EXPERT COMMITTEE ON
VENEREAL INFECTIONS AND
Treponematoses

Fifth Report

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EXPERT COMMITTEE ON
VENEREAil INFECTIONS AND TREPONEWATOSSES
Geneva, 21-26 September 1959

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EXPERT COMMITTEE ON VENEREAL INFECTIONS AND TREPONEMATOSES

Fifth Report *

The WHO Expert Committee on Venereal Infections and Treponematoses met in Geneva from 21-26 September 1959. The meeting was opened by Dr P. M. Kaul, Acting Director-General of WHO, who welcomed the members and mentioned some of the major current problems in the field of venereal infections and treponematoses.

The Committee unanimously elected Dr G. A. Canaperia as Chairman, Dr R. Wasito as Vice-Chairman and Dr L. M. Ram as Rapporteur, and adopted a working agenda. The following report was approved by the Committee.

* The Executive Board, at its twenty-fifth session, adopted the following resolution:

The Executive Board
1. NOTES the fifth report of the Expert Committee on Venereal Infections and Treponematoses;
2. THANKS the members of the Committee for their work; and
3. AUTHORIZES publication of the report.

1. THE BRUSSELS AGREEMENT OF 1924
AND MINIMUM REQUIREMENTS FOR MANAGEMENT
OF VENEREAL DISEASE IN SEAFARERS

The Committee noted the very complete review of historical and other
aspects of the 1924 Brussels Agreement respecting facilities for the treatment
of venereal diseases in merchant seamen (hereafter called the Agreement),
prepared by a Study Group which met to consider the Agreement in
Oslo in 1956. The subsequent discussion of, and observations on, the
report of this Group by the governing bodies of WHO were also noted
in regard to venereal diseases and the health of seafarers in general, particu-
larly the considerations of the WHO Executive Board (twentieth
and

1 The Executive Board, at its twenty-fifth session, adopted the following resolution:
The Executive Board
Having considered that part of the fifth report of the Expert Committee on
Venerable Infections and Treponematoses dealing with the International Agree-
ment of Brussels of 1924 regarding venereal disease treatment of seafarers,
1. TRANSFERS this report to the Thirteenth World Health Assembly; and
2. RECOMMENDS
(1) that the technical definitions, the minimum standards and the appraisal
scheme outlined therein be recommended by the Health Assembly to the States
Parties to the International Brussels Agreement as the basis for its application
and for venereal disease control practice in seafarers; and
(2) that the recommended technical definitions and standards be periodically
reviewed by WHO on the advice of its expert committee in the light of technical
progress.
The Thirteenth World Health Assembly adopted the following resolution:
The Thirteenth World Health Assembly
Considering that in accordance with Article 2 of the Protocol concerning the
Office International d’Hygiène publique, the World Health Organization has assumed
the duties and functions arising out of the administration of the International Agree-
ment Relating to Facilities to be Accorded to Merchant Seamen in the Treatment
of Venerable Diseases, signed at Brussels on 1 December 1924.
Considering that the Executive Board has recommended that the technical
definitions, the minimum standards and the appraisal scheme outlined in that part
of the Fifth Report of the Expert Committee on Venerable Infections and Trepnone-
matoses dealing with the Brussels Agreement of 1924, be recommended to the States
concerned as the basis for the application of that Agreement and for venereal disease
control practice in seafarers, and
Considering Article 23 of the Constitution,
1. RECOMMENDS to the States Parties to the Brussels Agreement of 1924 and to
the States which, as a matter of practice apply its provisions, the acceptance of the
technical definitions, the minimum standards and the appraisal scheme outlined in
the Fifth Report of the Expert Committee on Venerable Infections and Trepnone-
matos; and
2. RESOLVES that these technical definitions and standards be periodically reviewed
in the light of technical progress, on the advice of the Expert Committee.
(Resolution WHA13 52, Off. Rec. Wld Hth Org., 1960, 102

twenty-first ³ sessions) and the resolutions of the Health Assembly (Eleventh ² and Twelfth ⁹) leading to a study ⁴ by WHO of the broad health problems of seafarers and envisaging improvement of available health services in ports through further international co-operation between governments, WHO and the International Labour Organisation (ILO).

The Committee agreed with the broad views and recommendations of the Study Group given in its report.⁵ Presented from the point of view of health administration, the report is of considerable importance, if not indispensable, to other WHO governing bodies and other expert groups, which will study the question in the future.

The Committee decided not to reiterate in its report statements or recommendations already made by the Study Group, but only to include certain aspects of particular importance which required emphasis or to which new considerations applied.

In noting its terms of reference relating to the Agreement, the Committee proceeded (a) to define in some detail the technical implications of the Articles of the Agreement in the light of medical progress (see Appendix 1, page 11); (b) to suggest certain minimum standards of venereal disease control in seafarers, so as to make it possible for the health administrations adhering to the Agreement to have a fuller understanding of the provisions of the Articles (see Appendices 2, 3, 4, pages 12, 13, 14); and (c) to outline a scheme for assessing the work and worth of the Brussels Agreement (see Appendix 5, page 15).

1.1 The text of the Agreement

The Committee noted (as did the Oslo Study Group) that the original text of the Agreement of 1924 was in the French language and that the English translation of the original text—already in use prior to WHO's assumption of responsibility for the administration of the Agreement—in important respects did not appear to have the same meaning. After seeking competent advice, the Committee therefore decided to append to its report both the original French text and a comparable English and Spanish version of the Articles of the Agreement, so that in the future comparable value may be given to these languages and misunderstandings may be avoided.

1.2 Treatment in seaport clinics

The doctors responsible for the care under the Agreement of seafarers suffering from venereal diseases in ports fall into one of the following three categories:

(a) practising venereologists, who may also have public health responsibilities for venereal disease control;
(b) dermato-venereologists who may have hospital appointments;
(c) general medical practitioners who have received a varying amount of post-graduate specialized training.

From the first two categories, service of a reasonably high order is expected, but from all three the minimal training and other standards outlined by the Committee elsewhere (see Appendix 2, page 12) should be required.

1.3 Treatment aboard ship

The Committee noted that in addition to treatment at principal ports, there was also foreseen in the Agreement (Article 2) treatment aboard ships not carrying a doctor. During the last ten years there has been an increasing tendency to diagnose and treat suspected venereal diseases on board, without waiting for a medical opinion or the results of pathological investigations. In fact, it is likely with the simplified therapy now available that as many—if not more—venereal disease cases are treated afloat as ashore. In accordance with international practice the need for any medical treatment at sea is determined by the captain or by a person on board appointed for that purpose by the captain. This practice, if properly regulated, has much to commend it and has undoubtedly come to stay. An up-to-date definition of the Articles of the Agreement should make the practice reasonably efficient and safe, and should also ensure that a diagnosis of suspected venereal disease is always verified at the next port of call by laboratory tests, so that further treatment may be obtained as required. A smear should be taken of any urethral discharge for examination by the doctor at the next port, where a serological test also should always be carried out. While treatment of urethral discharge should be an immediate, adequate, dose of penicillin or similarly effective drug, genital sores should first be treated with sulphonamides and no antibiotic should be given if the next port of call can be reached within three weeks. If the distance is longer and the sore does not heal, further treatment by injections of an adequate dose of penicillin is justified—preferably a long-acting preparation such as procaine penicillin in oil and aluminium monostearate (PAM) or benzathine penicillin.
It was already pointed out in 1953 in the fourth report of the Expert Committee ¹ that there is a need for a specially trained individual—preferably a medical technician—aboard ships not carrying a doctor to be responsible for medical treatment. Every effort should be made to make this individual as efficient as possible in any situation. To improve his qualifications in venereal diseases and their management, he should have attended a short course of instruction at a well-conducted venereal disease clinic at a large seaport in his own country. He should have learned the importance of his own limitations, accurate diagnosis, and the damage that can result from haphazard methods. He should also know the potential danger and side effects of drugs used and how to handle them. Shipping companies and governments could with advantage encourage such training courses in ports in view of the great progress in the management of venereal disease during recent years.

1.4 The personal card

The Committee expressed the view that the use of a personal card, in which the patient is identified by number only and not by name, continued to be an important and useful part of the Agreement, and insisted in addition that the patient should not be identifiable by diagnosis. While the proposal by the Oslo Study Group of the introduction of a general health card for seafarers—into which also information on venereal disease could be incorporated—was welcomed, it was considered useful, in the meantime, to revise the personal card in use under the Agreement. The disease could be identified on the card by using the code number of the International classification of diseases, ² and to facilitate the work of doctors in ports, a list of these code numbers covering venereal conditions should be included in the World directory of venereal-disease treatment centres at ports. ³ The Committee noted in this connexion that several conditions with a venereal background were not contained as yet in the International classification of diseases. This should be arranged for as soon as possible by WHO. Furthermore, results of serological tests should be noted in accordance with the international designations as reactive, partially reactive or non-reactive. Laboratories in ports should adhere to approved serological methods and submit periodically batches of sera to national and international reference laboratories in order to assess test performance, and should also invariably make use of approved and tested reagents.

¹ World Health Organization. ¹953. 63
The evolution of cardiolipin antigens, based on the International Reference preparations of cardiolipin and lecithin, and of the International Standard of Human Syphilic Serum now available to all national health laboratories from the Department of International Standards, Statens Seruminstitut, Copenhagen, has made this possible.

1.5 The "World Directory of Venereal-Disease Treatment Centres at Ports"

The Joint ILO/WHO Committee on the Hygiene of Seafarers,1 and the fourth report of the Expert Committee on Venereal Infections and Treponematoses, as well as the Oslo Study Group, had recommended that the World directory of venereal-disease treatment centres at ports—of which a revised edition appeared in 1959—be included in the contents of the ship’s medicine chest. The Committee noted that the price of this revision of this publication had been considerably reduced, which should encourage health administrations and ship owners everywhere to implement this recommendation. The assistance of ILO might be sought in this connexion.

The Committee noted that five years had elapsed between the appearance of each of the two last editions of the Directory, and was of the opinion that this publication—useful as it already is—would be even more so if revised every three years as originally foreseen. A more frequent appearance would also make it possible to include new port areas opened to traffic from time to time, such as the St Lawrence Waterway.

1.6 Technical information

In view of the difficulty experienced by many doctors in charge of sea-port clinics in obtaining up-to-date literature on venereal disease management and control, it was strongly recommended that a biennial publication surveying recent advances in diagnosis, treatment and control be prepared by WHO and be made available to health administrations and the port doctors concerned. Very useful WHO publications of this type have already appeared.2 As a regular feature of the WHO programme, they could serve an important further purpose in the international control of venereal infections.

1.7 The assessment of the worth and work of the Brussels Agreement

The evaluation of the value and application of the Agreement might be based on four different approaches. It was considered that these four

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2 *Bull. Wld Hlth Org.*, 1954, 10, No. 4; 1956, 15, No. 6; 1958, 19, No. 3
approaches were supplementary to each other, and only by using them all could it be expected that a reasonable basis for the evaluation of the Agreement would result.

(1) *Initial survey*

Basic data should be collected from maritime Member States of WHO in an initial survey through a simple questionnaire requesting only the most essential information on the actual functioning of the Agreement. Data could be limited to the *principal sea and river ports* of States having ratified or acceded to the Agreement. The following points should be taken into account in the preparation by WHO of such a questionnaire:

(a) importance of traffic: tonnage volume and number of ships for the last 2-3 years, by national and foreign ships;

(b) nature of the services provided (specialized dispensary, health centre, polyclinic, hospital, private medical practitioner), their accessibility (distance from the port), number of staff (medical and auxiliary);

(c) coverage of diseases;

(d) laboratory facilities for diagnosis, routine examinations and treatment schemes;

(e) number of seafarers (national and foreign) examined and treated in the last 2-3 years (out-patients), and new cases of venereal infections by disease and by nationality;

(f) hospital treatment: availability of hospital beds for foreign seafarers, number of foreign seafarers hospitalized in the last 2-3 years (by diseases);

(g) number of personal cards given to patients, and number of seafarers with personal cards delivered by some other clinic;

(h) epidemiological investigations: are they carried out and promoted, and how is contact-tracing carried out? Is there exchange of national and international epidemiological information to promote case-finding?;

(i) health education activities and advertisement of facilities.

Health administrations should, at the same time, be invited to comment on the present working of the Agreement.

(2) *Consultant studies*

The services of WHO, in a consultative capacity, should be freely available and specifically offered to governments, so that various aspects of the Agreement can be studied in some sea and river ports chosen by WHO, and discussed on the spot by consultants drawn from WHO panel members and interested local clinicians and health administrators in the WHO Regions. Such an activity might be co-ordinated with the broader
inquiries envisaged in the study to be carried out by WHO into the general health problems of seafarers and the nature and extent of the services available to them in ports, as requested by the Eleventh World Health Assembly in the wider international approach to maritime health. By means of such surveys, valuable data contributing to the assessment of the working of the Agreement would be obtained.

(3) Yearly return forms

A return form should be brought into use on which governments adhering to the Agreement would be asked to furnish to WHO yearly information on certain minimal particulars for principal sea and river ports (see Appendix 3, page 15).

(4) Further survey

A second survey after 3-5 years, similar in nature and extent to those described under (1) and (2), should be carried out so as to provide comparative material for evaluation of the worth and work of the Brussels Agreement.

1.8 Recommendations

The Expert Committee on Venereal Infections and Treponematoses,

Having carefully studied historical and other developments relating to the Brussels Agreement of 1924, particularly the views and recommendations of the Study Group of 1956, and subsequently those of the WHO governing bodies;

Recognizing the importance of defining the implications of the articles of the Agreement in the light of medical progress and of establishing a basis for an evaluation of the worth and work of the Agreement; and

Noting that some large maritime nations have as yet not adhered to the Agreement,

RECOMMENDS

(1) that WHO encourage more governments of maritime countries to ratify the Agreement or to adhere to its practices;

(2) that the technical definitions of the Articles and the minimum standards outlined in the fifth report of the Expert Committee on Venereal Infections and Treponematoses be recommended to governments by WHO as the basis for the Agreement, and for venereal disease control practice in seafarers,1 and that these recommended definitions and standards be periodically reviewed and brought up to date by WHO on the advice of its Expert Committee in the light of technical progress every 3-5 years; and

1 Indicated in Appendices 1-4 inclusive (see pages 11-14)
(3) that the evaluation scheme for the work and worth of the Brussels Agreement outlined in the fifth report be based on a three-year survey period, and that a report on the findings be prepared for study by the WHO governing bodies.

APPENDIX I. BRUSSELS AGREEMENT ARTICLES

Definitions

Article
1. "Venereal diseases": To include syphilis (all forms), uncomplicated and complicated urethritis (any etiology), chancroid, lymphogranuloma venereum, granuloma inguinale and other local or general conditions with a venereal background.

2. "Services": The provision of specially trained and readily available medical and auxiliary staff, necessary medicaments, technical and non-technical equipment for the diagnosis and treatment of venereal diseases by up-to-date methods, as well as easily accessible public health or social workers necessary for control of the diseases, in addition to international exchange of epidemiological information in accordance with the practices of the countries concerned.

3. "Medical staff with specialized training": Duly qualified medical practitioners, legally authorized to practice medicine in the country where the services are provided and having post-graduate training, experience and ability in up-to-date methods of diagnosis, treatment, management and control of venereal diseases.


5. "Hospital beds": Occasionally required hospital beds for the treatment of, for example, syphilis complications, chancroid with suppurative adenitis, salpingitis, serious side effects of treatment, and similar conditions.

6. "Medical care and supply of medicaments": The free provision of all drugs, dressings, and other items needed for diagnosis and treatment, as well as the services of the doctor, the pathologist, and other staff.

7. "In-patient hospital treatment": Provision of all hospital care, including professional care, food, accommodation, nursing and attendance, etc., in accordance with the normal standards in the country concerned.

8. "Wassermann reaction": Implies up-to-date standardized, qualitative and quantitative, non-venereal tests for syphilis (reagin tests) using reagents referable to international standard reference preparations of cardiolipin, lecithin and human reactive sera, as well as specific tests using treponema immobilization (TPJ), fluorescent antibody tests, etc.) in problem cases, if practicable.
### APPENDIX 2. BRUSSELS AGREEMENT

**Minimum requirements for venereal disease management in seafarers:**

**Training of personnel**

**Medical practitioner in port**

Training always to include experience and proficiency in the following:

1. practical venereal bacteriology, regular and darkfield microscopy, and staining techniques;
2. the use and significance of *bacterial cultures*;
3. the principles and significance of qualitative and quantitative serological tests in the diagnosis of venereal diseases, including the TPI and similar tests, and the correct methods of collecting and dispatching serum for these tests;

**Medical technician at sea**

A specially trained person—preferably a medical technician—should administer treatment aboard, and his training should include a comprehensive course of instruction in a well-conducted venereal disease clinic in a seaport, before he is regarded as fit for these duties.\(^1\)

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\(^1\) As this work is of a responsible nature, it is important that the individual selected not only should be intelligent but should be a person likely to have the confidence of his shipmates.
(d) the significance and method of carrying out and reading skin tests in the diagnosis of lympho-granuloma venereum, chancroid, etc.;
(e) the use and application of all the medicines that are recognized internationally for the treatment of all venereal conditions;
(f) the significance of the side effects of treatment (e.g., hypersensitivity to antibiotics), their recognition and treatment;
(g) the performance of diagnostic lumbar puncture, prostatic examination, urethroscopy and the use of bougies for the assessment and dilatation of urethral strictures; understanding of the recognized criteria of cure in treated cases of all venereal disease;
(h) the internationally accepted public health and epidemiological methods for the control of the spread of venereal disease.

