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## EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

### Seventh Session

Geneva, 26-31 October 1953

#### Members :

- \*Dr. E. Dussert, Chief, Department of Control and Laboratories, Chilean Institute of Bacteriology, Santiago, Chile
- J. Gibbard, Chief, Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, Canada
- Professeur E. Grasset, Directeur de l'Institut d'Hygiène; Professeur de Bactériologie et d'Hygiène à l'Université de Genève, Geneva, Switzerland
- Dr. N. K. Jerne, Department of Biological Standards, Statens Seruminstitut, Copenhagen, Denmark
- Dr. O. Maaløe, Chief, Department of Biological Standards, Statens Seruminstitut, Copenhagen, Denmark (*Vice-Chairman*)
- Professor A. A. Miles, Director, Lister Institute of Preventive Medicine, London, England
- Professor A. B. Nichols, Secretary, United States Pharmacopeial Convention Inc., New York, N.Y., USA
- Dr. W. L. M. Perry, Director, Department of Biological Standards, National Institute for Medical Research, Mill Hill, London, England (*Rapporteur*)
- Professor R. Prigge, Director, Paul Ehrlich Institute, State Institute for Experimental Therapy, Frankfurt-on-Main, Germany
- Dr. A. W. Stableforth, Director, Ministry of Agriculture and Fisheries Veterinary Laboratory, Weybridge, Surrey, England
- Professeur J. Tréfouël, Directeur de l'Institut Pasteur, Paris, France
- Dr. P. M. Wagle, Director, Haffkine Institute, Bombay, India
- Dr. W. G. Workman, Chief, Biologics Control Laboratory, National Microbiological Institute, National Institutes of Health (Public Health Service), Bethesda, Md., USA (*Chairman*)

#### FAO Representative :

Sir Thomas Dalling, Chief Veterinary Consultant, Animal Production Branch, Agriculture Division, FAO

#### Secretariat :

Dr. W. Aeg. Timmerman, Director, Division of Therapeutic Substances, WHO  
Dr. E. M. Lourie, Chief, Biological Standardization Section, WHO

The report on the seventh session of this committee was originally issued in mimeographed form as document WHO/BS/252, 16 November 1953.

\* Was unable to attend.

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## EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

### Seventh Report \*

The seventh session of the Expert Committee on Biological Standardization was held in Geneva from 26 to 31 October 1953.

The Director-General welcomed the experts and thanked them for the work that they had already done in preparation for a long and difficult agenda. Their work aimed at making it possible for the potency of therapeutic, prophylactic, and diagnostic substances to be measured and described in terms which are accepted throughout the world. This is essential for orderly progress in human and veterinary medicine. It can be achieved to its maximum potential only if there are efficient working arrangements not only at WHO headquarters and at the two International Centres, in Copenhagen and London respectively, but also at the national control centres of the individual countries. He therefore welcomed the fact that

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\* The Executive Board, at its thirteenth session, adopted the following resolution:  
The Executive Board

1. NOTES the seventh report of the Expert Committee on Biological Standardization;
2. THANKS the members of the committee for their work;
3. AUTHORIZES publication of the report;
4. ENDORSES the recommendations of the expert committee that:
  - (1) the term "national control centres" be replaced by "national laboratories for biological standards"; and
  - (2) the status, privileges, and functions of national laboratories for biological standards be those proposed in Annex I to the report, i.e.:
    - (a) National laboratories should have scientific staffs qualified to deal with biological standardization in their own countries.
    - (b) National laboratories should as far as possible encourage the use of international units and the establishment of subsidiary standards with international unitage.
    - (c) National laboratories shall be entitled to receive specimens of the international standards for purposes approved by the Expert Committee on Biological Standardization. The international standards shall be used mainly for the calibration of subsidiary standards, in order to conserve the supply of the international standards.
    - (d) National laboratories shall receive from WHO reports describing the work and data on which the establishment and use of the international biological standards are based.
    - (e) The national laboratories should inform the World Health Organization about the establishment of any local standard, whether or not there exists an international standard for that substance.

(Resolution EB13.R11, *Off. Rec. Wld Hlth Org.* 52, 5)

the committee proposed to devote an important part of its time to considering means by which the system of national control centres, or national laboratories for biological standards, might be strengthened, so that all countries would be able to derive the fullest benefit possible from the international biological standards.

