COMMITTEE REPORTS

THE SECOND U. S. PHARMACOPŒIAL VITAMIN CONFERENCE.

BY E. FULLERTON COOK.

For many years the Committee of Revision has followed the policy of inviting into conference experts in special fields for their advice on standards and methods. Following this plan, an advisory committee on vitamin standards and assays was organized some time ago and a conference called last May.

The membership of this advisory committee includes about twenty-five of the leading workers in this field, within the United States, and also a number of foreign vitamin experts. The first meeting was held just prior to a similar conference, called by the Health Organization of the League of Nations in London on June 17, 1931. Doctors E. V. McCollum and H. Steenbock, who had been invited to attend the International Conference, were appointed to present the conclusions of our meeting at the London Conference. It was understood that, as soon as the conclusions reached at the London Conference were officially available, another meeting of the U. S. P. Advisory Committee would be called and an effort made to formulate standards and assay methods for immediate adoption in the U. S. P. X as an "interim revision." It was hoped, of course, that these standards could be in harmony with those recommended for international adoption.

The report of the London Conference was only recently made available and a second conference of the American members of our Advisory Committee was immediately called. The meeting was held on Friday, January 8, 1932, at the Hotel Pennsylvania and those present were: E. Fullerton Cook, Chairman of the U. S. P. XI Committee of Revision, presiding; John F. Anderson, of New Brunswick, N. J.; Charles E. Bills, of Evansville, Ind.; Archie Black, of New Brunswick, N. J.; R. A. Dutcher, of State College, Pa.; W. H. Eddy, of New York, N. Y.; A. D. Emmett, of Detroit, Mich.; George E. Ewe, of Cambridge, Mass.; M. S. Fine, of Battle Creek, Mich.; Mr. Goulden, of Newark, N. J.; Alfred Hess, of New York, N. Y.; Arthur D. Holmes, of Stoneham, Mass.; Charles W. Hooper, of New York, N. Y.; James H. Jones, of Philadelphia, Pa.; Robert L. Jones, of Detroit, Mich.; E. F. Kohman, of Washington, D. C.; Clifford S. Leonard, of Tuckahoe, N. Y.; Henry T. Mason, of Newark, N. J.; E. V. McCollum, of Baltimore, Md.; William J. Horn, of Bridgeport, Conn.; Lafayette B. Mendel, of New Haven, Conn.; A. Graeme Mitchell, of Cincinnati, Ohio; E. M. Nelson, of Washington, D. C.; Carl Nielsen, of North Chicago, Ill.; E. J. Quinn, of New York, N. Y.; H. W. Rhodehamel, of Indianapolis, Ind.; W. H. Sebrell, of Washington, D. C.; H. C. Sherman, of New York, N. Y.; Harry Steenbock, of Madison, Wisconsin; Julia B. Paton, of New York, N. Y.

The meeting was presided over by Chairman Cook, of the U. S. P. XI Committee of Revision, who had organized the Conference.

The London Conference had recommended the following:

The International Standard for Vitamin A.—"That carotene be accepted as an international provisional standard of reference for Vitamin A and that a selected sample of Cod Liver Oil be held in view as a possible secondary standard."

Definition of the Vitamin A Unit.—"The Unit of Vitamin A recommended for adoption is the Vitamin A activity of 1 γ (0.001 mg.) of the international standard."

The National Institute of Medical Research, in London, was requested to act as the central laboratory on behalf of the Health Organization of the League of Nations to undertake the final preparation of the sample of carotene to be used as the international standard for Vitamin A. Carotene is subject to deterioration unless carefully protected, and for that reason is not suitable for distribution. Therefore, it is proposed to determine the activity, expressed in international units, of a carefully selected Cod Liver Oil, and distribute that oil to laboratories as reference samples in standardizing Cod Liver Oil and related products for distribution and sale.

The International Standard for Vitamin D.—The International Conference also recommended, "that the standard solution of irradiated ergosterol at present issued by the National Institute of Medical Research, London, be adopted as international Vitamin D standard."

Definition of the Vitamin D Unit.—"The unit of Vitamin D recommended for adoption is defined as the Vitamin D activity of 1 mg. of the international standard solution of irradiated ergosterol."

The official report from London states that "the international standard at present recommended shall be regarded as provisional for the next two years, in the hope that a more stable crystalline substance may in the meanwhile become available."

The International Standard for Vitamin B_1.—The Conference recommended "the adoption, as international standard, of the adsorption product of the anti-neuritic Vitamin B prepared in the Medical Laboratory, Batavia (Java), by the method of Seídell, as described by Jansen and Donath."

Definition of the Vitamin B_1 Unit.—"The unit recommended for adoption is the anti-neuritic activity of 10 mg. of the international standard adsorption product."

