile products, thus indicating the probable presence in the preparation of traces of products derived from cod-liver oil.

The filtrate, from which the fatty acids and salicylic acid had been separated so far as possible, was evaporated to dryness, the residue dried at 98 C. and weighed. A residue of 0.2595 gm. was obtained. This residue did not give Pettenkoffer's reaction for bile salts. It consisted of salicylic acid, free fatty acids and undetermined substances. Since 0.8421 gm. salicylic acid was separated from the residue or 55.3 per cent. of the total, it follows that not more than 0.6804 gm. or 44.7 per cent. of the initial residue can possibly be free fatty acids, or 0.13 per cent. as calculated on the entire sample. This value is evidently much too high as it includes everything in the initial residue not obtained as crystallized salicylic acid. It was noticed during the examination that whenever a fatty acid residue was dissolved in alcohol a noticeable residue remained which was also insoluble in water. Adding the several residues obtained, 0.8421 gm., 0.0566 gm. and 0.2595 gm., the sum of 1.1582 gm., is obtained. Subtracting the sum from 1.5222 gm., the initial residue, a loss of 0.3640 gm., is noted. As a check on the above the total acids were determined in a sample of 100 c.c. An ether-chloroform soluble residue of 0.330 gm. was obtained.

who conducted a new series of experiments, and to a second referee (B), not a member of the Council, who investigated the product independently. The reports containing the findings of both these men were submitted to a third referee (C). The report of Referee C was submitted to the Council, together with the reports of Referees A and B and also letters from Mr. John E. Teeple, chemist for Mead Johnson & Co., and Professor Orndorff. The Council voted that all the matter submitted by Referee C should be published in pamphlet form and Referee C's individual report should in addition be published in THE JOURNAL. After this had been decided the manufacturers requested that publication be withheld until they had submitted new evidence, a request which the Council voted to grant for a specified time. At the end of this time Referee C submitted to the Council the following recommendation which was adopted and publication of the Cellasin report authorized. W. A. PUCKNER, Secretary.

RECOMMENDATION OF REFEREE C

To the Council: The accompanying letter, dated Aug. 13, 1909, from Mr. John E. Teeple, in behalf of Mead Johnson & Co., and addressed to the Secretary of the Council, has been transmitted to me:

Mead Johnson & Co. have handed me a copy of your letter to them of July 30, stating that further consideration of Cellasin has been postponed until August 15, and have asked me to write you regarding the matter.

I have worked on this subject in conjunction with bacteriologists a considerable portion of the time since I saw you in Chicago in April. I have been attempting to obtain a sterile solution by some means which would not at the same time interfere with the action of any enzyme which might be present.

From my conversation with you and others in Chicago I believed that there was not at present any question regarding the presence or absence of action on sugar, but that the question was now solely whether the action was bacterial or enzyme.

At the outset I assumed it would be comparatively easy to obtain a sterile solution by some means which would not interfere with the enzyme. I have not yet, however, succeeded in getting a satisfactory result. There are certain bacteria present which are evidently spore bearers and which resist any means of sterilizing so far tried, excepting means which would actually destroy enzyme.

More recently, I have been trying the possibility of sterilizing by repeated filtration through Birkhardt filters, but a very large number of filtrations, through a great many filters, with intervals to allow development of spore, has not yet produced a solution which is sterile.

I am at present endeavoring to isolate the bacteria and develop pure cultures and determine whether any of them have the same action on sugar and same resisting powers that the Cellasin itself seems to have.

It seems certain that we have here either an enzyme or a variety of lactic-acid-producing bacteria widely different from commonly known varieties, and much more active and resistant to chemicals than they are.

I expect to pursue this investigation until I can determine exactly what we have. If under these circumstances your committee cares

to leave the matter open a little longer, I shall be glad to report to you at frequent intervals just what results are being obtained. My only desire is to determine the exact truth in the matter.

Awaiting your advices, I remain,

Since Mead Johnson & Co. have on the market a product for which they made certain claims, which they are unable to substantiate in their letter of August 13, and as they themselves arrive at the conclusion that "it seems certain that we have either an enzyme or a variety of lactic-acid-producing bacteria widely different from commonly known varieties, and much more active and resistant to chemicals than they are," I would recommend the publication of the report on cellasin.

REPORT OF REFEREE C

Cellasin was submitted to the Council by Mead Johnson & Co., with the claim that it contained starch-converting and fat-splitting enzymes and an enzyme capable of converting sugar into lactic acid, together with small amounts of acetic and other acids. The report of the committee on chemistry showed that, so far as the action on sugar was concerned, these claims were not substantiated by the examinations made by its referee.

In view of the emphatic assertions of the manufacturer that the claims they made for the product were correct, the committee on chemistry again took up the matter, and after further investigation submitted a second report in which it is stated: "We have given an unusual amount of time to the investigation of cellasin and every opportunity has been afforded the firm to substantiate its claims. These claims could not be verified in any samples submitted, and the committee now and finally recommends the adoption and publication of the report."[1]

In the report on cellasin, as published in THE JOURNAL, it was stated that Mead Johnson & Co. claimed that "the action of cellasin on fats, carbohydrates in acid solution is most powerful." This evidently is an error, the word "acid" having been used when "alkaline" was meant. The firm having made no claim as to the activity of the product in *acid* media, this statement in THE JOURNAL should be corrected.

The consulting chemist of the firm, J. E. Teeple, presented arguments (Oct. 13, 1908) to show that the product contained or might contain an enzyme, and transmitted a report from Prof. W. R. Orndorff of Cornell University, who had examined cellasin with reference to its power to produce acid from sugar. Orndorff's experiments showed that the preparation would convert cane sugar into lactic acid when the

1. THE JOURNAL A. M. A., Sept. 12, 1908, p. 931.

media were apparently sterile and even in the presence of antiseptics, but apparently he made no examination of the substance itself or of the fermenting solutions for bacteria.[2]

On the receipt of this letter the matter was referred in accordance with the custom of the Council to the original referee (A) for reinvestigation. Referee A went carefully over the ground and reported in substance, that while cellasin has the power of converting sugar into lactic acid,[3] this action is due in the main to bacteria, of which cellasin contains about 500,000 per gram, and that these bacteria increase, *pari passu*, with the formation of acid. He found that when micro-organisms were removed by proper filtration the activity of the product becomes correspondingly decreased.[4]

In addition to the investigation by the referee, the product was referred to a second referee (B). His report confirmed the findings of the first referee.[5]

In accordance with the regular procedure of the Council, the reports of Referees A and B (the latter not a member of the Council) on cellasin, together with a letter, bearing date of Oct. 13, 1908, and signed by J. E. Teeple (consulting chemist, chemical engineer) in regard to the properties and claims made for the product, and accompanying this letter a report by Prof. W. R. Orndorff of Cornell University, were submitted to the third referee (C) for an additional opinion.

The report of Professor Orndorff goes to show that cellasin does possess considerable power of splitting up cane sugar into acid products, but singularly enough the report is lacking in a bacteriologic control of the results obtained. That he attempted to exclude *extraneous* bacteria is indicated by the statement: "Except in cases where antiseptics were used, all apparatus and chemicals were sterilized before cellasin was added." The possibility that *cellasin itself* might contain the responsible bacteria was seemingly excluded by a number of tests in which antiseptics were employed. The report tacitly as-

2. Mr. Teeple's letter and Prof. Orndorff's reports, pages 127 to 132.

3. The action of cellasin on a sugar solution is found to be slow at first. The examinations on which the first reports of the referee were based were made after an incubation for not more than 24 hours. The results were negative as to quantitative results. In the subsequent experiments a longer period of incubation gave considerable formation of acid. It is admitted by the manufacturers that the action of cellasin is too slow to be of use as an intestinal enzyme, but is claimed that it is an intracellular enzyme, similar to muscle enzymes, and acts after absorption into the blood. (As appears in Mr. Teeples' letter, page 127, and also report of Referee A, page 132.

