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1 April 1948

2. EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

REPORT ON THE SECOND SESSION¹

Held 18-23 March 1948, Palais des Nations, Geneva

The second session of the Expert Committee on Biological Standardization was held in Geneva from 18-23 March 1948. The following members were present:

Professor E. Grasset, Directeur de l'Institut d'Hygiène, Geneva, Switzerland

Dr. A. A. Miles, Director, Department of Biological Standards, National Institute for Medical Research (Medical Research Council), London, United Kingdom

Dr. J. Ørskov, Director, State Serum Institute, Copenhagen, Denmark

Major-General Sir Sahib Singh Sokhey, Director, Haffkine Institute, Bombay, India

Dr. W. Aeg. Timmerman, Director, Rijks Instituut voor de Volksgezondheid, Utrecht, Netherlands (Chairman)

Professor J. Tréfouël, Directeur de l'Institut Pasteur, Paris, France

Dr. M. V. Veldee, Chief, Biologics Control Laboratory, National Institute of Health (US Public Health Service), Bethesda, Md., United States of America

In addition, two experts on cholera—Dr. P. Bruce White, National Institute for Medical Research (Medical Research Council), London, United Kingdom and Dr. A. Bonnefoi, Chef du Service des Vaccins, Institut Pasteur, Paris, France—and two experts on BCG—Dr. J. Holm, Chief, Tuberculosis Division, State Serum Institute, Copenhagen, Denmark, and Dr. J. Bretey, Institut Pasteur, Paris, France—attended part of the session. Dr. A. A. Miles was appointed Rapporteur.

1. Cholera Vaccine

This problem was raised by the Expert Committee on Quarantine, which, at its October 1947 session, in connexion with the recent cholera

¹ This report was referred by the Interim Commission to the Health Assembly with the following comments:

- (a) Further expert study should be undertaken before deciding whether the International Salmonella Centre at the State Serum Institute, Copenhagen, should be taken over by WHO and, if so, whether its activities should be extended.
- (b) The work on the standardization of cholera vaccine should be continued.

epidemic in Egypt, recommended that the question of standardization of cholera vaccine be referred to the Expert Committee on Biological Standardization.² After full discussion of the problem, the committee agreed to defer the setting-up of an international standard for cholera vaccine until it had further information regarding the relation of immunizing potency in laboratory animals to that in man. To this end, the committee hoped that all facilities would be provided by the health authorities of India to Major-General Sir S. Sokhey for carefully controlled tests in man of the protective action of those cholera vaccines which show a high immunizing potency in animals and which contain all necessary smooth antigens.

In the meantime, the committee recommended the establishment of two reference preparations of cholera vaccine of the Ogawa and Inaba strains respectively. Dr. Veldee undertook to prepare batches of freeze-dried vaccine of proved immunizing potency in mice for these two types. These preparations would be tested by interested laboratories for their suitability as reference preparations which, when established, would be held and distributed by the State Serum Institute, Copenhagen.

To facilitate the use of the two reference preparations in comparative tests of potency, Sir S. Sokhey agreed to prepare freeze-dried living cultures of virulent Ogawa and Inaba strains, which would be held by the Kasauli Institute for distribution on request to national control-centres.

In response to a request made by Sir Aly Shousha, Pasha, during the fifth session of the Interim Commission for a diagnostic anticholera agglutinating serum,³ the committee decided that laboratory workers throughout the world would be better served by the establishment of a reference preparation of cholera O antigen, suitable for the immunization of rabbits, to produce antisera capable of distinguishing the true cholera and the El Tor strains from all other cholera-like vibrios. Dr. Bruce White agreed to prepare this material. Nevertheless, to facilitate the identification of Ogawa and Inaba strains within the groups of cholera vibrios, the committee recommended the establishment of reference

² *Off. Rep. WHO*; 8, 27

³ *Ibid* 7, 30

preparations of Inaba and Ogawa monospecific agglutinating antisera, to be prepared in India and held for distribution by the State Serum Institute, Copenhagen.

