

Biological Standardization

In 1921, the Health Organization of the League of Nations decided to study the possibilities of establishing international standards for certain substances which could be assayed only by biological methods. A permanent commission was appointed in 1924 to adopt international standard preparations and to define units of activity. In 1935, an inter-governmental conference was attended by members from 24 countries, and the obligatory use by all countries of international standard preparations and units was recommended. A year later, no less than 36 countries had officially adopted these standards. The conference also considered it essential that each country should possess an officially recognized centre with a trained staff in charge of the storage and distribution of the international standards. The burden on the two central laboratories, the State Serum Institute, Copenhagen, and the National Institute for Medical Research, London, was, in this way, to be relieved, since they would need only to maintain stocks of standard preparations at a single agency in each country. By 1939, 57 such centres had been created in 38 countries.

Biological standardization proved useful in three respects: it placed in the hands of clinicians weapons of well-defined calibre and range; it supplied health authorities with measures of the value of biological products placed on the

market; and it enabled manufacturers to express the potency of products marketed in different countries in the same units.

At the outbreak of war, 31 substances assayed by biological methods had been thus standardized. They comprised the principal sera, tuberculin, four of the vitamins, pituitary and steroid hormones, insulin, digitalis, ouabaine and the arsphenamines. During the war, three new substances — heparin, vitamin E and penicillin — were added to the list.

The International Health Conference having resolved to continue the technical work of the Health Organization of the League, the Interim Commission decided to establish an Expert Committee on Biological Standardization, composed of a maximum of eight members.²¹ The committee was to advise the Commission on the international standards and units which were most urgently required.²²

In December 1946, the Secretariat sent to the members of the committee²³ a note reviewing the existing international standards and containing proposals for future action. The necessity was emphasized for reaching some degree of standardization of vaccines and toxoids and of establishing an international standard for streptomycin. Amongst other subjects considered worthy of review were tetanus and gas-gangrene antitoxins, antivenins, antianthrax and antityphoid sera, tuberculin, neoarsphenamine,

¹⁷ To be published in *Bull. WHO*, 1948, 1

¹⁸ *Bull. WHO*, 1948, 1, 197

¹⁹ *Chronicle WHO*, 1947, 1, 182; *Off. Rec. WHO*, 6, 50

²⁰ *Off. Rec. WHO*, 6, 51

²¹ *Ibid.* 4, 164

²² *Ibid.* 5, 52

²³ For membership, see table XII, p. 84

to the minimum requirements for yellow-fever vaccine intended for use in conformity with the international sanitary regulations.

Streptococcus Antitoxin

An attempt to standardize this serum had to be abandoned in 1928, owing to lack of a sufficiently accurate test-method and the existence of patent rights covering production. Today these patents have expired and a satisfactory method of assay has been evolved, enabling a further review of this question. Samples of sera possessing high immunizing and flocculating potency would be examined in different laboratories with regard to their suitability to serve as international standard preparations.

Digitalis

The stock of international standard of *digitalis purpurea* being almost exhausted, the department of biological standards of the National Institute for Medical Research, London, had collected samples of powdered digitalis leaf from Switzerland, the United Kingdom and the United States. As the mixture had proved suitable for use as a standard preparation, it would be distributed to seventeen laboratories in the following countries: Canada, France, Hungary, India, Netherlands, Sweden, Switzerland, the United Kingdom and the United States, for collective assay to determine the unitage to be assigned to this new standard preparation.

Penicillin

The penicillin standard established in 1944 consisting of crystalline penicillin G (II) had shown itself to be satisfactory from all points of view. In spite of recent progress achieved in the identification of the different penicillins, any modification of the present standard was considered unjustifiable. On the other hand, the committee recommended that a substan-

tially pure sample of penicillin K (IV) should be set up as a reference preparation.

Streptomycin

In view of the impossibility of adopting as yet a standard, the committee limited itself to setting up a reference preparation. The activity was to be expressed both as milligram-equivalent of pure streptomycin, and in provisional units, which should have substantially the same value as the S unit originally proposed by Dr. S. Waksman.

Vitamins

Recent progress in research would necessitate the future replacement of existing standards for fat-soluble vitamins A and D by purer preparations (esters of vitamin A and vitamin D₃). This task was entrusted to a sub-committee which was to meet in the autumn of 1948.

Blood-groups

ABO system. The committee having decided to establish international standards for anti-A and anti-B agglutinating sera, large batches of pooled natural and stimulated material for each group had been collected in the United Kingdom and the United States. The pooled preparations, if proved suitable by concerted tests in different laboratories, would serve as international standards for these two sera.

Rh system. It was arranged that the problem of the Rh antigens should be examined by a sub-committee which would advise on the selection and designation of the sub-groups for which international standards were required.

International Salmonella Centre

The committee recommended that the Centre established in 1938 at the State Serum Institute, Copenhagen, should be taken over by WHO. If so desired, its field of activity could be extended at very little extra cost to cover other species of enteric bacteria.

Tuberculosis

As in the case of malaria, the Commission early decided that an expert committee should be appointed to advise on tuberculosis.²⁷ Two sessions of this committee²⁸ were held, the first in Paris from 30 July to 2 August 1947, and the second in Geneva from 17 to 20 February 1948.²⁹

An International Campaign

The work of the Expert Committee on Tuberculosis was based on the recognition that tuberculosis had reached epidemic proportions, and that international measures were urgently needed in addition to national efforts.

