properties of the liquid petrolatum solution of cod liver oil concentrate were found to be identical with those of the olive oil solution, and no evidence of any difference in activity between them could be found. Liquid petrolatum (Squibb) therefore seems to behave differently from the mineral oil used by Dutcher and his collaborators, and its presence appears to be unobjectionable from a vitamin nutrition standpoint, and even suitable as a vehicle for vitamin administration.

While the difference between our results and those of Dutcher and his collaborators is so far unexplained, the difference in source of vitamin or character of the liquid petrolatum used may furnish the answer. Whether these or other factors, yet unknown, are involved must be determined by further research.

RESEARCH DEPT. OF THE CHEMICAL & PHARMACEUTICAL LABORATORIES,
E. R. SQUIBB & SONS, BROOKLYN, N. Y.

WHAT THE FOOD, DRUG AND INSECTICIDE ADMINISTRATION IS DOING FOR PHARMACY.*[1]

Mr. Chairman and Members of the Section on Education and Legislation of the AMERICAN PHARMACEUTICAL ASSOCIATION:

Your secretary invited a representative of the Food, Drug and Insecticide Administration to address this section. When the invitation was referred to me the question arose as to which of the two chief lines of the Administration's activities would be of the greater interest to the members of the section. The one has to do with regulatory phases in connection with the administration of laws; the other with educational projects which the Administration has under way. These latter are designed to assist the pharmaceutical profession in improving manufacturing processes and laboratory control to the end that the public may be assured of meritorious articles which conform in all respects with the claims of potency made for them. I concluded that the members of this section would probably be more concerned in the last-named phase of the Administration's work than in a discussion of its regulatory features. It is my intention, therefore, to restrict my remarks to those research phases which are of practical interest to the laboratory control end of the pharmaceutical industry. As a matter of fact, I would not feel qualified to discuss the regulatory policies of the Administration since my own activities touch upon the law enforcing work of the organization only in very minor respects.

Possibly it should be mentioned at the beginning, in order to avoid confusion, that all of the law-enforcing powers which were formerly vested in the Bureau of Chemistry are now entrusted to the Food, Drug and Insecticide Administration. The laws which are of the most direct interest to Pharmacy and which are enforced by the Food, Drug and Insecticide Administration are the food and drugs act, the insecticide act and the caustic poison law. The tea act, the naval stores act and the import milk act are not of much greater importance to pharmacists than to other citizens.

The chief educational and research activities of the Administration which

* Section on Education and Legislation, A. PH. A., Rapid City meeting, 1929.

[1] An address by L. E. Warren of the Food, Drug and Insecticide Administration.

are helpful to Pharmacy may perhaps be considered under five divisions. After naming these, each will be discussed in greater detail. These are:

1. The work of the Drug Research Unit.
2. Coöperation on methods of analysis with the Association of Official Agricultural Chemists.
3. Similar coöperation with the Combined Contact Committee of the American Drug Manufacturers' Association and the American Pharmaceutical Manufacturers' Association.
4. Aiding in the revision of the Pharmacopœia.
5. Furnishing information on request concerning drugs, insecticides and caustic poisons.

THE DRUG RESEARCH UNIT.

The Drug Research Unit, which is one of the constituent parts of the Food, Drug and Insecticide Administration, was established in 1925. It had been recognized for a long time by the enforcement officials and chemists in control of pharmaceutical manufacturing plants that there was a vast amount of uncodified information in the literature concerning the assay of drugs and pharmaceutical preparations which was not readily available to drug analysts. Some of the needs which brought about the formation of the Unit are set forth in the two following paragraphs:

It is obvious that it is desirable and necessary to have dependable methods of analysis for potent medicinal substances. Without them it is impossible to guarantee the quality of crude drugs or to be assured of the reliability of pharmaceutical products. It has often happened that officials in Federal, state or municipal laboratories were handicapped in the enforcement of the drug laws by a lack of reliable methods of analysis for some of the medicines in every-day use.

For over a hundred years analysts in various countries have been engaged in studying the chemistry of drugs and in devising methods by which they might be evaluated. The publication of their findings has resulted in an extensive literature on the subject. These writings are scattered through many journals in numerous languages. Some of the recorded analytical methods are unreliable and misleading. Hitherto there has been no systematic and comprehensive effort made to collect the available information on the analysis of drugs, examine it critically and codify it for use. Several books covering certain phases of the analysis of drugs and medicines have been published, but there is no up-to-date monograph on the subject in which the information in the literature has been collected, criticised and coördinated. The Drug Research Unit was established for this purpose.

