Technical Preparatory Committee; No. 2 is the proceedings of the International Health Conference; and Nos. 3 to 7 inclusive contain the proceedings of the five sessions of the Interim Commission. No. 9 is Part I of the Interim Commission's Report to the First World Health Assembly, and contains a detailed account of the work of the Commission from the date of its establishment in 1946 to the end of April, 1948. A Supplementary Report, including information on the later phases of the Commission's work, was issued as No. 12. No. 10 was the Provisional Agenda, with recommendations for programme activities, presented by the Commission to the First World Health Assembly. The proceedings of the First and Second World Health Assemblies are printed as Nos. 13 and 21 of the series, and the reports of the first five sessions of the executive board appear in Nos. 14, 17, 22, 25, and 26. No. 16 is the *Annual Report of the Director-General to the World Health Assembly to the United Nations, 1948*, and covers the first four months' (September to December, 1948) work of the permanent Organization. The annual report for 1949 is No. 24.

Reports of expert committees and other advisory bodies were until the end of 1949 also published in the *Official Records* series (Nos. 8, 11, 15, and 19). At the beginning of 1950 these technical reports were published in a new series—*World Health Organization: Technical Report Series*—of which twenty-one have now either been printed or are being prepared for press.

Scientific papers relating to the work of the Organization are published in the *Bulletin of the World Health Organization*, and laws and regulations relating to health are reproduced, abstracted, or indexed in a separate publication—the *International Digest of Health Legislation*.

The *Weekly Epidemiological Record* contains notifications of first cases of pestilential diseases and other information of interest principally to quarantine authorities. The *Epidemiological and Vital Statistics Report*, which is published monthly, contains epidemiological and statistical information of wider interest. Non-serial publications, such as the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* and the *International Pharmacopoeia*, are also published. All W.H.O. publications are published in the English and French languages, and there are also Chinese, Russian, and Spanish editions of the *Chronicle*.

The Public Information Division issues a monthly *W.H.O. Newsletter*, an occasional Special Features series, and numerous Press Releases.

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THERAPEUTIC SUBSTANCES IN THEIR INTERNATIONAL ASPECTS

BY

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In its work in connexion with therapeutic substances the World Health Organization is undertaking duties that could be performed only by an international body. For this work a Division of Therapeutic Substances has been established within the Department of Central Technical Services of the World Health Organization (which also includes the Divisions of Epidemiology, Health Statistics, and Editorial and Reference Services), and this Division comprises sections for biological standardization, unification of pharmacopoeias, drugs apt to produce addiction, and co-ordination of research. All these activities call for the pooling of knowledge and experience obtained in various countries and a study of standards or control measures applicable and acceptable to all governments.

The work of the first three sections is described below. "Co-ordination of research"—a rather unsatisfactory designation which has been adopted for want of a better one—includes at present the activities of W.H.O.'s Tuberculosis Research Office at Copenhagen, which is also described below, and some work on antibiotics. Because the latter work is only in its initial stages of development, no account of it has been included here. The first meeting of the Expert Committee on Antibiotics of the World Health Organization took place only in April of this year, and the committee's report will be presented at the Third World Health Assembly in May. If approved it will later be published in the *World Health Organization: Technical Report Series*.

Biological Standardization

A comprehensive account of international work on biological standardization has been given by Gautier.* 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 fewer 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

*R. Gautier, *Bull. Hlth Org. L.o.N.*, 1935, 4, 497; 1945, 12, 1.

of the international standards. The burden on the two central laboratories—the National Institute for Medical Research, London, and the State Serum Institute, Copenhagen—was in this way relieved, since they would need only to maintain stocks of standard preparations at a single agency in each country.

Biological standardization proved useful in more than one respect: it enabled clinicians to administer accurate doses of substances whose weight bore no relation to the activity contained in different batches of the same

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 in November, 1946, adopted a resolution to establish an Expert Committee on Biological Standardization composed of a maximum of eight members. The committee was to advise the Commission on the international standards and units which were most urgently required. In December, 1946, the

W.H.O. Expert Committee on Biological Standardization.—First meeting in the Palais des Nations, Geneva, June 9–13, 1947. Left to right are: Dr. A. A. Miles, director, Department of Biological Standards, National Institute for Medical Research, Hampstead (London); Dr. W. A. Timmerman, chairman of the committee and director, Rijks Instituut voor de Volksgezondheid, Utrecht, Netherlands; Dr. J. Orskov, director, State Serum Institute, Copenhagen, Denmark; Dr. Raymond Gautier, counsellor of the W.H.O. Interim Commission and head of the Geneva office; Sir Sahib Singh Sokhey, director, Haffkine Institute, Bombay, India (now Assistant Director-General, W.H.O.); Dr. M. V. Veldee, chief, Biologics Control Laboratory, U.S. Public Health Service, National Institutes of Health, Bethesda, Md., U.S.A.; and Professor E. Grasset, directeur de l'Institut d'Hygiène, Geneva, Switzerland. Dr. Jacques Tréfoel, directeur de l'Institut Pasteur, Paris, seventh member of the expert committee, is not shown in this photograph.