4. Report of Referee A, page 132.

5. Report of Referee B, page 134.

sumes that the germicidal and antiseptic substance used either killed or held in check such bacteria as might be present, and, while it does not directly assert the presence of a "true enzyme," still it leads to such an inference. Thus, Mr. Teeple, referring in his letter of Oct. 13, 1908, to the tests made by Professor Orndorff and himself, states "that all of the experiments go to show that we have here a true enzyme whose action is roughly proportional to the amount of enzyme present." In these few words a tangible claim is made which must stand or fall with such experimental evidence as has been presented. The report of Professor Orndorff therefore requires particular attention.

In 8 out of the 12 experiments tabulated in the report of Professor Orndorff, phenol (in amounts of 0.03, 0.06 and 0.1 per cent.) was added to the cane-sugar solution clearly for the purpose of inhibiting the growth of bacteria. And yet, no control was made to ascertain whether the bacteria were actually inhibited, although it was noted that an increase in the amount of phenol retarded the reaction. The statement, made by way of comment on the results obtained, that "This retardation of *enzyme reactions* [Italics not in original] in the presence of antiseptics has been frequently observed," shows clearly that the possibility of *bacterial reactions* was entirely lost sight of.

As a matter of fact, Referee C, on repeating the phenol experiments under practically the same conditions as those which obtained in the experiments of Professor Orndorff, obtained an enormous development of bacteria, and as might be expected, a corresponding conversion of cane-sugar into acid products. The details of one experiment will be sufficient.

TEST WITH 0.1 PER CENT. PHENOL

To 392 c.c. of a sterile 2 per cent. solution of rock candy, 8 c.c. of a 5 per cent. solution of phenol was added. To this solution 2 c.c. of sterile normal sodium bicarbonate and 0.8 gm. of cellasin were added, and the whole mixture then incubated. In this, as in all other tests, made by Referee C, the solutions and containers were absolutely sterile, and special care was taken to avoid external contamination. Hence, the bacteria, if any developed, came from but one source—the cellasin.

Agar plates were poured at the times stated, and the kind and number of bacteria were noted. The clouding of the liquid soon indicated a rapid multiplication, and since the titration of a portion of the liquid showed considerable acid production, sterile normal sodium bicarbonate was added to the liquid

from time to time, in order to reduce the acidity. The total acidity at the end of 120 hours calculated as lactic acid, corresponded to 5.28 gm. of lactic acid. This result, as well as the bacterial count when compared with the control test given later on, where no antiseptic was used, shows an almost total absence of a supposed antiseptic action. The following table will serve to show the rapid growth of bacteria in this test:

MIXTURE PLATED	NO. BACTERIA PER C.C.
At once.	3,800
8 hours.	8,400
24 hours.	450,000
48 hours.	58,000,000
72 hours.	70,000,000
96 hours.	90,000,000

The obvious conclusion from this experiment is that 0.1 per cent phenol does not inhibit the action of the bacteria contained in the cellasin. It naturally follows that the 0.03 per cent. and 0.06 per cent. phenol would have even less inhibitory action, if any at all.

A similar experiment made with 0.5 per cent. phenol did show a complete inhibition of the growth of bacteria, and, paralleling this, a total absence of conversion of sugar into acid products. Agar plates made daily for a period of nine days showed about 100 colonies on each of the nine days. These were obviously derived from spores present in the cellasin. The spores, though resistant to 0.5 per cent. phenol, were unable to germinate in such a solution, whereas a 0.1 per cent. solution offered no such hindrance. The failure to effect a cleavage of the sugar can mean only one thing—the absence of a "true enzyme."

TEST WITH 0.5 PER CENT. SODIUM SALICYLATE

Two experiments of this kind are given by Professor Orndorff, who obtained about the same amount of conversion as with 0.1 per cent. phenol. Any one familiar with the antiseptic action of sodium salicylate would realize, as in the case of phenol, that very little, if any, inhibition of growth might be expected. Nevertheless, one test was made by Referee C under as nearly identical conditions as possible, and the result showed an even greater multiplication of bacteria than in the test with 0.1 per cent. phenol. The acid production corresponded to 3.78 per cent. lactic acid. It is therefore clear that cellasin contains bacteria which can multiply without apparent hindrance in the presence of 0.5 per cent. sodium salicylate, and hence such test can not be taken to indicate the presence of an enzyme other than that connected with the functional activity of the bacteria.

TEST WITH CHLOROFORM

Two tests were also made by Professor Orndorff using chloroform as an antiseptic, but here, as in other experiments, no controls were made. It is commonly assumed that chloroform water is an efficient antiseptic, and it is less generally known that there are bacteria which can thrive under such conditions. Cellasin, it will be seen, affords an interesting instance of this kind.

A number of tests made by Referee C, with varying amounts of chloroform and under varying conditions of agitation, showed an invariable and unhindered multiplication of the bacteria introduced into the sugar solution with the cellasin. One test will be sufficient to substantiate this point.

To 400 c.c. of a 2 per cent. solution of rock candy there was added 2 c.c. of sterile normal sodium carbonate, 40 c.c. of chloroform and 0.8 gm. of cellasin. Sterile conditions obtained as before except for the cellasin. The glass-stoppered bottle containing the liquid was placed on a mechanical shaker in an incubator and constantly agitated throughout the experiment. Sterile normal sodium bicarbonate was added from day to day to maintain an approximately neutral reaction. On titration at the close of the experiment the acidity produced corresponded to 2.88 gm. of lactic acid. The growth of bacteria can be seen from the following table:

MIXTURE PLATED	NO. BACTERIA PER C.C.
At once.	3,000
10 hours.	850,000
24 hours.	2,000,000
48 hours.	87,000,000
72 hours.	150,000,000
96 hours.	200,000,000
120 hours.	300,000,000

The constant presence of an excess of chloroform, therefore, does not materially interfere with the multiplication of the bacteria, and hence the conversion of sugar obtained under such conditions can not be ascribed to an enzyme contained with the cellasin.

TEST WITH HYDROCHLORIC ACID

The patent specifications describe an enzyme which is *indestructible* in a solution of 25 per cent. hydrochloric acid and it further specifies that the ferment has the empirical formula $C_{72}H_{112}N_{18}O_{22}S$. There are no tests, however, with 25 per cent.

acid,[6] and only one is given by Professor Orndorff with a concentration one-tenth that specified, and from his results he deduces the conclusion that "cellasin resists the action of 2.5 per cent. hydrochloric acid." This is quite true, but it does not prove that cellasin is an enzyme or even a mixture containing an enzyme. The presence of resisting spores offers an adequate explanation for the subsequent conversion of sugar.

Several tests were made by Referee C by treating 0.8 gm. of cellasin with 10 c.c. of 2.5 per cent. hydrochloric acid for one hour at 24 C., then neutralizing and adding the mixture to 400 c.c. of a 2 per cent. rock-candy solution. In one instance no growth was obtained and no cleavage of sugar resulted. In three other tests multiplication of bacteria occurred, though very slowly in the beginning, and at the same time sugar was split up into acid products. It is clear, therefore, that 2.5 per cent. hydrochloric acid may destroy all of the bacterial spores present in cellasin, but more often, either because of a large number or through mechanical protection, a few survive and slowly develop when placed under suitable conditions, resulting eventually in rapid growth and the conversion of sugar. Professor Orndorff in his experiment obtained complete conversion of the sugar contents, and although he noted "the only effect observed being a retardation of the reaction at the beginning," yet he failed, apparently, to note the significance of that delay.