The Drug Research Unit has been functioning for over three years and it is proper to survey what it has accomplished.

Since the number of drugs and pharmaceutical preparations for which improved assays were needed was very large, a list of drugs having extended use in therapy was prepared. The basis for this selection rested on information obtained from retail pharmacists in response to a questionnaire sent to representative dispensers in all parts of the country, on an examination of Dr. Charters' report,[2]

[2] W. W. Charters, A. B. Lemon and L. N. Monell, "Basic Material for a Pharmaceutical Curriculum" (1927).

and on opinions obtained from representative manufacturers. About 135 medicinal substances were chosen. Of these, some, like tincture of digitalis, tincture of strophanthus and tincture of cantharides, required bioassay procedures; others, like Dover's powder, syrup of white pine compound and compound tincture of gentian, are not amenable to any known satisfactory method of assay. The list did not include biological products, general anesthetics, solvents, vehicles or flavoring agents. Many requests have been received for this list.[1,2]

The drugs for which biological assays alone are known were placed in abeyance or brought to the attention of the Pharmacological Laboratory. The others were considered for study by the Drug Research Unit. The literature for each was searched and manufacturers were consulted so far as practicable to ascertain what methods they were using. If analytical methods were found, those which seemed worthy of trial were selected for each drug or preparation. Manuscripts of these were prepared and sent to two well-known drug analysts in the Administration for comment and criticism. In the light of the suggestions received the methods were revised and sent to a committee of 12 experienced analysts[3] with a request for critical revision and trial if convenient. The several members were asked to furnish other analytical methods for the drugs under consideration if in their opinions such methods were known. Analytical methods for over 100 drugs and pharmaceutical preparations are now in the hands of this committee. Comments on most of the topics have been received from the committee, and the preparation of a manuscript for a publication on the subject is under way. Although these methods as a whole are not yet ready for distribution I have sent many of them to various chemists on request.

Studies were undertaken to devise methods for some of the drugs in the list for which no satisfactory methods of assay were known. One of these is guaiacol carbonate. One of the chemists in the Administration has worked out a method for the determination of this substance which appears to be satisfactory. His report is in press. Another is resin of podophyllum, a satisfactory method for the assay of which was reported to the meeting of the American Chemical Society last April. Still another topic in this class is the Assay of Compound Jalap Powder. A method for this preparation has been devised and will be published in due course. Also investigators are urged to undertake research problems independently of the Unit or under its nominal direction only and several topics are being so studied. For such purposes the resources of the Unit are available in suggesting subjects and furnishing references and methods of analysis so far as practicable.

Of course the activities of the Drug Research Unit are not confined to the list of much-used drugs just discussed. If at any time a new or improved method for the assay of any drug is seen in the current literature, the fact is noted on an index card. If the drug be sufficiently important, the method is copied, filed for reference, and, if possible, tried in a collaborative way. In like manner the chemists for pharmaceutical manufacturers occasionally contribute methods which they have devised and which they have not considered sufficiently important to publish.

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[1] Proceedings, American Pharmaceutical Manufacturers' Association, 21 (1928) 285.

[2] JOUR. A. PH. A., 17 (1928) 737.

[3] Nine members of this committee are members of the AMERICAN PHARMACEUTICAL ASSOCIATION.

In these ways a great deal of information is being collected. The card index alone contains several thousand references to analytical methods new and old. The newer methods are tried out by collaborators. These collaborators are situated in the laboratories of pharmaceutical manufacturers, schools of pharmacy and the State and National Governments. Also the laboratories of the Department of Health of two states and the Board of Pharmacy of another have carried out collaborative studies.

Since the Drug Research Unit was established the following papers have been submitted for publication:

"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 Morphine in Presence of Atropine."
"A Note on the Assay of Trional Tablets."
"The Assay of Resin of Podophyllum."
"The Assay of Jalap."
"An Empiric Assay for the Resin Content of Compound Mercurous Chloride Pills."

COÖPERATION ON METHODS OF ANALYSIS WITH THE ASSOCIATION OF OFFICIAL AGRICULTURAL CHEMISTS.