2. Pertussis Vaccine

The committee reviewed the possibility of establishing an international standard for pertussis vaccine. In the absence of a test of recognized value for estimating immunizing potency, the committee decided that such a step would be premature.

For the same reason, the committee decided that it would be premature to establish standards for antipertussis sera, whether of human or animal origin, intended for the prophylaxis and therapy of pertussis.

3. Streptococcus Antitoxin (erythrogenic)

The possibility of establishing a standard streptococcus antitoxin had been considered in 1928 by the Permanent Commission on Biological Standardization of the League of Nations Health Organization and considered impracticable. Since then, it has proved possible to assay the potency of this antitoxin in laboratory animals with sufficient accuracy. In view of the continued therapeutic use of this antitoxin, the committee decided to reinvestigate the problem. A number of antitoxins of high neutralizing and flocculating potency would be examined in various laboratories for their suitability as a provisional international standard. The committee noted that, should an international standard be established, it would be desirable to equate the potency of the proposed standard with that of the US National Institute of Health.

4. Diphtheria Toxoid

The committee noted the progress made in implementing the recommendation made at its first session.⁴

5. Tetanus Toxin, Antitoxin and Toxoid

The committee reviewed the evidence that tetanus toxin and tetanus antitoxin were heterogeneous and that, as a consequence, the assay of potency of tetanus antitoxins in terms of the international standard might yield different results according to the preparation of toxin used. It recommended that a concerted attack should be made on this problem from the chemical, physical and physiological, as well as from the immunological, standpoints. To facilitate the provision for interested laboratory workers of samples of anomalous toxins and antitoxins, Dr. Trefouël agreed to undertake to receive and distribute such samples.

In view of the possible heterogeneity of tetanus toxin, the committee decided to rescind its former recommendation that an international standard for tetanus toxoid should be established. Never-

theless, it recommended that the highly purified sample of tetanus toxoid originally destined to serve as an international standard be investigated, with a view to its adoption as a reference preparation for characterizing the effective antigens in general use.

The committee considered the extensive use made of both the international and the US National Institute of Health units in designating the potency of tetanus antitoxin, and reviewed the circumstances in which the international unit had been defined in 1928. It recommended that, if informed opinion in interested countries were in favour of the step, the international unit for tetanus antitoxin should be redefined so as to equal the unit of the US National Institute of Health.

6. Blood-Groups

6.1 ABO System

The committee approved the steps so far taken in the preparation of international standards for anti-A and anti-B agglutinating sera by the Department of Biological Standards of the National Institute for Medical Research, London. Large batches of pooled natural and stimulated antisera for each group had been collected in the United Kingdom and the United States, and these will now be pooled. The pooled preparations, if proved suitable by the concerted tests, are intended for adoption as standards for A and B blood-groups.

6.2 Rh System

The committee took note of the report on the nomenclature of the anti-Rh typing serum made by the Advisory Review Board to the Surgeon-General of the US Public Health Service.

The committee recommended that, in the near future, bodies in other countries should similarly review the problems arising out of the clinical application of knowledge of the Rh blood-groups, with a view to obtaining representative opinions within these countries. It recommended that the Secretariat should then convene a meeting of a sub-committee to advise the Expert Committee on Biological Standardization on the following matters:

- (a) selection of sub-groups for which international standards are required;
- (b) technical problems in connexion with the preparation and designation of the standard antisera for sub-groups thus selected.

7. Digitalis

The committee approved of the action taken by the Department of Biological Standards of the National Institute for Medical Research, London, for establishing the third international standard for digitalis.

Three American, two British, and one Swiss sample preparation of digitalis powder had been

⁴ *Off. Rec. WHO*, 3, 6

assayed and found suitable for mixture into a standard preparation, samples of which will be distributed to 17 laboratories for collaborative assay against the second (1936) international standard for digitalis.

8. Fat-soluble Vitamins

The committee recommended that steps should be taken to appoint and convene as soon as feasible the sub-committee to advise the Expert Committee on Biological Standardization on the establishment of new standards for vitamin A and vitamin D.