APPENDIX 3. BRUSSELS AGREEMENT

Minimum requirements for venereal disease management in seafarers:

Equipment in ports

The following items to be provided for the use of the doctor and for the pathologist in, or readily accessible to, the premises where patients are examined and treated:

(a) a bacteriological microscope with darkfield and Abbé condensers, suitable lamps, and a sufficient supply of slides;
(b) the reagents and stains necessary for the Gram staining of smears;
(c) the reagents necessary for performing routine tests on urine;
(d) a supply of syringes and needles suitable for all purposes, e.g., intravenous, intramuscular, subcutaneous and intradermal use, and facilities for their proper sterilization, which should be adequate for bacterial, viral and chemical contamination (e.g., sensitizing antigens);
(e) proctoscopes, urethral bougies, vaginal specula sponge-holding forceps and platinum loops;
(f) the usual diagnostic instruments;
(g) supplies of long-acting penicillin preparations for the treatment of syphilis, e.g., PAM or benzathine penicillin, and of shorter-acting preparations of penicillin, streptomycin, sulfonamides, tetracycline preparations and possibly of erythromycin;
(h) supplies of appropriate restoratives to combat sudden anaphylactic and other reactions following treatment. Adrenaline (indispensable), steroid preparations, oxygen, aminophyllin, antihistaminic drugs (desirable);
Equipment in ports

(i) supplies of the usual preparations for the treatment of other venereal conditions, such as podophyllin for genital papillomatosis, benzyl benzoate for scabies, an efficient insecticide for pediculosis, peroxide of hydrogen for balanitis, trichomonal pessaries for trichomoniasis in females;

(j) suitable consulting-room furniture, office equipment and supplies;

(k) a copy of the latest edition of the WHO World directory of venereal-disease treatment centres at ports;

(l) a supply of the personal cards approved under the Agreement;

(m) a copy of the latest WHO publication reviewing recent advances in the diagnosis, treatment, management and control of the venereal diseases.

APPENDIX 4. BRUSSELS AGREEMENT

Minimum requirements for venereal disease management in seafarers:

Equipment at sea

The following items to be provided for the treatment at sea and eventual diagnosis of the venereal diseases on ships not carrying a doctor:

(a) a supply of microscopic slides;

(b) a supply of 10-ml all-glass, or preferably nylon, syringes and of stainless steel needles for intramuscular use (gauge 18-20 and at least 2 in. (5 cm) long);

(c) a small sterilizer or pressure cooker for sterilizing syringes;

(d) supplies of an easily handled penicillin preparation suitable for the treatment of gonorrhoea, e.g., aqueous procaine penicillin fortified;

(e) supplies of a long-acting sulfonamide preparation suitable for the treatment of gonorrhoea or other urinary infections (preferably one with a minimum tendency to cause crystalluria in the tropics);

(f) ampoules of an adrenaline solution immediately ready for use—preferably one with needle already attached, 1:1000;

(g) a copy of the latest edition of the WHO World directory of venereal-disease treatment centres at ports;

(h) a supply of the personal cards approved under the Agreement;

(i) a booklet giving simple descriptions of the various manifestations of the venereal diseases and clear, easily understood instructions for their treatment at sea. These instructions—which could with advantage be embodied in a general medical handbook—should forbid the treatment of venereal sores with antibiotics when the next port of call is to be reached within three weeks, and should explain why a urethral smear should be made before giving penicillin for suspected gonorrhoea.
APPENDIX 5

Yearly return forms to WHO from governments adhering to the Brussels Agreement of 1924, covering "principal sea and river ports" only

1. The numbers of seamen, by nationalities, dealt with annually in each such port, specifying the diagnosis for each case. The following headings would probably be adequate for this purpose:

(a) syphilis (primary and secondary);
(b) syphilis (all other forms);
(c) gonorrhoea;
(d) other forms of urethritis;
(e) other venereal conditions treated;
(f) conditions not needing treatment.

2. The ports, home or foreign, where the diseases were probably contracted.

3. The number of seamen seen in consultation who have undergone treatment at sea for urethritis or for venereal ulcers.

APPENDIX 6 A

Arrangement relatif aux facilités à donner aux marins du commerce pour le traitement des maladies vénériennes

Signé à Bruxelles, le 1er décembre 1924

Article premier

Les Hautes Parties contractantes s'engagent à créer et à entretenir dans chacun de leurs principaux ports, maritimes ou fluviaux, des services vénéréologiques ouverts à tous les marins du commerce ou bateliers, sans distinction de nationalité.

Ces services auront un personnel médical spécialisé et une organisation matérielle tenue constamment à jour des progrès de la science. Ils seront installés et fonctionneront dans des conditions telles que les intéressés y puissent avoir accès facilement. Leur développement sera proportionné, dans chaque port, au mouvement de la navigation et ils disposeront d'un nombre suffisant de lits d'hôpital.

1 L'application de l'Arrangement de Bruxelles et l'étude de ses implications techniques ont été prises en charge par l'Office international d'Hygiène publique à partir du moment où l'Arrangement a été soumis pour la première fois aux gouvernements; c'est-à-dire à partir de 1921. En vertu de l'Arrangement signé à New York, le 22 juillet 1946, par les gouvernements représentés à la Conférence internationale de la Santé, de même qu'aux termes du Protocole concernant l'Office international d'Hygiène publique, signé à New York à la même date, les responsabilités et fonctions de l'Office, y compris celles qui se rapportent à l'Arrangement de Bruxelles, ont été transférées à l'Organisation mondiale de la Santé et officiellement assumées par la Commission intérimaire au moment de l'entrée en vigueur du Protocole, le 20 octobre 1957.
Article 2

Les soins médicaux ainsi que la fourniture des médicaments seront gratuits ; il en sera de même de l'hospitalisation, lorsqu'elle aura été reconnue nécessaire par le médecin du service.

Les malades recevront également, à titre gratuit, les médicaments nécessaires aux traitements à suivre en cours de route et jusqu'à la prochaine escale prévue.

Article 3

Il sera délivré à chaque malade un carnet strictement personnel sur lequel il pourra n'être désigné que par un numéro, et où les médecins des diverses cliniques visitées par lui inscriront :

(a) Le diagnostic, avec l'indication sommaire des particularités cliniques relevées au moment de l'examen ;
(b) Les opérations faites à la clinique ;
(c) Les prescriptions à suivre en cours de route ;
(d) Les résultats des examens sérologiques pratiqués dans les cas de syphilis (Wassermann).

Ces carnets seront établis conformément au modèle ci-annexé. Ils pourront être ultérieurement modifiés par voie administrative.

Il est désirable, afin de faciliter la comparaison, que la recherche de la réaction de Wassermann soit faite, autant que possible, suivant une technique uniforme.

Article 4

Les capitaines de navires et les patrons de bateaux seront tenus de faire connaître à leur personnel l'existence des services visés dans le présent arrangement.

Au moment de l'arraisonnement du navire ou de sa première visite à bord, l'officier sanitaire remettra au personnel des notices indiquant les lieux et les heures de consultations.

Article 5

Les Etats qui n'ont pas pris part au présent arrangement seront admis à y adhérer sur leur demande. Cette adhésion sera notifiée par voie diplomatique au Gouvernement belge et par celui-ci aux autres gouvernements signataires.

Article 6

Le présent arrangement sera mis en vigueur dans un délai de trois mois à dater du jour de l'échange des ratifications. Dans le cas où l'une des Parties contractantes dénoncerait l'arrangement, cette dénonciation n'aurait d'effet qu'à l'égard de cette partie et cela une année seulement à dater du jour où cette dénonciation aura été notifiée au Gouvernement belge.

Article 7

Sauf décision contraire à prendre par l'une ou l'autre des Puissances signataires, les dispositions du présent arrangement ne s'appliqueront pas aux Dominions à gouvernement propre, aux colonies, possessions et protectorats des Hautes Parties contractantes et aux territoires à l'égard desquels un mandat a été accepté par les Parties contractantes au nom de la Société des Nations.

Cependant, les Hautes Parties contractantes se réservent le droit d'adhérer à la convention, suivant les conditions de l'article 5, au nom de leurs dominions à gouvernement propre, colonies, possessions ou protectorats, ou encore des territoires pour lesquels elles ont accepté un mandat au nom de la Société des Nations. Elles se réservent également le droit de la dénoncer séparément suivant les conditions de l'article 6.
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Article 8

Le présent arrangement sera ratifié et les ratifications seront déposées à Bruxelles dans le plus bref délai possible.

En foi de quoi les plénipotentiaires respectifs ont signé le présent arrangement et y ont apposé leurs cachets.

Fait à Bruxelles, le 1er décembre 1924, en un seul exemplaire, qui restera déposé dans les archives du Ministère des Affaires étrangères de Belgique, et dont une copie, certifiée conforme, sera remise à chaque Puissance contractante.

APPENDIX 6 B

Agreement respecting facilities for the treatment of venereal disease in merchant seamen

Signed at Brussels, 1 December 1924

Article 1

The High Contracting Parties undertake to establish and maintain in each of their principal sea or river ports venereal disease services open to all merchant seamen and watermen, without distinction of nationality.

These services shall have a medical staff with specialized training and technical equipment kept constantly abreast of the progress of science. They shall be so established and worked as to be readily accessible to those desiring to make use of them. Their size shall be proportionate in each port to the volume of traffic, and they shall have at their disposal a sufficient number of hospital beds.

Article 2

Medical care and the supply of medicaments shall be free of charge. The same shall apply to in-patient hospital treatment when it is considered necessary by the doctor of the service.

Patients shall also receive free of charge the medicaments necessary for the treatment to be followed on the voyage and as far as the next scheduled port of call.

1 Responsibility for the application of the Brussels Agreement and for the study of its technical implications were assumed by the Office international d’Hygiène publique from the time when the Agreement was first proposed to governments in 1921.

Under the Agreement concluded by the governments represented at the International Health Conference, signed at New York on 22 July 1946, and the Protocol concerning the Office international d’Hygiène publique, signed at New York on the same date, the duties and functions of the Office, including those relating to the Brussels Agreement, were transferred to the World Health Organization, these duties and functions being formally assumed by the Interim Commission upon the entry into force of the Protocol on 20 October 1947.
Each patient shall receive a card, which shall be strictly personal to himself, and on which he shall be designated by a number only. On the card the doctors of the different treatment centres visited by him shall enter:

(a) the diagnosis, with a summary of the clinical particulars noted at the time of the examination;
(b) the treatment carried out at the centre;
(c) the treatment to be followed on the voyage;
(d) the results of serological examinations undertaken in cases of syphilis (Wassermann).

These cards shall conform to the model annexed to the Agreement. They may be modified later by administrative action.

It is desirable, in order to make comparison easier, that the Wassermann test should be carried out so far as possible by a uniform method.

Ships' masters and skippers shall be required to make known to their crews the existence of the services mentioned in the present Agreement.

At the time of the vessel's sanitary inspection, or of his first visit on board, the sanitary officer shall furnish the crew with notices showing times and places for consultations.

States which are not Parties to the present Agreement shall be allowed to accede thereto at their request. Such accession shall be notified through the diplomatic channel to the Belgian Government and by them to the other signatory Governments.

The present Agreement shall enter into force three months after the date of the exchange of ratifications. Should one of the Contracting Parties denounce the Agreement, the denunciation shall have effect only as regards that Party, and not till one year after the date of the notification of the denunciation to the Belgian Government.

In the absence of a contrary decision by one or other of the signatory Powers, the provisions of the present Agreement shall not apply to self-governing dominions, colonies, possessions or protectorates of the High Contracting Parties or territories in respect of which a mandate has been accepted by the Contracting Parties on behalf of the League of Nations.

Nevertheless, the High Contracting Parties reserve the right to accede to the convention, in accordance with the provisions of Article 5, in the name of their self-governing dominions, colonies, possessions or protectorates or of territories in respect of which they have accepted a mandate on behalf of the League of Nations. They reserve also the right to denounce it separately, in accordance with the provisions of Article 6.

The present Agreement shall be ratified and the ratifications shall be deposited in Brussels as soon as possible.

In faith whereof the respective Plenipotentiaries have signed the present Agreement and have affixed to it their seals.
FIFTH REPORT

Done at Brussels, 1 December 1924, in a single copy, which shall remain deposited in the archives of the Belgian Ministry for Foreign Affairs, and of which a certified copy be communicated to each contracting Power.

APPENDIX 6 C

Acuerdo

relativo a las facilidades que han de darse a los marinos mercantes para el tratamiento de las enfermedades venéreas

Firmado en Bruselas el 1º de diciembre de 1924

Artículo 1

Las Altas Partes contratantes se obligan a establecer y a sostener en cada uno de sus principales puertos, marítimos o fluviales, servicios venéreológicos abiertos a todas las tripulaciones mercantes dedicadas a la navegación marítima y fluvial, sin distinción de nacionalidad.

Esos servicios contarán con un personal médico especializado y una organización material constantemente adaptada a los adelantos científicos. Estarán instalados y funcionarán de manera que el acceso para los interesados sea fácil. Tendrán importancia proporcional al movimiento de la navegación en cada puerto y dispondrán de un número suficiente de camas de hospital.

Artículo 2

La asistencia médica y los medicamentos serán gratuitos; también lo será la hospitalización cuando el médico del servicio la considere necesaria.

Los enfermos recibirán asimismo gratuitamente los medicamentos que requiera la continuación del tratamiento durante la travesía hasta la próxima escala prevista.

Artículo 3

Se entregará a cada enfermo una cartilla estrictamente personal, en la que podrá designárselle sólo con un número y donde los médicos de las distintas clínicas que visite inscribirán:

a) el diagnóstico y una breve indicación de las particularidades clínicas observadas en el momento del examen;

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1 Desde 1921, año en que por primera vez se propuso a los gobiernos el texto del Acuerdo de Bruselas, el Office International d'Hygiène Publique quedó encargado de velar por la aplicación del Acuerdo y de estudiar sus posibles consecuencias de orden técnico.

En ejecución del convenio firmado en Nueva York el 22 de julio de 1946 por los gobiernos representados en la Conferencia Internacional de la Salud, y del Protocolo sobre el Office International d'Hygiène Publique, firmado en el mismo lugar y en la misma fecha, las funciones y las atribuciones del OIHP fueron transferidas a la Organización Mundial de la Salud. El 20 de octubre de 1947, fecha de la entrada en vigor del Protocolo, esas funciones y esas atribuciones fueron oficialmente asumidas por la Comisión Interina de la OMS.
b) el tratamiento administrado en la clínica;

c) las prescripciones que deban seguirse durante la travesía;

d) el resultado de los exámenes serológicos practicados en los casos de sífilis (Wassermann).

Las cartillas se ajustarán al modelo adjunto, que podrá ser modificado ulteriormente por vía administrativa.

Será conveniente para facilitar las comparaciones que, siempre que sea posible, se practique la reacción de Wassermann según una técnica uniforme.

Artículo 4

Los capitanes y los patrones de barco deberán poner en conocimiento del personal a sus órdenes la existencia de los servicios mencionados en el presente Acuerdo.

Durante la inspección sanitaria del buque o en su primera visita a bordo, el funcionario de sanidad facilitará informaciones al personal sobre los lugares y las horas de consulta.

Artículo 5

Los Estados que no sean Partes en el presente Acuerdo podrán adherirse a él formulando la oportuna petición. La adhesión se comunicará por vía diplomática al Gobierno de Bélgica, que, a su vez, la pondrá en conocimiento de los demás gobiernos signatarios.

Artículo 6

El presente Acuerdo entrará en vigor en un plazo de tres meses a contar del día en que se haga el canje de ratificaciones. Si una de las Partes contratantes denunciara el Acuerdo, la denuncia no tendría validez más que para dicha Parte y sólo después de haber transcurrido un año desde el día en que hubiere sido notificada al Gobierno de Bélgica.

Artículo 7

Salvo decisión en contrario de una u otra de las Potencias signatarias, las disposiciones del presente Acuerdo no se aplicarán a los dominios autónomos, a las colonias, posesiones y protectorados de las Altas Partes contratantes ni a los territorios sobre los que las Partes contratantes hayan aceptado ejercer un mandato en nombre de la Sociedad de Naciones.

Ello no obstante, las Altas Partes contratantes se reservan el derecho de adherirse al Acuerdo, con arreglo a las condiciones del Artículo 5, en nombre de sus dominios autónomos, colonias, posesiones o protectorados, o de los territorios sobre los que hayan aceptado ejercer un mandato en nombre de la Sociedad de Naciones. Asimismo se reservan el derecho de denunciar esa adhesión por separado, con arreglo a las condiciones del Artículo 6.

Artículo 8

El presente Acuerdo deberá ser ratificado, y las ratificaciones se depositarán en el más breve plazo posible en Bruselas.

En fe de lo cual los plenipotenciarios respectivos han firmado y sellado el presente Acuerdo.

Hecho en Bruselas el 1 de diciembre de 1924 en un solo ejemplar que quedará depositado en los archivos del Ministerio de Asuntos Extranjeros de Bélgica, y del que se enviará una copia auténtica a cada una de las Potencias contratantes.
2. VENEREAL INFECTIONS

With the introduction of penicillin, which provided a quick, safe and rapid treatment for both syphilis and gonorrhoea, hopes were entertained a decade ago that these diseases might be eliminated as a public health problem, or at least controlled. A dramatic decline in the number of cases of early syphilis was initially apparent everywhere. However, a recent recrudescence has been noted in several countries. Although the fall in the numbers of reported cases of gonorrhoea was initially marked—e.g., a 56.8% decrease in Canada between 1946 and 1956—this decline has not been so apparent as in the case of syphilis. In many countries in Africa, the Americas, Europe, the eastern Mediterranean, south-east Asia and the western Pacific, the reservoir of gonorrhoea is in fact increasing. With regard to the non-gonococcal venereal infections, chancroid has declined further in incidence and is becoming less of a health problem; lymphogranuloma venereum and granuloma inguinale are becoming rare; while non-gonococcal urethritis appears to be an increasing health problem, the incidence in some countries approaching that of gonorrhoea.

