THE DRUG RESEARCH UNIT AND ITS VALUE TO THE PHARMACEUTICAL INDUSTRY.*

BY L. E. WARREN.[1]

"*Mr. President and Members of the American Pharmaceutical Manufacturers' Association.*—It is particularly gratifying to me to be with you to-day in order that I may explain to you something about the activities of the Drug Research Unit and the ways in which it is trying to be of help to manufacturing pharmacy. Let me say first, however, that Mr. Campbell, the Director of Regulatory Work in the Food, Drug and Insecticide Administration, wishes me to express to you his sincere regret that he could not be here to-day to address you as he had hoped. The pressure of work in connection with the closing of Congress and the problems arising out of the recently enacted Welch Law for salary increases necessitates his remaining in Washington. He sends you his best wishes for a successful and pleasurable meeting. Mr. Campbell has often expressed to his staff his gratification at the splendid work which is being accomplished by the Joint Contact Committees, one of which is supported by your Association. He particularly wanted me to emphasize his obligations to you for this service and to express his hope that the work may continue. As Director of Regulatory Work Mr. Campbell realizes that the pharmaceutical industry has many puzzling problems in connection with the interpretation of the law in respect to labeling. In this connection the enforcement officials have their uncertainties too. So far as the legal aspect is concerned the law merely intends that the manufacturer shall give his prospective customers products which are truthfully labeled—that is, a square deal is all that is expected. This being so, it would seem that the enforcement of the law would be a very simple matter. However, owing to the limitations of mechanics as applied to pharmaceutical manufacturing, to the instability of certain pharmaceutical preparations and to other factors, the proposition is far otherwise. In other words it is a difficult matter oftentimes to know exactly what the law means and to judge what deviations from the label may be permitted without injustice to the consumer. Since the manufacturers and enforcement officials each have problems to solve and interpretations to make, the more contacts which the two parties are able to establish, the better will they be able to appreciate the difficulties which the other has to meet. It seems to me that in no way can this be better accomplished than by the meetings of the Joint Contact Committees with the enforcement officials.

"Through the recent resignation of Dr. Hoover, the Food, Drug and Insecticide Administration has suffered a serious loss. Dr. Hoover had been in the Government service for more than twenty years and he had served continuously in the administration of the Food and Drugs Act ever since the law went into effect. From his long experience he probably had a broader grasp of the Law as it refers to drugs than any other official in the service. He interpreted the Law with rare judgment and administered it with tact.

"However, the Administration has been fortunate in securing an official to take Dr. Hoover's place who is a graduate both in pharmacy and in medicine. I

* An address before the American Pharmaceutical Manufacturers' Association at Lake Wawassee, 1928.

[1] Food, Drug and Insecticide Administration, Washington, D. C.

refer to Dr. Durrett, who entered the service less than a month ago and whom some of you have already met. Through his training in pharmacy, Dr. Durrett will undoubtedly have a more sympathetic understanding of the problems which the pharmaceutical industry is meeting than would be possible for one not so trained. In the appointment of Dr. Durrett I think the industry is fortunate.

"To return more particularly to the subject on which I am to address you. The Drug Research Unit is one of the constituent parts of the Food, Drug and Insecticide Administration. The Administration, as you know, is that part of the Department of Agriculture which is engaged in the enforcement of the Federal Food and Drugs Act and several other laws such as the Insecticide Act, the Caustic Poison Act, etc. For purposes of administration the regulatory staff is divided into a Washington force and a field force. The regulatory work in the field is carried out in three geographical areas called districts, each district having several station laboratories. The Washington force concerned with the Food and Drugs Act consists of two sub-divisions known as Food Control and Drug Control. Naturally, the Drug Research Unit is a part of Drug Control.

