REVIEW ARTICLE

INTERNATIONAL BIOLOGICAL STANDARDISATION

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Nobody would wish to deny that a stone's throw, a featherweight and a handful are very poor definitions of distance, weight or content. However, it was not until definite standards had been established and units of length, weight and volume related to them that it became possible to obtain accurate information about them. The foregoing is so evident that it would seem unnecessary to commit it to paper were it not that mankind has, as yet, not completely outgrown this stage and displays its conservatism by its refusal entirely to abandon archaic expressions such as pinches of salt and tablespoonfuls of medicine. Weight and bulk give information on the quantity of a certain substance, but tell us nothing of its composition. In order to obtain such information physical and, above all, chemical tests are indispensable. These alone may yield sufficient data regarding the composition and purity of a product. In fact, a large percentage of the drugs figuring in the pharmacopœias are satisfactorily defined in this manner. There are many pharmaceutical preparations, however, which cannot be characterised by means of chemical or physical tests alone. There may be various reasons for this. Sometimes the chemical composition of the drug is not known. Sometimes it contains impurities which interfere with the chemical tests and which may influence its activity. Again, it may be that such control tests are cumbersome and time-consuming. In all these cases alternative methods for measuring the specific activity of a certain preparation are indispensable. These have been found by making use of life itself, i.e. of the reaction of the living animal or of isolated living tissues to the administration of the drug. This type of assay is implied in the words biological standardisation.

Biological standardisation, therefore, involves the use of animals, which has the disadvantage of introducing a factor of considerable variability, since no two animals are identical in their reaction to a fixed amount of a drug. This variability can be reduced by the use of animals which are as uniform as possible as regards strain, weight, age, sex, etc., but it remains, nevertheless, a factor of great importance. For that reason it would be ineffectual to study the reaction of an animal or a group of animals to a certain drug without direct comparison of their reaction to a standard preparation, the potency of which is accurately defined. Such a standard preparation should be reasonably pure and it should, above all, be stable when stored at normal temperature.

The introduction of a biological standard preparation enables the comparison of a preparation of unknown strength with that of the standard, from which it may be concluded that both preparations are of the same

strength, or that one is stronger or weaker than the other. It is not possible, however, to draw any conclusions concerning the exact relations between the potencies of the two preparations. In order to overcome this difficulty it was necessary to assign units of activity to the standard preparation, such a unit representing the biological activity of a certain weight of the standard preparation. This weight is arbitrarily chosen, but it should be such that the number of units used in current practice is not too unwieldy. Thus it becomes possible to determine the weight of an unknown preparation which has the same activity as one unit of the standard. From this information the number of units per gramme of the unknown preparation can easily be calculated.

Much of biological standardisation work is based on Ehrlich's experiments of over fifty years ago with diphtheria antitoxin. Ehrlich carried out pioneer studies on the standardisation of this antitoxin. He first assigned a unit to diphtheria toxin which soon proved a failure. Toxin loses its toxicity on storage, but maintains its combining property with antitoxin. The unit, based on the toxic factor, was therefore far from stable. The antitoxic serum, however, remains unaltered for a long period of time, and for that reason is suitable as a standard. The unit was defined by Erhlich as the combining power (with diphtheria toxin) contained in a certain amount of antitoxic serum. This unit was later adopted as the International Unit of diphtheria antitoxin. The same principle has been applied to other immune sera for which international standards and their corresponding international units have been set up: the units are always expressed as the activity of the stable antiserum.

In the foregoing, the words "International Standards" and "International Units" have been used, thus showing that the work has left the national field and has entered the domain of international collaboration. This transition was undoubtedly highly desirable. The danger was by no means imaginary that each country, and even different laboratories within one country, would establish their own standards and units. This was, in fact, already taking place and threatening to lead to a highly undesirable state of confusion, thus defeating the unification at which the introduction of biological standards was aimed. Fortunately the Health Committee of the League of Nations, soon after its establishment, foresaw this imminent danger and decided to undertake a thorough investigation of the question. From 1921 onwards several conferences of experts were held at which many aspects of the problem were discussed, such as the standardisation of various sera and serological tests (1921: London[1]; 1922: Paris[2]; 1925: Geneva[3]); bloodgrouping sera (1930: Paris[4]); vitamins (1931: London[5]; 1934: London[6]); sex hormones (1932: London[7]; 1935: London[8]). Meanwhile the Health Committee had also established a Permanent Commission on Biological Standardisation which met usually every two years. At these sessions current problems of biological standardisation were discussed and recommendations were made concerning the setting up of new standards. Here, mention must be made of the important decision to convene an inter-governmental conference, the principal purpose of which was to promote the use of the international