Over the past ten years, the emphasis placed on venereal infections by health administrations has lessened after initial encouraging results in venereal disease control programmes. In this connexion, the Committee noted the sometimes extensive assistance programmes of WHO to develop national or local venereal disease control programmes in some 40 countries during this period, and expressed the view that further work is required nationally and internationally, and that planning is needed in areas where the reservoir of venereal infections has remained high and no active programmes have been undertaken. Surveys have shown that syphilis is still quite common in some countries, particularly in towns and seaport areas in Asia and South America. This also applies to clinical or infectious latent gonorrhoea. The economic importance of these diseases and their sequelae in reducing employability for work in industry and agriculture in the most productive age-group cannot be ignored. The considerations of the Sixth Health Assembly in its technical discussions on syphilis in this and other connexions are significant.1

Summing up, the Committee emphasized that venereal diseases are not dying diseases, but remain a public health problem in many areas.

2.1 Syphilis

The Committee reviewed the statements of previous Expert Committees,2 did not wish to restate recognized syphilis control procedures, and limited

1 Chron. Wild Hlth Org., 1953, 7, 195
itself to pointing out certain new developments and suggesting further avenues of approach.

Although there had been a spectacular decline in the incidence of early syphilis in many countries, in some areas it remains a public health problem. In the USA an increase of 15% of infectious cases was reported in 1959 over the preceding year. The disease has in fact been on the increase since 1954, and syphilis in all its stages ranks fourth in the USA among notifiable diseases. In some other countries also there has been a resurgence in recent years (e.g., Finland, France, Italy and various areas in Africa).

With improving economic conditions throughout the world, more and more persons with infectious syphilis are seeking treatment from private medical practitioners. As shown by surveys in areas where the disease is notifiable, it is estimated that only 25% of the cases diagnosed and treated by private physicians are reported. The Committee therefore wished to point out the need for health administrations to work closely with medical practitioners and offer epidemiological and possibly laboratory services to facilitate more effective venereal disease control.

In the field of epidemiology, paramedical lay personnel are in some areas being used for case-interviewing and investigating with considerable success. A new interviewing technique, the "cluster" technique, involving examination of persons moving in the same socio-sexual environment, has been shown almost to double the number of cases found.

In some areas the treatment of all verified contacts of infectious cases has been found to be an important measure in preventing the spread of infection. This technique should be given careful attention by health administrations in areas where the disease is a serious public health problem. The Committee took note of the international exchange of epidemiological information now used in several areas, and urged all health administrations actively to use this measure as a further aid in the world-wide control of syphilis.

New treponemal tests, such as the FTA (fluorescent treponemal antibody) and the RPCF (Reiter protein complement fixation), as well as non-treponemal tests, such as the RPRT (rapid plasma reagin test) and the PCT (plasmacrit test), have been developed in recent years. Because of rapidity, ease of performance, and low cost, they may be used in the screening of migrant groups, in field surveys and in mass campaigns, etc. These developments are important not only in syphilis, but also in the other treponematoses.

Penicillin PAM or benzathine penicillin remain the preparations of choice for the treatment of syphilis, and treatment schedules have remained essentially as suggested at the fourth meeting of the Committee,1 where

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1 World Health Org. techn. Rep. Ser., 1953, 63, 19
minimal requirements were reviewed. Penicillin reactions are reported to be increasing (see section 4, page 42) but have not reached any point of alarm. They can by no means be compared in incidence with reactions in the metal chemotherapy era, although sometimes as dangerous.

Although there have been advances in control methods and epidemiological, serological and laboratory techniques since the fourth Committee met in 1952, the present Committee, in observing the current unsatisfactory situation, urges that those measures which have proved successful be used more actively while T. pallidum is still highly susceptible to penicillin. Recent recrudescences in the incidence of syphilis show that intensified efforts are required both in developed and developing countries. In the African region, for instance, a concerted effort against syphilis is particularly desirable: the possibility that syphilis may spread into tropical rural areas, where yaws is being eradicated, cannot be ignored. In addition to the wider use of techniques available, research into many aspects (see section 8, page 61) are required, including the role of immunity, methods of cultivating T. pallidum, and epidemiological procedures.

2.2 Gonorrhoea

In many countries in recent years the numbers of reported cases of gonorrhoea have remained virtually static or have increased—in some countries substantially. Comparative data were presented to the Committee of the number of gonorrhoea cases reported in 22 countries and territories. In no less than 15 there has been a rise in numbers, and in four the situation appears static. The annual incidence ranges from 10 to 50 per 10,000 inhabitants. The magnitude of the reservoir of infection was also demonstrated by the morbidity statistics of gonorrhoea published in a recent ten-year review by WHO.¹

The limitations of figures of reported cases are well known, as many unreported cases of gonorrhoea are treated by private practitioners. For example, in the USA it is estimated that the incidence of gonorrhoea is five to ten times higher than is actually reported.

Available information indicates that gonorrhoea is widespread, remains uncontrolled, and is one of the most challenging health problems in many parts of the world.

2.2.1 Reasons for failure of control

The reasons for the lack of control include, in addition to general factors: difficulties in defining the reservoir of infection, difficulties in diagnosis, and increasing difficulties in the treatment and management of the disease.

¹ Epis. vital Statist. Rep., 1959, 12, 301
(a) Since treatment became simplified there has been a declining interest in, and a changed attitude to, gonorrhoea among the public. The same applies perhaps to the profession. Cases are under-reported by private physicians wherever the infection is reportable, and contact investigation is undoubtedly less vigorous in gonorrhoea than in syphilis.

(b) Venereal disease in young persons is an increasing problem in some countries and cannot be ignored as part of the “teenage” problems. Other problem groups include military personnel, seafarers, migrant labour groups, and promiscuous females. Repeated infections are common, and self-treatment is probably frequent.

(c) There is an important statistical difference between reported cases of gonorrhoea in males and females, signalling a failure to diagnose the disease in females, who may have few or no symptoms during infectious latency of long duration.

(d) The difficulties in diagnosis—again especially in the female—have long been recognized, as routine clinical and laboratory techniques fail to diagnose at least half of the cases. The limitations of smears and cultures are generally recognized, and “transportation media” introduce further difficulties.

(e) Difficulty in treatment has arisen as a contributory factor in the failure to control gonorrhoea. Lessened sensitivity—or resistance—to penicillin by the gonococcus has been observed in laboratories in several countries. The existence of penicillin-resistant strains of gonococci may become a growing problem, and increased failure rates with dosage schedules of penicillin previously adequate have been reported.

Proper tests of cure have once again, under these circumstances, assumed an increasing epidemiological importance. The management and follow-up requirements have thereby become even more complex.

2.2.2 Lack of parallel decline in gonorrhoea and syphilis

The following reasons have been advanced for this interesting epidemiological phenomenon:

(a) a higher proportion of infected contacts is secured in syphilis than in gonorrhoea, partly because a greater effort is made in syphilis, the latter being regarded as the more serious disease, and partly because the longer incubation period of syphilis allows a longer time for the finding of contacts before they become infectious;

(b) gonorrhoea is many times more frequent than syphilis, which, in addition to the shorter incubation period, enhances the statistical chance of spread of the infection. In addition it is also more infectious than syphilis;
(c) there is a greater chance that antibiotics will be given for unrelated conditions during the long incubation period of syphilis than during the short incubation period of gonorrhoea. On the other hand, particularly in the male, the shorter incubation period of gonorrhoea should allow fewer exposures before the patient has obvious symptoms and seeks advice;

(d) more persons are susceptible to gonorrhoea than syphilis, as some persons are immune to syphilis (e.g., seroreactors from past syphilis or other treponematoses). Immunity to gonorrhoea, though apparently present to a slight degree in experimental infections, is of little practical significance and repeated infections are common;

(e) gonorrhoea, unlike syphilis, is difficult to diagnose, especially in the female, and is very often not discovered by routine tests. This has reduced the feasibility of widespread or "target" case-finding surveys, such as can be made with syphilis;

(f) other possible reasons include the inadequacy of the penicillin treatment of gonorrhoea generally applied in the early period after the Second World War, as compared with that of syphilis, and last but not least the fact that epidemiological treatment of contacts is not generally applied.

In pre-sulfonamide days about one-fifth of male cases and over one-third of female cases developed complications. The incidence of complications declined markedly in the sulfonamide era and still further with the introduction of penicillin. Today it is agreed that serious complications are much less frequent. However, salpingitis is still quite common in the female. Indeed, in some developing areas female complications are known to reduce fertility, and in such areas, and others with a high endemicity of the infection, total mass treatment with penicillin has given interesting results.

Ophthalmia neonatorum is still a problem in some areas, and a recent rise in prevalence has been observed, e.g., in Singapore. In view of the increasing prevalence of gonorrhoea, gonococcal ophthalmia prophylaxis requires continued attention and its incidence should be carefully watched in many parts of the world.

2.2.3 Measures to improve control

Among the many factors mentioned, the limitations of diagnostic laboratory methods, the latent infectious reservoir in females, and the general complacency of the public are probably most important in the failure to control gonorrhoea. The lessened penicillin sensitivity of the gonococcus may also assume an increasing significance. In some countries, particularly in the USA, considerable efforts are made to meet the challenge. Thus "speed-zone" epidemiology has been tried, greater emphasis has been put on interviewing and investigation of contacts, and wider use is
made of epidemiological treatment. In some small communities in developing areas where gonorrhoea has been endemic, total mass treatment has been tried.

Of considerable importance are results of clinical and laboratory research. A promising tool for the fluorescent antibody identification of *N. gonorrhoeae* has been developed, which shows no strain differences. This fluorescent labelling antibody technique will allow the rapid and positive identification of *N. gonorrhoeae* and may be substituted for the more costly and slower culture method. It is recognized that in some countries the latter has fallen into disuse, since treatment of gonorrhoea is now frequently based on physical signs only, with little or no laboratory verification. The advent of new diagnostic techniques is therefore particularly useful. Studies of the endotoxin of the gonococcus suggests that it is a lipopolysaccharide. If confirmed, specific antigens for serologic testing of gonorrhoea might result and diagnostic skin tests might conceivably be developed.

Other areas of research in gonorrhoea which might be of practical value in the control of the disease were also discussed by the Committee, and ranged from the need to develop standardized methods for determining penicillin sensitivity of the gonococcus to the use of alternative antibiotics to penicillin.

The Committee expressed the view that intensified research on many basic and applied aspects of gonorrhoea was urgently required, and noted the recommendation of the First World Health Organization Venereal Disease Control Seminar of the Western Pacific Region,\(^1\) that an International Gonococcus Reference Laboratory be established. There is undoubtedly a need for such a centre which could be located in an existing institution, and which would work in collaboration with national laboratories in a co-ordinated programme. A scientific study group of laboratory experts in this field should be convened as soon as possible by WHO, under its intensified research programme, to outline plans and priorities for this activity.

The Committee also discussed the treatment of gonorrhoea in the male and female at some length, and considered that in view of the fact that instances of lessened sensitivity of *N. gonorrhoeae* to penicillin have been reported from various parts of the world, the total dosage of penicillin recommended in the fourth report of the Expert Committee on Venereal Infections and Treponematoses\(^2\) was no longer adequate. A minimal dosage of 1.8 mega units of penicillin should now be used. This total dosage may be given as 1.8 mega units or 1.2 mega units plus 0.6 mega units.


units and administered in not more than two injections on two consecutive
days, the first injection to consist of 1.2 mega units to provide an early
adequate blood level and the second injection to consist of 0.6 mega units
of PAM (or benzathine penicillin) so as to provide a persistent adequate
blood level for epidemiologic procedures to be carried out.

The Committee noted the various procedures followed when penicillin
treatment of gonorrhoea failed. These include treatment with higher doses
of penicillin, streptomycin, other antibiotics or sulfonamides. In view
of the fact that in some areas sulfonamide-sensitive gonococci had been shown
to be once more in a majority, a high degree of success might possibly be
achieved with adequate sulfonamide therapy, the long-acting sulfonamides
being especially useful for this purpose.

It was, however, considered that, as streptomycin had proved itself
a formidable rival to penicillin in the treatment of gonorrhoea over the
past ten years and had in fact been consistently and successfully used as
a routine in many clinics, this relatively safe—and not too costly—anti-
biotic is eminently suitable for the treatment of cases failing to respond
to penicillin. Moreover, streptomycin has the great advantage of being
injectable, so that in public health practice it can be made certain that the
patient actually gets his treatment. In all cases the dosage of streptomycin
should not be less than 2 g. It is still important that the usual post-treat-
ment procedures in gonococcal infections should be followed.

2.2.4 Recommendations

The Expert Committee on Venereal Infections and Treponematoses,

Noting the recent increase in prevalence of gonorrhoea in many coun-
tries, and observing that it represents one of the most widespread and
challenging public health problems of today,

RECOMMENDS

(1) that WHO give active attention to gonorrhoea as a world-wide
public health problem and be associated with epidemiological, diagnostic
and therapeutic measures in the promotion of gonorrhoea control;

(2) that a scientific study group on gonorrhoea be convened by WHO
as soon as possible to define the future role of WHO in research in
gonorrhoea under the Organization’s intensified medical research
programme; and

(3) that an International Gonococcus Reference Laboratory be
established in an existing institution to work with national laboratories
to foster microbiological and other research on *Neisseria*, particularly
to classify strains and types of the gonococcus; to watch for changes
in susceptibility to antibiotics, particularly penicillin; to standardize
techniques and methods.
2.3 Non-gonococcal venereal infections

Antibiotics and/or sulfonamides continued to be effective in chancroid, lymphogranuloma venereum and granuloma inguinale.

Chancroid is relatively the most important of these infections, both because of its higher incidence and because of differential diagnostic problems of penile ulcers and dual infection with syphilis. It was noted, however, that chancroid is declining in incidence in many parts of the world, including seaports in Asia.

Lymphogranuloma venereum and granuloma inguinale are rarely seen in most clinics. The excellent monograph published through WHO on the nature, extent, diagnosis and treatment of this latter condition was noted by the Committee.¹

The Committee also noted that in some countries the incidence of non-gonococcal urethritis in males approached, or even exceeded, that of gonorrhoea, and as the condition does not respond to penicillin and a certain etiological agent can hardly ever be identified, it presents a public health problem of considerable importance. Bacteria, spirochetes, pleuro-pneumonia-like organisms, trichomonads and virus inclusion bodies have all been found in the urethral discharge or in urethral scrapings from these cases, but none of these agents has as yet been certainly incriminated.

An attack of non-gonococcal urethritis subsides without treatment in about 30% of cases, but "cure rates" of 60%-80% have been reported after empirical treatment with streptomycin and sulfonamides (alone or combined) and with some of the so-called broad-spectrum antibiotics.

Though primary non-gonococcal urethritis is not uncommon, often an attack follows a known gonococcal infection after varying intervals.

Research into the etiological, diagnostic, therapeutic and epidemiological aspects of the urethritides is required, and it was thought that WHO might stimulate such research.

3. ERADICATION OF ENDEMIC TREPONEMATOSES: MASS CAMPAIGNS

3.1 Eradication

It was not until after the Second International Conference on Control of Yaws, Enugu, convened by WHO in 1955,² that the declared general purpose of endemic treponematoses campaigns changed from "control" to "eradication", and in considering the criteria necessary for the definition of eradication of endemic treponematoses, the Committee studied the

¹ Rajam, R.V. & Rangiah, P.N. (1954) Donovanasis (Granuloma inguinale, granuloma venereum), Geneva (World Health Organization: Monograph Series, No. 24)
² J. trop. Med. Hyg., 1957, 60, 27, 62
experiences in many campaigns against endemic syphilis and yaws after mass treatment. It was emphasized that these treatment campaigns had been eminently successful and that the ultimate disappearance of the “last cases” might well depend upon the improvement of the standard of living of the populations. Those “last cases” are not regarded as important provided that adequate surveillance of the population is maintained.

From a public health point of view it is recognized that there is likely to be an intermediate stage before complete eradication is achieved (see Fig. 1). This is named epidemiological eradication and is defined as having been reached when no indigenous infectious case has appeared in the population for three consecutive years, determined on the basis of the findings:

(a) at all medical centres in the country where proper records of cases of the disease are kept;

(b) at six-monthly medical examinations of all schoolchildren;

(c) at annual surveys of randomly selected villages remote from medical facilities, schools and towns; or

(d) reported from any reliable source of information.

The final achievement, complete eradication, is defined as having been reached when no indigenous active case has appeared in the population for a period of three years, information from all the above sources having been considered and no seroreactor in the age-group under five years having been found.

Either phase of eradication should apply only to large geographical or administrative areas, isolated geographically or surrounded by populations which have been under surveillance for at least a year. When either phase has been reached a senior national public health officer should be made responsible for surveillance, collection and correlation of reports on prevalence of the disease and for carrying out any action that may be required. He should prepare an annual report on the endemic treponematoses situation in the country.

In arriving at the above definitions, the recommendations of the Second International Conference on Yaws Control held at Enugu, Nigeria, in 1955 were taken into consideration.

