

I. EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

REPORT ON THE FIRST SESSION

Held 9-13 June 1947. Palais des Nations, Geneva

(presented to the Interim Commission at its fourth session).¹

The Interim Commission of the World Health Organization inherited the functions of the League of Nations Health Organization with regard to biological standardization.

Desirous of giving this work an adequate international technical direction, the Interim Commission adopted the following resolution during its second session (November 1946):

"The Interim Commission requests its Chairman and its Executive Secretary to appoint a small body of experts, whose number is not to exceed eight, to form the nucleus of the future Committee on Biological Standardization.

"These experts will define the subjects which appear to be the most urgent for study, and will draw up a plan of work covering the setting up of international standards and units in the fields selected, to be submitted to the Interim Commission for approval".

Acting upon this resolution, the Chairman and Executive Secretary appointed the following seven members, a seat being reserved for an expert from the Union of Soviet Socialist Republics:

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

Professeur Jacques Tréfouël, Directeur de l'Institut Pasteur, Paris, France;

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

Dr. W. Aeg. Timmerman, Director, Rijks Instituut voor de Volksgezondheid, Utrecht, Netherlands;

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

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

Dr. M. V. Veldee, Chief, Biologics Control Laboratory, United States Public Health Service, Washington, D.C., United States of America.

In December 1946, a note by the Secretariat reviewing the position regarding existing international standards and suggesting new substances for standardization was circulated to these experts.² On the basis of their comments, a provisional agenda was drafted, which was submitted to the Interim Commission at its third session (April 1947).³ At the opening meeting of its first session, held in Geneva 9-13 June 1947, the Expert Committee on Biological Standardization adopted this agenda, somewhat modified, and elected Dr. W. Aeg. Timmerman (Netherlands) to the Chair.

The report which follows is based on the decisions which were, without exception, unanimously taken by the Committee.

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1. National Control Centres.

The Committee approved the principle of the recommendation of the Inter-Governmental Conference on Biological Standardization of 1935⁴,

"That each country should have a national centre or centres, recognized by the competent authority, to take charge of the international standards and equivalent national standards;

"And that every such centre should have a qualified staff to control the application of the international standards in its own country, and thus to serve as the recognized national scientific authority in this field."

The Committee, however, considered that for simplicity and efficiency it was desirable to limit the number of control centres in each country to one, which would be solely responsible to the Committee for the custody and distribution of all international standards within its country's boundaries; the Committee also considered that such control centres should be established whether or not a particular country was able at the same time to maintain laboratories equipped to fulfil all the requirements laid down in the above resolution.

The Committee recommended that the Secretariat should

- (a) ascertain whether national control-centres designated before the war are still active,
- (b) approach the health authorities of interested countries in which there are no national control-centres with a view to establishing such centres, and
- (c) draw the attention of national control-centres to the need for all reasonable economy in the use of international standards and for establishing national standards in terms of international units.

2. Emergency Replacement of Standards.

The Committee approved the emergency action taken by the Department of Biological Standards of the National Institute for Medical Research, Hampstead, in replacing the following international standard preparations:

⁴ See "Report of the Inter-Governmental Conference on Biological Standardization, held at Geneva, 1-4 August 1935", *Quart. Bull. Hlth. Organ.* 1935, 4, 638-642 (Vol. 4, Extr. No. 11) (C.H.1178 (1)).

¹ *Off. Rec. WHO*, No. 6, pages 12, 53, 190, 214.

² WHO.IC/BS/1, an unpublished working document.

³ WHO.IC/BS/2, an unpublished working document.

1. The oestrus-producing hormone,
2. Androsterone,
3. Progesterone,
4. Pituitary (posterior lobe),
5. Neoursphenamine,

and in altering the method of dispensing the solution of β -carotene as the standard for vitamin A.

It also approved the measures taken by the Department of Biological Standards of the State Serum Institute, Copenhagen, in replacing the following standard preparations :

1. *Clostridium perfringens* antitoxin,
2. *Clostridium septicum* antitoxin,
3. Diphtheria antitoxin for the flocculation test.