standards in as many countries as possible. This conference was held in Geneva in the autumn of 1935. It recommended, amongst other things, that the use of international standards and units be made compulsory; that the distribution of standards continue to be free of charge, the cost being borne by the Health Organisation; and finally that a national centre be set up in each country for the storage and distribution of the preparations to interested laboratories within the various countries[9].

From the beginning of international co-operation an important part has been played by two central laboratories, the Statens Serum Institut, Copenhagen, and the National Institute for Medical Research, London. These Institutes acted, and are still acting, as centres for co-ordination. The usual procedure is as follows. When the Committee on Biological Standardisation considers that the setting up of a new international standard is warranted, one of the central institutes undertakes to obtain, and if necessary to prepare, the required material. It then distributes this material to different institutes experienced in this type of work for the testing of its suitability to serve as the international standard. The protocols of their assays are forwarded to the central institute, and are analysed statistically. It is on the basis of these analyses which are submitted to the Expert Committee on Biological Standardisation, that the suitability of the substance for adoption as the international standard is decided and the unit of potency is assigned to it.

It may well be that in the opinion of the Committee, the establishment of an international standard with a fixed unit of potency might be premature. It may be that they feel that the product in question is still in the research stage to some degree. Nevertheless, it would seem desirable that for the purpose of characterisation a good and stable sample of such a preparation should be made internationally available. In such a case the Expert Committee may decide to establish a reference preparation as an interim measure, which could, at a later date, be adopted as the international standard if the occasion arises. The central institutes are also responsible for the distribution of the standards to the various national centres. The Copenhagen Institute deals with all sera and bacterial products; the London Institute with hormones, vitamins, antibiotics and other drugs. The second world war caused many difficulties, but the work never completely ceased, and the distribution of standards continued as uninterruptedly as possible.

After the war the United Nations took over, and extended the work of the League of Nations. The World Health Organisation was created as one of the Specialised Agencies. It was at once understood by this body that the very important work of biological standardisation had to be continued. Therefore, from the very beginning of the World Health Organisation—during the Interim Commission—a new Expert Committee on Biological Standardisation was established, which continued to function when the World Health Organisation found its permanent form. The Committee met in 1947[10] and 1948[11] in Geneva, in 1949 in London[12] and in 1950 again in Geneva[13].

The principles laid down during the period of the League of Nations

were adhered to, an important one of which was that the Committee should remain averse to the prescribing of special methods or techniques for the assay of the various biological products for which standards have been established. It is felt that if laboratories use the technique to which they are accustomed, the best and most reliable results can be expected, and thus the door would always remain open to progress in methods of assay. Therefore, although in some cases a satisfactory method of assay may be indicated, hard and fast rules are never laid down. Although the setting up of biological standards and units is still the most important part of its work, the Committee has recently extended its field.

The use of BCG vaccine in the prevention of tuberculosis has considerably increased during the post-war years. Several of the United Nations International Children's Emergency Fund (UNICEF) anti-tuberculosis programmes include BCG vaccination in widely distant areas of the world. BCG vaccine cannot at present be preserved longer than approximately two weeks: therefore, owing to transport difficulties involved, decentralised manufacture is necessary. The preparation of BCG vaccine is a highly responsible task, the more so because it has to be distributed and used before the results of the various tests of innocuity and potency can be furnished, the time required for the performance of the tests being longer than that of the currency period of the vaccine. For this reason UNICEF has decided, in the interests of safety, to use only BCG vaccines which have been prepared in laboratories approved by the World Health Organisation. This very responsible task has been allotted to the Biological Standardisation Committee. Accordingly, during its 1949 meeting, it drew up minimal requirements for institutes engaged in the preparation of BCG vaccine. Approval by WHO is only given to laboratories complying with these requirements. This necessitates a careful inspection of the BCG-producing laboratory premises, of its staff and its methods of production and control investigation. This work is carried out either by a member of the Committee or by a staff member of WHO. The final approval is always given by the Committee itself.