In another experiment made by Professor Orndorff, the cellasin was digested with 0.2 per cent. hydrochloric acid in an incubator for five days, then neutralized and added to the sugar solution after which acid production was noted though in lessened amount. This test when repeated and controlled bacteriologically by Referee C showed an almost complete destruction of the bacteria present in cellasin. During the first 24 hours following neutralization there was no evidence of bacterial growth and no cleavage of sugar; after two days, however, the few surviving organisms multiplied sufficiently so as to split up the sugar present to a slight extent. At the end of five days the acidity corresponded to 0.9 gm. lactic acid, while the bacterial content was only four million bacteria per c.c., or about the number to be expected in a control at the end of about from 24 to 30 hours. The signifi-

6. In the earlier consideration of cellasin the Council having questioned the claim that cellasin was indestructible in 25 per cent. hydrochloric acid, Mead Johnson and Co. submitted, instead, the statement that cellasin is not destroyed by 2.5 per cent hydrochloric acid.

cant feature, here as in the other case, is the *absence of all signs of acid production prior to the establishment of a rapid multiplication of the bacteria.*

CONTROLS WITH UNALTERED CELLASIN

Since in the foregoing experiments with antiseptics it is apparent that the action of cellasin goes hand in hand with the growth and multiplication of bacteria, it is hardly necessary to show that cellasin when used direct, i. e., without an antiseptic, will give an equally rich bacterial development. One control of this kind, however, may be given. The test was carried out as in the case of the other experiments; 0.8 gm. of cellasin was added to 400 c.c. of a 2 per cent. solution of rock candy, to which was added 2 c.c. of normal sodium bicarbonate, everything being sterile except the cellasin. The liquid promptly became cloudy and the plate counts showed a rapid multiplication. The amount of acid produced corresponded to 5.4 gm. lactic acid. The increase in bacterial contents will be seen from the appended table:

MIXTURE PLATED	NO. BACTERIA PER C.C.
At once.	2,800
9 hours.	23,500
24 hours.	680,000
48 hours.	12,000,000
72 hours.	62,000,000
96 hours.	60,000,000

THE BACTERIAL CONTENT OF CELLASIN

The number of bacteria contained in cellasin is significant. The standard dilution of 0.8 gm. cellasin in 400 c.c. of sugar solution gave counts which averaged about 3,000 bacteria per c.c., or a total of 1,500,000 per gm. of cellasin. At no time did the samples contain less than 150,000 bacteria per gm. of product.

Of still further significance is the fact that one bacterial species predominated in all three samples of cellasin examined. Moreover, this form was present largely in the spore condition, a fact established by heating experiments, as well as by the behavior of the preparation in the presence of phenol and hydrochloric acid.

It should be stated further, that in plating out the various solutions of cellasin, referred to in the preceding tests, invariably one and the same organism was found. Isolated in pure cultures it was found to be a rapid spore producer. Control experiments made with the pure spores gave essentially the same result as with cellasin. The organism in pure culture splits up cane sugar into acid products, and there can

be no question as to the part it plays in the so-called action of cellasin.

That the action of cellasin depends on the presence and growth of this organism is evident also from filtration experiments. When a solution of cellasin is filtered through a Berkefeld candle into a sterile sugar solution no change whatever results. The solution, after incubation for weeks, remains clear, no acid is produced, and no bacteria can be detected. Were a "true enzyme" present, such would hardly be the case.

The evidence on hand goes to show that cellasin is a mixture of an acid-producing organism and a protein substance, presumably casein. Referee C can, therefore, only confirm the separate findings of Referees A and B, and recommend the rejection of the preparation.

LETTER OF MR. TEEPLE TO THE COUNCIL

NEW YORK, Oct. 13, 1908.

Gentlemen:—I am enclosing herewith a copy of the report of Prof. W. R. Orndorff of Cornell University concerning the action of cellasin on sugar solutions under various conditions. These are in confirmation of some of my own experiments. I have performed a great many others to determine the action of cellasin on cane sugar and glucose with the antiseptics used in the above report, as well as with other antiseptics, including toluene and thymol. I do not care to burden you with a lot more of this data, and I will simply say that all of the experiments go to show that we have here a true enzyme whose action is roughly proportional to the amount of enzyme present, and which is capable of splitting cane sugar and glucose into lactic acid, together with small amounts of volatile acids, and probably some polyoxy acids.

The production of enzymes under the conditions under which cellasin is produced is not entirely new. Buchner's work on the isolation of zymase is well known. Emerling (*Berichte der deutschen Chemischen Gesellschaft,* vol. xxxv, p. 649, 1902) stated "it is known that many bacteria, molds and fission fungi contain enzymes." Buchner & Meisenheimer (*Berichte,* vol. xxxvi, p. 634, 1903) have isolated an enzyme from lactic-acid-producing bacteria. Buchner & Spitta (*Berichte,* vol. xxxv, p. 1703, 1902) have shown that the zymase content of yeast varies a great deal according to the physiologic conditions of the yeast, and Pringsheim (*Berichte,* vol. xxxix, p. 4048, 1906) has shown that aside from the healthiness of the yeast it also varies a great deal in accordance with the food of the yeast. These are cited simply to show how the production of enzymes by fungus growths and the change of these enzymes by the change of condition of the growth have repeatedly been observed. The fact that cellasin acts slowly during the first twelve or fifteen hours is also in accordance with the observation of Buchner & Rapp (*Berichte,*

vol. xxxv, page 2376, 1902), who find that dauer-hefe, being the zymase precipitated by the alcohol-ether method, often acts very slowly for the first day or two.

As to the general rapidity of the action of cellasin, it will be noticed from the experiments that it decomposes nearly double its weight of sugar in twenty-four hours, and from four to five times its weight within forty-eight hours, which is fully comparable with the rapidity shown by ordinary zymase preparations and exceeds the rapidity shown by muscle ferments which have been isolated. If, however, it were to act only as an intestinal enzyme this would probably be too slow to be of any marked value. It is not claimed, however, that it does act in the intestines. It is claimed to be an intracellular enzyme similar to the muscle enzymes, and if this is true, its action should be gauged not so much by rapidity as by whether it is continuous or not. Our own experiments, as well as those of your committee, have shown that the cellasin can resist acidity of the stomach without retarding its later action. The amounts of alkali used during the experiments were often 0.2 to 0.3 per cent. of sodium bicarbonate present, and sometimes much more, so that it is not affected by the alkalinity of other digestive fluids which might reach it in the intestine or in the cells themselves.

Proteolytic enzymes have very little action on it. It is soluble, and from all these facts there is every reason to suppose that it would ultimately be absorbed and reach the blood stream without in any way losing its effectiveness. Our experiments show that its action is accelerated rather than retarded by blood serum. Harden (*Berichte,* vol. xxxvi, p. 715, 1903) has shown the same thing to be the case with zymase. There is then every reason to suppose that the enzyme present in cellasin can reach the cells of the body without losing its power of splitting sugar into acids. Its action and its products are similar to the action and products of enzymes which have actually been extracted from muscle by Stoklasa & Czerny (*Berichte,* vol. xxxvi, p. 4058, 1903), and by Cohnheim (*Zeitschrift für physiologische Chemie,* vol. xxxix, p. 336, 1903, and vol. xlii, p. 401, 1904).

The fact that cellasin is retarded in its action by some antiseptics is also not remarkable, since same facts have been found to be true in the case of other enzymes (see Cohnheim's book on Ferments and Effront on Enzymes) and in particular the action of muscle enzyme is stopped by so simple a thing as a physiologic salt solution (see Cohnheim's *Zeitschrift für physiologische Chemie,* vol. xliii, p. 547, 1904).

If we have an enzyme capable of reaching the cells of the body and of there converting either cane sugar or glucose into lactic acids and other acids, then its bearing on diabetes mellitus is to be considered. In this connection we quote from an article by Nencki & Sieber (*Journal für praktische Chemie,* vol. xxvi, p. 37, 1882), who performed a great many experi-

ments to determine the fate of sugar in the organism during diabetes, and as a result of his experiments states, "we do not doubt that if the diabetic patient was able to split sugar into lactic acid exactly as can be done with dilute alkaline hydroxid or ammonium bases, he would oxidize it completely," and again "so it seems as if the transformation of our foodstuffs into acid and their further change to neutral salts by the alkali carbonates of the blood and tissues is a condition essential to every combustion," and again "The cause of diabetes mellitus lies in the inability of the organism to transform glucose into lactic acid or other acids like, for example, Schmiedeberg's glycuronic acid," and again "reasoning from similar premises Schultzen expressed the view that sugar is eliminated unchanged in diabetes because the ferment is lacking which normally splits sugar into lactic acid and glyceric aldehyd." These same views regarding diabetes have been very frequently expressed and are approvingly discussed in detail in such recent works as the 1908 editions of Hammarsten's "Physiological Chemistry" and Abderhalden's "Lectures on Physiological Chemistry." All the above mentioned experiments and citations seem to me to lead to a very strong presumption that cellasin should be of a very marked value in cases of diabetes mellitus, although my primary object in taking the matter up was simply to point out what seemed to be an error in the report of your committee where they stated they could observe no quantitative change in cane sugar during twenty-four hours when treated with cellasin.