3. Adoption of International Standards.

The Committee approved the action of the Department of Biological Standards, Hampstead, in setting up the following provisional international standard preparations and defining the units thereof :

1. Vitamin E (1941),
2. Heparin (1942),
3. Penicillin (1944).

These three provisional standards were adopted as definitive international standards.

The Committee took note of the existence of a dry reference preparation of staphylococcus β -antitoxin, set up at the Copenhagen Institute, but decided to postpone the question of adopting it as an international standard.

The Committee wished to express its warmest thanks to the Directors of the Department of Biological Standards in Hampstead and Copenhagen for the initiative thus taken during the war emergency.

4. Replacement of Digitalis Standard.

An emergency measure, the Committee authorized the Department of Biological Standards, Hampstead, to proceed immediately with the preparation of the third international standard for digitalis to replace the second international standard, the stocks of which are almost exhausted. It also recommended that the new standard should consist of a mixture of a number of preparations of the powdered leaves of *Digitalis purpurea*, each preparation selected to conform as nearly as possible to the existing standard preparation, and that the final mixture of these preparations be subjected to comparative assays in a number of laboratories in various countries. The results of these assays should be submitted to the Committee with a view to the adoption of the final mixture of powdered leaves as the third international standard. In the meantime, the Department of Biological Standards, Hampstead, was authorized to issue the first international standard in place of the second international standard, when the stocks of the second were exhausted.

5. Replacement of Sulpharsphenamine Standard.

The Committee authorized the Department of Biological Standards, Hampstead, to proceed with the selection of a suitable batch of sulpharsphenamine

to serve as the second international standard for that substance, and to arrange for its assay in comparison with the first international standard in laboratories of various countries. The results of these comparative assays would be submitted to the Committee, with a view to the adoption of this preparation as the second international standard for sulpharsphenamine.

6. Standardization of Antigenic Substances.

(1) Toxoids.

The Committee recommended that international preparations of diphtheria and tetanus toxoids should be set up for reference in the biological assay of these antigens, and that the generous offer of Dr. Veldee to provide specimens of the highly purified toxoids recently prepared in the United States should be gratefully accepted. After a preliminary examination by the Department of Biological Standards, Copenhagen, these toxoids should be distributed to laboratories in interested countries for examination with a view to their suitability as international reference preparations. At the same time, opinions should be invited from interested workers on the desirability and possibility of adopting these preparations as international standards for diphtheria toxoid and tetanus toxoid respectively and of defining their activity in terms of units.

(2) BCG.

The Committee agreed that it was at present impracticable to set up a standard for BCG vaccine. However, in order to meet the urgent need for uniformity of the BCG vaccines in current use, the Committee recommended that :

- (a) the original strain of BCG kept at the Pasteur Institute, Paris, should be made internationally available,
- (b) the State Serum Institute, Copenhagen, which already distributes on behalf of the Committee a number of the international preparations, should also distribute the BCG strain,
- (c) the preparation and use of the vaccine in each country should be centrally co-ordinated.

(3) Old Tuberculin and P.P.D.

The Committee recognized that, in addition to the existing international standard for Old Tuberculin, there was a definite need for an independent international standard for the Purified Protein Derivative (P.P.D.) derived from *Mycobacterium tuberculosis*. A preparation of P.P.D. originally obtained by Dr. Madsen and stored for the duration of the war at the National Institute of Health, Bethesda, is available and has already undergone preliminary comparative tests. The Committee recommended :

- (a) that funds should be made available for the transport of this preparation from Washington to the State Serum Institute, Copenhagen, and
- (b) that the State Serum Institute should organize a comparative trial of this preparation by various workers, with a view to its adoption as an international standard.

The Committee recommended that, when sufficient experimental data on the P.P.D. preparation were secured, interested workers should be invited to express their opinion upon the desirability and possibility of defining the biological activity both of P.P.D. and of Old Tuberculin in terms of international units.