## IMMUNOLOGICAL

### 1. Blood-Typing Sera <sup>1</sup>

#### 1.1 *Proposed International Standard for Anti-Rh<sub>0</sub> (Anti-D) Blood-Typing Serum*

The committee noted that the International Blood-Group Reference Laboratory, London, in consultation with the National Institute for Medical Research, London, had now completed the preparation of the proposed International Standard for Anti-Rh<sub>0</sub> (Anti-D) Blood-Typing Serum. The committee authorized the Statens Seruminstitut, Copenhagen, to establish this material as the International Standard for Anti-Rh<sub>0</sub> (Anti-D) Blood-Typing Serum and to assign a unitage to it on the basis of the results of the collaborative study.

#### 1.2 *The International Blood-Group Reference Laboratory* <sup>2</sup>

The committee noted that the International Blood-Group Reference Laboratory had been established at the Medical Research Council's Blood-Group Reference Laboratory, London.

### 2. International Standard for Anti-*Brucella abortus* Serum <sup>3, 4</sup>

The International Standard for Anti-*Brucella abortus* Serum was established by the committee at its sixth session.<sup>5</sup> In the light of its decision to assign unitages to diagnostic sera (see section 15, page 13) and of the

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<sup>1</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/213

<sup>2</sup> Unpublished working document WHO/BS/240

<sup>3</sup> Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/223

<sup>4</sup> Stableforth, A. W., unpublished working documents WHO/BS/224, WHO/BS/228

<sup>5</sup> *Wld Hlth Org. techn. Rep. Ser.* 1953, 68, 9

fact that the mean weight of ampoules has been determined, the committee decided that one International Unit for Anti-*Brucella abortus* Serum is contained in 0.091 mg of the International Standard. This will mean that there will be the convenient number of 1,000 International Units in each ampoule.

### 3. Cholera Antigens, Diagnostic Sera, and Vaccines <sup>6</sup>

The committee considered the results of the collaborative studies organized by the Statens Seruminstitut and established the International Reference Preparations of:

- (a) Cholera Agglutinating Serum (Ogawa)
- (b) Cholera Agglutinating Serum (Inaba)
- (c) Cholera Antigen (Ogawa)
- (d) Cholera Antigen (Inaba)
- (e) Cholera Vaccine (Ogawa)
- (f) Cholera Vaccine (Inaba).

The committee also asked the Statens Seruminstitut to arrange for a further collaborative examination of the two proposed International Reference Preparations of Cholera Vaccines.

### 4. *Clostridium Perfringens* Antitoxins

The committee considered a suggestion from the Fifteenth International Veterinary Congress <sup>7</sup> that it should take steps towards establishing standards for *Clostridium perfringens* antitoxins, beta and epsilon, in

<sup>6</sup> Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/222

<sup>7</sup> The text of a resolution adopted at a plenary session of the Fifteenth International Veterinary Congress (held in Stockholm in August 1953) is as follows:

“Recognising the need for urgent action to establish international standards for biological products for veterinary use, the XVth International Veterinary Congress welcomes the extension of the work of the Committee on Biological Standardization of the World Health Organization to include such products. It suggests that this Committee be encouraged to extend as soon as possible its work towards the provision of international standards for other suitable veterinary substances, those meriting immediate attention being *Cl. welchii* (*Cl. perfringens*) antitoxins, beta and epsilon, and swine erysipelas antiserum. The XVth International Veterinary Congress also welcomes the work of the OIE [International Office of Epizootics] on the study of biological products for use in the control of animal diseases and suggests that the Office be encouraged to continue its activities on this subject.”

addition to the existing International Standard for Gas-Gangrene Antitoxin (*Perfringens*). These new standards would be required mainly for therapeutic purposes in veterinary practice, and the committee requested the Veterinary Laboratory, Weybridge, Surrey, England, to obtain suitable batches of serum for both the proposed new standards. It was further agreed that the Weybridge Veterinary Laboratory should be asked to arrange for a collaborative examination by interested workers throughout the world of the suitability of these preparations as International Standards. It was suggested that an examination should be made of potency and monospecificity of the proposed new standards and of the existing one.