"NOTE: A daily dose of 10 to 20 mg. of this preparation is required to maintain normal growth in a young rat on a diet deficient in the antineuritic Vitamin B but complete in all other respects, including the antidermatitis Vitamin (B_2); the curative 'day dose' for a pigeon (300 Gm. weight) suffering from polyneuritis on a diet of polished rice is about 20 to 30 mg."

The International Standard for Vitamin C.—The Conference recommends the adoption as international standard for the antiscorbutic Vitamin C, of the fresh juice of the lemon, *Citrus limonum*.

Definition of the Vitamin C Unit.—The unit of the antiscorbutic Vitamin C recommended for adoption is the Vitamin C activity of 0.1 cc. of fresh juice of the lemon, *Citrus limonum*.

The official report of the London Conference on Vitamins, as issued by the League of Nations, is available through the "Publication Department" with its United States agency at 40 Mt. Vernon Street, Boston 9, Massachusetts. The full report gives many additional details.

One of the first decisions at the London Conference was the agreement not to discuss or propose any detailed biological assay method for determining the exact Vitamin activity of the various products. It was believed that by the establishment of international standards and international unit values any approved biological method might be employed if in the hands of experienced operators and if the substance to be tested and the standard preparation were simultaneously assayed by the same method. This conclusion, reached by the London Conference, was not considered suitable for adoption by the Pharmacopœia. The U. S. P. standards are subject to enforcement under the Food and Drugs Act and it becomes necessary to establish an official method. The manufacturer will then know that his products will be evaluated by the same method by which they were standardized. This need was recognized by the New York Conference, and, after the consideration of the standards and units for Vitamins A and D, the detailed methods were studied.

Standards and Units for Vitamins A and D.—The New York Conference recommended the adoption by the U. S. P. Committee of Revision of the International standards and units for Vitamins A and D. It is expected that the Food and Drug Administration, Department of Agriculture, Washington, D. C., will distribute reference samples of Cod Liver Oil having a known value in relation to the international Vitamin A standard and also a standard irradiated ergosterol of known international Vitamin D unit value. It is yet to be determined whether this service can be rendered by the Food and Drug Administration, but their present efficient coöperation with the Pharmacopœia, in the distribution of standards for other official biological assays, points to this Governmental Bureau as the natural distributing organization for Vitamin standards.

Proposed U. S. P. X Methods of Biological Assay for Vitamins A and D.—The Conference considered the several methods of assay which had been proposed and, with slight modifications, recommend those offered by the Vitamin Committee of the American Drug Manufacturers' Association. These modified methods will soon be made available.

New U. S. P. X Cod Liver Oil Standards.—The standards and unit values and also the assay methods, approved by the New York Conference will promptly be submitted to the U. S. P. General Committee of Revision for their consideration. If accepted, these will be announced as the new standards for Cod Liver Oil, under the regulations of the U. S. P. X, and a reasonable time will be allowed to lapse before the new standards are enforced as the official requirements. These new standards will constitute an "interim revision" of the U. S. P.

Vitamins B_1 and C.—The New York Conference recognized that at the present time the Pharmacopœia is not required to adopt standards or assay methods for Vitamin B_1 and Vitamin C since no products containing these Vitamins are official. However, since so large a group were in conference, and as they represented many who are interested in Vitamin Standards within the United States, it was believed desirable that this Conference should also express its opinion concerning the international standards proposed for Vitamins B and C. The Conference thereupon voted its approval of the standards adopted by the International Vitamin Conference, at London, for these additional Vitamins.

FOOD AND DRUG UNIT APPROVES TOLERANCE AND ANALYSIS RULES.

Recommendations governing tolerances and analyses of certain drugs, and specifying that ampuls, or containers of drugs must carry a slight excess, but not a large one, over the amount stated on the label, have just been approved by the Federal Food and Drug Administration and copies distributed to the trade according to an oral statement January 12th by Dr. F. J. Cullen of the Drug Control Unit of the Administration.

"The recommendations," he said, "were formulated by the combined contact committee of the American Drug Manufacturers' Association and the American Pharmaceutical Manufacturers' Association in coöperation with the Drug Control Unit. They cover some of the more commonly used drugs, such as quinine, and some of the more powerful drugs always administered by a physician," he said. The following additional information was made available:

The recommendations cover methods of analysis or assay of quinine hydrochloride, commonly used to combat colds and malaria; sodium salicylate and iodide with colchicine, used in treatment of rheumatism and gout to relieve pain, procaine hydrochloride, used as a local anæsthetic for minor operations and by dentists; a glycerophosphates compound, used as a general tonic; strychnine, used as a heart stimulant in serious cases, as in operations or severe pneumonia cases; calcium chloride, used preceding operations to obtain increased blood coagulation, and sodium nitrite, used in cases of kidney disorder and high blood pressure.