preparation; it supplied health authorities with a means of evaluating biological products placed on the market; and it enabled manufacturers to express the potency of products marketed in different countries in the same units and research workers to determine the potency of unknown substances by comparison with the standard preparation and to measure this potency in terms of units irrespective of the method used.

At the outbreak of war international standards for 31 biological substances had thus been provided. During

Secretariat sent to the members of the committee a note reviewing the existing international standards and containing proposals for future action. On the basis of the replies received to this note a provisional agenda of the first session of the committee was held in Geneva, June 9–13, 1947. A second session was held in Geneva on March 18–23, 1948, and a third session took place in London on May 2–7, 1949.

National Control Centres.—The committee re-emphasized the principle that each country should have a single national

centre for the storage and distribution of the international standards. The results of an inquiry made by the Secretariat showed that 26 of the original 57 centres existing before the war were still in operation. In countries with no centres or where existing centres no longer operated health authorities were consulted and further centres established.

Vaccines and Sera

Cholera Vaccine and Reference Strains

In connexion with the cholera epidemic in Egypt the W.H.O. Expert Committee on Quarantine at its October session, 1947, had recommended that the question of the standardization of cholera vaccine be referred to the Expert Committee on Biological Standardization. The committee considered that a stock of dried Ogawa and Inaba vaccines should be obtained as reference preparations in order that workers might have a means of direct comparison of their observations. While it was desirable that the reference preparations should be typical cholera vaccines, it was not essential that they should be of the highest protective quality, provided that the protective value of other vaccines could be expressed as a fraction or multiple of that of the reference preparation. It was further recommended that preparations of freeze-dried cholera cultures should be made available for reference purposes in the production of prophylactic vaccines. Laboratories would thus, by starting afresh from a lyophilized culture, be able to produce a vaccine of a potency as nearly uniform as possible as often as required. It was felt that the adoption of these measures would constitute a primary step towards an attempt to raise the immunizing value of cholera vaccines in general.

Cholera Monospecific Diagnostic Antisera and O Antigens

The Expert Committee, in response to a specific request for the establishing of an anti-cholera agglutinating serum, decided that for cholera diagnostic purposes dry reference preparations should be obtained of the Ogawa and Inaba O antigens of the *Vibrio cholerae* suitable for the immunization of rabbits for the production of antisera capable of distinguishing the true cholera and El Tor strains from all other cholera-like vibrios. The committee considered that while availability of authentic dry O antigens would render the preparation of standard diagnostic sera superfluous, it was desirable that so-called monospecific Ogawa and Inaba type sera, obtained by the removal of the common cholera agglutinins from ordinary anti-cholera sera, should be available on demand for the rapid differentiation of the sub-types of *V. cholerae*.

These reference preparations have all been completed and are at present undergoing comparative testing in laboratories in different parts of the world. If these tests confirm their usefulness and quality they will shortly be made available by the committee to workers interested in this field.

Anti-Pertussis Vaccine

After a detailed examination of the question, the committee decided to defer the establishment of an international preparation for a *Haemophilus pertussis* vaccine until enough information was available on the following points:

- (1) The relation between the immunizing potency in laboratory animals and in man. Large-scale field tests with pertussis vaccine are at present in progress in Great Britain and other countries, and it is hoped that by the end of the year further information on this point will be available.
- (2) The consistency of results obtained by independent

workers when several vaccines are compared with a standard preparation.

Among the difficulties in reaching agreement about the potency of pertussis vaccines as measured by current methods are the variable interpretation of turbidity of vaccines in terms of bacterial content, and the variable results obtained in the intracerebral tests in mice. Samples were placed at the disposal of the interested workers by the National Institutes of Health of their turbidity standard—which is a suspension of particles of “pyrex” glass in water together with samples of the N.I.H. reference vaccine measured against this standard—with a view to obtaining opinions in various countries regarding the suitability of a pyrex glass suspension for a turbidity standard, and the N.I.H. laboratories further agreed to make available their strains of *H. pertussis* and mice for use in the intracerebral test.