The committee also discussed the need for these and other *Cl. perfringens* antitoxins for diagnostic purposes and asked the Weybridge Veterinary Laboratory to set up a small working group to examine this question and to prepare a report for an early future session of the committee.

## 5. Diphtheria

### 5.1 *Proposed International Standard for Diphtheria Toxoid, Adsorbed*<sup>8, 9, 10</sup>

The committee asked the Paul Ehrlich Institute, Frankfurt-on-Main, to prepare material for the International Standard for Diphtheria Toxoid, Adsorbed, and requested the Statens Seruminstitut to arrange for further studies of the stability of diphtheria toxoids at different temperatures, using for this purpose both the International Standard for Diphtheria Toxoid, Plain, and the proposed International Standard for Diphtheria Toxoid, Adsorbed.

The committee also discussed the general need for, and interpretation of, accelerated degradation tests for stability of standard preparations and decided to study this question in detail.

### 5.2 *Schick-test toxin*<sup>11, 12</sup>

The committee noted that in the collaborative investigation of various selected Schick-test toxins a freeze-dried purified preparation had shown the most consistent results, and authorized the Statens Seruminstitut to

<sup>8</sup> Greenberg, L. (1953) *Bull. Wld Hlth Org.* **9**, 829

<sup>9</sup> Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/193

<sup>10</sup> Prigge, R. (1953) *Bull. Wld Hlth Org.* **9**, 843

<sup>11</sup> Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/229

<sup>12</sup> Unpublished working document WHO/BS/247

proceed with a detailed collaborative study of the suitability of this preparation for an International Standard. The committee recommended that the examination should include tests of stability. The committee also asked the Paul Ehrlich Institute to draft a specification for the control and testing of such toxins by comparison with the proposed standard preparation. The committee further suggested that the Statens Serum-institut should examine the suitability of the proposed International Standard for preparing a Schick control reagent.

## 6. Pertussis

### 6.1 *Pertussis vaccine*<sup>13, 14, 15</sup>

The committee discussed the question of providing an International Reference Preparation of Pertussis Vaccine and decided that the preparation selected should, if possible, be made of material which had been subjected to a field trial of its immunizing efficacy. It was noted that the National Institute for Medical Research, London, would try to obtain part of a batch of vaccine that was to be used in the field trials at present being held in England. The committee decided to accept this offer and authorized the Statens Serum-institut to proceed with the collaborative examination of this proposed International Reference Preparation and to compare it with the standard pertussis vaccine of the National Institutes of Health, Bethesda, Md., USA, which is the only existing national standard.

The committee discussed the question of assigning a unitage to the proposed International Reference Preparation but, while agreeing that this would be desirable, deferred any decision until the results of the field and laboratory studies were known.

### 6.2 *Pertussis agglutinating serum*<sup>14</sup>

The committee noted that inquiries made by the Statens Serum-institut had shown that there was not a wide demand for an International Standard for Pertussis Agglutinating Serum, but agreed to accept the offer of the Institut Pasteur, Paris, to provide a high potency serum for further study. The committee authorized the Statens Serum-institut to arrange for this study and suggested that particular attention should be paid to

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<sup>13</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/203

<sup>14</sup> Statens Serum-institut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/216

<sup>15</sup> Pittman, M., unpublished working document WHO/BS/251

the reaction of the agglutinating serum with different serological varieties of *Haemophilus pertussis*. The committee decided to reconsider the establishment of this material as a standard when the results of such tests are available.

#### 7. Poliomyelitis Immune Globulin and Vaccine<sup>16</sup>

The committee noted preliminary reports on the standardization of poliomyelitis immune globulin and of poliomyelitis vaccine, but decided to defer consideration of these problems until further information was available.

#### 8. International Standard for Anti-Q-Fever Serum<sup>17</sup>

The committee noted that the preparation of freeze-dried bovine serum had been subjected to a collaborative examination of its suitability as an International Standard. The results of this study were discussed and the material was established as the International Standard for Anti-Q-Fever Serum.

It was decided that the International Unit should be a weight of dry material and the committee authorized the Statens Seruminstitut, in consultation with the Weybridge Veterinary Laboratory, to determine the average weight of the ampoule contents for this purpose. It was suggested that, for convenience in use, the International Unit should be such that each ampoule of the International Standard would contain approximately 1,000 International Units.