"Research has a proper and necessary place in regulatory work because the fundamental idea underlying enforcement activities—the ultimate protection of the consumer—is constructive in character. It is an essential part of such work to have accurate methods of analysis so that manufacturers may properly control their products and enforcement officials may check the claims of composition. The officials believe that in supporting research looking to improvement in analytical methods, the manufacturers will be better able to supply products which the public will accept with confidence as to their purity and reliability. It is obvious from its name that the Drug Research Unit is engaged in a search for new and improved methods for the analysis of drugs. The Unit is also undertaking to get together (so that the information may be available in one place) all of the methods for the analysis of drugs which it is believed will be of interest to pharmaceutical manufacturers, pharmaceutical chemists and enforcement officials. In explaining the necessity for work of this kind I can do no better than to quote from an address which I gave before the annual meeting of the American Drug Manufacturers' Association two years ago in New York.

> 'The desirability of having dependable methods available for the valuation of potent medicinal substances is obvious. The quality of the crude drugs supplied and the reliability of the output of pharmaceutical manufacturers are dependent, in a degree, upon the accuracy of the methods for the analysis of drugs which are available. Federal, state and municipal officials engaged in enforcement of drug laws, are often handicapped in not having reliable methods of analysis for many of the drugs and medicines in common use. Since the active constituent or constituents of some plant drugs are not even known with certainty at the present time, it is obvious that chemical analyses cannot yield unimpeachable valuation for their therapeutic efficacy.
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> 'Numerous analysts and many agencies, such as pharmacopœial revision committees, the laboratories of pharmaceutical manufacturers and schools of pharmacy, and Government Laboratories of various kinds, are conducting all over the world researches in the chemistry of drugs and the methods by which they may be assayed. In this way a very extensive literature in the subject has accumulated. However, the methods are widely scattered in numerous publications in several languages and some of them are misleading and unreliable. Search of the literature often reveals several

methods for the determination of the potent principle of a medicinal substance, yet the analyst may have no way of ascertaining which procedure is the most trustworthy without subjecting them all to trial. Sometimes no method applicable to the problem in hand can be found. Several books on the analysis of drugs and medicines have been published, but at present there is no up-to-date monograph or book in which the subject is given adequate treatment. That is, there is no comprehensive treatise in which the information in the literature has been brought together, critically examined and coördinated for use. In order to bring together the available information upon the subject, and to further conduct much needed investigations, a coördinating unit for systematic research in methods for the analysis of drugs was established.'

"After more than two years of operation it is meet that we inquire what has been accomplished by the Drug Research Unit, what it is doing now and what it proposes to do in the future. In this connection it might be of interest to you to know just how the Unit functions. At first the problems selected for study were taken up as a result of inquiries for analytical methods received from various agencies, such as the Joint Contact Committees, pharmaceutical manufacturers, Federal enforcement officials, etc. Later, a definite project was prepared which called for a study of drugs by classes, but owing to numerous, urgent calls for methods from many different classes, this project was placed in abeyance in part. Still later the drugs and pharmaceutical preparations were selected in the order of their relative uses in medicine and this is the plan now being followed.

"The number of drugs for which improved assays are desired is very large. Consequently in selecting those preparations for early study it seemed desirable to ascertain what preparations are most used. Accordingly a tentative list of approximately 275 drugs and pharmaceutical preparations was first prepared. The selection of these items was based on general knowledge of the uses of drugs in therapy and the prevalence of the various diseases for which the drugs are prescribed. It included some drugs described in the U. S. Pharmacopœia X, New and Nonofficial Remedies, the National Formulary and a few from other sources. It did not include biological products, general anæsthetics, solvents, vehicles or flavoring agents. This list was sent to a number of retail druggists situated in different parts of the country and each druggist was asked to indicate those drugs and preparations which he knew to be in considerable demand in his locality. Those preparations for which there was a very large demand were to be especially emphasized. Also if there were any drugs or preparations (not proprietary) for which the druggist had a large call and which were not included in the list sent him, he was asked to add these to the list and to indicate the frequency with which they were dispensed. From a study of the replies to this questionnaire, from an examination of Dr. Charters' report (Basic Material for a Pharmaceutical Curriculum) and from information received from the Joint Contact Committees, a second list consisting of about 135 drugs and pharmaceutical preparations was compiled. This list is believed to contain the medicinal substances which are being most used in the treatment of disease in this country; at least it includes drugs which are known to have a large use in therapy. It is from this restricted list that drugs are being selected for analytical study. I will include this list as a matter of record.