In Bosnia, where a mass treatment campaign was begun with international assistance as early as 1948, no new active case of endemic syphilis has been found for five years, in spite of careful surveillance, in a population of approximately a million people. On the basis of these findings, it is considered that complete eradication has been achieved. These findings aroused great interest at the Twelfth World Health Assembly,\(^1\) where it was emphasized that this was the first instance of the eradication of a

\(^1\) Off. Rec. Wld Hlth Org., 1959, 95
FIG. 1. THE COURSE OF YAWS ERADICATION CAMPAIGNS

Before campaign

No treatment campaign

Total active cases

Infectious cases

Individual eradication reached

Cumulatively reached

ITS = Initial Treatment Survey

RS1 = Resurvey 1, etc.

0-1 year

2-4 years

1-3 years

3 years

No active cases
communicable disease in a large area following a treatment campaign assisted by WHO. (Detailed data from a pilot area are given in Table I.)

At present, if the three-year criterion is accepted, in no large area or country has yaws been eradicated, either epidemiologically or completely. Examples among the many areas where yaws is receding as a result of treatment campaigns are given from Indonesia, Nigeria and Haiti in Tables II, III and IV.

**TABLE I. ERADICATION OF ENDEMIC SYPHILIS:**

**FIVE SURVEYS IN MNO* SAPNA, BOSNIA, 1949-58**

<table>
<thead>
<tr>
<th>Area **</th>
<th>Percentage prevalence of early infectious lesions</th>
<th>Percentage prevalence of seroreactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITS</td>
<td>RSI</td>
</tr>
<tr>
<td>1. Kraljevići</td>
<td>7.2</td>
<td>0.2</td>
</tr>
<tr>
<td>2. Ramći</td>
<td>9.3</td>
<td>2.2</td>
</tr>
<tr>
<td>3. Medvedja</td>
<td>6.7</td>
<td>1.1</td>
</tr>
<tr>
<td>4. Godus</td>
<td>4.5</td>
<td>0.3</td>
</tr>
<tr>
<td>5. Sapna</td>
<td>2.0</td>
<td>0</td>
</tr>
<tr>
<td>6. Andjevići</td>
<td>2.6</td>
<td>0</td>
</tr>
<tr>
<td>7. Mahmutovići</td>
<td>3.1</td>
<td>0</td>
</tr>
<tr>
<td>8. Kovačevići</td>
<td>2.3</td>
<td>1.3</td>
</tr>
<tr>
<td>9. M. Nezuk</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>10. Juslje</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

* "MNO" is a small administrative unit

**TABLE II. RESULTS OF REPEATED RESURVEY WITH THE CONTINUED FINDING OF FEW CASES (WRINGINANOM SUB-DISTRICT, INDONESIA)**

<table>
<thead>
<tr>
<th>Date</th>
<th>Surveys *</th>
<th>Coverage (%)</th>
<th>Non-infectious (%)</th>
<th>Infectious (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 1992</td>
<td>ITS</td>
<td>95</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>March 1993</td>
<td>RS I</td>
<td>94</td>
<td>1.3</td>
<td>0.32</td>
</tr>
<tr>
<td>January 1994</td>
<td>RS II</td>
<td>96</td>
<td>0.75</td>
<td>0.2</td>
</tr>
<tr>
<td>January 1995</td>
<td>RS III</td>
<td>94</td>
<td>0.2</td>
<td>0.03</td>
</tr>
<tr>
<td>June 1995</td>
<td>RS IV</td>
<td>91</td>
<td>0.2</td>
<td>0.04</td>
</tr>
<tr>
<td>January 1996</td>
<td>RS V</td>
<td>88</td>
<td>0.16</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* ITS = Initial Treatment Survey; RS = Resurvey
TABLE III. PERCENTAGE PREVALENCE OF INFECTIOUS YAWS AT INITIAL TREATMENT SURVEY (ITS) AND LAST RESURVEY (RS) IN NIGERIA

<table>
<thead>
<tr>
<th>Area</th>
<th>Number of last RS</th>
<th>ITS (%)</th>
<th>Last RS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasuuka</td>
<td>7th</td>
<td>3.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Udi</td>
<td>3rd</td>
<td>1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Afeunmai</td>
<td>3rd</td>
<td>7.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Ishan</td>
<td>3rd</td>
<td>6.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Owo</td>
<td>4th</td>
<td>3.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Igalia</td>
<td>3rd</td>
<td>10.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Koton Karifi</td>
<td>3rd</td>
<td>3.5</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* Interval between surveys was 6-12 months

TABLE IV. SAMPLE SURVEYS IN HAITI: 1958-59

<table>
<thead>
<tr>
<th>Department</th>
<th>Population</th>
<th>Population examined</th>
<th>Active yaws cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total yaws</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>North-west</td>
<td>200,673</td>
<td>4,950</td>
<td>20</td>
</tr>
<tr>
<td>North</td>
<td>606,484</td>
<td>14,900</td>
<td>58</td>
</tr>
<tr>
<td>Artibonite</td>
<td>607,188</td>
<td>15,100</td>
<td>26</td>
</tr>
<tr>
<td>West</td>
<td>1,325,150</td>
<td>27,355</td>
<td>96</td>
</tr>
<tr>
<td>South</td>
<td>844,716</td>
<td>21,000</td>
<td>71</td>
</tr>
<tr>
<td>Total</td>
<td>3,584,211</td>
<td>82,905</td>
<td>271</td>
</tr>
</tbody>
</table>

Comparable data for the earlier spot surveys in 1954 and 1955 were 91,624 persons examined; 0.65% of total active yaws and 0.15% of infectious yaws found. In mid-1957 it was estimated that the total yaws prevalence was 0.5%.

The eradication of yaws is the declared objective of all campaigns receiving international assistance, and the Committee considered that this was possible. Approximately 100 million people have so far been concerned in WHO-assisted campaigns, 70 million have been examined in initial surveys, and 86 million in resurveys. Some 40 million have been treated with long-acting penicillin PAM, and the work towards the declared objective should continue.
In conclusion, the Committee stressed that in many parts of the world available information indicates that the prevalence of yaws has also decreased without any effective campaigns, probably due to the improvement in standards of living. This recession is slow and may take generations, and every effort should therefore be made to reduce the prevalence of active yaws so that with the continued improvement in standards of living eradication can be anticipated also in these low-prevalence areas.

3.2 Epidemiological aspects

3.2.1 Yaws

The possibility of "giving every person in the community suppressive treatment regardless of whether signs of yaws could be found or not" had already been discussed in Sierra Leone in 1949, although this was before penicillin had come into general use and the eradication of yaws was not considered practicable at that time.

The widely accepted epidemiological points which are important in yaws campaigns are: (1) yaws is a contagious disease of childhood; (2) environmental factors favouring its transmission include warmth and humidity, scanty clothing, poor personal cleanliness and/or the absence of good soap, and low standards of living; (3) contacts outside the family are more important than familial contacts; (4) the prevalence of latent cases; usually 2-5 or more latent cases for every patient with active yaws lesions; and (5) the frequency of infectious relapses in latent cases within the first 3-5 years after infection.

The following points are taken into account in the treatment policies employing long-acting drugs drawn up by WHO for yaws eradication campaigns, directly based upon epidemiological knowledge: (1) high coverage at all surveys; (2) suitable treatment policies such as (a) total mass treatment (TMT), (b) juvenile mass treatment (JMT), (c) selective mass treatment (SMT); (3) expansion of campaign to cover compact areas; (4) resurveys at yearly intervals; (5) surveillance.

These principles have been widely adopted in yaws campaigns. An exception is Indonesia, which relies on treatment of patients with active yaws and of some contacts of infected patients, combined with regular resurveys, and requires 30% instead of 10% as the minimum prevalence of active yaws for total mass treatment. The resurveys in Indonesia are frequent, and rural health services are generally available.

The Haiti yaws campaign contributed considerably to the development of campaign techniques, particularly as regards total mass treatment, with emphasis on "contacts" defined as "everybody without lesions," which includes latent cases.

The great need at present is for careful studies of the transmission of yaws to find the crucial links in the chain of infection which could be broken
in inexpensive ways, thus stopping transmission. At present the emphasis is on the elimination of infectious cases. In areas of "receding yaws"—which will predominate in future campaigns—inexpensive, practical and acceptable environmental changes could be of very great value.

3.2.2 Endemic syphilis

Careful studies of population groups in Bosnia showed (i) the considerable chances of familial re-infection after clinical and serological cure if untreated infectious cases remained in the household, and (ii) the limited role of infectious relapses from latency in the spread of this treponematosis (as contrasted with yaws). The premises of the programme were epidemiological, and included clinical and serological examination of the entire population with adequate treatment of (a) all infected persons with clinical or laboratory evidence of the disease, and (b) all familial and other contacts at risk of infection.

Following the experiences in this endemic syphilis campaign, and in those in Bechuanaland, Syria, Iraq and French West Africa, it is now recognized that: (i) endemic syphilis is a contagious disease of childhood, non-venerally acquired; (ii) environmental factors favouring transmission include poor hygiene conditions and low standards of living: the disease is spread non-venerally by bodily contact with active lesions, perhaps via hands, or indirectly by utensils; (iii) contacts inside the family may in some areas be more important than extra-familial contacts; and (iv) the prevalence of latent cases for every infectious case varies from area to area depending on local conditions and the stage of the disease.

The principles of endemic syphilis eradication are similar to those for yaws.

3.3 Minimal dosage of PAM in endemic treponematoses

3.3.1 Yaws campaigns

An important aspect of yaws eradication campaigns is the size and frequency of injections of PAM, as well as the persons treated.

(a) Size and frequency of injections

Yaws was considered in 1949 by the WHO Expert Committee on Maternal and Child Health in a plan for the control of skin diseases in children, and it was suggested that a suitable adult dose was 1.2 mega units of PAM with lesser dosages for children. Longer observation than had by then been possible was, however, required, and pilot studies were at the time being made under WHO auspices on endemic treponematoses,

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1 World Health Organization (1949) *A plan for the control of skin diseases in childhood*, Geneva (Unpublished working document WHO/MCH/2)
and by the United States Public Health Service and others on venereal syphilis.

In the fourth report of the Expert Committee on Venereal Infections and Treponematoses\(^1\) it was recommended that the minimal total doses of PAM for adults with early infectious yaws should not be less than a single injection of 1.2 mega units, and children should receive smaller doses; contacts should be given a dose not less than half that for adult infectious patients (all references to PAM imply PAM of satisfactory standards, as recommended by WHO).

At the Second International Conference on the Control of Yaws\(^2\) this dosage was further defined in regard to age-groups, as follows:

<table>
<thead>
<tr>
<th>Age-group (years)</th>
<th>early and late active cases</th>
<th>latent cases and contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 15</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>15 and over</td>
<td>1.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

However, from the start of the Haiti yaws campaigns, the dose used for patients with active yaws was 0.6 mega units and for contacts, 0.3 mega units. This was based upon unpublished reports on the treatment of early syphilis in Guatemala with a single dose of PAM, and of yaws in Venezuela. This “Haitian” dose has since been maintained there. In the conclusions of the Regional Seminar on Treponematoses Eradication (excluding venereal syphilis) in Haiti in 1956, it was considered that “the minimum satisfactory dose required for mass treatment in a yaws campaign cannot be based on rigid criteria. Although the Haitian eradication programme demonstrated that a campaign can be successfully carried out using 0.6 mega units of procaine penicillin G in oil with 2% aluminium monostearate (PAM), it was accepted that the use of 1.2 mega units as recommended by the WHO Expert Committee would give greater security.” Some national yaws programmes in the Americas, e.g., Brazil, are being carried out using 1.2 mega units for adults.

At the Second International Conference on the Control of Yaws in 1955, a proposal was made by the Eastern Nigeria Health Administration to carry out parallel clinical trials with the larger WHO-recommended usage and the smaller Haiti dosage. These trials showed that there is little or no difference in the results in early cases of yaws after 0.6 or 1.2 mega units, but in late lesions the results after the larger dose are better.

\(^1\) *Wild Hith Org. techn. Rep. Ser.*, 1953, 63
\(^2\) *J. trop. Med. Hyg.*, 1957, 60, 27, 62
The following tabulation sets out basic differences in these two dosages:

<table>
<thead>
<tr>
<th>Age-group (years)</th>
<th>WHO-recommended dosage (in mega units)</th>
<th>Haiti dosage (in mega units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>active cases</td>
<td>latent cases and contacts</td>
</tr>
<tr>
<td>Under 15</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>15 and over</td>
<td>1.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

It will be seen that the difference in the two schemes is that "active cases" and "latent cases and contacts" aged 15 or more years received twice the amount of PAM in the WHO dosage than in the Haiti dosage. As regards the effect on early (infectious) yaws, this would probably not be important since early active yaws and early latency from which infectious relapses may stem are most frequent in children, for whom the dosages are identical in both schemes.

Experience in yaws eradication campaigns in other parts of the world support the adequacy of the WHO-recommended dosage, and the Committee was of the opinion that this dosage in endemic treponematoses campaigns should continue as at present.

(b) Persons treated

The effectiveness of "abortive", "prophylactic" or "preventive" treatment of household contacts was first demonstrated in the Bosnian endemic syphilis campaign and recommendations for contact treatment were included in the fourth report of the Expert Committee. In the Haiti yaws campaign, two broad categories were treated: (i) patients with active yaws, and (ii) "contacts", that is, those living in permanent contact with patients. As children are frequently exposed to infections, all under 16 years of age received the same dose as "contacts".

On the basis of available data, it was recommended by WHO in 1955 that when the prevalence of clinically-active yaws is over 10%, total mass treatment (TMT) be given; that is, all patients with clinically-active yaws should be treated and the remainder of the population given half doses. Where this prevalence is 5%-10%, in addition to patients, all children should be given half doses, and where this prevalence is under 5%, in addition to patients, all household and other obvious contacts should be given half doses. These two treatment policies were for easy reference called "juvenile mass treatment" (JMT) and "selective mass treatment" (SMT) respectively.

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1 World Health Organization (1955) Some important aspects of yaws control, Geneva (Unpublished working document WHO/VDT/135)
These recommendations have been generally followed, except in the treponematoses control project in Indonesia. There selective mass treatment is generally carried out and only where the prevalence of clinically-active yaws is over 30% or where the population is difficult of access is TMT carried out. No great importance has been attached to household contacts, and relatively few have been treated. Furthermore, the pattern of the yaws work in Indonesia—of djuru pateks (yaws scouts) and nurses (who are usually only employed part-time on yaws)—does not lend itself to the adoption of TMT. On the other hand, few other yaws campaigns have been carried out where it has been possible to undertake such systematic periodical resurveys and case-finding in the population, and the achievements of the yaws campaign in Java are excellent.

These three recommended treatment policies (TMT, JMT and SMT) have been widely adopted elsewhere with complete satisfaction, and were approved by the Committee.

(c) The future

About half the 200 million people in yaws-endemic areas have, over the last 10 years, been covered by eradication campaigns; prevalence of clinical lesions of yaws has been mostly over 10% in these populations. In the remaining 100 million in yaws areas the prevalence is probably less than 10% and the present WHO recommendations should certainly be effective. However, the lower prevalence must certainly be due to differences, in environment or other factors, from those where the prevalence is high, and it may therefore be necessary to modify the present recommendations or practices for low prevalence areas in order to keep the costs as low as possible. These modifications may include:

(1) TMT in low-prevalence areas (e.g., 3%-7%) and postponement of RS until the second or even third year, instead of JMT or SMT and first RS the following year;

(2) in very low-prevalence areas (under 3%) it may only be necessary to ensure that free PAM is available at rural dispensaries, health centres, etc. Alternatively, and preferably, the anti-yaws work could be carried out in the course of activities against another disease.

3.3.2 Endemic syphilis campaigns

The dosages used in campaigns in which WHO has assisted have varied in Bosnia, Syria, Iraq, Bechuanaland and French West Africa. The tendency has been towards decreasing the dosages to 1.2 mega units for adults and smaller doses for children and infants.

In populations with endemic syphilis, it is usual to find a relatively low prevalence of clinically-active cases with varying relationships to sero-reactors. Thus clinical prevalence is not a satisfactory guide to treatment
policy. In view of the wide disproportion between the prevalence of active disease and that of seroreactors, in the scattered or nomadic populations, which often comprise most of those suffering from endemic syphilis, and in the absence of preliminary serological surveys it is considered that TMT with WHO-recommended minimal doses should be practised when clinical prevalence is over 3%.

3.3.3 In pinta campaigns

In 1952 a single injection of 1.2 mega units of PAM or four injections of 0.3 mega units at weekly intervals were found to give satisfactory results in the treatment of pinta. Later, however, a single dose of 1.2 mega units of PAM in mass treatment has been used in the Americas.

The Committee expressed considerable interest in pinta, its nature, extent and possible eradication, and the failure of research workers to isolate the treponeme in the experimental animal. It was noted that at least one national campaign was going forward in the Americas and that preliminary results were promising.

It was considered that further information on pinta would be of great scientific and public health interest in view of the several aspects differentiating it from the other treponematoses. The Committee was of the opinion, therefore, that a thorough review of pinta—diagnosis, treatment and control, including epidemiological and research aspects—should be entered on the agenda for the next meeting of the Expert Committee on Venereal Infections and Treponematoses.

3.4 Surveillance

In the course of an endemic treponematoses eradication campaign the time comes when it is not economical to continue periodical resurveys because the prevalence of active lesions is low and thus to find each case becomes relatively expensive. Ideally the measures against endemic treponematoses might then continue as part of a mass action against another disease ("sequential approach"), as in Bosnia, where, after retraining of field teams, following the endemic syphilis campaign, mycosis of the scalp is being attacked on a mass basis. If adequate rural health facilities are available, the surveillance necessary to ensure at the same time the eradication of the endemic treponematosis should also be undertaken. In the absence of either of these conditions, some reduced action should be instituted.