Smallpox Vaccine

The committee considered the question of the investigations necessary for the definition of minimum requirements for smallpox vaccines. To this end it recommended that seed vaccinia virus used in different countries for the preparation of smallpox vaccines be tested in rabbits for its immunizing potency against freshly isolated variola virus.

Yellow Fever

The committee felt that close consultative liaison should be established with the W.H.O. Yellow Fever Panel, particularly with regard to the minimum requirements for yellow fever vaccine intended for use in conformity with the international sanitary regulations.

B.C.G.

In view of the fact that B.C.G. is a live organism the committee considered the establishment of a B.C.G. vaccine reference preparation as premature, but on account of the necessity for uniformity with regard to the vaccines in current use it recommended that the original B.C.G. strain kept at the Institut Pasteur should be made available to all countries, and that the preparation and utilization of the vaccine in each country should be centrally co-ordinated through the National Control Centre. The committee noted that the Institut Pasteur was now ready to prepare, and to distribute monthly, freeze-dried cultures of living B.C.G. for use as seed material to the laboratories producing B.C.G. upon the recommendation of the National Control Centres.

In 1948 Unicef addressed a request to the Expert Committee on Biological Standardization that the laboratories producing B.C.G. for the Unicef International Anti-Tuberculosis Campaign should be approved by that committee. The Expert Committee, therefore, at its third session in London, discussed the conditions necessary for the production of a safe and effective vaccine, and drew up a set of minimum requirements with which the laboratories producing B.C.G. should conform in order to afford a guarantee of safety for the vaccine. These minimum requirements are published as an annexe to the committee's report (W.H.O. Technical Report Series No. 2). Furthermore, the committee has sent to each laboratory engaged in the production of B.C.G. for use in the Unicef campaign one of its members to carry out an inspection on the spot of the conditions under which the vaccine is produced; it is on the basis of a favourable report by the member that the vaccine is released for general use. The Institut Pasteur is at present engaged in the production

of freeze-dried B.C.G. vaccine, and the committee hopes that when certain problems in this connexion are settled it may be possible to review the position of the setting-up of a reference standard preparation for B.C.G. vaccine.

Tuberculin

In 1931 an international standard for old tuberculin was adopted—the unit being left undefined. The Expert Committee at its second session (1948) considered that the time had come 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 micromillilitres of the international standard preparation.

Purified Protein Derivative of *M. tuberculosis* (P.P.D.)

The committee at its first session recognized, in addition to the existing international standard for old tuberculin, that there was a definite need for establishing a separate international standard preparation for the Purified Protein Derivative (P.P.D.) obtained from *Mycobacterium tuberculosis*. A batch of P.P.D. preparation had previously been selected and retained to serve as the standard, should it prove suitable. The first testing of this material seemed to indicate that it possessed excessive sensitizing properties, and the committee at its second session entrusted the State Serum Institute, Copenhagen, with the distribution, for the purpose of comparative tests, of a new preparation as free as possible from sensitizing properties. Further tests of various preparations of P.P.D. have shown that their sensitizing properties do not debar them from use as standard preparations. The reaction that they produce in hypersensitive animals and man, however, are qualitative in a significant degree. Moreover, P.P.D. and similar materials prepared in different ways contain variable proportions of active fractions of different molecular weight. The committee therefore decided to defer the establishment of a reference preparation until its next session, and meanwhile recommended and arranged for a comparative biological and physiochemical examination of representative types of purified tuberculo-proteins in several laboratories.

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. To-day these patents have expired and a satisfactory method of assay has been evolved, enabling a further review of this question to be made. A suitable preparation of streptococcus antitoxin has been procured by the Department of Biological Standards of the National Institute for Medical Research, London. Preliminary tests indicate that this preparation is suitable for an international standard. Estimation of its potency in terms of the U.S. National Institutes of Health standard streptococcus antitoxin is to be made by laboratories in different countries.

Tetanus Antitoxin, Toxin, and Toxoid

In the past the Permanent Commission on Biological Standardization has devoted much work to the assay of tetanus antitoxin. An international standard was adopted in 1928 defining the international unit as 0.1547 mg. At its second session, in 1948, the Expert Committee on Biological Standardization 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 may 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 the immunological, standpoints. To facilitate the supply for interested workers it was arranged that samples of anomalous toxins and antitoxins should be collected and distributed on request.

The committee considered the extensive use made both of International and U.S. National Institutes of Health units in designating the potency of tetanus antitoxin and reviewed the circumstances in which the international unit was defined in 1928. On the basis of an inquiry instituted in various countries it was decided to re-define the international unit for tetanus toxin so as to bring it into equality with the U.S. National Institute of Health unit. This change has been duly advertised, and as from July 1, 1950, the international unit for tetanus antitoxin will be the specific neutralizing activity for tetanus toxin contained in 0.3094 mg. of the standard preparation.