Another new field of activity concerns the bacteriological diagnosis of tuberculosis. The WHO Expert Committee on Tuberculosis has asked the Expert Committee on Biological Standardisation to draw up a set of minimum requirements for laboratories occupied in this work. At its last session (November, 1950) the Expert Committee on Biological Standardisation discussed this problem and laid down some general guiding principles. This work in the diagnostic field is still in its initial stages but may be expected to widen considerably in the near future.

For another reason the duties of the Standardisation Committee are expanding. More and more other expert committees of WHO are beginning to seek advice on various subjects. During its 1950 meeting many questions were referred to the Committee by the Expert Committee on the Unification of Pharmacopœias, on Tuberculosis, and the Sub-Committee on Serology and Laboratory Aspects of the Expert Committee on Venereal Infection. These few examples serve to demonstrate that the

importance and the responsibilities of the Expert Committee on Biological Standardisation are constantly growing.

It is interesting to note the substances for which international standards and units have been established. For the purposes of clarity it is desirable to divide these into the following groups: (1) sera and bacterial products; (2) antibiotics; (3) vitamins; (4) hormones; (5) other drugs. These groups will be discussed separately.

Sera and Bacterial Products

As already mentioned, the first international standard and unit established concerned *diphtheria antitoxin* (1922). From then onwards standards for several other sera have been set up, together with the corresponding units. All these standards have served a very useful purpose. In view of the development of other therapeutic methods some are at present of less importance. Others are still indispensable, such as *tetanus antitoxin*, which is mostly administered as a prophylactic measure. The international unit assigned to the standard preparation has recently been changed. A dual notation of potency existed; the international unit and the United States unit, the latter being twice as big as the former. The Committee decided that the weight of the international unit be doubled, so as to make it equal to the U.S. unit (1949).

In view of the fact that *Streptococcus antitoxin* is still in continued therapeutic use, the establishment of a standard preparation is under consideration. Difficulties arising out of methods of assay have not, as yet, been overcome.

At its session in 1949 the Committee decided to re-embark upon work in the field of agglutinating sera, already begun by the League of Nations in 1932. Such sera are used for the diagnosis of infectious diseases, and it would be of great benefit if international standard preparations were available. This would increase the comparability of results of agglutination tests obtained in different laboratories. Agglutinating antisera for various *Salmonella* antigens and for the specification of the *X-strains of Proteus* are being prepared. The preparation of uniform agglutinating sera for the diagnosis of *cholera* has been promoted by making available dried cultures of both types of vibrio choleræ to be used in the preparation of such sera in the rabbit.

Work on bloodgrouping sera had already started in 1927. It was then restricted to questions of nomenclature. After the war the Committee considered the time ripe to establish Anti-A and Anti-B agglutinating serum standards. Large quantities of pooled anti-sera were collected and assayed in eleven laboratories. At its 1950 meeting the Committee assigned as international unit of *Anti-A agglutinating potency* the activity contained in 0·3465 mg. of the standard preparation, and as international unit of *Anti-B agglutinating potency* the activity contained in 0·3520 mg. of the standard preparation.

The Rh-factors have also attracted the attention of the Committee. At its 1949 meeting it occupied itself with attempts at unification of the systems of notation employed, and also recommended the inter-

national adoption of the term " Rh-negative " for which it formulated a definition, both for the blood donor and for the recipient. At its 1950 meeting the Committee went a step further and authorised the central institutes to undertake the establishment of standards for *anti-rh'* (*anti-C*), *anti-Rh°* (*anti-D*) and *anti-rh''* (*anti-E*) blood grouping sera of the blocking variety.

The trend of modern medicine is more and more towards the direction of prevention of diseases, leaving therapy to situations where preventive measures have failed or have been neglected. Thus, the use of bacterial products has come to the fore. Most of these are of an antigenic character and are therefore suitable for inducing immunity, thus preventing outbreaks of infectious diseases or diminishing their danger. For this reason the standardisation of antigens has become urgent, and the Committee devotes much time to the study of this problem. The difficulties are considerable, progress is very slow, and the majority of the problems is still in the stage of collaborative study.

Diphtheria toxoid and *tetanus toxoid* have been discussed at all meetings held since the war. At its last session (November, 1950) the Committee decided to establish a provisional reference preparation of diphtheria toxoid, plain, and a provisional reference preparation of diphtheria toxoid, aluminium phosphate adsorbed. Realising that many important questions are still open, it requested its Copenhagen Centre to study these and to obtain opinions of interested workers on the unitage of immunising power to be assigned to these preparations.