1 The Bosnian endemic syphilis campaign is the only one in which systematic serological surveys have been carried out—initially and on subsequent resurveys—over several years. The results of TMT in a pilot area of this campaign were described in the fourth report of the Expert Committee (Wild Hth Org. techn. Rep. Ser., 1953, 63, 9)
The point at which resurveys can safely be stopped and replaced by a simple surveillance activity has not been defined in endemic syphilis or yaws. In yaws, this question is of considerable practical importance, and the point at which the resurveys can be replaced by the simpler activity should be defined. In Indonesia, the consolidation phase of the yaws campaign begins immediately after the completion of a resurvey in which at least 80% of the population were covered, and in which the prevalence of active yaws did not exceed 2%, and that of infectious cases not more than 0.5% of the people examined.

The Committee approved that surveillance should consist of: (1) constant watching of yaws attendances at rural health centres, such as dispensaries, etc., where the village from which each yaws patient comes would be reported; (2) regular surveys of schoolchildren; (3) immediate reporting of yaws cases by village officials to their nearest medical officer; (4) occasional surveys of villages with few schools and at a distance from the health centres, and where no case of yaws has been reported for one year.

3.5 Evaluation

One of the essentials for evaluation is reliable comparative data at various stages of the campaigns. This has been started by the introduction of the form WHO/YAWS/101 (see Annex 1, page 66) on which are reported data under the same headings for different resurveys of the same population. The basis for evaluation of endemic syphilis is contained in the fourth report of the Expert Committee.¹

A deterrent to evaluation is "error in diagnosis". Under optimal conditions, diagnostic errors in yaws may be as low as 10%. There are a number of non-specific lesions, however, especially of the soles and palms, which are not affected by penicillin, and might thus still be present at resurvey, so that the effect of the previous treatment on the population would be underestimated. In one area these errors at an initial treatment survey were at least half of all "diagnosed" active cases so that at the resurvey the prevalence had only fallen by half and the medical officer complained that the PAM had no action on hyperkeratoses. Another error is to regard all persons who say they have had yaws ("history, latent") as patients with "active yaws". Other diagnostic errors occur which can be avoided by adhering strictly to the principle that "active yaws" patients must have clinically recognizable active yaws lesions.

During yaws surveys patients are also seen with lesions other than yaws but which will respond to PAM—e.g., tropical ulcers, or widespread

¹ *Pub Health Off. tech. Rep. Ser.*, 1953, 63, 9
septic skin lesions. These should, of course, always be treated but they should not be recorded with the yaws figures.

Though excessive diagnosis can only benefit the course of the campaign because more persons will be given larger doses as active yaws patients than they would receive as "latent cases and contacts", evaluation is made more difficult. To help in avoiding these diagnostic errors WHO has published an illustrated monograph on the nomenclature and classification of yaws.1

The simplest and minimal evaluation may be made, as indicated above, by comparing similar data from the same populations at different times. Evaluations of such data have been published by WHO staff members, consultants and others over the years, for both yaws and endemic syphilis. Finally, it should be noted that for a complete evaluation, factors which are concerned with improvements in health, standard of living, etc., are difficult to measure and are usually not available for the start of treponematoses or other communicable disease campaigns.

3.6 The introduction of venereal syphilis

Where the prevalence of endemic treponematoses has recently been high, or is so still, there is little or no venereal syphilis. Yaws tends to be prevalent in populations having relatively little contact with modern developments. The increase of venereal syphilis in such populations has been attributed to a relaxation of tribal taboos and moral standards. In some yaws populations, however, there has been a high prevalence of gonorrhoea which has apparently benefited considerably from total mass treatment with PAM given to eradicate yaws.

Studies of infection with T. pertenue followed by T. pallidum in animals and in man support the existence of cross immunity after from six to twelve months. The protection against venereal syphilis afforded by childhood yaws infections has been generally confirmed by observations in the field. If this protection is real, then the risk of the introduction of venereal syphilis into rural populations from whom yaws has been eradicated, or at least greatly reduced following national mass campaigns, has considerable interest and has already been anticipated.

From 10% to 30% seroreversal has been reported in early yaws up to two years after treatment. Of greater importance are the children reaching sexual maturity who have not had yaws and are thus susceptible to venereal syphilis. Thus from about 1965 onwards, with the increasing "unprotected" rural populations, venereal syphilis may extend from the urban to the rural people. The importance of this will depend upon the prevalence of infectious

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1 Hackett, C. J. (1957) An international nomenclature of yaws lesions, Geneva (World Health Organization : Monograph Series, No. 36)
venereal syphilis in the towns and cities. Since the eradication of endemic syphilis in Bosnia where seroprevalence had fallen from more than 20% to less than 1% since 1948, only sporadic cases of venereal syphilis have so far been observed, but here the prevalence is very low in towns and cities. The prevalence of syphilis in the urban populations of countries in which yaws is disappearing is not generally known. However, a useful indicator of the general prevalence of syphilis in a population is the seroreactivity in pregnant women. Randomly selected groups of apparently healthy pregnant women in several parts of West Africa gave a seroprevalence of about 20%. In Surabaya, Indonesia, a seroprevalence among *primiparae* of about 16% was found, of which about half was possibly due to yaws and not syphilis. Biological false-positive reactions are probably not important in these countries at present. From the scanty evidence available it appears that they represent about one-twentith of all reactors (reagin tests).

To start to define this problem WHO is approaching health administrations to provide information about the prevalence of seroreactors among pregnant women, since complete information on the new early cases of infectious syphilis cannot be obtained from most areas. In Indonesia, studies are being made in one area to ascertain how much—if any—venereal syphilis is entering now that yaws has been eradicated. Periodic serological testing of individuals is being undertaken.

3.7 Recommendations

The Expert Committee on Venereal Infections and Treponematoses, Noting the great progress made in national campaigns, with and without WHO/UNICEF assistance, during the past 10 years in the eradication of endemic treponematoses in the high-prevalence areas, the continuing effectiveness of long-acting penicillin, the possibility of increase of hypersensitivity to penicillin and development of resistance by the treponemes, and considering the possible risk of extension of venereal syphilis from the towns into rural populations in which endemic treponematoses, particularly yaws, have been eradicated,

RECOMMENDS

(a) that there should be no delay by health administrations in extending the campaign for the world-wide eradication of yaws and endemic syphilis which is a feasible undertaking from a technical point of view, and

(b) that the prevalence of venereal syphilis in towns and rural areas be studied by ascertaining initially the prevalence of seroreactors among unselected pregnant women—as an index of the overall prevalence of the infection—so that necessary public health measures may be taken in time.
4. PENICILLIN REACTIONS

World production of penicillin now surpasses many hundreds of tons yearly and the antibiotic is widely available. It has been used and misused in many countries over the last few years, and various side-effects have been observed. Indeed, many reports have been published on untoward penicillin reactions. They have recently been evaluated in a comprehensive review by WHO which focuses attention on the side-effects from an individual and public health viewpoint, as well as on the apparent increase in their incidence. While the toxicity of penicillin is insignificant, its antigenic sensitizing potential is considerable. The most important side-effects of penicillin as contrasted to other antibiotics, where true toxicity and microbiogenic reactions prevail, are of an allergic, and in particular anaphylactic, nature.

Although the classification of reactions to antibiotics as toxic, microbiogenic or allergic is acceptable from a systematic viewpoint, it would appear logical from a public health point of view to distinguish between:

(a) the rare life-threatening reactions, most serious of which are anaphylactic reactions, and conditions such as severe exfoliative dermatitis, serious super- and cross-infections, and other potentially dangerous conditions (e.g., renal damage), and

(b) the much more frequent, non-serious and mild eczematous and urticarial reactions and the ordinary microbiogenic sequelae (e.g., transitory gastro-intestinal reactions).

In the first group must also be included the occasional Jarisch-Herxheimer reactions of microbiolytic nature occurring in debilitated infants with congenital syphilis.

4.1 Nature and incidence

It is emphasized that drug reactions become a true public health problem only when their incidence and seriousness, in relation to total consumption of the drug, expose a number of people to unacceptable risks, and not merely because scattered fatalities attract attention.

On the basis of published data it has been estimated that the rate of fatal anaphylactic reactions following penicillin is slightly more than one per million injections. The incidence of non-fatal anaphylactic reactions is probably at least ten times that figure.

While penicillin is responsible for most of the total anaphylactic reactions caused by all antibiotics, a survey in the USA in 1957 indicated that this drug also causes almost all the severe angioneurotic oedemas which occur

in one-tenth of the reactions to all antibiotics. Acute hypotension without any other symptoms can also be caused by penicillin. A mortality of 13% is estimated to be associated with angioneurotic oedema, 10% with severe skin reactions, 47% with microbial superinfection, and 40% with blood dyscrasias, although the rarity of these conditions should be kept in mind.

The known total deaths from penicillin—in connexion with all syndromes and types of reactions—are some 90-115 yearly in the world. There are undoubtedly more.

These data per se may appear not to constitute a serious risk to the health of the public. In appraising the question further, however, it should be recognized that: (1) the calculations are averages, based on minimal information available; (2) the data are compiled from restricted areas, predominantly countries with a high consumption of penicillin; and (3) the great majority of reactions are allergic and occur in individuals following repeated sensitizing exposure to the drug, suggesting an increasing number of penicillin reactors in the future. That such reactions—all types—are increasing has been shown in two studies of venereal disease patients in the USA in 1954 and in 1959, the results of which were as follows:

<table>
<thead>
<tr>
<th>Year of study</th>
<th>Total patients treated</th>
<th>Total patients reacting number</th>
<th>Rate per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1954</td>
<td>19,510</td>
<td>116</td>
<td>5.95</td>
</tr>
<tr>
<td>1959</td>
<td>20,687</td>
<td>206</td>
<td>9.96</td>
</tr>
</tbody>
</table>

In the vast WHO-assisted anti-treponematoses campaigns in rural underdeveloped areas many millions of people had their first dose of penicillin in endemic treponematoses campaigns, and reactions were extremely rare. Reports from members of the WHO Expert Panel on Venereal Infections and Treponematoses consulted in 1959 also emphasized the rarity of serious reactions in countries where penicillin infiltration of a large proportion of the population has only recently begun.² On the other hand, there are reports from other countries with a high penicillin consumption over many years that serious—occasionally fatal—reactions may be provoked by penicillin dust in hospital wards, by penicillin-contaminated syringes, and penicillinized agricultural products, such as milk, meat, etc. It is likely also that sensitization to penicillin occurs in this way in at least a part of the population.

The possibility of penicillin reactions becoming a problem of wider public health importance in the future should under these circumstances not be underestimated, wherever the antibiotic is reaching, or is expected to reach.

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the public in increasing amounts, such as may be the case in countries with rising economic standards, expanding public health programmes and improved distribution of the drug.

4.2 Sensitizing factors

Available information indicates that sensitivity to penicillin can be induced by any penicillin salt or preparation, by any mode and route of administration and probably by any dosage, however small. Repeated small dosages are evidently more sensitizing than a few large ones.

There is convincing evidence that allergic diathesis—particularly bronchial asthma—predisposes to penicillin reactions. Such conditions are counter-indications for the use of penicillin.

From a recent study of penicillin reactions in the USA in a venereal disease clinic population injected with penicillin for venereal infections, it appears that the incidence of reactions increases with age. This was also evident from a similar study made in the USA in 1954 (see Table V). The age factor, however, is complicated by the amount of treatment administered. The younger patients, in general, represent gonorrhea and low-dosage schedules; the older patients, syphilis and higher-dosage schedules.

<table>
<thead>
<tr>
<th>Age</th>
<th>1959 study</th>
<th></th>
<th>1954 study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cases</td>
<td>Cases reactive</td>
<td>Total cases</td>
<td>Cases reactive</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>Rate per 1000</td>
<td>Number</td>
<td>Rate per 1000</td>
</tr>
<tr>
<td>10-19</td>
<td>3,031</td>
<td>12 4.0</td>
<td>3,908</td>
<td>12 3.1</td>
</tr>
<tr>
<td>20-29</td>
<td>6,741</td>
<td>53 7.9</td>
<td>9,512</td>
<td>37 3.9</td>
</tr>
<tr>
<td>30-39</td>
<td>2,566</td>
<td>29 11.2</td>
<td>3,574</td>
<td>34 9.3</td>
</tr>
<tr>
<td>40-49</td>
<td>857</td>
<td>22 25.7</td>
<td>1,252</td>
<td>21 16.8</td>
</tr>
<tr>
<td>50 and over</td>
<td>597</td>
<td>22 36.9</td>
<td>1,102</td>
<td>11 10.9</td>
</tr>
</tbody>
</table>

The fact that therapeutic and prophylactic administration of penicillin may constitute the main source of penicillin-sensitization does not mean it is the only source from a public health viewpoint. Penicillin-sensitization is an occupational hazard to persons who handle drugs, i.e., drug plant workers (12%-15% sensitivity), doctors, nurses, etc., and special measures may be required. Furthermore, “hidden contacts” with penicillin often
occur, and extremely small amounts (0.000003 units) are capable of provoking reactions in sensitized people. Important among these “hidden contacts” are the following:

(a) *Market milk*. In the USA, in a survey of 1706 samples of milk in 1956, 5.9% was found to be contaminated with from 0.003 to 0.55 units of penicillin per ml (3-500 units per litre) as a result of intramammary penicillin treatment of bovine mastitis. This is sufficient to induce penicillin sensitivity in milk-consuming individuals and to provoke reactions in those already sensitized to the drug. Penicillin-contaminated milk has also been found in England, and is undoubtedly present in other countries where penicillin is commonly used in early cases of mastitis due to machine milking.

(b) *Virus vaccines*. There may be between 0.001 and 20 units of penicillin per ml of vaccine, and the risk of penicillin reactions after vaccination against poliomyelitis has been emphasized since anaphylactic reactions have been reported from Denmark, England and the USA. Urticarial reactions also have been reported from the USA. Persons with allergic diathesis predisposing to reactions may thus show penicillin reactions on vaccination, while on the other hand the possibility of actual induction of penicillin sensitivity by such virus vaccines must be kept in mind.

(c) *Penicillin-contaminated syringes*. Trials have shown that sterilizer water from syringes sterilized by the usual boiling methods contained antigenically potent penicillin capable of provoking reactions in passively sensitized individuals. A case of systematic reaction—undoubtedly due to traces of penicillin in a syringe used for penicillin injections and sterilized by boiling—was also observed. These observations, suggesting that all-purpose syringes are often chemically unclean, are of practical as well as epidemiological interest and call attention to current procedures of syringe sterilization. The fact that boiling for sixteen hours does not completely destroy the antigenic properties of penicillin is noteworthy. In some areas “throw-away” types of syringes and needles are being used.

(d) *Penicillin-contaminated dust*. Unintentional inhalation may give rise to severe anaphylactic reactions in sensitized persons; such hidden contact with the antibiotic may also facilitate sensitization with the allergen. Skin contact with penicillin-contaminated dust (e.g., from hospital floors) may sometimes have similar effects.

4.3 Prevention

The discovery of new antibiotics has led to the supplanting of penicillin in some branches of medicine. Generally, however, it has remained the “queen of drugs”. In treponematous no remedy can so far replace it as the drug of choice and it will undoubtedly continue to be used for some time to come for individual treatment as well as in mass campaigns, the
increased importance of reactions notwithstanding. Only in cases of known sensitivity (or in therapy resistance) do other drugs now take the place of penicillin.

It has been suggested that "new" penicillin preparations—resulting from the recent discovery of penicillinic acid nucleus—may not give rise to reactions in persons sensitized to previous preparations, but the appearance of reactions due to such new preparations would probably only be a matter of time. More promising in outlook are entirely new antibiotics with antitreponemal properties equal to those of penicillin and without serious side-effects.

4.4 Measures by health administrations

Health administrations in all countries should be concerned in the prevention of penicillin reactions. Reasonable regulations should be made requiring prescription by a doctor before sale of penicillin preparations, while at the same time the medical profession should confine its use to conditions consistent with its known therapeutic properties, in order to prevent or delay as long as possible the process of sensitization of the population at large.

Efforts should be made to prevent the production of penicillin preparations of questionable therapeutic value, such as penicillin lozenges and penicillin toothpaste, which, because of the likelihood that they would be used continually, would have particular allergenic effects. Furthermore, precautions are necessary to prevent contamination by penicillin from undefined, hidden sources. This may imply regulations for the use of penicillin in agriculture, veterinary medicine, and food preservation, with particular attention to milk. Consideration might be given to the production of penicillin-free vaccines, available at least for individuals with a history of allergy or penicillin sensitivity. Care should be exercised in general during vaccinations. Measures are necessary to protect employees in the drug industry and professional people who handle penicillin regularly from contamination by penicillin dust and other penicillin residue.

Certain health programmes at present highly effective—for example, yaws eradication campaigns—should be undertaken and carried through as quickly as possible. The use of intensive foreshortened treatment schedules in such campaigns would reduce the risk of sensitization.

4.5 Prevention at the patient level

Sounder indications for the use of penicillin than at present would be the best prophylaxis against reactions in individual patients, and its use in trivial conditions, topical application and self-medication should be severely discouraged. The widespread preventive use of penicillin before and after surgical operations should be limited to special cases where it is
medically and bacteriologically indicated. Strictly conservative aseptic surgical methods would help to reduce the hazard of development of penicillin-resistant staphylococcal infections in hospitals.