A batch of tetanus toxoid prepared by the Pillemer method has been presented to the Expert Committee by an American firm. This preparation is being examined by various laboratories to test its suitability to serve as a reference preparation for characterizing the effective antigens in general use.

Diphtheria Toxoid

The committee has obtained a batch of highly purified diphtheria toxoid, which is undergoing collaborative testing in laboratories in different countries. This preparation may eventually be adopted as the international reference preparation.

It is to be hoped that these tests of the toxoids may also provide a solution to several outstanding difficulties which have arisen in connexion with the standardization of toxoids—principally that of whether the establishment of a unit of diphtheria toxoid, representing a certain weight of a standard preparation, will enable the potency evaluation to be made of all kinds of adsorbed diphtheria toxoids in terms of this unit. It is intended to hold a special subcommittee meeting of the Expert Committee on Biological Standardization in the near future, at which the whole question of the assay of toxoids will be discussed with a view to arriving at a solution to this problem.

Drugs

Digitalis

At the second session of the Expert Committee, the Department of Biological Standards, National Institute for Medical Research, was authorized to replace the second international standard of digitalis, which was nearly exhausted. A large blend of one British, two Swiss, and three American batches was made. The assays for determining its suitability and the ultimate designation of potency were carried out on frogs, cats, guinea-pigs, and pigeons. Statistical analysis showed that the method was sufficiently standard to permit a valid combination of results. The potency was assigned on the basis of the overall weighted mean; thus one international unit is contained in 76 mg. of the new preparation.

Sulpharsphenamine

The existing international standard for sulpharsphenamine having become exhausted, the committee had received a donation of a large and satisfactory batch of material from a British firm. On preliminary testing it had been found that the quality of this batch was superior to that of the old standard; it would seem fitting, therefore, that

the committee should fix a higher standard of potency for the new standard. To this end tests are in progress whereby the unitage of the new standard will be defined in terms of the old, using a new and better-designed test method for the assay of the activity and toxicity.

Hormones

Oestrone and Oestradiol Monobenzoate

The committee recognized that preparations of oestradiol monobenzoate and oestrone were no longer necessary as biological standards, owing to their synthetic production and to the fact that their characteristics can now be determined by physico-chemical means. The committee recommended, therefore, that the issue of international standards for oestrone and oestradiol monobenzoate should cease on January 1, 1951, and that this fact should be duly advertised. (See *W.H.O. Chronicle*—General Notices, July, 1949, Vol. 3, No. 7, p. 164.)

Androsterone

The international standard preparation is mainly used as a pure chemical standard, and as such it is obsolete as a biological standard. However, since the standard is still apt to be used for the assaying of androgen content of body fluids and the stocks of the standard are nearing exhaustion, it was recommended that the supplies of androsterone should be temporarily replenished, but that users would be warned that the distribution of this standard, when stocks again become low, will be restricted to those using it for biological assay.

Thyrotrophin

The committee considered the need for continuing with the preparation of a standard for thyrotrophin recommended by the Third International Conference on the Standardization of Hormones (1938) and interrupted by the war. The committee recommended that the opinion of interested workers should be sought on this matter.

Corticotrophin

The recent extension of the therapeutic uses of this hormone and improved methods of assay have made the provision of an international standard a matter of urgency. Negotiations are at present in progress for the procurement of a sufficiently large batch of substance suitable to serve as the international standard preparation.

Vitamins

Vitamin A and Vitamin D

It had long been recognized that beta-carotene was not the ideal standard of reference for determining Vitamin A, and in 1947 the question was referred by the Accessory Food Factors Committee of the M.R.C. to the Expert Committee on Biological Standardization. Owing to recent progress in our knowledge of the synthesizing of vitamins A and D₃, it was decided that a subcommittee meeting on fat-soluble vitamins should be convened to advise the Expert Committee on Biological Standardization on the establishment of new standards both for vitamin A and for vitamin D. This subcommittee meeting was held in London on April 26–29, 1949, in connexion with the third session of the Expert Committee on Biological Standardization, which it immediately preceded. On the basis of the subcommittee's report, the Expert Committee recommended that the international standard for vitamin A should be crystalline all-trans vitamin A acetate and that the international unit should be the activity of 0.344 microgram of the standard preparation of crystalline vitamin A acetate.

The existing standard preparation of pure all-trans beta-carotene should cease to be the international standard for vitamin A and should become the international standard for provitamin A.