Please command me in any way in which I can be of service in this matter.

J. E. TEEPLE,
(Consulting Chemist, Chemical Engineer).

LETTER OF PROF. ORNDORFF TO MR. J. E. TEEPLE

ITHACA, N. Y., Oct. 8, 1908.

Dr. J. E. Teeple:—I have examined the sample of cellasin which you submitted to me with a request that I test its action on solutions of cane sugar, and beg to report as follows:

The solutions tested in each case consisted of 400 c.c. of approximately 2 per cent. cane sugar solution made from pure "rock candy," to which 0.8 gm. of the cellasin had been added. The solutions were made distinctly alkaline to litmus paper by the addition of 2 c.c. of normal bicarbonate of soda solution and were then placed in an incubator and kept at a temperature of 39-40 C. during the entire experiment. The solutions were contained in Erlenmeyer flasks of resistance glass which were closed with plugs of cotton. Except in cases where antiseptics were used, all apparatus and solutions were sterilized before the cellasin was added. In cases where volatile antiseptics were used, such as chloroform and toluene, care was taken to keep the solution saturated by repeated additions of the antiseptic.

As the reaction proceeds, the bicarbonate is decomposed by the acids formed, and the solution becomes acid to litmus paper, a further addition of normal bicarbonate of soda solution was made sufficient to make the solution distinctly alkaline. The general progress of the reaction can be followed quite closely by observing the amount of bicarbonate solution required to keep the solution alkaline. At the end of definite periods of time exact titrations were made on portions of the solutions by adding an excess of standard hydrochloric acid, boiling for a short time to remove carbon dioxid and titrating the excess of the hydrochloric acid with standard alkali, using phenolphthalein as an indicator. From the total amount of alkaline bicarbonate neutralized, the acid formed during the experiment is computed as lactic acid which was shown to be present qualitatively in considerable quantity by means of Uffelman's reagent. Small quantities of volatile acids are also formed during the reaction. Another portion of the test solution was treated with basic lead acetate solution filtered and the sugar present determined with a polariscope reading to hundredths of a degree in the usual manner. In case reducing sugars (invert sugar) were also present, determinations were made both before and after inversion in order to obtain the amount of invert sugar as well as cane sugar present. The amount of sugar present deducted from the amount in the original solution (also determined by the polariscope) gives the amount of sugar converted into acids by the cellasin. Below are given some of the experiments in detail:

No. 1.—No antiseptic, 400 c.c. of solution containing 7.70 grams of cane sugar ("rock candy") and 0.8 gm. cellasin. Kept at a temperature of 39-40 C. for 109 hours. The amount of acidity developed in terms of normal acid at successive periods was as follows: In 11 hours, 3 c.c.; 14 hours, 4 c.c.; 43 hours, 21 c.c.; 57 hours, 35.5 c.c.; 64 hours, 42.5 c.c.; 81 hours, 62 c.c.; 109 hours, 81 c.c. At the end of this period no sugar was left in the solution, and hence there had been a conversion of 7.7 grams of cane sugar into acids. Computing the total acidity as lactic acid shows the formation of 7.3 gm. of this acid. If we plot the additions of alkaline bicarbonate against the total time elapsed in each case, it will be observed that the velocity of the reaction is fairly uniform after the first 12 or 13 hours until the sugar is nearly entirely converted into acids.

No. 2.—With 0.03 per cent. phenol and containing 7.61 grams cane sugar, otherwise exactly the same as No. 1, the amount of acidity developed at successive periods in terms of normal acid, was as follows: In 11 hours, 4 c.c.; 13 hours, 5 c.c.; 34 hours, 34 c.c.; 43 hours, 43 c.c; 57 hours, 55 c.c.; 64 hours, 59 c.c.; 82 hours, 72 c.c.; 109 hours, 74 c.c. At the end of this period no sugar remained in the solution, hence 7.61 gm. of cane sugar, which were present originally in the solution, were converted into acid, forming 6.67 gm. of lactic acid. Plotting the acidity against time elapsed, as in experiment No. 1, we find again a fairly uniform velocity after the thirteenth hour until the sugar is nearly all converted into acid, but in this case the velocity is greater than in experiment No. 1, as will readily be seen by comparing the acidity

at the end of the forty-third, fifty-seventh and sixty-fourth hours. A duplicate experiment of No. 2 gave practically the same results as detailed above. Other duplicates of No. 2, which were stopped at shorter intervals gave the following results:

No. 2 A.—In 24 hours, 1.22 gm. cane sugar converted 1.13 gm. acid formed.

No. 2 B.—In 39 hours, 3.84 gm. cane sugar converted 3.58 gm. acid formed.

No. 2 C.—In 48 hours, 3.60 gm. cane sugar converted.

No. 3.—With 0.06 per cent. phenol and 7.54 gm. cane sugar, otherwise same as No. 2. At the end of 65 hours, 3.20 gm. cane sugar converted into acids.

No. 4.—With 0.1 per cent. phenol, otherwise same as No. 3. At the end of 65 hours, 2.71 gm. of cane sugar converted into acids. It will be seen from experiments No. 3 and No. 4 that an increase in the amount of the phenol retards the reaction, but that even with 0.1 per cent. of phenol the velocity of the reaction is still considerable. This retardation of enzyme reactions in the presence of antiseptics has been frequently observed.

No. 5.—With 0.5 per cent. sodium salicylate, otherwise same as experiment No. 2. After 131 hours 2.76 gm. cane sugar converted, 1.98 gm. acid formed.

No. 6.—With a few drops of chloroform always present in the flask, which was thoroughly shaken several times a day, otherwise same as experiment No. 2. After 131 hours, 3.96 gm. of cane sugar converted, 3.58 gm. of acid formed. It will be noted that the reaction is retarded in experiments No. 5 and No. 6 in the presence of the antiseptics, just as it is in No. 3 and No. 4.

No. 7.—Same as No. 1, excepting that the 0.8 gm. of cellasin was treated for one hour at room temperature, 24 C., with 10 c.c. of 2.5 per cent. hydrochloric acid. At the end of this time the acid was neutralized before adding the sugar solution. After 131 hours in the incubator 7.70 gm. of cane sugar were converted, forming 6.73 gm. of acid. This experiment shows that the cellasin resists the action of 2.5 per cent. hydrochloric acid, the only effect observed being a retardation of the reaction at the beginning. In another experiment the cellasin was digested in the incubator in a 2 per cent. sugar solution containing 0.2 per cent. hydrochloric acid for five days without showing any conversion of sugar into acid. The solution was then made slightly alkaline with sodium bicarbonate and at the end of 19 hours showed the formation of 0.17 gm. of acid. This shows that even prolonged digestion with 0.2 per cent. hydrochloric acid does not prevent the action of the cellasin on the cane sugar when the solution is made slightly alkaline.

Experiments conducted in the same way as those enumerated above, with no antiseptic, with phenol, sodium salicylate, or chloroform, only using caustic soda instead of bicarbonate, gave similar results, excepting that the velocity of the reaction was much slower. For example: with no antiseptic in 131 hours, 6.33 gm. of cane sugar were converted, forming 5.25 gm. of acid. Using toluene as the antiseptic and caustic soda, a very marked retardation of the reaction was noticed. The formation of acid in 131 hours was only 1.01 gm. as against 5.25 gm. of acid with no antiseptics. The following table gives the results of some of the experiments:

Antiseptic.	Hours.	Alkali.	Sugar Converted. Gm.	Acid as lactic. Gm.	Total sugar. Gm.
1. No antiseptic ...	109	$NaHCO_3$	7.70	7.30	7.70
2. 0.03% phenol ...	109	$NaHCO_3$	7.61	6.67	7.61
2. Dupl. 0.03% phenol	131	$NaHCO_3$	7.61	6.39	7.61
2A. 0.03% phenol ..	24	$NaHCO_3$	1.22	1.13	7.54
2B. 0.03% phenol ..	39	$NaHCO_3$	3.84	3.58	7.61
2C. 0.03% phenol ..	48	$NaHCO_3$	3.60	...	7.54
3. 0.06% phenol ...	65	$NaHCO_3$	3.20	...	7.54
4. 0.1% phenol	65	$NaHCO_3$	2.71	...	7.54
5. 0.5% sod. salicyl.	131	$NaHCO_3$	2.76	1.98	7.61
6. $CHCl_3$, few drops	131	$NaHCO_3$	3.96	3.58	7.61
7. With HCl (2½%)	131	$NaHCO_3$	7.70	6.73	7.70
7A. With 0.2% HCl	19	$NaHCO_3$	...	0.17	7.61
8. No antiseptic ...	131	NaOH	6.33	5.25	7.70
9. 0.03% phenol ...	131	NaOH	2.91	2.12	7.61
10. 0.05% sod. salicyl.	131	NaOH	1.97	1.62	7.61
11. $CHCl_3$	131	NaOH	1.27	...	7.61
12. Toluene	131	NaOH	...	0.01	7.61

W. R. ORNDORFF.
Professor of Organic and Physiologic Chemistry, Cornell University.

REPORT OF REFEREE A, AFTER REINVESTIGATION

The substance cellasin has been before the Council, and after full investigation was rejected. Recently the manufacturers, through a chemist in their employ, have submitted what they seem to consider new evidence as to the merits of this product. At the same time more samples of cellasin have been received, which the referee has tested. Samples have also been purchased in the open market for experiments.

The first samples submitted had no action whatever on starch paste, and no measurable action on sugar, although great activity in both directions was claimed. The last samples sent have not been tested with starch, as this is not referred to in the recent correspondence, but have been tested with reference to action on sugar. A marked inverting action on cane sugar is now found, and acid is formed in appreciable amount, as the chemist writing for the firm claims. But the interpretation offered by this chemist seems to be wrong, in the main, as the whole of the activity which he ascribes to enzymes may be due, and probably is largely due to the bacteria and molds present. I have had a considerable number of bacteriologic examinations made in our laboratory and learn that the bacteria per gm. run as high as 500,000. It is also true that the molds are still alive, and not destroyed by the final treatment, as the claims of the manufacturers would indicate. We have made cultures of the bacteria and find with them a decided sugar-splitting power. It is quite likely that some enzymes are also present. It would be strange if a product made in this way should not contain some enzymes. But when precautions are taken to inhibit the action of bacteria and molds by proper means the activity of the product becomes correspondingly decreased.

But the cellasin, as last submitted, is evidently a mixture and a mixture of which the composition must vary with each lot made. The effects secured are due to the several agents present, and not to enzymes in any marked degree. The manufacturers have no right to put forward their claims as strongly as they do until they can define the cause of the activity more accurately. The chemist employed by the manufacturers has taken the trouble to quote literature showing that enzymes may be formed from molds. This was quite unnecessary as the point is well known. But all the literature quotations are valueless in proving that the action claimed can extend beyond the intestines. The manufacturers assume, and the chemist assumes that the enzymes may pass from the intestines, through the liver presumably, into the circulation and assist in sugar splitting in the remote tissues. This is very interesting—if true—and has been dreamed of before. The burden of proof here is on the manufacturers. Admittedly, the cellasin has no value as an ordinary ferment, as it is too slow. It is expected to work in the blood or tissues, but the manufacturers must give us some tangible proof that it actually gets there.

The use of such a product is not unattended with danger. Cellasin is produced under conditions which apparently make a high bacterial content possible, and until the firm can give some positive assurance of the absence of pathogenic bacteria, and of the fractions of the activity belonging to (a) bacteria, (b) molds and (c) enzymes, and also that they are able to turn out a product in which these fractions shall remain practically constant, they have no right to force the article on the public. A mixture whose properties depend so largely on unknown and variable quantities has at present no place in medicine.

A chemical analysis of one of the last samples examined gives the following results:

Residue insoluble in water at 40 C	58 per cent.
Total nitrogen in original substance	10.3 per cent.
Nitrogen in soluble part	2.4 per cent.
Nitrogen in insoluble part	8.4 per cent.
Ether extract	3.4 per cent.
Ash	6.5 per cent.

A consideration of the patent under which the product is supposed to be made, and which has recently come to my attention, suggests something as to the nature of the nitrogenous substances shown by the above analysis. Some of the samples examined contained very considerable quantities of the remains of fungus growths, along with the living forms, and these are present in this last sample, to some extent. The portion soluble in water contains some kind of a proteose and inorganic matter making up a good part of the ash. The part insoluble in water contains a very considerable quantity of a protein, which is evidently casein. It dissolves in weak alkali, and the viscous solution secured is precipitated by very

dilute acids just as casein is. I have found further that this precipitated flocculent matter, when redissolved in standard tenth-normal alkali in presence of phenolphthalein combines with the alkali almost exactly in the proportions which has been found to be characteristic for pure casein from cow's milk.

The patent specifications state that the mold and other organisms used in producing this substance are grown finally on a culture medium consisting largely of milk. Under the conditions of working there must be a rich bacterial flora present, in consequence of which acid is liberated and the casein of the milk precipitated. The patent formula would therefore account for the findings, as secured in the last samples examined which apparently correspond to the product described as No. 2 in the patent.

But the patent describes as No. 1 a preliminary product which may also be marketed, and which has the properties of No. 2, but in weaker degree. This product does not appear to be grown on milk, and would not, therefore, contain casein. These conditions, as explained in the patent, may account for the marked variations in the nature of the substance, as illustrated by the different samples analyzed in the last eighteen months.

The patent is, however, a singular jumble and too much importance should not be attached to the statements in it. Considering all the evidence at hand it is plain that the product is far from constant and is a mixture of inert nitrogenous matters in which are lodged the bacterial and other organized forms to which the chemical activity is due. It must be recalled that the first samples of cellasin submitted to us were supposed to act as ordinary digestive ferment, and stress was laid on the power of digesting starch, fats and proteins as well as of decomposing sugars. This last point seems to be the one for which the strongest claims are now made, and the mixture is advertised as a diabetes cure, on the assumption that it can follow up the sugars and split them in the tissues, as intimated above. No tangible proofs have ever been offered to support any of these claims, and I recommend that the product be rejected as unworthy of further consideration.

REPORT OF REFEREE B

The sample of cellasin submitted to me gives on examination the following results:

I have satisfied myself concerning the general nature of cellasin and its action on sugar solutions, but am somewhat uncertain as to the form in which report should be made. I will endeavor briefly to communicate the result of the few experiments made. All tests were made on the sample labeled "Cellasin (sent by Dr. J. E. Teeple)," sent me by Referee A.

1. Cellasin contains about 500,000 living micro-organisms per gm. (560,000 and 680,000 on two counts made).

2. Several species are present, among them a white mold, bacteria which liquefy gelatin rapidly producing an alkaline reaction, and bacteria which do not liquefy gelatin but produce a marked acid reaction in lactose litmus media. Of this last type there are about 14,000 per gm. of cellasin.

3. Cellasin is acid to litmus paper.

4. Cellasin produces acid in a 2 per cent. cane sugar solution at a temperature of 37 C. when all other sources of bacterial contamination have been eliminated. This action is at first slow but later proceeds at a more rapid rate, provided the acid is neutralized by sodium carbonate every twelve hours. The acid production is accompanied by the multiplication of bacteria. Thus in such a mixture when first made there were found 1,240 living micro-organisms per c.c. After 17 hours, 8,000,000 living micro-organisms (chiefly acid formers). After 25 hours, 75,000,000 living micro-organisms (chiefly acid formers). At this time the liquid had become quite cloudy, the cloudiness proving to be due to bacteria on direct microscopic examination. Later a scum formed on the surface and a gelatinous sediment in the bottom of the vessel resembling "mother of vinegar" in appearance. Microscopic examination showed bacteria of different kinds but no molds.

5. When the cane sugar is dissolved in 50 per cent, glycerin solution this action is very slow or entirely inhibited, no acid formation taking place at 37 C. after a week's observation. (Starch paste and saliva mixture made up with 50 per cent. glycerin, parallel with the above test, showed entire conversion of the starch in ten minutes).

6. Cellasin sugar mixture, rendered slightly alkaline and then sterilized in the autoclave, shows no appreciable acid production after 4 days at 37 C.