Safe, practical and objective methods to disclose sensitivity before penicillin administration are still not available. Skin tests give a positive result in only about half of the reactors, but may be dangerous, and should not be made if there is a history contra-indicating the use of penicillin. Positive immediate skin tests usually contra-indicate the use of penicillin, but negative skin tests do not exclude penicillin sensitivity. In addition to the immediate false negative reactors there are also delayed intradermal reactors. The delayed intradermal test discloses latent penicillin sensitivity capable of developing into active epidermophytid-like eruptions. Recent research work concerns the development of more sensitive testing methods on the one hand (gamma globulin-penicillin-antigen, the "pressure patch tests") and of new methods for detection of penicillin-antibodies on the other hand (the "geldiffusion method", the "red-cells agglutination method", and passive transfer tests).

In the absence of exact objective methods, precise history-taking, aimed at disclosure of previous penicillin exposure, previous penicillin reactions or evidence of allergic diathesis, is obviously imperative for the prevention of reactions. Surveys show that if patients are carefully questioned, almost 50% have a history of previous penicillin treatment, and 5% disclose side-effects associated with penicillin administration. These details should be routinely introduced into, and clearly indicated on, the medical records of the patients.

The possible preventive function of antihistaminics given concurrently with penicillin is of some interest. Experimental and clinical experience is not, however, unanimous as to their usefulness. There is evidence that when given before, with or immediately after penicillin, they may, to some extent, suppress or delay allergic symptoms and the danger of fatal shock may be mitigated. However, sensitized patients, for whom penicillin treatment is considered of vital importance, could possibly be carried through with the help of antihistamines and steroids (ACTH and cortisone). An antihistamine-penicillin salt in a long-acting preparation without procaine (APM-Megacillin) and suspended in oil with 1% aluminium-monostearate has recently appeared on the international market and meets the WHO minimum requirements for treatment of treponematoses.

In the treatment of manifest penicillin reactions, immediate and repeated injections of adrenalin are the "sheet-anchor". Prolonged medication of antihistaminics is also indicated, particularly in cases of urticaria and angio-oedema. An emergency kit consisting of suitable anti-shock drugs and portable oxygen should be available for immediate use.

The outlook for a causative treatment of penicillin reactions may be improved by the appearance of penicillinase, a bacterial enzyme which,
in vivo, hydrolyzes penicillin to inactive penicilloic acid. Single injections of 5000 units of penicillinase have been shown to inactivate 100,000 units of crystalline penicillin G. Penicillinase does not apparently produce its effect immediately after injection but acts slowly and remains active in the body for 4-7 days. Its domain therefore appears to be penicillin-urticaria and angio-oedema, while in anaphylactic shock reactions where the patient may die within a few minutes after penicillin medication, its benefit is questionable. It is obvious that anti-shock treatment—particularly adrenaline and other resuscitating drugs, together with antihistamines and steroids—should be administered immediately. This may be followed by penicillinase for the purpose of hastening recovery. It is noted, however, that allergic anaphylactic reactions to repeated penicillinase injections may follow, and caution is therefore necessary until further experience is gained with this new preparation.

Individual and public health measures for the prevention of penicillin reactions and procedures for treatment of shock reactions have been summarized below, and take into account the views of the First World Health Organization Venereal Disease Control Seminar held in Tokyo in 1958.

A. At the public health level

(1) Regulate use of penicillin in agriculture and veterinary products, and food preservation, particular attention being paid to milk and dairy products.
(2) Regulate distribution of drug and sale on prescription by doctor only.
(3) Caution the medical profession and limit the use of penicillin to clinical and public health indications.
(4) Lessen therapeutic abuse, and reduce to a minimum the possibilities for hidden contamination (milk, syringes, virus vaccines).
(5) Take occupational health measures to protect from contamination by penicillin dust and other residue employees and workers in the drug industry and professional people who handle penicillin regularly.
(6) Implement fully and as soon as possible those health programmes which depend on penicillin therapy, such as syphilis control and yaws eradication, using adequate dosages and simple injection techniques.
(7) Undertake health education of the public to recognize dangers of misuse of antibiotics.

B. At the patient level

(1) Prophylaxis

(a) Exact past history in regard to previous contact with penicillin, previous penicillin reactions, allergic diathesis.
(b) Avoid skin-testing of patients with history of previous penicillin reaction.
(c) No penicillin treatment of patients with previous reactions or allergic diathesis (e.g., bronchial asthma).
(d) Assure complete sterilization of all-purpose syringes which have been used for penicillin treatment, when used for injections of other drugs. Possible use of disposable syringes and needles.
(e) Retain all patients for half-an-hour in the clinic after injection if possible (most anaphylactic reactions occurring shortly after injection).
(2) Treatment

(a) Emergency kit

(i) 1:1000 solution of adrenalin hydrochloride (epinephrine) ready to use (disposable-type syringes and needles desirable);
(ii) an antihistamine preparation for intramuscular injection;
(iii) 2-× 2-ml syringes and hypodermic needles.
Also if possible:
(iv) portable oxygen;
(v) cortisone for intramuscular, or a suitable hydrocortisone preparation for intravenous injection;
(vi) aminophylline up to 0.5 g for intravenous injection;
(vii) penicillinase.

(b) Procedure

(i) immediately on appearance of signs of reaction, patient should be made to lie down (head down, feet up);
(ii) 0.5-1.0 ml of adrenalin in the upper arm;¹
(iii) if immediate response not obtained: adrenalin repeated or cortisone (25-100 mg intramuscular or hydrocortisone intravenous);
(iv) in angio-neurotic oedema, urticaria, conjunctivitis; antihistamines intramuscular or intravenous;
(v) where coughing, dyspnoea, respiratory distress, substantial discomfort: a slow intravenous injection of 0.25-0.5 g aminophylline can be used.

4.6 Recommendations

The Committee noted the increasing significance of allergic reactions to penicillin, particularly in areas where it has been used (and misused) for a long time. While so far of little public health significance in mass campaigns against the endemic treponematoses in developing countries, and few in number in the light of the enormous quantities of penicillin used, they may conceivably become sufficiently significant to prejudice the smooth development of venereal syphilis control programmes, and perhaps also of eradication campaigns based on the use of penicillin. It should be noted that the reactions are by no means comparable in incidence, severity or mortality with those experienced in the arsenicals era, and there is at present no cause for alarm. No known means exists, however, for certain advance detection of penicillin reactors. The best means of prevention lies in the avoidance of the indiscriminate use of antibiotics and in measures to prevent "hidden contacts".

The Expert Committee on Venereal Infections and Treponematoses RECOMMENDS

(1) that the attention of health administrations be drawn (a) to the increasing number of penicillin reactions in the hope that the practice of a number of countries of restricting the use of antibiotics, except

¹ Peroral use of adrenalin by atomiser has recently been reported to give good results.
on prescription by a physician, might be extended; (b) to the necessity of limiting the use of antibiotics to well-established clinical and public health indications; (c) to the desirability of taking all individual and public health measures for prevention of penicillin reactions, as set out in this report;

(2) that research be undertaken on the nature of sensitizing reactions and to evolve a practical testing procedure, suitable for individual and mass use and capable of determining latent penicillin sensitivity; and

(3) that the attention of other relevant WHO expert committees, study groups, etc., be drawn to this report, since the problem of penicillin sensitivity reactions concerns many other fields of medicine.

5. DRUGS OTHER THAN PENICILLIN
IN THE TREATMENT OF THE TREPONEMATOSES

In spite of the seriousness of some of the side-effects of penicillin, it continues to hold its unique position as the least dangerous, most effective, least expensive and most easily administered treponemicidal antibiotic available. It is likely that it will remain so for some time to come, but certain problems are emerging—namely:

(1) the choice of drug for the treatment of the individual patient with syphilis (or other treponematoses) already known to react to penicillin and in whom serious—even fatal—side-effects may occur on further penicillin therapy (for this or any other condition);

(2) the long-term problems which may result from: (a) exposure to the sensitizing effect of penicillin of increasingly large numbers of people, resulting in an increasing incidence of reactions; (b) cross- and super-infection by certain penicillin-resistant micro-organisms, possibly on an increasing scale; and (c) manifestations of penicillin resistance in the treponeme (not yet observed) and decreased susceptibility of the gonococcus to the antibiotic (now emerging).

It cannot be excluded that penicillin therapy of treponematoses (and gonorrhoes and other conditions as well) may in the future become a real risk to individuals and the population in general as well as to the medical profession and the health authorities. Although such a development is by no means inevitable if all measures are taken on the public health as well as on the patient level—and in any case would need considerable time to evolve—this possibility was considered by the Committee in connexion with the eventual use of alternative drugs. Signs would be expected to manifest themselves first in countries where penicillin has been used (and misused) the longest, and in the urban earlier than in the rural areas. In the view of the Committee this aspect is of some importance from a public health
point of view, in as much as internationally-assisted mass campaigns against the endemic treponematoses, particularly yaws, are carried out in rural areas of tropical countries where penicillin has not previously been generally available and where, therefore, frequent serious side-effects are unlikely to be encountered for some time to come.

5.1 Antitreponemal antibiotics

A wide range of antibiotics other than penicillin has been shown to have antitreponemal effects in laboratory experiments. Some of these antibiotics, such as gliotoxin, aspergilllic acid, neomycin, novobiocin, polymyxin B and bacitracin, have shown antitreponemal effects comparable to that of penicillin, but have been excluded from further consideration for reasons of scarcity, or because their toxicity did not justify further clinical trials. Experience with symenam B is negligible although it has been observed to have antitreponemal effect in vitro and in vivo, and to be less toxic than penicillin.

The present appraisal includes chlortetracycline (Aureomycin), oxytetracycline (Terramycin), tetracycline (Achromycin), chloramphenicol (Chloromycetin), erythromycin (Ilotycin), and carbomycin (Magnamycin), all of which are treponemical, and are presumably the most promising in a “second-string” approach to treponematoses therapy. Some consideration has also been given to spiramycin, oleandomycin, kanamycin and cyclamycin. The Committee observed that so far there were only few trials and experiences with these antibiotics in the treponematoses and that observation time in such trials was short.

5.1.1 Treponeme disappearance time

The studies of the tetracyclines, chloramphenicol, erythromycin and Magnamycin in regard to disappearance of treponemes in primary and secondary syphilis show that in 96.8% of the 515 cases reported, darkfield negativity was attained within 18-72 hours (average 30 hours).

Similar data for yaws are available where darkfield negativity was usually obtained in early lesions within 24-48 hours following similar dosages of chlortetracycline and oxytetracycline and in 42 hours in the isolated cases of pinta examined by the darkfield method after chlortetracycline had been administered.

The Committee noted from these observations that the broad-spectrum antibiotics are effective in man. It appears that their action is weaker than that of penicillin, where 0.8 g (0.3 mega units) will destroy surface treponemes in 12-16 hours. From these limited data on clinical trials, particularly those in syphilis, no preference among the new broad-spectrum antibiotics can be established. It is noteworthy, however, that the total dosages of erythromycin and Magnamycin were lower than that of the
other antibiotics, although the effects were equally good. This observation should be seen in the light of the more exact experimental evidence in animals from the International Treponematosis Laboratory Center, ranking the antibiotics investigated for treponemical effect in the following order: (1) penicillin; (2) carbomycin and erythromycin; (3) oxytetracycline and chlortetracycline; and (4) Chloramphenicol and streptomycin.

5.1.2 Healing of lesions

While the disappearance time of treponemes from lesions is shorter after penicillin than after the administration of other antibiotics, these lesions heal at least as rapidly with other antibiotics.

5.1.3 Serological response

Very few patients treated with broad-spectrum antibiotics for seropositive early syphilis have been observed over a sufficient period to fulfill the criteria on which the extensive trials of penicillin-treated cases have been based. In a study of 410 cases of early syphilis treated with various antibiotics, where monthly observations and serological response at the end of each period were noted, it was found that the cumulative failure rate after up to two years' observations was 8.7%.

Comparison of the long-term effect in early syphilis of the various antibiotics is of limited value, because of the dissimilarity of mode of administration, dosages, observation periods, etc. The limitations of the material are also indicated by the fact that failures were observed only in patients who were kept under surveillance for from one to two years. With these reservations in mind, it is nevertheless noticeable that in the cases treated with erythromycin and Magnamycin no failures were observed during observation periods up to 12 months and six months respectively.

The information available on broad-spectrum antibiotics and their effect on the serological pattern in yaws is very limited, and does not warrant conclusions.

5.1.4 Pre-natal syphilis, neurosyphilis and late manifestations

Very few patients in any of these categories have been reported as having been treated with other antibiotics than penicillin. However, chlortetracycline and chloramphenicol have been shown to penetrate the placenta and to exert their influence in the syphilitic foetus. Other antitreponemal antibiotics may behave similarly. In neurosyphilis treated with substantial dosages of chlortetracycline, satisfactory response was observed. The same applied to late lesions adequately followed.

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5.1.5 Dosage forms and administration

The total dosages in the 410 patients referred to under 5.1.3 varied from 3.4 g to 70 g administered over three to 15 days. Limitations of material and observation time do not, however, permit conclusions about therapeutic dosage schedules and their adequacy.

Broad-spectrum antibiotics are in most instances given orally, although the parenteral route is feasible. Chlorotetraycine is given intramuscularly and difficulties are sometimes encountered in application. Oxytetracycline, tetracycline and sometimes chloramphenicol, erythromycin, spiramycin and carbomycin may all, to a varying degree, be painful by intramuscular injection and are not recommended for children. Kanamycin is given only by deep intramuscular injections, sometimes painful. On the other hand, the tetracyclines parenterally produce fewer gastro-intestinal complications. The blood dyscrasias resulting from chloramphenicol are apparently not influenced by the route of administration.

It must be assumed that the curative effect also of the broad-spectrum and other antibiotics depends on persistent treponemical blood and tissue concentrations, such as result from long-acting penicillin preparations. There are, however, considerable limitations in present assay methods for determining blood duration levels of such antibiotics, particularly as regards methods with fiducial limits which would allow analysis of dosage requirements in relation to the infection in the body. Furthermore, long-acting parenteral preparations have not yet been developed permitting rational dosage forms to be used for public health purposes in the treponematoses.

Less information is available on the treatment, with antibiotics other than penicillin, of yaws and pinta than of syphilis.

The view was expressed that a long-acting inexpensive preparation of a suitable alternative antibiotic for intramuscular use should be developed, suitable for application for public health purposes in venereal syphilis, as well as against the endemic treponematoses.

5.1.6 Side-effects

Several untoward reactions are attributable to antibiotics other than penicillin. There have already been some fatal reactions, and indiscriminate use of these antibiotics also may prove a hazard to patients. This is illustrated by a nation-wide survey in the USA during 1953-57, where 18% of 1070 severe reactions were caused by antibiotics other than penicillin. The severe and fatal reactions caused by the broad-spectrum antibiotics are almost entirely of toxic and microbiogenic nature. They are, in contrast to penicillin reactions, rarely allergenic and should, therefore, tend to increase with increased dosage.

No serious reactions have so far been observed following erythromycin treatment, orally or parenterally, and although oral administration of the
drug may alter the intestinal flora, gastro-intestinal disturbances are rare and of little significance unless more than 300 mg of the drug are used every six hours.

The Committee noted reports on 516 patients with syphilis and gonorrhoea treated with chlorotetracycline, oxytetracycline, tetracycline, chloramphenicol, erythromycin, carbomycin, streptomycin, novobiocin, oleandomycin, spiramycin and kanamycin. Gastro-intestinal disturbances were encountered in 90% of the 157 patients treated with chlorotetracycline, in half of the six patients treated with oxytetracycline, and in 1.05% of 132 treated with chloramphenicol. Of those treated with chloramphenicol, 5.3% had mild cutaneous reactions, as was the case in 8.3% of those with streptomycin. None suffered blood dyscrasias. 17.3% and 3.7% respectively of the chlorotetracycline and chloramphenicol patients had Herxheimer’s reaction.

5.1.7 Cost

Broad-spectrum and other antibiotics are at present many times more costly than penicillin, regardless of the type of preparation or route of administration. Some broad-spectrum antibiotics in the dosages recommended for syphilis by some practitioners would cost at least between 10 and 15 times the price of adequate penicillin treatment. Erythromycin and spiramycin are approximately from three to four times as costly.

5.2 Recommendations

The Committee noted the increasing need for alternative drugs to penicillin for use in the individual patient with treponematoses, who is allergic to penicillin, and suggested that such alternatives should be available should the problem of penicillin reactions in the future assume importance in syphilis control programmes and in mass campaigns against the endemic treponematoses. A number of antibiotics had been shown to be treponemicidal, but no suitable parenteral preparations were available which could be considered practicable for public health use.