The committee recommended that the international standard for vitamin D should be a preparation of crystalline vitamin D₃ and that the international unit should be the vitamin D activity of 0.025 microgram of the international standard preparation of crystalline vitamin D₃. The existing standard preparation of irradiated ergosterol should cease to be the international standard for vitamin D, but would be maintained as a reference preparation.

Anti-pernicious-anaemia Factor

The committee had at its second session discussed the unsatisfactory position with regard to national units of activity for liver extract preparations. It noted that a unit of activity based upon admittedly variable interpretation of the clinical effect of liver extracts on patients with pernicious anaemia instead of in terms of a standard preparation was not in accordance 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. It was further aware of the possible dangers of adulteration of the extracts by the addition of folic acid in quantities sufficient to stimulate a reticulocyte response comparable to that induced by the anti-anaemic principle of liver extract. Owing to the absence of a satisfactory animal assay of anti-pernicious-anaemia potency at that time, it was difficult for the committee to take any action with regard to the establishment of an international standard. However, the subsequent isolation of vitamin B₁₂ in 1949 provided a substance which might prove suitable as a standard preparation for the assay of the anti-pernicious-anaemia potency of extracts of liver and other animal tissues. The committee authorized the Department of Biological Standards, N.I.M.R., London, to procure enough pure crystalline vitamin B₁₂ to serve as a standard preparation for the assay of anti-pernicious-anaemia factors and to ascertain the opinion of interested workers on the preferred size of a unit of activity.

Antibiotics

Penicillin

As the stocks of the international standard for penicillin were running low the committee had procured a preparation of pure penicillin G (II) to serve as the second international standard for penicillin, and authorized in laboratories of various countries an assay of the proposed second international standard in terms of the existing standard.

Streptomycin

The committee decided that the reference preparation of streptomycin held by the Department of Biological Standards, N.I.M.R., London, since 1948, should now be established as the international standard for streptomycin, and recommended that a preparation of dihydrostreptomycin should be obtained and held as a reference preparation. It was recommended that the potency of the international standard should be expressed either as units or as gram-equivalents of streptomycin base, or as both. Unit activity should, in the first place, be assigned to that weight of standard preparation which, so far as can be ascertained, contains one microgram of streptomycin base, thereby making the international unit as nearly as possible equivalent to the original Waksman unit.

Blood Groups**ABO**

International standards for anti-A and anti-B agglutinating sera have been set up. Large batches of natural and stimulated antisera for each group were collected in the United Kingdom and the United States. These preparations were pooled and submitted for testing to 11 different laboratories in various countries. On the basis of these tests it has been proposed to assign to each antiserum an agglutinating potency of 256 international units per ml. of reconstituted serum. The avidity of the anti-A serum for A and A₁B cells, and of anti-B serum for B cells was found to be high enough to serve as a standard to be equalled by diagnostic antisera; and the avidity of the anti-A serum for A₂B cells, measured by the time taken for slide agglutination, is about one-third that desirable in diagnostic antisera.

Rh

It was not considered expedient at present to establish international standard preparations of the various anti-Rh sera, nor did the committee wish to make any recommendation about the notation of the Rh groups. It considered, however, that a universally acceptable definition of the term "Rh-negative" was desirable, and recommended that the following definitions should be adopted universally:

"The term 'Rh-negative' should, whenever possible, be applied to a human blood donor only if his erythrocytes are not agglutinated by three anti-Rh sera—namely:

(1) Anti-Rh₀ (Wiener notation); anti-D (Fisher-Race notation).

(2) Anti-Rh' (Wiener notation); anti-C (Fisher-Race notation).

(3) Anti-Rh" (Wiener notation); anti-E (Fisher-Race notation).

"Tests for the antigens represented by antisera (1) and (2) are conveniently made by the mixed serum anti-Rh₀' (Wiener)—anti-D+C (Fisher-Race)—and for the antigens represented by antisera (1) and (3), by the mixed serum anti-Rh₀" (Wiener)—anti-D+E (Fisher-Race).

"The antisera (2) and (3), however, are not always available. In this case, tests with antiserum (1) may be considered sufficient for specifying an Rh-negative donor, but it should be realized that the risk of incompatibility is thereby slightly increased. Tests with antiserum (1) anti-Rh₀ (Wiener)—anti-D (Fisher-Race)—are indispensable.

"The term 'Rh-negative' should be applied to a human blood recipient when his erythrocytes are not agglutinated by an anti-Rh₀' (Wiener)—anti-D (Fisher-Race)—serum. An Rh-negative recipient is not necessarily an Rh-negative donor."