The same Institute was authorised to obtain a *pertussis vaccine* of proved protective value in man for distribution among interested workers for collaborative study with a view to establishing it as an international reference preparation.

The question of *smallpox vaccine* was also raised. In connection with the definition of minimum requirements for this vaccine it was recommended to test against human variola virus, the immunising potency of vaccinia virus used for the preparation of smallpox vaccine (1949). In 1950 the value of dried smallpox vaccine was discussed. The Committee described the requirements which the dried vaccine should satisfy.

Considerable work has been done in connection with the important and complex problem of *cholera vaccine*. Provisional reference preparations and three freeze-dried cholera vaccines of unknown potency were prepared. The Copenhagen Centre was authorised to institute a collaborative assay of the unknown vaccines in terms of the provisional reference preparations with a view to establishing the latter as definitive international reference preparations. Furthermore, freeze-dried cultures of its challenge strains of vibrio choleræ have been put at the disposal of interested workers by the Haffkine Institute, Bombay. Investigations are under way. It is expected that the results obtained will enable an increase in the immunising potency of cholera vaccines.

The question of *BCG vaccine* has already been mentioned. At its last meeting (1950) the Committee discussed the problem of dried BCG

vaccines. The chief advantage is their presumed keeping quality. This important point certainly needs additional clarification. Further research, concerning both liquid and freeze-dried BCG vaccine, is urgently required.

Tuberculin is a bacterial product used for the detection of allergy to tuberculo-proteins. A standard preparation for old tuberculin was established as early as 1931, and a unit assigned to it in 1948 described as being the activity contained in 10 micrograms of the standard preparation.

PPD (purified protein derivative) prepared from tuberculin is used for the same purpose. At various sessions the Committee discussed the desirability and feasibility of establishing a standard for PPD. As these are not the only purified tuberculo-proteins in current use, it was decided (1950) before further steps are taken that a collaborative comparison of various representative types be made.

ANTIBIOTICS

The Committee obviously recognises the necessity of devoting great attention to this new and enormously important development.

The desirability of an international standard preparation for *Penicillin* was already evident during the war. Accordingly in 1944, a conference was held in London at which it was decided that a pure crystalline preparation of a sodium salt of Penicillin G should serve as provisional international standard and that the activity contained in 0·6 microgram of this preparation should be the provisional international unit. This action was approved in 1947. The stocks are now running low and at its meeting in 1950 the Committee authorised the National Institute for Medical Research (a) to obtain a new standard preparation, (b) to organise a collaborative assay, and (c) to establish it as the second international penicillin standard.

As regards *Streptomycin* the Committee at its 1947 meeting considered that it was at that time impracticable to establish an international standard for this preparation. However, in order to promote uniformity in the assay of streptomycin potency it was considered necessary to establish an international reference preparation. In 1949 the Committee decided that the U.S. Food and Drug Administration working standard should be established as the international standard, and in 1950 it assigned to it a potency of 780 international units, or microgram equivalents, per milligram.

At this same meeting the Committee also authorised its London central institute to obtain a standard preparation of *Dihydrostreptomycin* and to assign to it a unitage or microgram equivalence. Since the preparation adopted is a pure and homogeneous preparation of one streptomycin, it is felt that the gramme equivalent notation of potency can legitimately be used in the description of its activity.

Several other important decisions were taken during the 1950 meeting. The establishment of international standards for *Aureomycin* and *Terramycin* was authorised.

Although it is possible to characterise *Chloramphenicol* by chemical

and physical means, it was considered convenient for workers engaged in production by fermentation methods to have an international preparation of reference. Accordingly the establishment of such a preparation was authorised.

The Committee also authorised the establishment of an international reference preparation for *Bacitracin*.

Other decisions made were that the Committee considered it desirable to have for distribution to interested workers specimens of certain antibiotics whose clinical and scientific status would justify their inclusion in a collection of " author's preparations." It decided (a) to invite authors who have described such antibiotics in the scientific journals to contribute specimens of their antibiotics to this collection, and (b) to advertise the collection as widely as possible among workers in the field of antibiotics.