#### 9. Proposed International Standard for Antirabies Serum<sup>18, 19</sup>

The committee noted the proposal of the Expert Committee on Rabies that a standard for antirabies serum should be set up, and asked the Secretariat to obtain material for a standard along the lines suggested by the Expert Committee on Rabies. The committee suggested that the material obtained should be examined not only for its potency but also for its stability by accelerated degradation tests.

<sup>16</sup> Workman, W. G., unpublished working documents WHO/BS/234, WHO/BS/235

<sup>17</sup> Stableforth, A. W. & Kaplan, M. M., unpublished working document WHO/BS/230

<sup>18</sup> Kaplan, M. M., unpublished working document WHO/BS/231

<sup>19</sup> *Wld Hlth Org. techn. Rep. Ser.* 1954, **82**, 9 (section 4)

The committee also discussed the possibility of providing a standard for rabies vaccine but agreed that there was still insufficient information to allow of the provision of an adequate standard.

#### 10. Proposed International Standard for Anti-Swine-Erysipelas Serum<sup>20</sup>

The committee, acting on a recommendation of the Fifteenth International Veterinary Congress (see footnote 7, page 7) that an International Standard for Anti-Swine Erysipelas Serum should be established, and noting that the Paul Ehrlich Institute uses a German national standard which they established some 40 years ago, asked the Institute to provide similar material for an International Standard.

The committee authorized the Weybridge Veterinary Laboratory to proceed with the organization of a collaborative assay of this preparation in terms of the existing German national standard, and agreed that the International Unit should be equated to the existing national unit.

### 11. Syphilis

#### 11.1 *Cardiolipin and lecithins*

The committee noted the progress made in thermostability tests of cardiolipin and lecithins<sup>21</sup> and asked the Statens Seruminstitut to continue the study.

The committee also noted the results of the collaborative assays of the proposed replacements for the Provisional International Reference Preparations of Cardiolipin and Lecithins,<sup>22</sup> and authorized the Statens Seruminstitut to establish them as International Reference Preparations of Cardiolipin and Lecithins subject to results obtained in the collaborative assay.

#### 11.2 *Syphilitic sera*<sup>23</sup>

The committee considered the progress made with the collection of freeze-dried sera from syphilitic and non-syphilitic donors by the Subcommittee on Serology and Laboratory Aspects of the Expert Committee

<sup>20</sup> Prigge, R. & Eissner, G., unpublished working document WHO/BS/246

<sup>21</sup> Unpublished working document WHO/BS/238; Reyn, A., Rasch, G. & Bentzon, M., unpublished working document WHO/VD/SERO/27

<sup>22</sup> Unpublished working document WHO/VD/SERO/44

<sup>23</sup> Unpublished working documents WHO/BS/239, WHO/VD/95, WHO/VD/SERO/28; Rasch, G. & Bentzon, M., unpublished working document WHO/VD/SERO/20

on Venereal Diseases and Treponematoses. It was originally planned that, after a preliminary study of the stability of such freeze-dried sera, the collection should be used for the evaluation of the various serological methods for the diagnosis of syphilis. The committee noted that, in the pilot trial of the stability of the sera, there was evidence that sera from syphilitic donors were stable, but advised that the pilot experiment should be extended to obtain further evidence about the stability of sera from non-syphilitic donors.

The committee also noted that considerable progress had been made with the collection of sera for the main experiment and recommended that this should be proceeded with as soon as the collection included a representative sample of each type of serum.

The committee further agreed that there was an urgent need to provide international reference preparations of sera from syphilitic donors and asked the Subcommittee on Serology and Laboratory Aspects of the Expert Committee on Venereal Diseases and Treponematoses to provide suitable material for this purpose. It was suggested that three sera of a varying degree of activity in commonly used serological diagnostic tests be selected. The committee authorized the Statens Seruminstitut to establish these three sera as International Reference Preparations.

## 12. Tetanus<sup>24, 25, 26</sup>

The committee noted reports indicating that, in assays with plain or adsorbed tetanus toxoid, potency ratios and the divergence of the slopes of the dose-response curves may differ when mice are used instead of guinea-pigs, and considered that the provision of the International Standard for Tetanus Toxoid<sup>27</sup> would facilitate investigations of such heterogeneities.