7. Same mixture as employed in 6, sterilized and inoculated with one platinum loopful of the fermenting mixture of 4, above, shows marked acid production, similar to that observed in 4, but rather energetic.

The other tests I have undertaken add little or nothing to the above data. The preparation hardly seems worthy of further attention, but I shall be glad to undertake any further tests which the Council deems desirable.

RESINOIDS AND CONCENTRATIONS

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., Nov. 13, 1909.)

In view of the fact that there is much misunderstanding as to the character of the so-called resinoids and concentrations, and also as to the meaning of the suffix "in," as used in pharmacology, it has been recommended that the following report be published. The recommendation was adopted.

W. A. PUCKNER, Secretary.

MISUSE OF THE ENDING "IN" AS APPLIED TO SO-CALLED RESINOIDS AND CONCENTRATIONS

The endings "in" and "ine" are commonly used in connection with the names of definite chemical substances. In naming the vegetable principles (substances), the ending "ine" has

commonly been used to indicate basic (alkaloidal) substances and the ending "in" to identify non-basic (glucosidal, neutral, bitter) substances, and this system of nomenclature is followed in the U. S. Pharmacopeia. While both endings have thus been used to indicate definite, chemical substances much confusion has been caused by using the ending "in" in connection with a class of pharmaceutical preparations (galenicals) known as "resinoids" or "concentrations." This class of preparations is obtained by preparing an alcoholic tincture of a drug, reducing the tincture to a soft extract and collecting the precipitate which is formed when the extract is poured into water. "Podophyllin" may be taken as the type of this class of preparations. "Podophyllin" is not a definite chemical substance, as the ending "in" would imply, but a somewhat variable mixture of the resinous constituents of the drug podophyllum (Mandrake). The name "resin of podophyllum" applied in the U. S. Pharmacopeia to an almost identical product, is more rational. While the term "podophyllin," therefore, is unscientific and incorrect, it has been established through usage by which the term "in" has come to be applied to non-alkaloidal mixtures known to contain the active constituents of the drug, and in a measure has ceased to be misleading.

There is no justification, however, for a considerable number of titles included with "resinoids" or "concentrations" by some manufacturing pharmacists. While such drugs as juglans (butternut bark), aletris, baptisia, etc., do not contain any appreciable amount of resinous material and do not, therefore, owe to their resin, to any extent, any medicinal activity they may possess, yet the title, "juglandin," "aletrin," "baptisin," etc., are given by the manufacturers to the "concentrations" or "resinoids" of these drugs. From the general descriptions of the "concentrations" or "resinoids" which appear in the catalogs of the manufacturers referred to it is evident that they realize the inconsistency of their position in the matter, for the attempt is made to assign a new meaning to the term "resinoid" or "concentration." Thus the following description of these products is found in the price list of a well-known manufacturing firm and agrees in general with the descriptions found in the price lists of other manufacturers of this class of preparations: "While some of these (resinoids and concentrations) represent a pure resin and others an impure alkaloid, by far the greater number are a combination of the various active proximate principles contained in the drug which they represent."

When it is considered that the chemical nature of the active principle or principles of the drugs, from which these preparations are made, if they possess any, has not been determined, the reliance which is to be placed on the claims of the manufacturers is obvious. While it is not definitely so stated, it is to be inferred from the descriptions that these products are, in the main, extractive preparations of the drugs. It should be noted, however, that the drug strength (the amount of drug represented by a given amount of the preparation) is not stated; such preparations are thus secret in their composition and should be classed with other preparations of unknown composition, that is, as nostrums.

MEAT AND BEEF JUICES

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., Nov. 20, 1909)

The following was submitted to the Council by a subcommittee:

To the Council: While meat extracts contain only traces of coagulable proteids and have little food value, meat juices are prepared by a process which ensures the presence in the finished product of considerable quantities of coagulable proteids and they therefore have considerable value as foods. Many preparations which are sold as beef juices or meat juices have no right to these designations. Since the public and physicians are likely to be misled by the names given to these products and by the false claims which are made for them as foods and depend on them in the nourishment of the sick, it is important that their composition and their value as foods should be known.

In the following report is presented the results of an examination of some of the commercial products found on the American market. The report shows that *Wyeth's Beef Juice* (John Wyeth & Bro., Philadelphia), *Bovinine* (The Bovinine Co., New York), *Carnine* (Carnine Co., Fougera & Co., New York), and *Valentine's Meat Juice* (M. J. Valentine, Richmond, Va.) are sold under names which are incorrect, that their composition is not correctly stated by the manufacturers and that false and misleading statements are made in regard to their value as food.

It is recommended that the products named be refused recognition for conflict with rules 1, 6 and 8. Since these preparations are typical of many others on the market, and as their use is a menace to the public health it is recommended that the report be published.

This report was adopted by the Council.

W. A. PUCKNER, Secretary.

Beef or meat juices are clearly to be distinguished from beef or meat extracts. The word "juice" applies solely to the fluid portion remaining in fresh meat after proper cooling and storing and may be obtained by pressure or diffusion with or without a low degree of heat. Under heavy pressure freshly chopped meat will yield from 25 per cent. to 40 per cent. of a thick reddish juice and if the meat is previously frozen or heated to 60° C., as much as 50 per cent. may be obtained. This gives some idea as to the probable cost of preparing beef juice at home. The chief charactertistics of meat juice are the presence of a considerable proportion of coagulable protein and a low content of meat bases. The above represents the nature of these commodities as usually understood by the medical profession as is clearly shown by this quotation:[1]

"One or two teaspoonfuls of this (meat juice) are added to a teacupful of cold or warm water, which, however, must not be boiling, or otherwise the albumin would be coagulated, but it may, however, be sufficiently warm to drink comfortably."

Beef juice is considered by some physicians of much dietetic service and believed to represent liquid food in concentrated form. W. O. Atwater,[2] relative to this product, says:

"Beef juice obtained from the best steak which has been merely warmed through over the coals and then entirely deprived of soluble substances by a screw press, is undoubtedly the most concentrated of the liquid foods."

The latter authority gives a number of analyses of beef juices prepared under known conditions.

DEFINITION OF MEAT JUICE

Meat juice is defined by the standards committee of the Association of Official Agricultural Chemists as the fluid portion of muscle fiber obtained by pressure or otherwise, and may be concentrated by evaporation at a temperature below the coagulating point of the soluble protein. The solids contain not more than 15 per cent. of ash, not more than 2.5 per cent. of sodium chlorid (calculated from the total chlorin present), not more than 4 nor less than 2 per cent. of phosphoric acid (P_2O_5), and not less than 12 per cent. of nitrogen. The nitrogenous bodies contain not less than 35 per cent. of coagulable proteins and not more than 40 per cent. of meat bases.

---

1. Brunton, Sir Lauder: "Disorders of Assimilation, Digestion, etc.," p. 183.
2. Bull. No. 21, U. S. Dept. Agricult., Office of Experiment Stations.

Meat juices of commerce are supposed to be made by subjecting properly prepared meat to heavy pressure with subsequent concentration of the juice *in vacuo* at a low temperature. The latter is necessary because if the temperature is raised to any material extent the valuable coagulable, soluble proteins referred to above, are precipitated and lost. In order to establish a basis of comparison relative to the composition of natural raw beef juice a number of samples were prepared under known conditions and submitted to analysis. The results contained in the subjoined table clearly show that meat juices made under known conditions vary according to the mode of preparation, but it is evident that practically one-half of the nitrogen is present as coagulable protein.

FOOD VALUES

In order to arrive at the food value of any commodity it is necessary to consider its chemical composition, available potential energy, absorbability, etc. On referring to the analytical table it will be found that the amount of inorganic material in meat juices Nos. 7 and 10 is unduly high. It appears that sodium chlorid, *per se*, has been added to both Bovinine and Wyeth's Beef Juice probably as a preservative in the latter and for condimental purposes in the former. The relative and absolute proportions of phosphatic material in both products is excessive. The other constituents present in the ash are those usually found in meat products.

The amount of sugar and glycerin in Carnine is interesting. These agents may be added for preserving purposes but the resulting product, on account of its syrupy appearance, leads to the belief and is so represented, that it is a concentrated food. Glycerin is also present in Bovinine and Valentine's meat juice. Bovinine in addition contains about 8 per cent. alcohol.