Finally, the Committee studied the existing anomalies in the nomenclature of units in scientific literature. It recommended that it should be made widely known among authors and editors of scientific journals, that (a) when there was an official description of an authentic unit (e.g., an international or a national unit) the unit should be so described, and (b) when any other unit of potency was cited it should be fully described in the context, or proper reference made to a published description.

VITAMINS

In the field of vitamins the Committee established between 1931 and 1938 international standards and units for preparations of A, B_1, C, and D vitamins.

As regards the *Vitamin A* standard, at first a mixture of the α- and β-isomers of carotene was adopted (1931). As this proved not entirely satisfactory it was replaced in 1934 by a pure β-carotene preparation. Further, at its 1947 meeting, the Committee recommended its replacement by a standard consisting of a vitamin A ester. To study this problem a Sub-Committee on Fat-Soluble Vitamins was set up and its conclusions were adopted[14]. Accordingly the new international standard for Vitamin A is a crystalline all-trans vitamin A acetate. The international unit is the activity of 0·344 microgram of this preparation.

An adsorption product was used in 1931 as *Vitamin* B_1 standard. When it became possible to synthesise pure vitamin B_1 this latter preparation replaced the adsorption product. The international unit is contained in 0·003 mg. of the standard.

An international standard of pure fresh lemon juice was employed as a provisional standard of *Vitamin C*. However, after ascorbic acid, which could be chemically defined, was discovered, the provisional standard was replaced by a definitive international standard consisting of *l*-ascorbic acid, one international unit being contained in 0·05 mg.

The first preparation used as a *Vitamin D* standard was an irradiated ergosterol solution (1931). This was soon replaced by calciferol (1934). However, after it had come to light that the results of assays were greatly influenced by the species of animal used in the test, it became necessary to reconsider the problems. On the basis of extensive investigation

carried out in pre-war years, it was recommended by the above-mentioned Sub-Committee on Fat-Soluble Vitamins to replace the existing standard by a preparation of crystalline vitamin D_3. This proposal was adopted by the Expert Committee on Biological Standardisation (1949). The unit assigned to the new standard is the activity contained in 0·025 microgram of the standard preparation.

During the war a provisional international standard for *Vitamin E*, consisting of α-tocopherol acetate was set up (1941). At the time sufficient international contact was not possible, and it was not until 1947 that this action of the Department of Biological Standards, London, could be approved by the Committee on Biological Standardisation of the Interim Commission at its first session, thus adopting this provisional standard as a definitive international standard preparation.

The isolation of *Vitamin* B_{12} gave the Expert Committee the opportunity to discuss the suitability of this preparation as a standard for anti-pernicious anæmia factors.

Thus the National Institute for Medical Research was authorised to study the problem and to ascertain the opinion of workers in the field. At its 1950 meeting the Committee noted that the material had been acquired, and invited the said Institute to proceed with the characterisation of a standard preparation. The establishment of an international standard is undoubtedly very urgent, and the action taken by the Committee means a big step forward in this direction.

Hormones

Two international conferences on sex hormones were held in London in 1932 and 1935, under the auspices of the Permanent Commission of Biological Standardisation of the Health Organisation of the League of Nations, at which it was decided to adopt international standards for the *œstrus-producing hormones* obtained from the urine of pregnant women; one for the keto-hydroxy form and, later, a standard for the esterified form consisting of the monobenzoate of the dihydroxy form.

The former international standard was in such demand that by 1939 the supplies became so low that it was necessary to renew them. In 1949 the stocks of both these standards again became reduced and the Expert Committee on Biological Standardisation considered the desirability of replacing them. However, in view of the fact that all these substances are now made synthetically, their characteristics being perfectly definable by physical and chemical methods, the Committee felt that biological standards for these preparations were no longer necessary and their issue has, in fact, ceased from 1st January, 1951.

The first male sex hormone to be established in 1935 was the crystalline substance from male urine, named *androsterone* by Butenandt. It was realised, of course, that although androsterone was probably not the primary male testicular hormone, it was necessary as a reference preparation for the estimation of androgenic activity in blood, urine or other body fluids. This hormone was also renewed during the war years. In 1949, stocks were again renewed but it was decided that this should be for the

last time, androsterone now being generally considered to be an excretory product of testosterone, the latter being produced synthetically as a pure chemical and requiring no biological assay. When the present supplies are exhausted it will be withdrawn.

