Dr. I. M. Kolthoff said the Pharmacopœia of the Netherlands was being revised very much along the lines of the U. S. Pharmacopœia.

Chairman Ruth of the Section on Practical Pharmacy and Dispensing presided during the discussion of the report of the Committee on National Formulary by Chairman W. L. Scoville. See report and abstract of discussion in October JOUR. A. PH. A., pp. 972–974.

After the discussion of the report on the National Formulary, Chairman J. P. Snyder resumed the chair. He introduced Dr. J. C. Munch as the next speaker.

BIOASSAY STANDARDS.

BY J. C. MUNCH.*

The variation in strength of pharmaceutical preparations on the market is uniformly recognized as undesirable and, in many instances, as dangerous. Much effort has been directed toward reducing this variation. Most manufacturers are attempting to produce pharmaceutical preparations in compliance with definite specifications, both qualitatively and quantitatively. The various steps in manufacturing processes and the factors affecting subsequent deterioration have been closely studied. More uniformity has been obtained where accurate methods of assay are available, such as those used in testing strychnine preparations, than in connection with preparations for which no definite assay methods have been worked out.

Chemical methods of assay have been worked out, tested and adopted, for a number of drugs and their preparations. For a group of products, however, chemical assays are not at present feasible. The active principle (or principles) of such products may be unknown, or it may not be possible by present methods chemically to separate their physiologically active constituents. Included in this group are some of the most-used drugs, such as digitalis and pituitary extract. Their clinical importance has led to extensive investigation of means of assay, and in assaying certain of these drugs the reactions of animals have been utilized.

The necessity for providing adequate assay methods in order to reduce variability to commercially feasible limits has been under consideration by several pharmacopœial revision committees. The Committee of 1890 reported (Preface, U. S. P., 7th Revision, 1890, p. XXIX):

> "Among the subjects brought prominently to the attention of the Convention of 1890 was the establishment of a fixed proportion, or of fixed limits, of the active principles in preparations made from the more energetic drugs capable of being assayed. * * * the Convention finally decided to refer the introduction of assay processes and of so-called standardized preparations to the discretion of the Committee. The Sub-Committee, which was subsequently appointed to take charge of this work, * * * finally came to the unanimous conclusion that reliable methods of assay * * * are available at the present time, for only a few drugs. * * * after a careful study of the subject, it was resolved to apply processes of assay, in this revision, only to cinchona, Nux Vomica, and Opium. * * * There is a fair prospect, however, that a further, extensive study of the problem will render it possible to increase the number of assayed preparations materially at the next revision."

The following statement was made in the "Abstract of the Proceedings of the National Convention of 1900," U. S. P., 8th Revision, 1900, page XXXI:

> "4. *Assay Processes.* The Committee is instructed to append assay processes to as many of the potent drugs and preparations made therefrom as may be found possible, provided that the processes of assay are reasonably simple (both as to methods and apparatus required) and lead to fairly uniform results in different hands. As regards the products of such assays, tests of identity and purity should be added wherever feasible. Physiological tests for determining strength should not be introduced by the Committee."

In the "Abstract of the Proceedings of the Ninth Decennial Convention, 1910," U. S. P., 9th Revision, page XXXIII, the following recommendation occurs:

> "10. *Assay Processes.* * * * it is recommended that biological tests or assays, when accurate and reliable, may be admitted."

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* Bureau of Chemistry, U. S. Dept. of Agriculture.

Bioassay methods for aconite, cannabis, digitalis, epinephrine and pituitary preparations were included in U. S. P. IX. The 1920 Convention of the German Pharmacopœial Revision Committee considered the inclusion of bioassay standards in the 6th Revision of their Pharmacopœia and apparently decided to include the methods listed in U. S. P. IX.

The matter of bioassays was thoroughly discussed at the 1920 Convention of the 10th Revision Committee. The sub-committee on bioassays recommended that bioassay methods for aconite, cannabis, digitalis, epinephrine, ergot and pituitary preparations be required in U. S. P. X. The methods recommended have been tested and have been found to be practical and to yield reasonably consistent results in the hands of adequately trained workers.

The Bureau of Chemistry was asked by the sub-committee whether it would consider furnishing prototype standards for use in standardizing those drugs and preparations which require bioassay. After considering the matter from various aspects the bureau finally decided that it would be feasible to do so and that supplying these standards would lead to uniformity in application of bioassay methods. It was believed that such action would tend to reduce the variability and to improve the general character and quality of these drugs as marketed, and would materially aid in the enforcement of the food and drugs act. Accordingly, the bureau is prepared to test, pack and distribute such prototype standards as the revision committee decides on to manufacturers and others requesting them. A statement such as the following will be contained in the preface of U. S. P. X:

> "In order to facilitate the adoption of the standards for biological assays prescribed by the Pharmacopœia, the Bureau of Chemistry of the United States Department of Agriculture has indicated its willingness to supply, upon application, for the purposes of comparative tests, substances conforming to said pharmacopœial standards." (Circ. 333, p. 1827.)