Sodium Bicarbonate
Acetylsalicylic Acid
Codeine Sulphate
Acetphenetidin

Tincture of Nux Vomica
Ammonium Chloride
Sodium Bromide
Salol
Sodium Salicylate
Bismuth Subnitrate
Mild Mercurous Chloride
Phenol
Caffeine Citrated
Potassium Citrate
Tincture of Camphorated Opium
Tincture of Belladonna
Strychnine Sulphate
Tincture of Iodine
Triple Bromides
Quinine Sulphate
Spirit of Ethyl Nitrite
Syrup of Ipecac
Petrolatum
Camphor
Cascara Sagrada
Zinc Oxide
Tincture of Aconite
Liquid Petrolatum
Phenolphthalein
Solution of Magnesium Citrate
Chloral Hydrate
Syrup of White Pine Compound
Ampuls of Sodium Cacodylate
Ointment of Zinc Oxide
Heroine
Ointment of Sulphur
Cod-Liver Oil
Hydrogen Peroxide
Sodium Cacodylate
Magnesium Sulphate
Syrup of Iron Iodide
Solution of Iron and Ammonium Acetate
Dover's Powder
Guaiacol Carbonate
Spirit of Chloroform
Sodium Iodide
Strontium Bromide
Cerium Oxalate
Acetanilid
Resorcin
Cocaine Hydrochloride
Milk of Bismuth
Chloroform Liniment
Amidopyrine
Nitroglycerin
Infusion of Digitalis
Compound Syrup of Squill
Sodium Borate
Ointment of Ammoniated Mercury
Barbital
Ammonium Bromide
Arsphenamine
Sodium Sulphate
Compound Mixture of Glycyrrhiza
Chalk Mixture
Compound Effervescing Powder (Seidlitz Powder)
Resin of Podophyllum
Opium
Syrup of Squill
Potassium Iodide
Tincture of Iron Chloride
Morphine Sulphate
Potassium Acetate
Metheneamine
Ammonium Acetate Solution
Compound Tincture of Gentian
Methyl Salicylate
Silver Protein, Mild
Tincture of Hyoscyamus
Salicylic Acid
Potassium Arsenite Solution
Tincture of Digitalis
Tincture of Opium
Extract of Belladonna
Zinc Sulphate
Castor Oil
Potassium Bromide
Antipyrine
Syrup of Hydriodic Acid
Bismuth Subcarbonate
Aromatic Fluidextract of Cascara
Aromatic Spirit of Ammonia
Extract of Nux Vomica
Milk of Magnesia
Lime Water
Elixir of Iron, Quinine and Strychnine
Wine of Colchicum Seed
Solution of Boric Acid
Codeine Phosphate
Bismuth Subgallate
Procaine Hydrochloride
Atropine Sulphate
Caffeine
Sodium Benzoate
Soap Liniment
Spirit of Camphor
Silver Protein, Strong
Mercurial Ointment, Stronger
Silver Nitrate
Phenobarbital
Lead Acetate
Camphorated Oil
Cinchophen
Tincture of Cantharides
Tincture of Strophanthus

Ointment of Boric Acid
Santonin
Calcium Lactate
Potassium Permanganate
Bismuth Subsalicylate
Syrup of the Bromides
Compound Jalap Powder
Trional
Effervescent Sodium Phosphate
Aromatic Tincture of Rhubarb
Ointment of Phenol
Monobromated Camphor
Mass of Mercury
Caffeine Sodium Benzoate
Compound Powder of Glycyrrhiza
Mercury with Chalk
Sodium Chloride
Chloramine
Barium Sulphate
Acriflavine
Solution of Phenol
Benzyl Succinate

"The relative frequency of prescribing is approximately indicated by the order of naming. It will be seen that the list contains some drugs for which reliable chemical assays are not known.