In 1935 it was decided to establish an international standard for the hormone of the corpus luteum-*progesterone*. At first, considerable difficulty was experienced in obtaining sufficient quantity of the material, only 3 g. becoming available. Later, in 1941, a total quantity of 50 g. of material was obtained and adopted as the second international standard for progesterone.

In 1937 a questionnaire was sent out by the Permanent Commission on Biological Standardisation to ascertain opinion in favour of the standardisation of *Gonadotrophic hormone* from the urine of pregnant women and pregnant mare serum and also whether standards should be provided for thyrotrophic and lactogenic hormones of the anterior pituitary lobe. As a result of a conference held in 1938, it was decided to establish two gonadotrophic hormone international standards, one for gonadotrophin obtained from the urine of pregnant women and the second from the serum of pregnant mares. The question of a revision of the methods of assay of gonadotrophic hormone was referred to the Expert Committee on Biological Standardisation. It is felt that the test dependent on the ovary weights or the cornification of the vaginal epithelium in immature rats yields less accurate results than that of the weights of the seminal vesicles in immature rats. The Committee recommended that a collaborative investigation should be made of the accuracy and precision of the methods in current use.

An international standard for the lactogenic hormone of the anterior pituitary lobe was set up in 1938 for the assay of *Prolactin*.

In 1938 it was recommended that an international standard for *Thyrotrophic hormone* should be established, but due to the scarcity of suitable material it was not possible to put this decision into effect until 1950. A reference preparation will be available shortly. At the same meeting the Expert Committee recommended that a reference preparation of growth hormones should be procured.

Owing to the recent clinical interest in *Adrenocorticotrophic hormone* and the availability of highly purified preparations, the Committee, at its last meeting in 1950, decided to set up a standard for adrenocorticotrophic hormone and to assign to it as a unit of potency the activity contained in 1 mg. of the international standard preparation.

Ever since 1925 an international standard preparation has existed for the assay of the *anti-diuretic, oxytocic* and *pressor principles* of the posterior pituitary lobe. This preparation consists of a quantity of acetone-extracted powder prepared from fresh ox pituitaries.

Perhaps the accurate biological standardisation of *Insulin* is of greater importance clinically than for any other substance, overdosage being no less dangerous than underdosage. The stocks of the present international standard of the pure crystalline hormone from the zinc salt, originally prepared by the Insulin Committee of Toronto University, are running

low, and the Expert Committee at its last meeting (November, 1950) authorised the National Institute for Medical Research, London, to obtain a preparation of insulin. It is especially important that the introduction of a new standard should in no way affect the value of the present unit of activity, and an extremely careful assay will be carried out comparing the proposed Third International Standard for Insulin with the existing Second International Standard.

Other Drugs

The first standard preparation for *Digitalis* was set up by the Commission on Biological Standardisation in 1926. It consisted of a mixture of 10 samples of dried and powdered leaves of *Digitalis purpurea.* The requests for this standard preparation were numerous and it had to be replaced by a second standard in 1935. After the war replacement was again necessary. The preparation of the new standard was entrusted to the National Institute for Medical Research which assayed six samples of digitalis powder. These were found suitable for mixture into a standard preparation. Collaborative assay of this mixture was carried out in 17 laboratories. After a full statistical analysis of the results of these investigations this mixture was adopted by the Committee as the third international standard for digitalis. The international unit is contained in 76 milligrams of this preparation.

A *Sulfarsphenamine* standard preparation was established in 1925. This was exhausted and replaced before the war. Recently replacement again became necessary, and a new batch was procured by the National Institute for Medical Research. This has proved suitable for the third international standard, which will be established shortly.

The Committee at its Fourth Session (1950) decided to proceed with the establishment of international standards for *Oxophenarsine* and Dimercaprol, and further to establish an international standard for *d-Tubocurarine,* and to assign to it a potency of 1 unit or 1 milligram-equivalent per milligram.

During its meeting in 1950 the Committee also discussed several other preparations. Among these were *Hyaluronidase, Streptokinase, Thrombin* and *Prothrombin.* No definite international action was taken, but the National Institute for Medical Research was invited to investigate the possibility of setting up international standards for *Hyaluronidase* and *Thrombin.*

On re-reading this article the writer is painfully aware of its incompleteness. Only some of the activities with which the Expert Committee on Biological Standardisation occupies itself have been mentioned. Those reviewed here have only been dealt with in a very cursory and superficial manner. It would not have been possible to treat the extremely complicated problems involved within the scope of the present short article.