## 13. Proposed International Standard for Purified Protein Derivative of Avian Tuberculin<sup>28</sup>

The committee noted that the Weybridge Veterinary Laboratory had prepared a batch of purified protein derivative of avian tuberculin which

<sup>24</sup> Prigge, R. (1953) *Bull. Wld Hlth Org.*, **9**, 843

<sup>25</sup> Greenberg, L. (1953) *Bull. Wld Hlth Org.* **9**, 837

<sup>26</sup> Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/194

<sup>27</sup> *Wld Hlth Org. techn. Rep. Ser.* 1952, **56**, 5

<sup>28</sup> Veterinary Laboratory, Weybridge, Surrey, unpublished working document WHO/BS/227

had been freeze-dried in ampoules and which was considered likely to be suitable as an International Standard. The committee asked the Weybridge Veterinary Laboratory to arrange for a collaborative examination of the specificity and potency of the proposed standard.

#### 14. Typhoid and paratyphoid fevers

##### 14.1 *Standardization of typhoid vaccines*<sup>29, 30, 31</sup>

The committee noted the progress made by the Central Public Health Laboratory, London, in making a stable typhoid vaccine. It was agreed that any standard for typhoid vaccine should preferably be made of material tested for immunizing efficacy in the field. The committee recommended that, in any such field trial that might be made, large samples of the vaccines used should, if possible, be held in reserve for possible subsequent use as reference preparations.

##### 14.2 *Typhoid and paratyphoid agglutinating sera*<sup>32, 33</sup>

The committee noted that seven of the eight sera prepared by the Central Public Health Laboratory, London, were now available, and authorized the Statens Seruminstitut to arrange for a collaborative examination.

### GENERAL

#### 15. The Unit Notation for Diagnostic Sera<sup>34, 35, 36</sup>

The committee discussed the general problem of using a unit notation for diagnostic sera. The principal advantages of the system lie in its simplicity in practice, with the consequent ease of comparison of results obtained in different laboratories, and in the fact that it avoids certain logical inconsistencies of other systems of notation. The disadvantages are those which inevitably result when a concept, well established as it may be in other fields, is introduced into a field in which it is unfamiliar.

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<sup>29</sup> Unpublished working document WHO/BS/182

<sup>30</sup> Felix, A., unpublished working document WHO/BS/226

<sup>31</sup> Spaun, J., unpublished working document WHO/BS/217

<sup>32</sup> Felix, A. & Bensted, H. J., unpublished working document WHO/BS/218

<sup>33</sup> *Wld Hlth Org. techn. Rep. Ser.* 1950, 2, 6

<sup>34</sup> Stableforth, A. W., unpublished working document WHO/BS/228

<sup>35</sup> Jerne, N. K., unpublished working document WHO/BS/200

<sup>36</sup> Miles, A. A., unpublished working document WHO/BS/201

The committee considered, however, that positive advantages would result from the introduction of the system, and agreed that, when practicable, international units should be defined for the international standards for diagnostic sera as and when they are established.

This decision is in accordance with the principles followed for the international standards for therapeutic substances and for the international standards for blood-grouping sera.

#### **16. International Reference Preparation for Opacity<sup>37</sup>**

The committee noted that the Statens Seruminstitut, in consultation with the National Institutes of Health, Bethesda, had obtained a new batch of material similar to the standard for opacity used by the National Institutes of Health. It was agreed that this material was equivalent to the standard of the National Institutes of Health, and the committee established it as the International Reference Preparation for Opacity and assigned to it an opacity of ten International Units per ml.

#### **17. Stability of Serum Standards<sup>38</sup>**

The committee noted the results obtained by the Statens Seruminstitut in the investigation of the stability of some serum standards. The results confirmed the previous conclusion that these dried standard preparations are very stable, and that the stability of solutions as dispensed for international use is satisfactory.

### **PHARMACOLOGICAL**

#### **ANTIBIOTICS**

#### **18. International Standard for Aureomycin<sup>39</sup>**

The committee noted that the International Standard for Aureomycin had been established and that the International Unit had been defined as

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<sup>37</sup> Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/198

<sup>38</sup> Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/199

<sup>39</sup> Humphrey, J. H., Lightbown, J. W., Mussett, M. V. & Perry, W. L. M. (1953) *Bull. Wld Hlth Org.* **9**, 851

the activity of 1 microgram of the International Standard Preparation. The committee also noted that the International Standard for Aureomycin could be regarded as substantially pure.