The Expert Committee on Venereal Infections and Treponematoses:

RECOMMENDS

(1) that the attention of manufacturers be drawn to the need for safe, inexpensive, quickly acting repository antibiotic preparations other than penicillin, which are effective against the treponematoses, and which could be used in public health programmes in treatment procedures similar to those now in current use with PAM and benzathine penicillin, and

(2) that co-ordinated studies be undertaken or arranged by WHO of the therapeutic efficiency of such preparations in all stages of the treponematoses, and that co-operation with national health administrations be sought as required.
6. INTERNATIONAL STANDARDIZATION

6.1 International reference preparations for PAM

In the fourth report of the Committee it was strongly emphasized that preparations of PAM (procaine penicillin in oil and aluminium monostearate)—to be recommended to governments, WHO and UNICEF for use in venereal disease and treponematoses programmes—should meet certain provisional, minimum requirements, since it had been shown by WHO that, when using the same dosages, there were great differences in the blood duration levels resulting from PAM preparations of different origin. The use of inferior preparations might jeopardize the outcome of mass treponematoses campaigns, since increased relapse rates might result. Certain provisional international minimum requirements which PAM preparations should meet were therefore proposed in co-operation between the Expert Committees on the International Pharmacopoeia and on Venereal Infections and Treponematoses.\(^1\)

These minimum requirements have been utilized since 1952, although the WHO testing programme of PAM on the international market began as early as 1949. PAM to an estimated value of 3 million dollars has been procured by governments, UNICEF and WHO for treponematoses programmes; and about 40 million people have been treated among the 100 million examined in internationally-assisted endemic treponematoses programmes alone between 1949 and 1958. In this period a total of 663 lots of PAM have been tested co-operatively by WHO and the United States Food and Drug Administration. The Antibiotics Laboratory of the latter acted as reference laboratory for WHO in this regard. Of the 663 lots tested, 21.4\% failed to meet the provisional international minimal requirements referred to above.

The Committee considered that the WHO testing programme of PAM has proved its value. It is believed that it has provided more certainty to health administrations, in the sense that the therapeutic basis for treponematoses campaigns and control programmes has been sound, and that the relapses which have occurred were not due to inadequacies of the penicillin preparations used, including possible deterioration after the “expiration date” of products stored under tropical conditions.

The text describing the provisional minimum requirements considered by the Expert Committee on the International Pharmacopoeia\(^2\) was studied by the Expert Committee on Biological Standardization, which

was of the opinion that there should be devised (a) a modified laboratory assay method which had fiducial limits, (b) an animal test for the persistence of small amounts of penicillin in the blood as a referable substitute for similar tests in man, and (c) an international reference preparation of PAM. The Committee recommended that the Medical Research Council’s National Institute for Medical Research, London, be asked to investigate the matter.

The Expert Committee on Biological Standardization considered the progress made in implementing these recommendations in its ninth and tenth reports. A suitable method for determining persistence of penicillin in the circulating blood was developed in 1956 and was subsequently published by WHO.

The problems encountered in the study of establishment of an animal test for the persistence of small amounts of penicillin in the blood have proved complex. In 1959 the Expert Committee on Biological Standardization studied these problems in detail, and requested the National Institute for Medical Research, London, to analyse further available data, considered that further research was required, and recommended that the work to establish an international reference preparation of PAM proceed as soon as possible, in view of its anticipated continued and widespread use in the treatment of treponematoses.

The present Committee expressed its agreement with the views of that Expert Committee and urged that WHO adequately support this important research activity.

6.2 Benzathine penicillin

The prolonged acting properties of benzathine penicillin are inherent in the substance itself and not dependent upon the vehicle, as in the case of PAM. There is therefore no need for an international reference preparation for this penicillin salt, when used in an aqueous suspension. The potency of preparations of benzathine penicillin can be assayed against the International Standard for Penicillin. These considerations have been taken into account by the Expert Committee on Biological Standardization. Benzathine penicillin is now available also in oil and aluminium monostearate in a gelled preparation, suitable for use under tropical conditions, in addition to the presuspended aqueous preparations.

3 *Bull. Wld Hlth Org.*, 1957, 17, 553
6.3 International reference preparations of cardiolipin and lecithin

The reference preparations established by the Expert Committee on Biological Standardization in 1951 and referred to in its fifth report\(^1\) were distributed to national laboratories from the International Laboratory for Biological Standards at the Statens Serum Institut, Copenhagen. The first replacement was found to be necessary in 1953,\(^2\) the next one in 1957-58.\(^3,4\) On all occasions international collaborative assays were established and members of the Expert Advisory Panel on Serology and Laboratory Aspects were participants.

As the requests for beef-heart lecithin since 1954 have been less numerous than those for egg lecithin, no steps have been taken for replacing the beef-heart lecithin. An international reference preparation of egg lecithin has been established.\(^5\)

The monograph on cardiolipin published in 1951 has been of such interest that a second impression was arranged in 1953 and a second edition with various improvements in laboratory techniques was issued in 1955.\(^6\) The Expert Committee on the International Pharmacopoeia arranged for an annex to be inserted in the second volume of the Pharmacopoea Internationalis,\(^7\) which gives instructions on the types of tests needed to ensure that cardiolipins and lecithins conform to the international reference preparations now available to all national laboratories.

6.4 International Standard for Human Syphilitic Serum

Studies on the use of freeze-dried sera in the serology of the treponematoses have been carried out since 1952, and a collection of freeze-dried sera has been established at the WHO Serological Reference Centre in Copenhagen since 1954.

Close co-operation with the Expert Committee on Biological Standardization has led to the establishment of an International Standard for Human Syphilitic Serum. The serum pool used was tested in a large

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\(^1\) *Wld Hlth Org. techn. Rep. Ser.*, 1952, 56


\(^3\) *Wld Hlth Org. techn. Rep. Ser.*, 1958, 147


\(^7\) *Pharmacopoea Internationalis ... International Pharmacopoeia*, 1955, vol. 2, World Health Organization, Geneva
international collaborative assay, in which eight laboratories took part.\(^1\)\(^2\) The testing comprised not only the proposed standard itself, but also, under code numbers, dilutions of the standard and a series of strongly, moderately and weakly reactive sera. For each of the 18 serological methods used in the assay, the differences in average values per method became greatly reduced when calculated on the basis of the titre of the proposed standard. The International Standard was formally established at a meeting of the Expert Committee on Biological Standardization in 1959.\(^3\) An article in the WHO Bulletin\(^4\) presents the historical facts of the setting-up of this International Standard for Human Syphilitic Serum, gives the technical details of the assay, describes the reactivity of the serum, and gives instructions for its use in establishing national standard sera as well as for expressing the level of reactivity in a national laboratory by means of the standard.

It is therefore now possible to express the serological reactivity of a national test in international units.

The Committee suggested that WHO should consider what further reagents in treponemal and non-treponemal tests are ready for international standardization.

7. SEROLOGICAL AND LABORATORY ASPECTS OF THE TREPONEMATOSES

7.1 Perspectives and developments

The Committee noted the third report\(^5\) of the Subcommittee on Sero-
logy and Laboratory Aspects which met in 1953, and observed that several of the recommendations of the Sub-Committee were being or had been implemented. The establishment of the International Standard for Freeze-Dried Human Syphilitic Serum now available to national laboratories from the Department of International Standards, Copenhagen, is an important step forward in the international efforts to standardize serological methods.

The Committee also studied the reports of the WHO Serological Reference Centres in Copenhagen (Statens Seruminstitut) and in Chamblee, Ga., USA (the Venereal Disease Research Laboratory of the Communic-
able Disease Center), noting the important contributions of these centres to research, exchange of scientific information, training and other activities.

Emphasis, for the last few years, has been on the development of specific serum tests, using treponemal antigens, among which the *Treponema pallidum* immobilization (TPI) test has proved to be the most sensitive and specific. There is an increasing need in developing countries for TPI testing. This has become clear as the high prevalence of seroreactors is being reduced in such areas under the effect of mass campaigns against the endemic treponematoses, and the general use of penicillin, in venereal disease control and otherwise. In certain areas international assistance for the establishment of TPI testing and the furnishing of supplies and equipment is highly desirable, provided competent personnel can be trained. The problem of the specificity of partial seroreactivity with lipoidal antigens in developing areas where the endemic treponematoses are receding can hardly be solved unless facilities for treponemal tests are available. Apart from the increasingly wider use of TPI testing throughout the world, further tests have been developed, such as the *Treponema pallidum* immune adherence (TPIA), *Treponema pallidum* agglutination (TPA), *Treponema pallidum* complement fixation (TPCF), and the development of a protein antigen from the Reiter treponeme (RPCF) and its use in several complement fixation procedures. Such tests may eventually become as specific as the TPI test. They have the advantages of easy performance and low cost, but further research is needed. The antibodies detected by the RPCF, the TPCF and the TPI tests are not identical. The RP antibodies appear earlier in the disease than the immobilisin. The RPCF test has a specificity superior to that of the reagin tests. It shows false positive and false negative results in comparison with TPI tests.

Besides its usefulness in research, the RPCF test is of value in laboratories where TPI testing is not feasible, but only within the above limitations.

The Committee noted with great interest the development of several “screening” tests for syphilis such as the rapid plasma reagin test (RPR), the rapid plasma reagin test using unheated serum (USR), and the plasmacrit tests (PCT). These and similar tests should now be studied in the field under tropical conditions, aiming at their use for survey purposes and evaluation by national field teams and for WHO treponematoses advisory teams (TAT). There is a great need for such testing, particularly for evaluating the later stages of yaws campaigns.

The Committee in its fourth report in 1953 set forth the need for a rapid screening test which could be used for general public health purposes as well as for mass campaigns. Such tests should be easily performed, inexpensive, and should compare favourably with standard tests for syphilis. The three tests, RPR, USR and PCT, all compare satisfactorily with the VDRL test and are applicable for screening in treponematoses mass campaigns and in migrant groups. The RPR and USR require quantities
of blood obtainable only by venipuncture, whereas the PCT is performed on a small quantity of blood serum for which a sufficient quantity may be obtained by a finger puncture, although high-speed centrifugation is necessary.

The Committee took note of, and studied in some detail, what appears to be the most significant recent development in this field, namely the fluorescent treponemal antibody (FTA) technique, which permits rapid recognition of specific antibody in the serum. This technique should now be introduced in all areas, and steps should be taken to have reagents manufactured on a large scale.

In other fields of research progress was noted also in regard to several fundamental aspects of the biology of the treponematoses. New knowledge of the interrelationship of these infections has become available. On the basis of the research work at the International Treponematoses Laboratory Center at Johns Hopkins University, USA, where a deep-freeze library of treponeme strains is being built up in co-operation with WHO, strains of treponemes can be classified into three categories. The differences apparently reside in the character and amount of capsular mucopolysaccharide that each strain produces. The S type includes most strains of venereal syphilis, the Y type most yaws strains, and the M type most endemic syphilis strains. A WHO monograph on this subject has been published.\(^1\)

Several WHO laboratory assistance projects in the venereal diseases and treponematoses field have gone forward since 1952, and the Committee expressed the view that these had undoubtedly contributed in establishing facilities and in improving test performances in areas where this is most needed. Assistance by WHO and UNICEF had been rendered in several instances also to establish the manufacture of cardiolipin and lecithin, e.g., in India and Iran.

Since 1952 a self-contained mobile laboratory unit has been developed by WHO for field purposes. This type of equipment is essential, for example, in sample surveys, during the later stages of eradication campaigns, for the use of the treponematoses advisory teams (TAT) now being furnished by WHO to health administrations. Advantage should be taken of this type of equipment by health administrations, and with the newer type of simple field serological tests available, proper evaluation has been greatly facilitated.

### 7.2 Recommendations

The Expert Committee on Venereal Infections and Treponematoses,

Noting the important progress which is now taking place on several serological and laboratory fronts in the treponematoses, pointing to the

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continued need for international co-operation and co-ordination of activities in this field, and observing that the last report of the Sub-Committee on Serology and Laboratory Aspects appeared in 1954,

RECOMMENDS

that the Sub-Committee be convened at the earliest possible date

(a) to review the newer specific tests for treponematoses;
(b) to consider further the existing as well as planned international reference preparations and standards; and
(c) to study other laboratory activities where international co-operation is desirable.

8. RESEARCH

8.1 The Committee welcomed the plans for an intensified medical research programme in many fields studied by the Twelfth World Health Assembly, and expressed its satisfaction that it was the intention of WHO during the initial year of this programme to study the means by which its existing programme in venereal disease and treponematoses might be most productively extended. Furthermore, it noted that a Scientific Group on Treponematoses would, for this purpose, be convened in 1959 to advise on specific plans.

In its review of the gonorrhoea problem, the Committee had already made certain suggestions for research. As regards treponematoses, many suggestions for research, including serology and laboratory aspects, have been made by previous expert committees. The first International Symposium on Yaws Control held in Thailand in 1952, the second International Conference on the Control of Yaws held in Africa in 1955, and other meetings which WHO has convened—or in the organization of which it has participated or was represented—have made several research proposals. The members of the WHO Expert Panel on Venereal Infections and Treponematoses and other leading workers have also been widely consulted on research problems in 1958-59, as a preliminary to the envisaged research programme. Important study material was thus available to the Committee, and is summarized in Annex 2 (see page 67).

Microbiological studies and experimental animal infections must be based upon suitable laboratories, while epidemiological, clinical and preventive studies, including experimental human infections, would be carried

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1 Off. Rec. Wld Hlth Org., 1959, 95, 504
out mainly in the field. Some of the knowledge obtained through further research would have immediate application in the control and eradication of the treponematoses; some may open up other aspects of practical value; most of it may have wider application also with regard to other communicable diseases.

The Committee considered that in regard to studies of the treponeme, continued research work on the culturing of pathogenic treponemes and the study of their antigenic structure is of paramount importance, as well as serological identification of active components in the treponemal body and capsular material for differentiation between different groups and types of this micro-organism. Studies on survival of treponemes away from the body under different environmental conditions should also be given a high priority in the research programme. In the epidemiology of the endemic treponematoses, studies on modes of transmission and factors favouring them, as well as on the extension of venereal syphilis into areas cleared of yaws and endemic syphilis (immunity) are important. In venereal syphilis, search for factors other than antibiotics which have brought about a decline in prevalence of syphilis, and the reasons for the recent increase in early syphilis in some areas, should be undertaken. In the pathology of the treponematoses the survival of treponemes in the body and their localization in latency should receive attention in the research programme.

On the clinical side, it was considered that the importance of cardiovascular and neurological involvement, as well as congenital transmission in all of the treponematoses in relation to the duration of infection and age of the patient in treated and untreated diseases should be studied. The growing use of surgical methods in the treatment of aneurisms and valvular deformation was mentioned, and the importance of correct serology and adequate preliminary penicillin therapy in these cases was stressed. In the diagnostic field continued work to evolve a simple, specific, sensitive, reproducible and inexpensive serum test employing treponemal antigens should be given the highest priority, and it was felt that the need for study of the nature and extent of biological false positive reactions in mass and other venereal disease and treponematoses campaigns in developing areas is becoming increasingly urgent. In the field of therapy, the Committee had already pointed out the need for the development and assessment of other antibiotics than penicillin, effective in all stages and manifestations of the treponematoses. The need for research into the nature and extent of penicillin sensitization and the significance of humoral penicillin antibodies has also been referred to elsewhere in this report. In the prevention of endemic treponematoses evaluation by clinical and serological surveys of results of campaigns against the treponematoses after 5-10 years would be of great importance. In regard to venereal syphilis, sex-behaviour and other studies are desirable in the younger age-groups, where the attack-rates of the infection are the highest.
9. EXCHANGE OF SCIENTIFIC INFORMATION

The role of WHO in the exchange of information among venereal disease and treponematoses workers has been considerable since the Expert Committee on Venereal Infections and Treponematoses issued its fourth report in 1953. The technical documents, monographs, survey of existing world-wide venereal disease legislation, published articles, reprints of original investigations, field and laboratory studies, epidemiological and vital statistics, and other publications of WHO in this field, which appear in English, French and Spanish, prepared by WHO Headquarters often in collaboration with regional offices and based on data collected from many parts of the world, have proved to be of great value. The hope was expressed by the Committee that these might obtain the widest possible distribution to health administrations, interested institutions and workers in the field.

It was thought that the issues of the WHO Bulletin ¹ which have been devoted to syphilis, yaws or serological and laboratory aspects since 1952 were particularly valuable, both from the point of view of the overall perspective given to the problems treated, and of their scientific content.

Since 1952, WHO has convened many meetings of scientific workers and public health experts on venereal infections and treponematoses. The value of these meetings, for giving guidance to the WHO programme as well as for contributing to knowledge on many aspects of complex technical questions, needs no further comment. It was felt that personal contact is undoubtedly one of the best ways of useful exchange of scientific information.

In looking to the future, the Committee believed that the proposal for the third International Conference on the Control of Yaws to be held in Brazil or Indonesia in 1961 is sound, and that the World Health Organization, in co-operation with the International Union against the Venereal Diseases and the Treponematoses, and the United States Public Health Service, might sponsor a second International Symposium on Venereal Diseases in 1962 or 1963.

10. NOMENCLATURE AND CLASSIFICATION IN YAWS AND SYPHILIS

10.1 Nomenclature and classification

The Expert Committee on Venereal Infections and Treponematoses, in its fourth report, had recommended that a special corresponding group of experts be set up by WHO to propose a suitable standard nomenclature

¹ See page 67, footnote ¹¹.
for yaws lesions based on the grouping of lesions proposed at the first International Symposium on Yaws Control held in 1952. In co-operation between the corresponding group and an international group of experts on yaws and participants at the International Conference on the Control of Yaws in Africa in 1955, an illustrated, international nomenclature had been established and published by WHO.\footnote{Hackett, C. J. (1957) An international nomenclature of yaws lesions, Geneva (World Health Organization: Monograph Series, No. 36)} The relationship to the classification of yaws patients for mass campaigns has also been included. This work has proved most useful for professional and auxiliary workers in the field, and has contributed to improved diagnosis, classification of lesions and evaluation from a scientific as well as from a public health point of view.

The Committee considered the necessity for a similar international nomenclature and classification for syphilis, and was of the opinion that there is a need for this in view of the multiplicity of descriptive and other terms employed for this treponematoses in many countries. There was also noted a wide variety of grouping of lesions and stages of syphilis used in countries where this infection is reported for statistical purposes to national health administrations.