For those interested a thorough study of the numerous documents published since the beginning of the Committee is essential. It is hoped, however, that these lines will be sufficient to demonstrate the importance

and extent of the work on Biological Standardisation undertaken by the World Health Organisation.

References

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12. Report of the Expert Committee on Biological Standardisation, 3rd Session, London, 1949 *(WHO Tech. Rep. Ser., 2).*
13. Report of the Expert Committee on Biological Standardisation, 4th Session, Geneva, 1950 *(document WHO/BS/112). Corr. 1.*
14. Report of the Sub-Committee on Fat-Soluble Vitamins *(WHO Tech. Rep. Ser., 3).*

International Standard Preparations and Units Established by the World Health Organisation

International standard preparations	*International units*	
Diphtheria antitoxin	0·0628	mg.
Tetanus antitoxin	0·3094	mg.
Anti-dysentery serum (Shiga)	0·0500	mg.
Scarlet fever antitoxin	—	*
Staphylococcus alpha antitoxin	0·5000	mg.
Anti-pneumococcus serum (Type I)	0·0886	mg.
Anti-pneumococcus serum (Type II)	0·0894	mg.
Gas-gangrene antitoxin (Perfringens)	0·2660	mg.
Gas-gangrene antitoxin (Vibrion septique)	0·2377	mg.
Gas-gangrene antitoxin (Œdematiens)	0·2681	mg.
Gas-gangrene antitoxin (Histolyticus)	0·3575	mg.
Gas-gangrene antitoxin (Sordelli)	0·1334	mg.
Anti-A blood Group agglutinating serum	0·3465	mg.
Anti-B blood group agglutinating serum	0·3520	mg.
Old tuberculin	0·01	mg.
Diphtheria antitoxin for flocculation test		
Vitamin A acetate	0·000344	mg.
Provitamin A (beta-carotene)	0·0006	mg.

* Unit potency to be assigned at the next session of the Expert Committee on Biological Standardisation.

Vitamin B_1 (Pure synthetic vitamin B_1)	0·003	mg.
Vitamin B_{12} (Pure crystalline)	—	*
Vitamin C (*l*-ascorbic acid)	0·05	mg.
Vitamin D_3 (crystalline)	0·000025	mg.
Vitamin E (alpha-tocopherol acetate)	1·0	mg.
Neoarsphenamine	—	
Sulfarsphenamine	—	
Insulin (Pure crystalline insulin)	0·0455	mg.
Pituitary (Posterior lobe) powder	0·5	mg.
Digitalis	76·0	mg.
Ouabain	—	
Androsterone	0·1	mg.
Corpus luteum hormone (Progesterone)	1·0	mg.
Chorionic gonadotrophin	0·1	mg.
Serum gonadotrophin	0·25	mg.
Prolactin (galactin or mammotrophin)	0·1	mg.
Heparin	0·0077	mg.
Penicillin G	0·0006	mg.

At its Fourth Session, held in Geneva, November 6-11, 1950, the Committee on Biological Standardisation established, or authorised the establishment of:

A. INTERNATIONAL STANDARD PREPARATIONS FOR:

1. *Adrenocorticotrophic hormone.* The international unit of potency is the activity contained in 1 mg. of the international standard preparation.
2. *Streptomycin,* with a potency a 780 international units or microgram equivalents per milligram.
3. *Dihydrostreptomycin.*
4. *Aureomycin.*
5. *Terramycin.*
6. *d-Tubocurarine.* The international unit is the activity contained in 1 mg. of the international standard preparation.
7. *Cardiolipin.*
8. *Lecithin.*
9. Anti-rh′ (anti-C) bloodgrouping serum.
10. Anti-Rh° (anti-D) bloodgrouping serum.
11. Anti-rh″ (anti-E) bloodgrouping serum.

B. INTERNATIONAL REFERENCE PREPARATIONS FOR:

12. *Thyrotrophin.*
13. *Growth Hormone* of the *anterior pituitary.*
14. *Chloramphenicol.*
15. *Bacitracin.*

C. PROVISIONAL REFERENCE PREPARATIONS FOR:

16. Diphtheria Toxoid, Plain.
17. Diphtheria Toxoid, Aluminium Phosphate Adsorbed.

* Unit potency to be assigned at the next session of the Expert Committee on Biological Standardisation.