#### 19. International Standard for Bacitracin<sup>40</sup>

The committee noted that the International Standard for Bacitracin had been established and that one International Unit is contained in 0.0182 mg of the International Standard (55 International Units per mg).

#### 20. International Reference Preparation of Chloramphenicol<sup>41</sup>

The committee noted that the National Institute for Medical Research, London, had obtained a synthetic preparation of pure chloramphenicol and established this material as the International Reference Preparation of Chloramphenicol. The committee further agreed that as this material was an authentic chemical substance it should properly be held as one of the collection of authentic chemicals which the Expert Committee on the International Pharmacopoeia proposed to set up in the near future. It was agreed, however, that the material should be held and distributed by the National Institute for Medical Research, until such time as this collection is established.

#### 21. International Standard for Dihydrostreptomycin<sup>42, 43</sup>

The collaborative assay of the proposed International Standard for Dihydrostreptomycin has now been completed, and the committee established the material as the International Standard. One International Unit is contained in 1.316 micrograms of the International Standard Preparation (760 International Units per mg). The committee also noted that the International Standard could be regarded as containing 760 micrograms of dihydrostreptomycin base per milligram.

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<sup>40</sup> Humphrey, J. H., Lightbown, J. W., Mussett, M. V. & Perry, W. L. M. (1953) *Bull. Wld Hlth Org.* **9**, 861

<sup>41</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/212

<sup>42</sup> Humphrey, J. H., Lightbown, J. W., Mussett, M. V. & Perry, W. L. M., unpublished working document WHO/BS/241

<sup>43</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/242

## 22. Proposed International Standard for Oxytetracycline<sup>44</sup>

The committee noted that further investigations of the first batch of material prepared as the International Standard for Oxytetracycline had shown that the heterogeneity between ampoules was due to variations in the moisture content ; the committee also noted that the National Institute for Medical Research, London, had therefore obtained another batch of material for the proposed International Standard and that preliminary studies of its suitability were in progress.

The committee authorized the National Institute for Medical Research to proceed with the collaborative examination of this material, to establish it as the standard, and to assign a unitage to it.

## HORMONES

### 23. Insulin and Insulin Preparations

#### 23.1 *Proposed Fourth International Standard for Insulin*<sup>45</sup>

The committee noted the progress made by the National Institute for Medical Research, London, in consultation with the Insulin Committee of the University of Toronto, Canada, and the United States Pharmacopeia Revision Committee, in the collection of material for the Fourth International Standard for Insulin. The committee decided that, when this large quantity of insulin had been re-crystallized, only those ampoules filled in a single run would be considered for the International Standard Preparation, and that the remaining material ampouled for international use should be designated as the International Working Standard.

#### 23.2 *Preparations of insulin ; and the International Reference Preparation of Protamine*<sup>46</sup>

The committee decided not to establish a standard either of globin alone or of globin-zinc insulin. The committee also decided that there

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<sup>44</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/211

<sup>45</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/205

<sup>46</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/204

was insufficient evidence of the stability of protamine-zinc insulin to justify the establishment of an international standard of this substance, but accepted the offer of the United States Pharmacopeia Revision Committee to make available a quantity of protamine to serve as an International Reference Preparation of Protamine. The committee asked the National Institute for Medical Research, London, to proceed with a collaborative examination of the suitability of this material and authorized the Institute to establish it as the International Reference Preparation of Protamine subject to the results of the collaborative examination.

### 23.3 *Glucagon*<sup>47</sup>

The committee considered a request from a number of experts at the Nineteenth International Physiological Congress to provide an International Reference Preparation of Glucagon. The National Institute for Medical Research, London, was requested to ask these experts to provide material for an author's preparation, which would be held and distributed to interested workers for further studies.