Serodiagnosis of Enteric Infections

The Permanent Commission on Biological Standardization of the League of Nations had initiated an international inquiry with a view to the standardization of the serum diagnosis of enteric fever and the Widal test in particular. This work had been interrupted by the war. At its third session the Expert Committee recommended that eight horse antisera for the specification of agglutinating suspensions for use in the serodiagnosis of typhoid and paratyphoid infections should be prepared. Antisera specific for the following antigens will be made: *Salmonella typhi* (H), *Salmonella typhi* (O), *Salmonella typhi* (Vi), *Salmonella paratyphi A* (H), *Salmonella paratyphi A* (O), *Salmonella paratyphi B* (H), *Salmonella paratyphi B* (O), *Salmonella paratyphi*, non-specific (H). These antisera will be examined in different laboratories and, if suitable, they will be adopted as international standard preparations.

Serodiagnosis of Rickettsial Infections

Owing to the difficulty and impracticability of preparing purified rickettsial suspensions for serological diagnosis of typhus the committee recommended that it would be useful to prepare horse antisera for the specific identification of the X strains of *Proteus* for specifying agglutination suspensions to be used in routine serodiagnosis of rickettsial infections. Antisera for the following antigens will be made: P.OX19, P.OXK, and P.OX2. If found suitable they will be adopted as international standard preparations.

The committee wound up their discussions at their last session by reviewing the circumstances in which the three current methods of designating the potency of biological substances are valid. They considered these circumstances are:

(1) Whether or not the active principles in biological substances have been characterized by chemical and physical means, the potency of such substance should be expressed in *units* wherever the active principle of both standard preparation and preparations to be assayed may be heterogeneous.

(2) The expression of potency in *gram-equivalents* is valid, although not always desirable when the active principle in the standard preparation is known to be homogeneous and free from inert material, and the active principles in preparations to be assayed may be heterogeneous.

(3) Designation of potency in *grams* is justified only when the active principle in the standard preparation is known to be homogeneous and free from inert material and when the active principle in the preparations to be assayed is known to be homogeneous. In such circumstances, however, biological assay will be necessary only when expense prohibits the routine characterization of preparations by physical and chemical means.

Unification of Pharmacopoeias

The need for unification in the field of therapeutic substances has been increasing rapidly in the last decades owing to the development of science, to international research, and to the increase in travel and commercial exchanges between nations.

An international conference on the unification of formulae of potent substances was held in 1902, and a further conference was held in 1925 with representation from 31 nations. Shortly afterwards an agreement, giving the strength and description of 77 potent substances, was signed by a number of countries. This was revised in 1929; in the same year the Council of the League of Nations examined the question of the creation of a permanent secretariat for the Unification of Pharmacopoeias, and a technical commission of Pharmaceutical Experts was set up in 1937 by the Health Organization of the League of Nations to prepare a limited International Pharmacopoeia. This Commission had made considerable progress when the work had to be interrupted in consequence of the second world war.

In 1947 the Interim Commission of the World Health Organization resumed the work and established an Expert Committee of seven members, under the chairmanship of Dr. C. H. Hampshire, in order "to produce a draft international agreement for the unification of pharmacopoeias modifying and extending the existing agreement for the unification of all the formulae for potent drugs, and to present the draft agreement as an international pharmacopoeia, similar in form to the present national pharmacopoeias" (*Off. Rec. World Hlth Org.*, 10, 12, 19, 22). This committee has worked continuously since that time

and has met on five occasions. It is now approaching completion of its work for the first volume of an *International Pharmacopoeia*, to be published this year in English and in French, followed by a Spanish edition. This volume will contain descriptions of standards for some 200 drugs in general use, giving titles, definitions, and standards for identity, quality, strength, and purity.

Close contact with all other units working in related fields is being effected through the secretariat of the organization, particularly with other W.H.O. Expert Committees on Biological Standardization, Malaria, Venereal Infections, Antibiotics, etc.

Valuable information is also being received from other international organizations on subjects of common interest—e.g., symbols, reagents, weights and measures, doses, nomenclature, etc., from the International Union of Chemistry, the International Bureau of Weights and Measures, the World Organization on Standardization, and the World Medical Association. Moreover, the members of the Expert Committee can rely on the wealth of scientific information available from the pharmacopoeial commissions in their respective countries.

The articles in this first edition will consist mainly of drugs of established therapeutic value common to a number of national pharmacopoeias. The rapid advances in certain aspects of medical science make it difficult to lay down definite fixed standards at present for certain drugs, particularly among the antibiotics, and in order not to delay the publication of the first volume it has been found advisable to defer them to the addenda, which are to be published later on.