9. National Control-Centres

The committee received a report of the Secretariat—made in accordance with the desire expressed at the first session—on national control-centres still in operation. It re-emphasized the need for organizing the distribution of international standards in each country through a single agency.

10. Liver Extract

The committee took note of the fact that a unit of activity for liver-extract preparations had been accepted by the US Pharmacopœia, based upon admittedly variable interpretation of their clinical effect on patients with pernicious anæmia and not in terms of a standard preparation. This practice did not accord with the internationally recognized principles governing the establishment of standards and the measurement of potency in terms of units of activity based on a given weight of these standards. The committee therefore recommended that :

- i. the Expert Committee for the Unification of Pharmacopœias be asked to consider the matter at its next meeting in connexion with monographs on liver preparations ;
- ii. the Committee of Revision of the Pharmacopœia of the United States be informed, through its Chairman, of this proposed action, in the hope that the requirements of the US Pharmacopœia authorities in respect of liver-extract preparation might be modified so as to exclude reference to a unitage based on a biological assay, for the precision of which there was no standard preparation yet available.

The committee also desired to draw the attention of the Expert Committee on the Unification of Pharmacopœias to the need in all countries for assuring the clinical efficacy of liver-extract preparations by tests on pernicious-anæmia patients, and to the possible dangers of adulteration of the extracts by the addition of folic acid in quantities sufficient to stimulate a reticulocyte response comparable with that induced by the anti-anæmic principle of liver extract itself.

11. Dextro-tubocurarine

The committee noted that the Department of Biological Standards of the National Institute for Medical Research had established a provisional British standard for *d*-tubocurarine and had defined a provisional British unit of activity.

12. Oxophenarsine

The committee noted that the Department of National Health and Welfare of Canada and the Department of Biological Standards of the National Institute for Medical Research, London, intended jointly to adopt a Canadian-British standard for oxophenarsine hydrochloride. It did not consider that international action on the matter would be justified at this stage, but accepted the offer made by the two countries to place their standard at the disposal of the committee as a reference preparation for oxophenarsine.

13. Dimercaptopropanol (British Anti-Lewisite, BAL)

The committee considered that there was at present no need for an international standard or reference preparation for this substance.

14. Salmonella Centre

The committee re-emphasized its recommendation that the International Salmonella Centre at the State Serum Institute, Copenhagen, should be taken over by WHO, and wished to point out that the activities of such a centre could at small cost be extended, if it were so desired, to cover other species of enteric bacteria.

15. Purified Protein Derivative (PPD)

At its first session, the committee had recommended that the preparation of PPD originally obtained by Dr. Mačsen should be tested for its suitability as an international standard.⁵ The tests so far made showed that the material had excessive sensitizing properties. After a full discussion of the characteristics required of an international standard preparation of PPD, the committee decided to rescind its recommendation that an international standard should be established. It nevertheless recommended that a typical preparation of PPD, as free as possible from sensitizing properties, should be distributed by the State Serum Institute, Copenhagen, for comparative tests, with a view to its establishment as a reference preparation of PPD.

16. Tuberculin

The committee recommended that an international unit be established for the international standard for Old Tuberculin, and proposed that

⁵ *Off. Rec. WHO*, 3, 6

this unit be defined as the activity contained in ten micrograms of the international standard preparation.

17. BCG

The problems arising out of the preparation and assay of BCG vaccine were fully discussed. The committee decided that it could not at present usefully add to or modify the recommendations made at the last session with respect to the standardization of BCG vaccine. It took note of the fact that the Institut Pasteur, Paris, hoped in the near future to be able to distribute on

request a freeze-dried viable preparation of the original BCG strain.

18. Liaison with the Expert Committee on Tuberculosis

The committee welcomed the recommendation made by the Expert Committee on Tuberculosis at its second session for a joint meeting of representatives of the two committees to discuss common problems in the standardization of BCG and PPD.⁶

⁶ See p. 6