## 24. Anterior Pituitary Hormones

### 24.1 *Proposed Second International Standard for Adrenocorticotrophic Hormone*<sup>48</sup>

The committee considered a report from the National Institute for Medical Research, London, on the progress made in collaboration with the United States Pharmacopeia Revision Committee in obtaining material for the Second International Standard for Adrenocorticotrophic Hormone and noted that there had been significant advances in the knowledge of this hormone since its last session. It was accordingly decided to use as the material for the new standard two new contributions which had been offered and which are crude extracts prepared by the Astwood process. The committee authorized the National Institute for Medical Research to proceed with the preparation and collaborative assay of the proposed new Standard, to establish it, and to assign a unitage to it on the basis of the collaborative assay against the existing International Standard.

The committee decided to defer further investigation of material purified by the oxycellulose method as an additional standard.

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<sup>47</sup> Reinert, H. H. R., unpublished working document WHO/BS/244

<sup>48</sup> Perry, W. L. M., unpublished working document WHO/BS/249

#### 24.2 *Proposed International Standard for Growth Hormone*<sup>49</sup>

The committee noted that material for the proposed International Standard for Growth Hormone had now been obtained, and authorized the National Institute for Medical Research, London, to arrange for a limited collaborative examination of the material, to establish the Standard, and to assign to it a unitage of convenient size.

#### 24.3 *Proposed Second International Standard for Prolactin*<sup>50</sup>

The committee noted that supplies of the existing International Standard for Prolactin were running short and decided that, although the demand for it is relatively small, it should be replaced.

The committee asked the National Institute for Medical Research, London, to collect and study suitable material for a Second International Standard.

#### 24.4 *Proposed International Standard for Thyrotrophin*<sup>51</sup>

The committee noted that the proposed International Standard for Thyrotrophin had been prepared in co-operation with the United States Pharmacopeia Revision Committee and was being subjected to a collaborative examination of its suitability by comparison with the existing thyrotrophin reference substance of the United States Pharmacopeia.

The committee authorized the National Institute for Medical Research, London, to establish the Standard and to assign a unitage to it based on the results of the collaborative assay.

### MISCELLANEOUS

#### 25. *Dextran Sulfate*<sup>52, 53</sup>

The committee noted that the collaborative examination of the author's preparation of dextran sulfate was in progress, and decided to defer con-

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<sup>49</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/250

<sup>50</sup> Perry, W. L. M., unpublished working document WHO/BS/208

<sup>51</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/210

<sup>52</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/207

<sup>53</sup> Grasset, E., unpublished working document WHO/BS/220

sideration of its establishment as an International Standard until the results of this collaborative study were available.

#### 26. Proposed International Standard for Hyaluronidase<sup>54</sup>

It was noted that the pilot trial of the methods of assay of bovine testicular hyaluronidase had been completed and that the results were satisfactory.

The committee also noted the progress made by the National Institute for Medical Research, London, in consultation with the United States Pharmacopeia Revision Committee, in the collection of material for the proposed International Standard for Hyaluronidase.

#### 27. Proposed International Reference Preparations of the Melaminyl Trypanocides<sup>55</sup>

The committee noted the progress made by the National Institute for Medical Research, London, in the collaborative study of the proposed International Reference Preparations of the Melaminyl Trypanocides.

#### 28. Pyrogens<sup>56</sup>

The committee noted that two preparations of pyrogens were now available for study and requested the National Institute for Medical Research, London, to distribute them to interested workers throughout the world for examination of their suitability as International Reference Preparations.

#### 29. Secretin<sup>57</sup>

The committee noted a proposal made by a group of experts at the Nineteenth International Physiological Congress that an International Standard for Secretin should be considered. The committee asked the

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<sup>54</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/232

<sup>55</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/202

<sup>56</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/206

<sup>57</sup> Perry, W. L. M., unpublished working document WHO/BS/233

National Institute for Medical Research, London, to obtain a suitable batch of secretin as an author's preparation and to hold and distribute it to interested workers throughout the world.

### 30. Proposed International Standard for Vitamin B<sub>12</sub><sup>58</sup>

The committee noted the progress made in the preparation of the proposed International Standard for Vitamin B<sub>12</sub>, and authorized the National Institute for Medical Research, London, to establish the material as the International Standard for Vitamin B<sub>12</sub> subject to the results of the collaborative study.

## GENERAL

### 31. National Laboratories for Biological Standards

The committee discussed a report by Dr. N. K. Jerne on his visit to the South-East Asia Region in the capacity of a temporary Consultant in Biological Standardization of the World Health Organization. On the basis of this report the committee made the following recommendations.