"In the quest of analytical methods for the drugs in this compilation the literature has been searched, pharmaceutical manufacturers and others interested have been consulted and, as a result, a great deal of information has been obtained. This information has been collated to some extent and certain methods of analysis are being selected which appear to be more promising than others. The manuscript for these methods is then sent to a committee of two analysts in the Government service for criticism and revision. In the light of the revisions received from these chemists, the manuscripts are edited, mimeographed and the revised copies sent in the form of bulletins to a committee composed of pharmaceutical chemists who have had much experience in the analysis of drugs. This committee is composed of twelve chemists, nine of whom are associated with pharmaceutical manufacturers and three from Government laboratories. Your association is represented on this committee by chemists from three of your active members and one associate member. In other words, one-third of the membership of the committee is furnished by your association. Each bulletin gives one or more methods for the assay of about 10 drugs or preparations. The members of the committee are asked to read the methods as sent out in the bulletins, note errors and make such suggestions and improvements as are indicated by their judgment, experience and knowledge. Also each member is requested, if practicable, to try such methods as apply in the control of his own products and to report his opinions of their general serviceability. Also each member is asked to furnish assay methods for the particular drugs under consideration if in his opinion he knows of methods which are likely to be of greater applicability. Already six bulletins have been sent to this larger committee and two more are in process, one of which is nearly ready to be mimeographed. The most searching criticisms are invited.

"Although these mimeographed bulletins are not for general distribution as yet, I have sent out a good many of the methods which they describe to chemists as a result of requests.

"It is expected that after the methods for about 100 drugs and preparations have been criticized and re-edited, a bulletin will be published giving these selected methods in their revised forms. Such bulletin will, of course, be intended for general distribution.

"I have stated these details to you at considerable length even at the risk of wearying you, because I want you to know that this work is being taken seriously

by the regulatory officials and that every activity in the Administration, so far as drugs are concerned, is contributing to carry it on successfully.

"It must not be supposed that the activities of the Unit are confined entirely to the collection of methods for the assay of drugs in this list. Whenever a method is found in the literature for any drug that is much used it is copied, placed in the files for reference, and tried out when possible. Here is an illustration: A few months ago a modified method for the assay of jalap appeared in an English journal. I have requested several collaborators to try this method in comparison with the U. S. P. X method and I have tried it myself. It is too early to make a positive statement concerning the value of the method but the indications are that it is more reliable than the U. S. P. method. It is expected that this type of work will be continued.

"There is another feature of this work of which I have not spoken and that is the collaborative investigations. New methods for the analysis of drugs or those of uncertain status are tried out by a corps of collaborators. A method is selected from the literature, edited if necessary, or a new method is devised in the Unit. This is then sent to about six collaborators for analytical trial either accompanied by material of known composition or by directions to try the method on preparations from stock. For the most part these collaborators are situated in the laboratories of pharmaceutical manufacturers or in schools of pharmacy. The Laboratories of the Department of Health of one state and the Board of Pharmacy of another have carried out collaborative studies. Such of the Station Laboratories of the Food, Drug and Insecticide Administration as have specialized in drug control work have also contributed. A list of the institutions doing collaborative work might be of interest.

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CHICAGO STATION, FOOD, DRUG AND INSECTICIDE ADMINISTRATION.
NEW ORLEANS STATION, FOOD, DRUG AND INSECTICIDE ADMINISTRATION.
SAN FRANCISCO STATION, FOOD, DRUG AND INSECTICIDE ADMINISTRATION.