The recommendations specify that ampuls are considered as containers of medicine and not as measures of the dose, but they recognize that physicians frequently use the containers as measures. They therefore specify limits by which an ampul may contain an excess or deficiency of the drug above or below the amount stated on the label. Since it is impossible to withdraw from the ampul with a syringe all the drug it contains for injection into a patient, the recommendations state that it is necessary that an ampul should contain certain percentages, varying with different drugs, above the stated contents.

COMMITTEE EXPLAINS DECISION.

The Committee's explanation of its report and the reasons for its decisions follow in full text:

The Committee's report on the volume of contents of ampuls is based upon extensive experimental data designed to determine the volumes of different types of liquids which any specified ampul should contain to permit the physician to withdraw and administer to his patient the indicated dose.

While the Committee regards the ampul as a container of medicine, not as a measure of the dose, it recognizes that among physicians there is not always this definite understanding. It is accordingly undesirable to place in an ampul an indefinite excess over the intended dose of a drug. Moreover, it has been customary to designate ampuls by the volume of the intended dose to be taken from them as "1 cc.," "5 cc.," etc. Such labeling on ampuls containing materially more than the indicated volume would conflict with the provisions of the Federal Food and Drugs Act.

On the other hand it is obviously impossible to withdraw from an ampul into a syringe and to administer to a patient the entire contents of an ampul. It is therefore necessary to provide a slight excess of the medication in the ampul.

The amount of this excess in the case of viscous liquids is greater than in the case of more limpid drugs. As typical of these classes the Committee used in its experiments camphor in oil, sodium, cacodylate solution, ovarian extract, and quinine and urea hydrochloride solution.

The Committee has recommended that ampuls be designated as "1-cc. size," "2-cc. size," "3-cc. size," etc., and, based upon a large amount of data which have been submitted to the Food and Drug Administration in detail, that in order to permit the administration of the dose as indicated by the "size" mentioned an excess of the medicament be filled into the ampul in accordance with the following table:

Ampul size, A; Excess recommended, limpid solutions, B; Viscous solutions, C:

A.	B.	C.
0.5 cc.	0.1 cc.	0.12 cc.
1 cc.	0.1 cc.	0.15 cc.
2 cc.	0.15 cc.	0.25 cc.
3 cc.	0.25 cc.	0.4 cc.
4. cc.	0.25 cc.	0.4 cc.
5 cc.	0.3 cc.	0.5 cc.
10 cc.	0.5 cc.	0.7 cc.
20 cc.	0.6 cc.	0.9 cc.
50 cc.	1.0 cc.	1.5 cc.
100 cc.	2.0 cc.	3.0 cc.

In the case of ampuls of sizes other than those specifically mentioned commensurate excess of solution in such ampuls is recommended.

It is the opinion of the Solicitor of the Department of Agriculture that such designations upon ampul lables as "1-cc. size," will not violate the spirit of the Federal Foods and Drugs Act if the volume of content of the ampul exceeds the indicated volume by only a sufficient amount to insure the practicability of obtaining and administering the stated volume by means of a syringe. The Fool and Drug Administration will be guided by the Solicitor's opinion.

In connection with the enforcement of the Food and Drugs Act the Administration will give careful consideration to the recommendations embodied in this report.

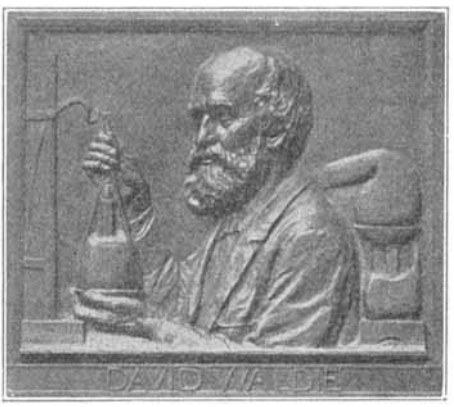
MEMORIAL TO DAVID WALDIE.

In a daily newspaper, *The Englishman*, of May 1898, there is an article by William Mair, our honorary member, in which the centenary of chloroform, in prospect, is referred to. There seems to be no other claim for the first surgical use of chloroform than that of Sir James Y. Simpson, professor of Obstetrics, University of Edinburgh.

In his original pamphlet on the subject of chloroform he includes a footnote—"Talking over with different chemists what fluid might be sufficiently volatile to be respirable and hence desirable of being experimented upon, Mr. Waldie first named to me the perchloride formyle (chloroform), as worthy of a trial."

A bronze plaque "Chloroform Pharmacy" is set over the doorway of the old shop at Linlithgow, near Edinburgh in which the suggestion was made. Waldie's father was a surgeon apothecary in whose shop David Waldie made the suggestion to Dr. Simpson. Mr. Waldie had had some experience in the production of chloroform and on his being asked for his opinion by Dr. Simpson, David Waldie especially recommended that Dr. Simpson try chloroform.

There are various phases of history in connection with discoveries and in this instance the



DAVID WALDIE BRONZE.

one who had recommended the use of chloroform rendered a part, however small, in a very great service.