(4) Other Antigenic Preparations.

After detailed discussion, the Committee considered that it was at present impracticable to set up standards for:

- (a) *Haemophilus pertussis* vaccine,
- (b) *Vibrio cholerae* vaccine,
- (c) *Pasteurella pestis* vaccine,
- (d) Smallpox vaccine,
- (e) Yellow-fever vaccine.

The Committee was of the opinion, however, that progress in these fields would be greatly facilitated by exchange of the relevant strains of bacteria and viruses, and comparison of their antigenic potency and its methods of assay.

As regards yellow-fever vaccine, the Committee felt strongly that this vaccine, among others, should be standardized as soon as it is practicable to do so. In the meantime, close consultative liaison should be established between the Expert Yellow-Fever Panel (to be set up by the Expert Committee on Quarantine) and the Expert Committee on Biological Standardization, particularly with regard to the minimum requirements of yellow-fever vaccine intended for use in conformity with the international sanitary regulations.

7. Human Blood Antigens.

(1) The A B O System.

The Committee recommended that international standards for Anti-A serum and Anti-B serum should be established. To this end, a pooled sample of high potency human Anti-A serum and one of Anti-B serum should be submitted to comparative tests by various workers and their potency expressed in appropriate units.

(2) The Rh System.

The Committee recognized two urgent problems concerning the Rh antigens, namely:

- (a) The provision of an agreed international nomenclature;
- (b) The establishment of standard antisera for those Rh antigens which are important in medical and obstetrical practice.

The Committee decided to create an Expert Sub-Committee on Rh Antigens to study these two subjects and report on them. This Sub-Committee is to consist of geneticists and hæmatologists, to be proposed after consultation with interested workers in the various countries.

8. Antibiotics.

(a) The Penicillins.

The Committee considered that recent progress in the identification and definition of the different penicillins does not at present justify any change

in the International Standard for Penicillin (1944) or any redefinition of the unit of activity.

It was, however, considered desirable to set up as a reference preparation a substantially pure specimen of penicillin K (IV).

(b) Streptomycin.

The Committee considered that it was at present impracticable to establish an international standard for streptomycin.

Nevertheless, to promote uniformity in the assay of streptomycin potency, it is necessary to establish an international reference preparation. The activity of this preparation should be expressed both as milligram-equivalents of pure streptomycin base, according to current practice in the United States of America, and in provisional international units, which should have substantially the same value as the S-unit originally proposed by Dr. S. Waksman.

9. Vitamins.

The Committee considered that the following problems in the domain of vitamins were the most urgent:

(a) The replacement of the present international standard for vitamin A, which is a preparation of β -carotene, by a standard consisting of a vitamin A ester.

The existing international preparation of β -carotene should then be established as an international standard for β -carotene, for agricultural purposes.

(b) The replacement of the existing international standards for vitamin D, which were respectively preparations of calciferol (vitamin D₂) and irradiated ergosterol, by an international standard consisting of vitamin D₃.

The Committee decided to create an Expert Sub-Committee on the Fat-soluble Vitamins to study these two subjects and report on them, the members of the Sub-Committee to include experts already at work on these problems.

The Committee also discussed the vitamins not yet standardized and considered that they were either sufficiently well characterized by physical and chemical means or at this stage so ill-defined in their biological action as to preclude any attempt at standardization.

10. International Salmonella Centre.

The Committee discussed the proposal of Dr. J. Ørskov that the International Salmonella Centre established in 1938 at the State Serum Institute, Copenhagen, should be taken over by the World Health Organization and its scope extended, under the name of International Enteric Centre, to include the dysentery, coliform and *Proteus* groups of bacilli.

The Committee recommended that the International Salmonella Centre should be taken over as such by the WHO but that consideration of the proposed extension of its activity to include the dysentery and other intestinal bacilli should be deferred until the Committee had consulted other experts in these fields.