For more than twenty years the Association of Official Agricultural Chemists has been conducting researches in methods for the analysis of drugs, as a part of its work. During all of this time the staff of the Bureau of Chemistry (and later the Food, Drug and Insecticide Administration) has been collaborating in these studies and many important contributions to the subject have been published. As an example of the scope of the researches on drugs by this Association it may be mentioned that the work last year was conducted by a referee and fifteen associate referees. They were aided by thirty-four individual collaborators, those assisting on more than one topic not being enumerated twice. Of the total of fifty referees and collaborators who worked on drugs, twenty-six are on the staff of the Food, Drug and Insecticide Administration. The report of the referee on drugs for 1928, which has just been published, occupies 53 pages of the Journal of the Association of Agricultural Chemists. Reports were submitted on such topics as:

Alcohol in Drugs, Chloroform and Carbon Tetrachloride, Microchemical Methods for Alkaloids, Santonin, Ether, Ephedra, Pilocarpine in Tablets, Thymol, Menthol, Chenopodium Oil, Sabadilla.

COLLABORATION WITH THE COMBINED PHARMACEUTICAL CONTACT COMMITTEES.

Another line of constructive, educational work upon which I wish to touch is that which concerns the studies undertaken by the Administration in coöperation with what is known as the Combined Pharmaceutical Contact Committee of the American Drug Manufacturers' Association and the American Pharmaceutical Manufacturers' Association.

As soon as the Food and Drugs Act was passed in 1906, the question arose as to what tolerances above and below the declared strength should be permitted in pharmaceuticals. The law intends merely that the manufacturer shall furnish

his customer with products that are truthfully labeled. In the case of drugs the law does not require a declaration of quantity or count on the labels, but if these be given, the statements must be true. Because of mechanical limitations and other uncontrollable factors in manufacture, it is impossible to produce pharmaceutical preparations each of which shall contain exactly 100 per cent of what is claimed for it.

The Bureau of Chemistry had collected a vast amount of analytical data concerning almost every type of marketed pharmaceutical product. From time to time this information had been tabulated and studied. The enforcement officials were thus enabled to obtain a fairly accurate concept of the degree of manufacturing accuracy which was being attained in commercial practice. However, it was considered desirable to obtain still more information on the subject from first-hand sources. In 1924 the enforcement officials communicated their desires to the two associations of pharmaceutical manufactuers, *viz.*, the American Drug Manufacturers' Association and the American Pharmaceutical Manufacturers' Association. The two Associations appointed a joint committee to work in coöperation with governmental agencies. This is called the Combined Pharmaceutical Contact Committee. This Committee has been very active in conducting research with a view of determining the limits of manufacturing accuracy. Hypodermic tablets, compressed tablets and ampules have been studied and the investigation is being extended to other pharmaceutical products. The enforcement officials have coöperated with this Committee by furnishing analytical data, suggesting methods of analysis when requested and conducting coöperative assays.

From time to time the Committee has submitted reports to the Administration indicating the degrees of accuracy within which, in the opinion of the Committee, properly manufactured medicinal products can be made under present-day methods. The reports also include methods of analysis. The Administration has made these reports public through mimeographed notices, and has assured the Committee that in applying the terms of the Federal Food and Drugs Act to the articles concerned careful consideration will be given to the tolerances recommended. The Administration takes pride in assisting in this meritorious program for the benefit of pharmacy.

AID IN PHARMACOPŒIAL REVISION.

Ever since the Food and Drugs Act was passed, the officials of the Bureau of Chemistry have taken much interest in the revision of the Pharmacopœia and usually some of its staff have held membership on the Committee of Revision. A great mass of information relating to the status of drugs has been collected through the years. Some of this was gained as a result of researches, necessitated by a lack of suitable standards for drugs, and a part was obtained through the examinations of thousands of samples of drug products. This information had to do with the botanical and geographical sources of drugs, their collection and curing, changes in shipment and storage, analytical and pharmacological tests, etc. By placing digests of this information at the disposal of the Committee of Revision it is believed that more equitable standards for drugs have been made possible.

At the request of the Chairman of the Committee of Revision of the Pharmacopœia the Administration is undertaking to prepare a critique of the methods for

the proximate assay of the most important drugs. The literature since 1924 is being carefully searched, and digests prepared of the available papers dealing with the subject. Particular attention is being paid to the reports dealing with comparative assays. The more promising methods are being tested by collaborators. From the data already collected it is believed that this report will be of considerable value to the Committee of Revision and incidentally to Pharmacy.

REPLIES TO INQUIRIES ABOUT DRUGS.