Addiction-producing Drugs

The tasks which W.H.O. has to fulfil in this field are of different character. It inherited from the League of Nations and the Office International d'Hygiène Publique at Paris certain obligations deriving from the different Opium Conventions. So far as the new synthetic substances of the methadone and pethidine type are concerned, a new Protocol was signed in Paris in 1948 and came into force on December 1, 1949, complementing these older Conventions. In all these cases W.H.O. is the competent authority for deciding whether a new substance is addiction-producing or not. Advice as regards this decision, which in part has binding legal force for the United Nations and the parties of the corresponding treaties, is given by the Expert Committee on Drugs Liable to Produce Addiction of W.H.O.

Two meetings of this committee have been held so far—one in January, 1949, and the second in January, 1950. Among the questions considered during these meetings the following might be mentioned: the consumption of diacetylmorphine has increased during the last few years in some countries to surprising levels. This fact seemed still the more alarming to the committee, as on the occasion of the 1931 Convention emphasis was already laid on "the highly dangerous character of diacetylmorphine as a drug of addiction and the possibility, in most if not all cases, of replacing it by other drugs of a less dangerous character." Although in the last year the situation so far as the consumption is concerned had improved to some degree, the committee expressed grave concern over this situation, particularly as some important countries continue to maintain that their physicians consider this drug indispensable for certain medical uses. Therefore Governments have been asked for information on the use or dispensability of this drug.

Another important task concerns the new synthetic substances of methadone, morphinan, and pethidine type. The addiction-producing character of the compounds of those types employed up to the present is without question, and one pethidine derivative, known under the designation "keto-bemidone," seems to be particularly dangerous from the standpoint of addiction liability. In general, W.H.O. recommended precautionary measures to be taken with regard to these substances. This recommendation has been accepted by the Economic and Social Council of the United Nations. The idea is to place substances of a particular chemical type under control until such time as they have been shown not to be addiction-producing.

Another item which should be mentioned is the definitions which had to be formulated for the new unified convention in the process of being elaborated by the Commission on Narcotic Drugs, United Nations. For "drug addiction" the following was accepted.

"Drug addiction is a state of periodic or chronic intoxication, detrimental to the individual and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include: (1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means; (2) a tendency to increase the dose; (3) a psychic (psychological) and sometimes a physical dependence on the effects of the drug."

It was also decided that expressions such as "habit-forming" should be replaced by "addiction-producing." There are many habits which are not addictions. Furthermore, the important principle was accepted that, according to all available evidence at the present time, any substance which is able to sustain an established addiction—i.e., will adequately replace the drug that has produced the addiction—must be regarded as also capable of producing an addiction.

This Expert Committee recommended, further, that every addiction-producing drug should be given a recognized common name by some authoritative body, in order to avoid long chemical designations as well as many different registered trade names for the same chemical substance. The realization of this proposal has been entrusted to the Expert Committee on the Unification of Pharmacopoeias, W.H.O., with the result that common names will be proposed not only for addiction-producing drugs, so that the international understanding in such a complicated matter as medicamentation will be simplified.

Attention is drawn to the development of the chemical, pharmacological, clinical, medico-social, and legal aspects of drug-addiction questions in their widest sense, also to substances which at present do not fall under the activities of W.H.O. but which may do so in the future.

Moreover, alcoholism, which had not been considered by earlier international health organizations, has become the concern of W.H.O. The effects of alcohol on the human organism, the aetiology of alcoholism, the determination of its nature and extent, the study of somatic as well as psychic and social factors which contribute to the development of this scourge, and the improvement of methods of treatment and of prophylaxis, are on the programme of studies to be undertaken.

B.C.G. Vaccination

Recognizing the need for scientific research in connexion with the mass B.C.G. vaccination programme of Unicef and Scandinavian Voluntary Organizations, and the unparalleled opportunity such a campaign offers for the world-wide study of tuberculosis, the Executive Board of the World Health Organization created a Tuberculosis Research

Office at its Second Session in November, 1948. In February, 1949, the Tuberculosis Research Office was established in Copenhagen in order to permit close working co-operation with the Joint Enterprise of Unicef and the Scandinavian Voluntary Anti-Tuberculosis Organization, and to undertake the responsibility of directing and supervising the tabulation and analysis of the statistical material collected in the B.C.G. campaign in various countries.