"As a result of these coöperative studies and of analyses that I have found time to make personally, six papers involving analytical procedures have been published or are now in press. The titles are included herewith:

The determination of cinchophen in tablets
A comparison of several processes for the assay of podophyllum
The constants of chloroform liniment
A note on the assay of tablets of sulphonal
The determination of atropine in presence of morphine
A note on the assay of trional tablets

Reprints of some of these have been distributed by your association.

"Considerable work has been done on a number of other subjects including the following:

The detection and determination of cocaine in presence of procaine and trional
The assay of lozenges of sulphur and cream of tartar
Further observations on the determination of cinchophen in tablets
The assay of compound cathartic pills
The assay of jalap
The assay of emulsions
The assay of syrup of white pine compound for codeine, morphine and chloroform
The determination of bismuth in pharmaceuticals
The determination of strychnine in Blauds pills with strychnine

"Several months ago your Secretary was kind enough to briefly mention the work of the Drug Research Unit in one of your bulletins. Attention was called to the fact that the Unit would be willing to furnish whatever information on analytical methods which it might have to any member of your Association who cared to call for it, the understanding being that the requests should concern methods for specific drugs. In other words not all of the information in the files could be furnished to any individual because it was widely scattered and much of it not sufficiently codified for distribution. As a result of Dr. Vanderkleed's bulletin several of your members have availed themselves of this opportunity. In addition to these, many inquiries have been received from chemists all over the country asking for methods for the assay of particular drugs or drug preparations. Of

course the desired information could not be furnished in every instance, either because no method had been edited for our files or because no satisfactory method was known. However, the bibliographic files of the Unit contain several thousands of references to sources of information pertaining to analytical methods for drugs, so that in many cases the inquirer could be referred to the original sources for the information wanted.

"At present there is a large sale for medicines in ampules. There is a great deal of confusion in the manner in which these ampules are labeled. Undoubtedly a great deal of coöperative work between physicians, the industry and the regulatory forces will have to be done before these difficulties can be eliminated. Some time ago the Joint Contact Committees of the two associations considered the advisability of taking up the study of ampules in a collaborative way. The regulatory forces of the Department are also considering this class of products. In anticipation of this expected action I have prepared methods for the assay of six drugs which are sold in ampules. Methods for the assay of others are under investigation. This information is in the files subject to call from anyone interested. The ampules for which tentative methods of assay are available are as follows:

Sodium Iodide	Potassium Iodide
Caffeine and Sodium Benzoate	Iron Cacodylate
Sodium Cacodylate	Quinine Dihydrochloride

"Now, Mr. President, I have too long taxed the patience of this audience. I am indeed very grateful that your members have listened with such forbearance to this outline of what the Drug Research Unit is trying to do to aid the industry. In closing there are three principal thoughts that I would leave with you: First, that the officials of the Food, Drug and Insecticide Administration are very desirous that the work of the Joint Contact Committees shall continue. We believe that the contacts established are of mutual benefit to the industry and to the enforcement officials. I think that I may assure you that the resources of the Drug Control will continue to be at your service for coöperative studies. Second, that the Drug Research Unit is collecting information from a great many sources concerning the analysis of drugs. Such information as we have is yours for the asking. Third, that the Government is spending a great deal of time and energy in an earnest, whole-hearted attempt to ascertain what are the best methods for the analysis of drugs and to devise shorter methods for chemical control. It is trying to aid the industry by supplying these methods. This policy is the outcome of the belief of the Administration officials that the most effective way to insure compliance with the law is by striving by every means within their power to aid the industry in the production of medicines of controlled purity and accuracy.

"I thank you for your attention."

CORNIN: A GLUCOSIDE FROM *CORNUS FLORIDA* L.

BY EMERSON R. MILLER.

The dogwood family, *Cornaceæ*, comprises fifteen genera and about one hundred species which are shrubs and trees growing principally in temperate regions. Two of these genera, *Cornus* and *Nyssa*, are represented in the United