There is still another avenue through which the Administration benefits Pharmacy. The Department of Agriculture receives many inquiries concerning the sources, preparation, uses and marketing of drugs. These inquiries are of infinite variety and interest. They come from other departments of the Government, from members of Congress, from pharmaceutical manufacturers, wholesale druggists, retail pharmacists, citizens engaged in welfare work and others. Some of these are referred to the Bureau of Plant Industry (U. S. Department of Agriculture) and a few to the Department of Commerce for reply, but most of them are answered in the office of the Food, Drug and Insecticide Administration. To show their interest to pharmacists a few typical queries are submitted:

> Is there any known process for making heroin synthetically without the use of products from the poppy plant? If so, is the process commercially feasible?
>
> Can morphine be made from codeine? If so, is the process commercially feasible?
>
> How do you determine the therapeutic value of ichthyol? Upon what does the medicinal value of ichthyol depend?
>
> What is bulbocapnine? Is it used in medicine?
>
> Has the capsicum grown in Louisiana the same medicinal value as the African grown drug?
>
> What is the toxicity of paratoluenediamine? In other words, is it dangerous to use this in hair dyes?
>
> What is the value of plasmochin in the treatment of malaria?
>
> What species of plants are the sources of chaulmoogra oil?
>
> What is the value of the oil from *Oncoba echinata?*
>
> Are the synthetic local anesthetics habit forming?

ADVICE IN REVISING PHARMACEUTICAL CURRICULUMS.

In some instances teachers in schools of pharmacy, when revising their courses in pharmaceutical assaying, have sought the advice of Administrative officials. This probably came about because there are some teachers who have had very little experience in practical drug assaying (either in the control laboratories of manufacturers or in the laboratories connected with law enforcement agencies). It is well known that the assay methods in the Pharmacopœia and National Formulary represent no more than a tithe of the problems which the drug analyst meets. Most of these assays are determinations of a single substance and do not involve analytical separations to any considerable extent. Consequently, if an advanced course in drug assaying be confined to selections from the U. S. Pharmacopœia and the National Formulary preparations, the student will miss numerous puzzling types of assays which he will later encounter in practice. Consequently these teachers wished to revise their courses of study to include more problems of the kind which the drug analyst is likely to encounter. In such instances the

Administration officials have been able to suggest analytical problems representative of practical conditions. A few examples are cited:

The qualitative detection of methenamine and cinchophen in mixtures.
The assay of calomel and soda tablets.
The assay of calomel and bismuth tablets.
The assay of phenacetin and salol tablets.
The determination of barbital and related compounds in elixirs.
The assay of ampuls of sodium cacodylate.

SUMMARY.

The Food, Drug and Insecticide Administration, apart from its strictly regulatory functions, aids Pharmacy by maintaining a Unit for collecting, codifying and distributing information on the analysis of drugs; by coöperating with the Association of Official Agricultural Chemists, and with the Combined Pharmaceutical Contact Committee of the American Drug Manufacturers' Association and the American Pharmaceutical Manufacturers' Association in research on methods for the analysis of drugs; by aiding in the revision of the Pharmacopœia of the United States; and by furnishing information to inquirers about new, rare or little used drugs.

L. L. Walton assumed the term "Drug" was used by the author in the legal sense. He also asked the author for a list of the drugs for which assay processes are to be studied.

THE CHEMISTRY OF NATURE.*

BY CHARLES H. MAYO, M.D.

Rochester, Minnesota.

After interesting remarks relating to friends and members of the ASSOCIATION and the section of the country and city in which the meeting convened and a reference to his experience in pharmacy, Dr. Mayo said:

"I am intensely interested in the scientific side of medicine. Long ages ago, the doctor of the period knew such science as was known. As knowledge through investigation progressed, science became specialized along many lines. Linnæus took up botany two hundred years ago, and science gained from the study of his work. When Aristotle had claimed, hundreds of years before, that two bodies of equal size, but of different weight, would not fall with the same rapidity, it was thought true. Long afterward Galileo said they would fall with the same rapidity and he was threatened with being burned at the stake because it was against religious teaching. Under his breath he said, 'It is so, just the same'. I think that showed what kind of a man he was. Some men are pleased to become martyrs, but you need to have a tremendous lot of religion to be a martyr to-day.

"About 1686 study of single cells began. The existence of non-motile bacteria was not appreciated, but there were certain types of single cells that had motion. It was 1818 before any scientist attributed disease to bacteria and recognized that diseases could be reproduced by bacteria. There was no broadcasting of scientific

* Part of an address before the AMERICAN PHARMACEUTICAL ASSOCIATION, Rapid City, South Dakota, August 30, 1929.