The B.C.G. campaign includes plans to tuberculin-test 50,000,000 children and young adults in Europe, and estimates that 15,000,000 persons will be vaccinated with B.C.G. By the first half of May, 1949, about 9,000,000 were tested and 4,000,000 vaccinated in Finland, Poland, Czechoslovakia, Yugoslavia, Hungary, Greece, Bulgaria, Austria, and Italy. The campaign has also been started in India, Ceylon, and North Africa, and plans are ready for the Middle East countries. It is expected that before long the work will be extended to East Asia and Central and South America. The wide geographical area involved, the large numbers to be tested and vaccinated, and the uniformity of procedures and materials used in the campaign are unique and unprecedented. An enormous number of observations on tuberculin sensitivity as well as records of vaccination have already been collected.

The compilation and analysis of these data require the greatest care and attention, and should provide not only an adequate documentation of the work of the campaign but also a valuable permanent record of the findings of the prevaccination tuberculin testings performed in various countries and areas.

During recent years much information has been accumulating which suggests that B.C.G. vaccination affords some protection against the development of tuberculosis, but decisive proof of this and the exact degree of protection are lacking. The statistical analysis of the records of vaccination and tuberculin testing carried out by the W.H.O. Tuberculosis Research Office should provide useful data on the protective powers of B.C.G. vaccine.

In order to encourage young people to gain wider experience in their work and improve their knowledge of languages by taking employment abroad, the Brussels Treaty Powers—Belgium, France, Luxembourg, the Netherlands, and the United Kingdom—have agreed on a Convention to facilitate exchanges of student employees between the five countries and to establish the principles by which such exchanges should be regulated. The Convention was signed by the Foreign Ministers at the meeting of the Consultative Council held in Brussels on April 17. It concerns student employees of either sex who may be employed in either manual or non-manual work. In general they will not be more than 30 years of age. The five Governments will exempt any necessary permits enabling student employees to stay in their countries and to take employment there from all taxes or charges other than purely nominal charges. In general the period for which they can stay in the country will be not more than a year, but in exceptional cases it could be extended for a further six months. No fixed numbers of student employees are laid down in the Convention, but it provides methods for regulating the numbers to be admitted by the various countries. The five Governments also agree to facilitate the exchanges of student employees either by setting up a central agency to supervise the application of the Convention or by other appropriate means with the help of organizations concerned with such exchanges. The Convention can be extended to nationals of any other country with the consent of all the five Governments. Last year the United Kingdom was visited by 704 student employees from the Brussels Treaty countries, of whom 101 came from Belgium, 241 from the Netherlands, 359 from France, and 3 from Luxembourg.

MEDICAL STATISTICS AND WORLD HEALTH

BY

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A World Health Organization could not function effectively without the aid of some medical statistics from most of its member States: as well try to conduct a global airway system without the aid of telecommunication. It is not enough to give directions and get the units moving; it is also necessary to measure their progress and know where they are. The Health Section of the League of Nations established an information system for epidemic diseases which proved its usefulness and continued to operate until it was incorporated in the World Health Organization. But the aims of W.H.O. extend far beyond the circulating of information on which countries can take action if they wish, and the "control" of epidemic diseases forms only a fraction of the whole programme of action.

The Aims of W.H.O.

Child health may be taken as an example, for it is known to be closely correlated with the infant mortality rate, which is not difficult to estimate. When countries are arranged in ascending order of this rate they fall into several broad groups. First come those with fairly complete medical certification of the cause of death and well-organized systems of vital statistics; next come those with poorly developed medical certification and vital statistics; and then those countries not yet possessing any system of registration but where infant mortality is known to be very high. It is not by accident that infant mortality and quality of medical statistics tend to run together, nor is this merely due to both being by-products of the quality of social and sanitary services. Whilst it is true that infant mortality can be brought down a long way by improving social conditions, guided by the experience of other countries who have had the advantage of good medical statistics, a point is reached beyond which a country is unable to reduce its rate further without guidance from *its own* statistics of mortality from different causes in various groups of its population.

The statistical concern of W.H.O. in this question of child health consists, therefore, in (a) assembling the national data in existence and drawing such conclusions as can be drawn from the imperfect material; (b) considering the faults in the data and how they can be removed by (i) international rules regarding definitions and mode of presentation of vital statistics, and (ii) advice and help to countries in establishing or improving their systems of collecting data; (c) enabling countries to benefit as fully as possible from experiences of other countries which have advanced further in the improvement of child health; (d) encouraging statistical researches into the various factors associated with child mortality and morbidity through the agency of National Committees on Health Statistics or their equivalents; (e) statistical supervision of international projects for improving child health so that their effectiveness may be measured and waste of money and effort minimized.

It is one thing, however, to make a tidy statement of aims such as the above, and another thing to see them realized, not only for child health, but also for other great problems such as tuberculosis and cancer. There is a natural inertia concerning statistics in any medical