(1) The committee recommended that the term "national control centres" should be replaced by "national laboratories for biological standards". The committee discussed the status and functions of these laboratories, and recommendations on this subject are given in Annex 1 to this report (see page 22).

(2) The committee asked WHO to prepare, in consultation with the International Centres in London and Copenhagen, a booklet on the principles of biological standardization and of the selection of substances requiring standardization, and containing information on the way in which WHO takes action in this field.

(3) The committee discussed the question of providing a series of minimum requirements for therapeutic and prophylactic substances of biological origin, but decided that it was not the appropriate body to deal with this matter. The committee agreed that help should be provided for health authorities in various countries in devising their own minimum requirements, and that help of this kind would be forthcoming if the recommendations given in (4) and (5) below were accepted.

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<sup>58</sup> National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/209

(4) The committee recommended that WHO should if possible arrange, at the request of governments concerned, for short-term consultants in biological standardization to spend several months in individual national laboratories for biological standards in order to give assistance and advice.

(5) The committee recommended that WHO should consider providing financial support for an active laboratory in India which would, at the request of individual governments, undertake the training of personnel engaged in the control of biological substances in the other Member States of the South-East Asia Region, and suggested that, during the training period, the individuals concerned should carry out such control testing as might subsequently be necessary for biological products used in their own countries.

(6) The committee recommended that, in drawing up memoranda describing the individual international standards, the International Centres in London and Copenhagen should endeavour to give detailed descriptions of suggested methods of assay. The committee discussed the possibility of collecting such memoranda in the form of a loose-leaf publication.

(7) The committee considered the need for standardizing plague, dysentery, and smallpox vaccines, and antivenines, and decided to consider these matters in detail as soon as possible.

The committee recorded its appreciation of the excellent work done by Dr. Jerne in his capacity as a WHO Consultant in Biological Standardization during his visit to the South-East Asia Region.

### 32. Collection of Authentic Chemical Substances<sup>59</sup>

The committee noted the progress made by the Expert Committee on the International Pharmacopoeia in the establishment of a collection of authentic chemical substances, and agreed to advise the Expert Committee on the International Pharmacopoeia on the substances which should be included in such a collection.

### 33. Recommended Diagnostic Methods<sup>60, 61</sup>

The committee considered the information which had been collected on the need for a compilation of recommended diagnostic methods. It

<sup>59</sup> Unpublished working documents WHO/BS/243, WHO/Pharm/250, WHO/Pharm/266

<sup>60</sup> Unpublished working document WHO/BS/175

<sup>61</sup> Unpublished working document WHO/VD/SERO/26

was decided that the committee was not the appropriate authority to prepare such a compilation, although the need for it was fully recognized.

### 34. Questions Submitted by the Expert Committee on the International Pharmacopoeia

The committee approved the draft amended monograph on antitetanus serum<sup>62</sup> and the draft appendix on the biological assay of injection of ouabain<sup>63</sup> for the *Pharmacopoea Internationalis*, and recommended that the monograph on suramin sodium<sup>64</sup> should include a test for therapeutic potency.

#### Annex 1

### PROPOSALS FOR THE STATUS, PRIVILEGES, AND FUNCTIONS OF NATIONAL LABORATORIES FOR BIOLOGICAL STANDARDS

(a) National laboratories should have scientific staffs qualified to deal with biological standardization in their own countries.

(b) National laboratories shall be designated by the governments concerned, and should as far as possible encourage the use of international units and the establishment of subsidiary standards with international unitage.

(c) National laboratories shall be entitled to receive specimens of the international standards for purposes approved by the Expert Committee on Biological Standardization. The international standards shall be used mainly for the calibration of subsidiary standards, in order to conserve the supply of the international standards.

(d) National laboratories shall receive from WHO reports describing the work and data on which the establishment and use of the international biological standards are based.

(e) The national laboratories should inform the World Health Organization about the establishment of any local standard, whether or not there exists an international standard for that substance.

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<sup>62</sup> Unpublished working document WHO/Pharm/252 Add. 1

<sup>63</sup> Unpublished working document WHO/Pharm/269

<sup>64</sup> Unpublished working document WHO/Pharm/Mon/273 Rev. 3

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