The bioassay sub-committee of the revision committee selected the following standards:

(1) For digitalis, strophanthus and squill: Ouabain.
(2) For cannabis sativa: Fluidextract of Cannabis.
(3) For ergot: Fluidextract of Ergot.
(4) For epinephrine preparations: Epinephrine powder.
(5) For pituitary preparations: Pituitary powder.

Inquiries were sent to manufacturers and bioassayists as to the quantity of each standard they would need per year. Estimates of the total amounts required per year have been based upon the replies.

The question as to the cost to the bureau of procuring and preparing these standards and what charge ought to be made for such samples then arose. To facilitate the use of common standards for these products the bureau desired to distribute them (with the possible exception of ouabain) without charge. The chairman of the bioassay sub-committee, Dr. C. W. Edmunds, and the chairman of the revision committee, Dr. E. Fullerton Cook, have given careful consideration to this matter. Steps have been taken toward the establishment of coöperative relations in accordance with which certain manufacturers would furnish the bureau sufficient quantities of the necessary materials from which to prepare the prototype standards. In case full coöperation is arranged, it is hoped that reasonable quantities of such standards can be furnished without charge. In case of excessive requests for standards, it may be necessary to make some charge.

The bureau is ready at all times to coöperate in any movement which tends to improve the quality of drug products on the American market and to assist manufacturers in decreasing the variability of marketed preparations. The highest degree of coöperation has always been extended to the bureau by manufacturers. Every facility has been placed at its disposal in conducting investigations of this character. Willingness on the part of the manufacturers to furnish material for preparing sufficient standards for distribution exemplifies such helpful coöperation.

The standards set for these preparations in U. S. P. X have recently been published by the revision committee and are essentially the same as those contained in U. S. P. IX.

For aconite preparations the dose required to kill two out of three guinea-pigs within six hours after subcutaneous injection has been chosen. Certain figures have been adopted as M. L. D. standards.

For digitalis, strophanthus and squill preparations, figures are adopted for the minimum systolic dose of ouabain required to stop the heart of a frog in 1 hour, under specified conditions.

For this assay, a standard preparation of ouabain is needed. The Bureau of Chemistry has been able to obtain supplies of this drug from various sources and has collected an amount deemed sufficient for use as the official standard. Nevertheless, the utmost economy in its use is desirable. In the interest of conserving the supply, the bureau can only furnish it to meet definite needs. It is proposed to distribute it to manufacturers so that they may be assured that they are using the same unit of measure for testing their products. For experimental work and for demonstrations in pharmacy and medical schools, other substances of similar action, such as a standardized tincture of digitalis or of strophanthus, can be used instead of ouabain.

Cannabis is to be tested upon dogs, and ergot upon white leghorn cocks. The effects in each instance will be compared with the effects produced upon the same animals by prototype standards in the form of fluidextracts. Fluidextract of Cannabis should produce the same degree of incoördination in dogs after a dose of 0.03 cc./Kg. of standard as is produced by the same dose of the test sample. In case the effects produced by 0.03 cc./Kg. of prototype standard are not considered satisfactory for assay purposes, larger doses of the standard may be used to produce the desired end-reaction, which is then to be duplicated by the test sample. However, such doses must not exceed 0.10 cc./Kg.

Test samples of Fluidextract of Ergot should produce the same darkening of the comb that the standard produces.

Test samples of epinephrine are to be assayed biologically by determining the effect upon the blood pressure of dogs, as compared with the effect of a standard epinephrine preparation.

The standard for pituitary preparations has been carefully studied by the sub-committee. The standard adopted as a result of their investigations consists of the dried, fat-free, ground posterior lobe, to be prepared in accordance with certain specifications. The bureau is now engaged in preparing a batch of this material. It is proposed to supply the powder in 100 mg. lots in ampuls.

In recapitulation, in order to be of more specific assistance to manufacturers in their efforts to reduce the variation in bioassay drugs and in order better to assure the stability and potency of the Nation's drug supply as was contemplated by the provisions of the food and drugs acts, the Bureau of Chemistry will furnish upon request prototype samples of ouabain, F. E. cannabis, F. E. ergot, epinephrine and pituitary powder. Probably no charge will be made for these samples, with the possible exception of ouabain. In undertaking this distribution, the bureau is not unmindful of the difficulties involved. Many helpful suggestions have already been received, ranging from those regarding the source of ampuls to be used, to those relating to methods of conserving ouabain. The rate of deterioration of these standards and the frequency of their replacement are now being studied by the bureau. Any suggestions in connection with this project, such as the date at which standards will be desired, etc., will be greatly appreciated.