There were not enough trained doctors and other medical workers in the wide areas where tuberculosis was rampant, and no substantial

improvement in the situation could be expected without an increase in their numbers.

It was therefore agreed that one of the important functions of WHO should be to provide travelling fellowships, principally to train medical officers in administration, epidemiology, and laboratory and clinical work. The number of fellowships which should be provided by the organization during the first year was estimated at fifty, fellowships for experts and senior workers being given priority. In this connexion, the need was stressed for impressing national health-administrations with the great advantages of releasing key-workers for relatively short periods of time for study.

²⁷ For report on first session, see *Off. Rec. WHO*, 8, 49; report on second session, not yet published or considered by Commission at time of going to press

²⁷ *Off. Rec. WHO*, 5, 137

²⁸ For membership, see table XII, p. 84

vitamins A, D and K, and the anterior-pituitary-lobe hormones. On the basis of this note, the agenda of the first session²⁴ of the committee, held in Geneva, 9 to 13 June 1947, was framed. A second session was held from 18 to 23 March 1948.²⁵

National Control Centres

The committee re-emphasized the principle that each country should have a single national centre for the storage and distribution of international standards.

The results of an inquiry made by the Secretariat showed that 26 of the national centres existing before the war were still functioning. It was agreed that, in countries where no centre existed, health authorities would have to be approached with a view to establishing such centres.

Toxoids

A highly purified diphtheria toxoid has been obtained by a new method involving the use of benzoic acid. It was agreed that a toxoid sample so prepared should be distributed to various laboratories in order to determine its suitability as a reference preparation. Should these tests prove the material to be satisfactory, its adoption as the international standard would be considered.

A similar procedure would in all probability be followed with regard to tetanus toxoid. In view of the accumulated evidence of the heterogeneity of tetanus toxin, a property of significance in the assay of the sera, it seemed desirable that this toxin should be further analysed from a chemical, physical, physiological and immunological standpoint.

Cholera Vaccine

The consideration of the possible establishment of a standard for this vaccine was referred to the committee by the Expert Committee on Quarantine during the Egyptian cholera epidemic in October 1947.²⁶ Before endeavouring to establish a standard vaccine, the committee considered that further information was required regarding the relation between immunizing potency in animals to that in man. The hope was therefore expressed that the health authorities in India would provide all facilities to Sir Sahib Singh Sokhey, for the carrying-out of the inquiries on this subject that he was about to undertake.

In the meantime, the committee entrusted Dr. M. V. Veldee with the preparation of vaccines from the Ogawa and Inaba strains which, after having been examined for stability in different laboratories, would be held for distribution by the State Serum Institute, Copenhagen, for comparative tests. In order to facilitate the use of these vaccines in assays of activity, the Kasauli Institute would hold freeze-dried living Ogawa and Inaba cultures at the disposal of interested workers.

Following the cholera epidemic in Egypt, Dr. Shousha Pasha requested that anticholera agglutinating sera should be made internationally available as an aid to diagnosis. It was, however, considered more expedient to establish a preparation of O antigen, suitable for the immunization of rabbits, in order to produce antisera capable of distinguishing the true cholera and the El Tor strains from other cholera-like vibrios. Furthermore, to facilitate the differentiation of Inaba and Ogawa strains, monospecific agglutinating sera of the two types should be prepared in India and held by the State Serum Institute, Copenhagen, for distribution.

Tuberculin

In 1931, an international standard for old tuberculin was adopted — the unit being left undefined. The moment seemed opportune for assigning a unit of activity to this preparation, and it was accordingly proposed that this unit be defined as the activity contained in 10 micrograms of the international standard preparation.

The committee, at its first session, had recognized the necessity for establishing a separate international standard for the Purified Protein Derivative (PPD), obtained from *Mycobacterium tuberculosis*. A batch of PPD preparation had been previously selected and retained to serve as the standard, should it prove suitable. Comparative assays, however, showed that this material possessed excessive sensitizing properties, and, at its second session, the committee therefore rescinded its previous decision to establish a PPD standard. Nevertheless, it entrusted the State Serum Institute, Copenhagen, with the distribution of a new preparation as free as possible from sensitizing properties for the purpose of comparative tests.

BCG

The committee considered the establishment of a BCG standard premature, but, in view of the necessity for uniformity with regard to the vaccines in current use, it recommended that the original BCG strain kept at the Institut Pasteur, Paris, should be made available to all countries, and that the preparation and utilization of the vaccine in each country should be centrally co-ordinated.

Other Antigens

It was considered impracticable as yet to standardize pertussis, plague, smallpox and yellow-fever vaccines. Nevertheless, progress would be greatly facilitated by exchange of the relevant strains.

As regards yellow-fever vaccine, the committee felt that close consultative liaison should be established between the Yellow Fever Panel and the committee, particularly with regard

²⁴ For report, see *Off. Rec. WHO*, 8, 5; and *Bull. WHO*, 1948, 1, 7

²⁵ Report not yet published or considered by Commission at the time of going to press

²⁶ See pp. 35, 48