10.2 Recommendations

The Expert Committee on Venereal Infections and Treponematoses recommends

that WHO take steps to establish, through a corresponding group of experts—possibly in co-operation with the International League of Dermatological Societies and the International Union against Venereal Diseases and Treponematoses—suitable standard nomenclature for scientific, clinical and public health purposes in syphilis. Consultation with the relevant WHO expert committees or other bodies might be sought.

11. TRAINING

The Committee referred to the extensive discussions of this problem in reports of previous expert committees in several fields of health, including venereal diseases and treponematoses. Over the last ten years, WHO has awarded in many parts of the world more than three hundred fellowships for advance study of venereal infections and treponematoses, often combined with broader public health training, thus making a significant contribution to the training of professional personnel.
There is a great need in many countries for auxiliary personnel, and in the mass campaigns against endemic treponematosis this question is of particular importance. While multipurpose training of permanent auxiliary personnel is to be preferred to training of temporary personnel for specialized campaigns, this is not always practicable. But specialized training of short duration for personnel in yaws eradication programmes may, for example, be the basis for subsequent broader training.

The Committee welcomed the project of WHO, as part of its training and education programme, to study on a world-wide basis the training of auxiliaries and their teachers. It was noted that this study is to include—within the public health programme—an assessment of the types of auxiliaries needed and the adjustment of the required training accordingly. Re-training facilities for specialized programme workers should then become available, and avenues of promotion for such workers should be opened, so that they might eventually be integrated into general health services.

It would be useful if scientific aid materials could be made available by an established unit in the central health administration, for the use of teachers in training courses for auxiliary workers.

12. HEALTH EDUCATION AND VENEREAL DISEASE INFORMATION

Health education is mainly concerned with the attitudes of the public to a disease and its effect on acceptance of early treatment, surveillance and prevention. Very few systematic studies exist of public attitudes towards venereal diseases.

The furnishing of venereal disease information to age-groups younger than in the past is required, in the light of the higher attack rates of venereal disease in these age-groups within the last few years. In the endemic treponematoses, educational work to ensure full participation in mass treatment campaigns is needed, to establish confidence between the health team and the population, after which little further education or publicity might be necessary because of the spectacular and rapid effect of penicillin on surface lesions.

The Committee desired to draw the attention of the International Union against Venereal Diseases and the Treponematoses and the International Union for Health Education of the Public—both non-governmental international organizations in official relationship status with WHO—to the continued need for informational and educational work in the venereal disease and treponematoses fields, including family education of “teenagers”.
# Annex 1

## AREA RESURVEY RETURN FORM

WHO Project No. ..........................
UNICEF Project No. ..........................
Area of operation: ..........................
Number of villages in the area: ..........................
Name of largest village: ..........................

**YAWS CAMPAIGN:** Country ..........................
Form: WHO/YAWS/101

### AREA RESURVEY RETURN

**Date** ..........................

I. FIRST □ SECOND □ THIRD □ FOURTH □ RESURVEY (3) RETURN

**Months after ITS** ..........................

<table>
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<th>AGE (years)</th>
<th>SEX</th>
<th>POPULATION</th>
<th>PERSONS SEEN AND TREATED</th>
<th>INACTIVE LATE YAWS</th>
<th>NO YAWS LESIONS PRESENT</th>
<th>PERSONS NOT SEEN</th>
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<th>AGE (years)</th>
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<th>PERSONS SEEN AND TREATED</th>
<th>INACTIVE LATE YAWS</th>
<th>NO YAWS LESIONS PRESENT</th>
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### II. CORRESPONDING DATA FROM INITIAL TREATMENT SURVEY (ITS) RETURN

**For same population as above**

<table>
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<th>AGE (years)</th>
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<th>PERSONS SEEN AND TREATED</th>
<th>INACTIVE LATE YAWS</th>
<th>NO YAWS LESIONS PRESENT</th>
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### NOTES TO AREA RESURVEY RETURN

**Column 2:** Census figures or estimated population.

**Column 9:** Inactive late yaws to be kept separately but to be treated as latent cases.

**Columns 10 and 12:** In areas of low or medium prevalence where only those under puberty or household and other obvious contacts or infectious patients are protected as latent cases and contacts, that is, column 11.

**Percentage at foot of column:**

- 4 = percentage of column 3
- 5-12 = percentage of column 4
- 13 = percentage of column 3

**NOTE:** Any difference between persons treated and persons seen, not accounted for by the treatment policy being used, should be given in a footnote.
Annex 2

A GENERAL REVIEW OF TREPONEMATOSES RESEARCH

The following is a summary of suggestions and views concerning treponematisos research expressed in reports of the WHO Expert Committees concerned with this field, and in reports of the Sub-Committee on Serology and Laboratory Aspects. In addition are incorporated views expressed at the following international meetings: the tenth International Congress of Dermatology, London (1952); the first International Symposium on Yaws Control; the Second International Conference on the Control of Yaws, Enugu, Nigeria (1957); the First International Symposium on Venereal Diseases and the Treponematoses, Washington, D.C.; the Eleventh International Congress of Dermatology, Stockholm (1957); the First WHO Venereal Disease Control Seminar of the Western Pacific Region; the Inter-Country Yaws Control Co-ordination Meeting for Asia, Kuala Lumpur, Malaya; and also at the meetings of the International Union against the Venereal Diseases and the Treponematoses held in Monaco in 1954, Naples in 1955, Stockholm in 1957 and Brussels in 1958.

Also included are some considerations contained in special numbers of the Bulletin of the World Health Organization devoted specifically to treponematoses, and other issues devoted largely to syphilis; previous

1 Off. Rec. Wild Hith Org., 1948, 8, 60
2 Off. Rec. Wild Hith Org., 1949, 15, 18
6 Wild Hith Org. techn. Rep. Ser., 1951, 33
14 Bull. Wild Hith Org., 1954, 10, No. 4; 1956, 14, No. 2; 15, No. 6
15 For example, Bull. Wild Hith Org., 1952, 5, No. 4
WHO documents on the subject of research;¹ and monographs published by WHO, particularly Biology of the treponematoses.² Furthermore, the summary contains proposals made to WHO by the WHO Expert Panel on Venereal Infections and Treponematoses and other leading workers on the invitation of the Secretariat.

The following subjects require further study:

Treponemes

The basic biological, pathological, immunological and biochemical characteristics and differences of treponemes from all of the treponematoses. Studies should include the morphology of treponemes, examined by electronic and protonic microscopy, and their behaviour in man and animals. Animal spirochaetes should be included as their study might provide useful knowledge.

Studies on the survival of treponemes away from the body, e.g., in soil, sweat and insects, and on healthy skin, under different environmental conditions.

Human inoculations with different treponemes to study transmission and cross-immunity, as related to environment, stage of infection and treatment. This work is important to assess the potential dangers of the spread of venereal syphilis in rural areas when non-venereal treponematosis has been eradicated. What protection against venereal syphilis follows childhood yaws? To what extent does venereal syphilis occur in yaws and endemic-syphilis areas?

Immunoochemical studies of pathogenic treponemes to identify serologically active components in the treponemal body and/or the capsular material for improved methods of demonstration of group- or species-specific antibody.

The studies on penicillin sensitivity of treponemes on a world-wide scale to be repeated at regular intervals. The present absence of penicillin resistance and factors that might produce resistance—such as long-continued exposure to subminimal doses of antibiotics—should be investigated.

Studies on mutation in pathogenic treponemes and the part that might be played by antibiotics and radioactivity.

Continued work, by the chemist, biochemist and microbiologist on growing the pathogenic treponemes, employing recently-developed tissue

⁴ Pangborn, M. C. et al. (1955) Cardiolipin antigens, Geneva (World Health Organization : Monograph Series, No. 6, 2nd ed.)
and virus culture methods, and the study of the antigenic structure of treponemes. Success in this would be of paramount importance in many respects. It would increase our knowledge of the individual treponematoses and their relation to each other. Practical aspects such as specific serological tests and possibly skin tests and immunization might then also be considered.

Epidemiology

(a) Endemic treponematoses

Studies on mode of transmission and of factors favouring transmission and high prevalence. The mode of entry of treponemes into the body.

The influence of climatic (skin temperature), hygienic and socio-economic conditions and other environmental factors, including local customs, on the geographical distribution, transmission and persistence of these diseases.

Prevalence studies of endemic treponematoses in virgin areas.

"Improved standards of living", including social, hygienic and economic factors, improved communications; and the part played by "unaccountable penicillin administration"—including penicillin-like substances in the food—in producing recession or low prevalence in untreated areas.

Significance of varying ratios of the prevalences of different clinical lesions of the endemic treponematoses to each other and to seroreactivity. Studies to determine whether an increase of active cases in the wet season is due to latent cases becoming overt or to other reasons.

The significance of raised prevalence in young adults aged 20-30; the effects of other diseases upon prevalence in treated populations.

Studies on the presence of venereal syphilis in yaws and endemic-syphilis areas, and cross-immunity between them. These are important in relation to possible spread of venereal syphilis into the rural areas which have been cleared of endemic treponematoses. How long after yaws is eradicated and at what level of venereal syphilis in the towns does this become a danger? Search for areas where this might have taken place.

(b) Venereal syphilis

Search for factors other than penicillin which have brought about the decline in prevalence of syphilis, and the reasons for the recent increase in early syphilis in some areas. Continued surveys are required to define the problem in all parts of the world.

Studies to determine whether the use of short-acting penicillin or other antibiotics in gonorrhoea would tend to increase the prevalence of venereal syphilis.

Studies of local factors, e.g., religious, social or local customs, which influence the spread of venereal syphilis.
Pathology

Distribution of treponemes in the body of infected individuals, starting from the entry of the treponeme into the host. Comparative studies of the various treponematoses as causes of death and of lesions of syphilis, yaws and pinta in treated and untreated individuals.

The survival of treponemes in the body and their position in latency. The number of treponemes in the body at different stages of infection, without or after treatment, and the presence of treponemes and their infectivity in seroreactive treated cases.

Immunity to further infection, and cross-reactions to treponemal tests and factors which may modify these responses.

The effects of temperature, humidity and other environmental influences in animal infections with the treponematoses to ascertain whether long-continued environmental influences alter infectivity or clinical manifestations. The possibility of various types of treponemes to pass the placental barrier in animal infections. Serological and immunological changes in rabbits infected with heat-killed or avirulent treponemes.

Factors influencing antigen/antibody relationship, and their importance in relapses; these would include other infections, nutrition, seasonal changes, inadequate treatment. Frequency of spontaneous cure.

Studies of the nature of the Wassermann antibody (Reagin) to elucidate the mechanism of its production and the significance in treponemal and other chronic diseases, special attention being given to "sero-fast" subjects. Precise studies, using quantitative tests, of the results of therapy of endemic treponematoses.

The determination of the duration of the early stages of the endemic treponematoses. The recognition of early and late stages of an infection in the absence of clinical lesions. The frequency of spontaneous cure. Changes in the cerebrospinal fluid in all stages of the different treponematoses, treated and untreated.

The part played by trauma and superinfection in the production of late lesions. The infectiveness of late ulcers. Why in some yaws areas adult populations may have 50% seroreactivity while there may be little active yaws and this comprising mainly plantar changes.

Clinical aspects

Mortality studies of the endemic treponematoses and their effect on life expectancy, of the role of treponematoses as causation of miscarriages, abortions, sterility. The clinical pattern of the different treponematoses in different races under different conditions. The effects of race, other infections and disease; nutrition; temperature, humidity and seasonal changes; infectivity and course of the disease, and mucosal lesions in relation to geographic distribution; studies on the course of the diseases
when patients were moved from one area to another. Possibility of transition from endemic to venereal syphilis.

The lowered severity of yaws at the present time compared with twenty years ago in the absence of mass campaigns or much “casual” treatment.

The clinical and pathological nature of the hyperkeratoses, digital contractures, goundou, and dyschromias in relation to geographical distribution and environmental factors. Pathological studies to differentiate early from late lesions of hyperkeratosis. Clinical and pathological studies of palmar and plantar changes not due to endemic treponematoses, and differentiating criteria.

Cardiovascular and neurological involvement and congenital transmission in all of the treponematoses in relation to duration of infection and age of the patient in treated and untreated disease. The significance of seroresistance in relation to complications.

The possibly allergic nature of interstitial keratitis, nerve deafness in venereal syphilis, and of gummata in all the treponematoses, reappraisal of the incidence of paresis and other forms of neurosyphilis in the tropics; the relation of tabes dorsalis and other parenchymatous lesions to blood groups; and the pathology of optic atrophy.

**Diagnosis**

Criteria for diagnosis at various stages in the evolution of endemic treponematoses. Differential diagnosis in yaws eradication campaigns. Improved differentiation of yaws and syphilis, especially serologically.

Value of serological surveys in campaigns against yaws and endemic syphilis. Comparative studies of different serum tests. Serological activity and the occurrence of relapses. Significance of varying prevalences of clinically active disease to serological reactivity.

The influence of racial groups and other diseases on serological findings. Biological false-positive reactions in mass and other venereal disease and treponematoses campaigns, and their significance in clinical medicine. The establishment of an adequate international supply of sera from all stages of treponematoses and of biological false-positive reactors.

Use of the treponemal immobilization tests, and other tests employing treponemal antigens, in all stages of the various treponematoses. The use of *T. pertenue*, as well as *T. pallidum*, as antigens for such tests—and also for skin tests. Continued work to evolve a simple specific sensitive reproducible inexpensive serum test employing treponemal antigens. Continued standardization of reagents and reactive sera (e.g., freeze-dried sera).

Suitable methods to transmit blood, plasma and sera without deterioration. Development of a simple, specific inexpensive micro-test for mass screening. Periodical international evaluation studies of sensitivity, specificity and reproducibility of the various qualitative and quantitative serological tests and their relation to the TPI test.


Therapy

Long-term assessments, at five- and 10-year periods, of existing penicillin treatment of all stages of all treponematoses, including latency, neurosyphilis and cardiovascular syphilis.

Evaluation of newer long-acting penicillin preparations (e.g., benethamine penicillin, benzathine penicillin in aqueous suspension and in oil with aluminium monostearate (BOM), antihistamine penicillins, etc.), and their value in mass campaigns. Definition of standards of height and duration of penicillinemia following specified single doses of newer preparations in man. Further development of an animal test for such work. The effects of the addition of steroids to penicillin in certain manifestations of treponemal diseases.

The nature and extent of penicillin sensitization and the significance of humoral penicillin antibodies. The extent to which mass campaigns may produce penicillin sensitivity. The development of a test to indicate penicillin sensitivity.

Assessment of all other antibiotics effective in all stages and manifestations of the treponematoses. Minimal standard data required for that purpose. Mode of action of such antibiotics. Development of a suitable painless injectable repository preparation to be held in reserve should sensitivity reactions or penicillin resistance become important.

Prevention

(a) Endemic treponematoses

Studies on the public health activity required at different prevalences of clinically active disease and/or serological reactivity. The definition of minimal public health activity. The prevalence below which regular surveys can be replaced by surveillance. The prevalence below which no special public health activities are indicated. The source of clinically active endemic treponematoses cases which are found in the later surveys and in surveillance of eradication campaigns.

The part played by "unaccountable penicillin administration" and improved standards of living in yaws eradication in areas where no mass campaigns have been carried out.

The factors in "improved standard of living" that are most effective in reducing transmission of yaws; these may be social, economic and hygienic, and may include communications.

Once the prevalence of yaws has been reduced to a low level, what factors favour its increase and how great is the risk of such increase?

Economic consequences of yaws eradication campaigns.

Evaluation by clinical and serological surveys of results of campaigns against the treponematoses after five and 10 years. Improved assessment and statistics of yaws campaigns.

The development of effective and economical methods to stop transmission (see under Epidemiology, page 69).

Vaccine immunization against the treponematosis (see under Treponemes, page 68).

International nomenclatures for the clinical manifestation and stages of each treponematosis. Agreed terms for use in field campaigns and in the laboratory. The time relationship of late latency remains to be defined.

(b) Venereal syphilis

Social, psychological, and sex-behaviour studies are required on the factors leading to promiscuity, delinquency and venereal disease in young persons (e.g., “teenagers”), and studies of the factors leading to high incidence of venereal disease in migrants and ethnic minorities, both before and after entry to the host country.

Studies of prostitution as the cause of venereal disease and a comparison of the prostitute with the “good-time girl” in this respect in different countries. Social and psychological factors of prostitutes and their clients. Effect of closure of brothels on venereal disease situation in relation to facilities available.

Evaluation studies of tangible effects of venereal disease legislation; study groups to study public health aspects of venereal disease control and the various methods used in different countries, including newer case-finding methods such as “speed-zone epidemiology” and “cluster testing” with a view to assessing possibilities or otherwise of application of these or other methods elsewhere. Studies of returns in relation to cost of new cases found by mass blood-testing of special population groups. Selection of most profitable groups in different areas.

Studies on how much syphilis is concealed, or is being treated by private practitioners, or by self-medication in countries where antibiotics are obtainable without a doctor’s prescription. Studies to see how contact-tracing services could best be extended to private practitioners.

Studies to evolve methods best suited to particular areas of ensuring prompt attendances at clinics of patients and contacts and of preventing default; of the most effective means of health education applied to specific groups.

Further investigations into the efficacy or otherwise of existing methods of local and systemic prophylaxis, suitable for particular circumstances and the evaluation of these methods. Evaluation of such methods in persons frequently exposed (e.g., prostitutes), special consideration being paid to the possible increase of strains of gonococci less sensitive to penicillin now in circulation (see under Gonorrhoea, page 26).