ABSTRACT OF DISCUSSION.

Paul S. Pittenger felt assured that the coöperation of the Bureau of Chemistry in this work marks an epoch in physiologic standardization. He dwelt upon the importance of having a central bureau for issuing the standards, so there may be uniformity in the preparations of different manufacturers. He gave several illustrations drawn from past experiences to emphasize this point, relating to the standardization of cannabis preparations.

L. W. Rowe said he had nothing to add except to say that the troubles of manufacturers have largely been due to various sources of standards which will now be uniform. He considered that ergot presented the greatest difficulties, because of the uncertain rate of deterioration—the standard suggested by Dr. Munch is probably the best possible.

D. M. Copley was pleased with the report; Frederic Fenger was satisfied with the pituitary standards.

Chairman Cook called attention to the international interest of the subject; a committee of the League of Nations decided to recommend the plan under discussion to all countries. The U. S. Pharmacopœia will make the first set of standards available and may become an international factor and thus, through the coöperation of the Bureau of Chemistry, the U. S. Pharmacopœia will render a world service.

H. A. B. Dunning asked relative to the sources of supply of ouabain. W. L. Scoville asked whether there would be discrimination between varieties of ergot and of cannabis; his understand-

ing was that fresh Spanish ergot is more active than Russian but the rate of deterioration is greater and, in his opinion, an investigation of this would be of value. E. L. Newcomb referred to domestic ergot and cannabis. E. A. Ruddiman had nothing to add; he desired to know when the standard would be obtainable. H. A. B. Dunning asked whether investigations are going on with a view of improving the preparations of the drugs under consideration.

Dr. Munch replying said that the questions presented were concerned with deterioration, the source and time of supplying standards. He stated that manufacturers were giving much attention to deterioration and that the subject would in that way be taken care of, at least to some extent. It is the purpose to provide composite fluidextracts (of ergot and of cannabis) each from ten different lots of the respective drugs. Combining these there will be precipitation, but one precipitate is better than ten. This composite fluidextract will be aged, decanted and sealed; as soon as a standard falls below a desired strength a new standard will, in like manner, be prepared—the assays are being made at regular intervals.

The speaker referred to the international significance of the work, as mentioned by Chairman Cook.

When he left Washington (two weeks prior to convention) eight lots of ouabain from Germany were being assayed; other lots had come from manufacturers. A supply of pituitary powder was on hand, which should last for four years. Ergot must be aged; this is not the case with cannabis, so this will be available earlier. It may be possible to grow strophanthus in the United States and steps are being taken to make that possible; if that is feasible the supply of ouabain will be assured. Dr. Munch concluded by saying that he had received full coöperation of manufacturers in every way and he wished to publicly and definitely go on record expressing thanks to the manufacturers for the coöperation they have extended to the Bureau.

Dr. Munch was given a vote of thanks and the session was adjourned.

SECTION ON PRACTICAL PHARMACY AND DISPENSING.

The first session of the Section on Practical Pharmacy and Dispensing was convened by Chairman Robert J. Ruth at 9:35 A.M., August 28. Owing to the absence of the Secretary, Ivor Griffith was asked to serve in that capacity, and F. W. Nitardy presided during the reading of the Chairman's address, which follows:

CHAIRMAN'S ADDRESS.

BY ROBERT J. RUTH.

It was with a feeling of deep appreciation that your Chairman assumed the responsibilities of the office which you entrusted to him and he has at all times endeavored to serve you to the greatest extent of his humble capabilities, mindful of your reposed confidence and of the resultant effects of either the failure or success of his administration.

It is appropriate at this point to express the appreciation and thankfulness that your Chairman feels for the staunch support of his associates and Delegate Irwin A. Becker and their spirit of close coöperation and helpfulness, all of which has made the work of your Chairman a pleasure to him and has assisted greatly in the smooth functioning of the affairs of the section and accounts in no small degree for the success of our program. Your Chairman feels that this occasion should not pass without special reference being made of our fellow member Edward Swallow, who, although a bed-ridden invalid, fights valiantly with his pen for pharmaceutical prestige and recognition, and his many letters expressing his optimism and high ideals have ever been an inspiration to your Chairman in carrying on his duties. Your Chairman would like to continue on with a long list of those who have so kindly and willingly helped him throughout the past year in the preparations for this meeting, but as time does not permit, he sincerely hopes they will know that he does not minimize the value of their service or fail to appreciate it, and this pertains also to the President and Secretary of the Association and to the Editor of the JOURNAL.

During the past year, Chairman Snyder and Secretary Pittenger of the Scientific Section met with President Arny in New York City and drafted proposed By-Laws for the Scientific Section. Your Chairman was called into conference when these proposed By-Laws were given final consideration before being presented before the Scientific Section for adoption at this meeting and it was then suggested by your Chairman that they be made the model By-Laws for all of the