The total nitrogen content of the trade products excepting Carnine, is greater than the amount of nitrogen present in meat juices proper, but the relative amount of nitrogen present as coagulable protein—the valuable part of meat juice—is much greater in the latter. In fact, the amount of coagulable protein present in Valentine's Meat Juice may be considered *nil*, which indicates that an unduly high temperature is used in its preparation. In this connection it should also be noted that even a moderate elevation of temperature influences the chemical composition of meat juices. For example, the coagulable matter present in Nos. 3, 4 and 5, is approximately one-half that present in Nos. 1 and 2, which appears to indi-

cate that the best product can be made without the use of any heat whatever. Several of the trade products, namely Nos. 7, 8 and 9, contain about as much coagulable material as meat juice made by heating beef to 60 C. According to the formula appearing in a circular of the Bovinine Company, a part of the coagulable matter is present in the form of egg albumin, but the company claims egg albumin is not used at present. In the case of Carnine, the coagulable matter appears to be introduced by the use of blood itself. The exact nature of the coagulable protein matter in Wyeth's Bef Juice has not been ascertained. It is well-known to manufacturers and physiologic chemists that it is practically impossible to manufacture a genuine meat juice possessing a reasonable amount of coagulable proteins, which is stable, without a preservative.

Meat juices, in addition to the coagulable protein material, contain other protein bodies such as albumoses and peptones. These bodies are largely formed from the original protein bodies present in the meat juice during the process of manufacture. They are highly nutritious and largely and readily absorbed from the alimentary canal but the amount of these bodies present in the trade products is relatively small excepting in Bovinine, which is not a meat juice, particularly when the high prices are considered.

A considerable proportion of the nitrogenous matter contained in Valentine's and Wyeth's products is present in the form of amino bodies frequently included in the general term, "extractives." These bodies may be oxidized in the body and thus supply heat in a manner similar to alcohol, but it should be remembered that there still appears to be a wide difference of opinion among various observers on this point. Some appear to be of the opinion that the amino bodies are devoid of food value in that these bodies appear in the urine practically unchanged. It would, therefore, appear that the value of the amino bodies is largely of a stimulant character.

The food value of meat juices, therefore, resides largely, if not solely, in the coagulable and other protein material present. Comparing the calorific value or potential energy available in meat juices proper on this basis with that present in the commercial products, excluding Bovinine, it will be seen that on the average the genuine meat juices—that is, those made by pressure direct from the meat itself as wanted—are much superior to the commercial products, notwithstanding the marked concentration in some cases. The calories given in the accompanying table do not include sugar, alcohol or any other added material of this character.

COMPOSITION OF MEAT JUICES

Number.		Name of Preparation.	Volatile matter 100 C.	Inorganic matter.	Sodium chlorid.	Phosphoric pentoxid (P_2O_5).	Ether extract, Glycerol and undetermined matter.	Total nitrogen.	Coagulable proteins (N x 6.25).	Other proteins (N x 6.25).	Amino bodies (N x 3.12).	Calories per 500 gm. obtained from protein factor 4.8.	Calories per 500 gm. obtained from amino bodies factor 0.56.
			Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.			
1	Made in Laboratory.	Chuck beef, cold pressed..	86.85	1.86	.20	.31	1.32	1.74	6.13	2.94	.90	217.68	2.52
2		Round beef, cold pressed..	85.76	1.53	.12	.37	.75	2.08	8.56	2.37	1.03	262.32	2.88
3		Chuck beef pressed at 60 C.	91.90	1.29	.19	.29	.81	1.09	2.56	2.50	.84	121.44	2.35
4		Chuck beef pressed at 60 C.	89.56	1.27	.16	.37	2.98	1.09	3.00	2.63	.56	135.12	1.57
5		Round beef pressed at 60 C.	90.65	1.36	.16	.36	2.09	1.16	4.25	.31	1.34	109.44	3.75
6		Chuck beef heated 6 hours before pressing 60-100 C.	98.11	.39	.05	.12	.25	.24	....	1.00	.25	24.00	.70
7	Trade Products.	Beef Juice, John Wyeth & Bro., Philadelphia, Pa...	58.84	16.21	6.71	3.27	12.51	3.15[1]	2.88	3.56	6.00	154.56	16.8
8		Bovinine, The Bovinine Co. 75 W. Houston St., New York City	80.40[3]	1.55	1.05	.09	3.64[5]	2.36	3.38	10.75	.28	339.12	.78
9		Carnine Co., Lefranco, Paris, France; Imported by Fougera & Co., Agts., New York City.....	24.80[4]	.86	0.09	0.33	68.94[6]	.96	2.25	2.56	.59	115.44	1.65
10		Meat Juice, M. J. Valentine, Richmond, Va.....	57.64	10.26	1.77	3.41	20.41[7]	3.06[2]	.19	5.44	6.06	135.12	16.97

1. Including .20 per cent. as NH_3; 2, including .22 per cent. NH_3; 3, 8.17 per cent. alcohol found; 4, vacuum 70 C.; 5, 3.1 per cent. glycerol found; 6, 47.50 per cent. cane sugar—14.2 per cent. glycerol found; 7, 8 per cent. of glycerol found.

The several samples of beef juice were prepared from practically fat free, finely comminuted, chuck and round beef, first by pressure at the ordinary temperature; second, by heating the prepared meat for several hours at 60 C., then submitting to pressure. Sample No. 6 was made from chuck beef, prepared as above, by heating six hours at from 60 to 100 C., and expressing after cooling. It is not a beef juice proper but was prepared, analyzed and added to the list for information. Its composition resembles several commercial articles closely. A number of products represented and sold as meat juice in the United States were analyzed and the results recorded in the accompanying table.

WYETH'S BEEF JUICE

"Wyeth's Beef Juice" is not a true beef juice, but resembles rather a diluted meat extract. It contains much added inorganic matter, is low in coagulable proteins, and considering the degree of concentration, relatively deficient in nutritive value. Some of the claims contained in the circular accompanying this preparation, in view of its composition set forth above, may be of interest:

"Wyeth's Beef Juice . . . containing two fluid ounces and representing three pounds of prime lean beef, . . ."

" . . . beef extracts made by the Liebig process are utterly devoid of the valuable and nutritious albuminous constituents of meat. . . ."

[Wyeth's Beef Juice] "should not be compared with ordinary beef extract, . . ."

BOVININE

Bovinine, advertised as a "condensed beef juice prepared by a cold process" is a mixture of alcohol, glycerin, added sodium chlorid, and apparently some form of defibrinated blood. According to the manufacturer's literature egg albumin was used formerly but this ingredient is said to be no longer employed. It is not a meat juice in any sense of the word. Numerous misrepresentations will be found on the label and in the literature of Bovinine, of which the following are typical:

"The blood of selected steers prepared by a cold process, furnishing a perfect food, free from insoluble elements."

"The rapidity with which Bovinine is absorbed and assimilated in the stomach . . ."

"It supplies complete nutrition to the patient."

"Bovinine contains all the elements of the animal, vegetable and mineral kingdoms for the production of new blood with great rapidity. Its principal constituents have been selected with a view to furnish the largest amount of nutriment in the most condensed form and all the resources of modern chemical analysis have been brought to bear on this important problem."

A series of experiments carried out with dogs under anesthesia, by injecting Bovinine into the stomach, the pyloric end of which was ligated, shows that Bovinine is not readily absorbed and assimilated by the stomach as claimed. The amount of protein material found in the stomach at the end of one-half hour to one hour and a quarter was practically equal to the amount introduced by the Bovinine.

It is also represented that Bovinine is of great service in case of an irritable stomach. This is not borne out by experiment. Bovinine fed to dogs by the mouth, either alone or mixed with food, induced vomiting, which was less marked when Bovinine was given with the regular diet. An examination of the urine of these animals showed a marked diminution of the amount of indican, while the ethereal sulphates

were enormously increased, both absolutely and relatively, when Bovinine was given. Experiments on rabbits have shown that Bovinine injected into the peritoneal cavity was invariably followed by large quantities of albumin in the urine, which persisted for from 24 to 48 hours. Thirty to 50 c.c. per kilo given by mouth daily caused emaciation and weakness; in some cases, irritation of the gastrointestinal canal, with death of the animal in from 7 to 12 days.

CARNINE

Carnine is a French preparation imported into the United State by Fougera & Co., of New York City. In physical appearance it looks like highly concentrated food, but analysis shows that it consists of a small proportion of defibrinated blood dissolved in a mixture of syrup and glycerol, the whole agreeably flavored. It is represented as a "juice of rare meat, prepared by cold process. Each tablespoonful represents 100 gm. of raw meat, or 3½ ounces." It is clear that Carnine is not a meat juice in any sense of the word.

VALENTINE'S MEAT JUICE

Valentine's Meat Juice resembles in physical appearance, taste, odor and by chemical analysis a diluted meat extract. The nutritive value of meat extracts is virtually *nil*, as is well-known by the medical profession. Notwithstanding the composition of Valentine's Meat Juice and the fact that beef extract represents little nutritive value, the manufacturer makes the following misleading representations:

"The two-ounce oval bottle, adopted for the Meat Juice contains the concentrated juice of four pounds of the best beef, exclusive of fat; or the condensed essence of one and a half pints of pure liquid juice which is obtained from the flesh of beef."

"The use of *hot water* with the Meat Juice *changes its character and impairs its value.*" [Italics in original.—ED.]

The company must certainly be aware of the fact that its product contains little, if any, coagulable proteids.

CONCLUSIONS

In conclusion; neither Bovinine nor Carnine is a meat juice, the former is anything but palatable and the latter soon cloys. "Valentine's Meat Juice" and "Wyeth's Beef Juice" are virtually diluted meat extracts which are known to possess little food value. A physician depending on any of the foregoing products to supply material nourishment, in case of serious illness, is deceiving himself, starving his patients, and may be lessening their chances for recovery. If a patient recovers while using these commodities, it is certainly not due to the food value contained in them.

ECHINACEA CONSIDERED VALUELESS

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., Nov. 27, 1909.)

The Council has voted to reject several non-proprietary articles and has recommended that the reasons for their rejection be given in THE JOURNAL; among these is echinacea. The following paper has been submitted by a subcommittee with the recommendation that it be published. This recommendation was adopted.

W. A. PUCKNER, Secretary.

ECHINACEA

When this drug was first introduced, it was a typical nostrum, with exaggerations regarding its therapeutic value that were somewhat more gross than usual. It was later adopted by the eclectic school without being freed from the stigmata of its origin. It was also pressed into use as the main ingredient of such proprietary preparations as echafolta, ecthol, eusoma, etc. Efforts have been made to get the regular profession to use it in these various forms.

According to J. U. Lloyd (*Pharm. Review*, vol. xxii, p. 9-14), the introduction of echinacea into eclectic medicine is due to the efforts of Dr. H. F. C. Meyer to increase the sale of Meyer's Blood Purifier, a secret remedy containing it. The following is a literal copy of the label on this nostrum:

MEYER'S BLOOD PURIFIER

DIRECTIONS

Take one ounce three times every day in the following cases: *Rheumatism, Sick Headache, Erysipelas, Dyspepsia, Old Sores* and *Biles, Open Wounds, Dizziness, Scrofula* and *Sore Eyes.*

In case of *Poisoning by Herbs, & C.,* take the double dosis, and *Bites of Rattlesnakes* take three ounces three times a day, until the swelling is gone. This is an absolute cure within 24 hours.

After Lloyd had identified the plant, Meyer put the preparation out under another form with the following label:

ECHINACEA ANGUSTEFOLIA

This is a powerful drug as an Alterative and Antiseptic in all tumorous and Syphilitic indications; old chronic wounds, such as fever sores, old ulcers, Carbuncles, Piles, eczema, wet or dry, can be cured quick and active; also Erysipelas. It will not fail in Gangrene. In fever it is a specific; typhoid can be adverted in two to three days; also in Malaria, Malignant, Remittent and Mountain fever it is a specific. It relieves pain, swelling and inflammation, by local use, internal and external. It has not and will not fail to cure Diphtheria quick. It cures bites from the bee to the rattlesnake, it is a specific. Has been tested in more than fifty cases of mad dog bites in human and in every case it prevented hydrophobia. It

has cured hydrophobia. It is perfectly harmless, internal and external.

Dose.—One half to one fluid-drachm 3 or 4 times a day.

Manufactured by H. C. F. Meyer, M.D.

PRICE, $ PAWNEE CITY, NEB., U. S. A.

Patent

These absurd claims of an evidently ignorant man have passed into the more recent proprietary advertising matters and into much of the eclectic writings. Indeed, the seemingly impossible has been attained by even surpassing Meyer's all-but-all-embracing claims. Not content with endorsing echinacea as a positive and speedy "specific" for rattlesnake bite, syphilis, typhoid fever, malaria, diphtheria and hydrophobia, later enthusiasts have credited it with equally certain curative effects in tuberculosis, tetanus and exophthalmic goiter, and with the power of retarding the development of cancer.

It is worth noticing—although it is not surprising—that these far-reaching claims have been made on no better basis than that of clinical trials by unknown men who have not otherwise achieved any general reputation as acute, discriminating and reliable observers. No attempt seems to have been made to verify these claims by accurate scientific methods, clinical or otherwise, although this could very easily have been done.

Not one of the eulogistic reporters and exploiters seems to have considered it worth while to determine by the simplest control experiments whether the drug possesses any bactericidal or antiseptic powers whatever. It is therefore not very strange that discriminating physicians have failed to show much enthusiasm. One of the warmest endorsers of echinacea, C. S. Chamberlain (who later became the president of the Eusoma Pharmaceutical Company), complains that he has been unable to interest regular physicians in the remedy. He reviews the statements of previous authors and reports eight cases of infection, only two being acute or extensive, in which he used it with asserted success.

In view of the lack of any scientific scrutiny of the claims made for it, echinacea is deemed unworthy of further consideration until more reliable evidence is presented in its favor.

REFERENCES

Meyer, H. F. C.: *Eclectic Med. Jour.*, 1887; Goss: *Chicago Med. Times*, 1888; Hages: *Eclectic Med. Jour.*, 1888; Shelly: *Medical Gleaner*, 1894; Lloyd, C. G.: *Eclectic Med. Jour.*, 1897; Lloyd, J. U.: *Eclectic Med. Jour.*, 1897; Lloyd, J. U.: *Pharm. Review*, xxii, 9-14; Schultz, Elsie M.: *Wis. Med. Recorder*, 1898, ii, 202; White, J. N.: *Texas Med. News*, 1898-8, viii, 110-113; Stinson, J. C.: *Therap. Gazette*, 1900; Hale, E.: *Lancet-Clinic*, March, 1901; Thielen, B. F.: Echafolta, Its Uses in Dental Surgery, *Dental Reg.*, 1903, vii, 462-465; Gorse, C. A.: *New Albany Med. Herald*, 1903-4, xxii, 384; Chamberlain, C. S.: *Louisville Monthly Jour. Med. & Surg.*, 1904-5,

xi, 219-223; *Lancet-Clinic*, 1905, M. S., liv, 279-283; Ellingwood, F.; *Therap. Gazette*, 1905, 3, S., xxi, 298-300; French, J. M.: *Med. Brief*, 1905, xxxiii, 537; Mathews, A. B.: *Georgia Pract.*, 1905, i, 137-140.

FALSE UNICORN (HELONIAS)

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., Nov. 27, 1909)

The Council voted to refuse to recognize false unicorn as a non-proprietary article and the following statements, submitted by a subcommittee, were ordered published.

W. A. PUCKNER, Secretary.

FALSE UNICORN—HELONIAS

Helonias dioica, or more properly *Chamælirium luteum*, is a plant, preparations of which enter into various proprietary mixtures for diseases of the female pelvic organs. In the advertisements of these preparations it is usually credited with hemostatic powers and is asserted to be a uterine tonic.

There is practically no reference to this drug in reliable medical literature, and as there is no evidence worthy of credence to support the claims made for it, the drug was not considered deserving of a place in the Pharmacopeia. Hence, it may be regarded as a drug not worthy of attention of physicians.

INDEX