EXPERT COMMITTEE ON VENEREAL INFECTIONS AND TREPONEMATOSES

Fourth Report

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EXPERT COMMITTEE ON VENEREAL INFECTIONS
AND TREPONEMATOSES

Fourth Session
London, 28 July - 2 August 1952

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EXPERT COMMITTEE
ON VENEREAL INFECTIONS
AND TREPONEMATOSES

Fourth Report

1. INTRODUCTION

The Expert Committee on Venereal Infections and Treponematoses met in London from 28 July to 2 August 1952.

The committee unanimously elected Dr. G. L. M. McElligott as Chairman and Professor M. Soetopo as Vice-Chairman. Dr. T. J. Bauer was elected Rapporteur. Several members of the WHO Expert Advisory Panels on Venereal Infections and Treponematoses, including Serology and Laboratory Aspects, attended some of the meetings.

This was the fourth session of the committee and the first for which the terms of reference formally included the non-venereal treponematoses, in accordance with the decision of the Executive Board at its fifth session. A number of panel members (from 44 countries), including experts on serology and laboratory aspects, had been appointed by WHO to advise on venereal infections and treponematoses. Twenty-five members of this panel who had attended the Tenth International Congress of Dermatology in London during the week preceding the session of the committee held consultations on technical and other matters of interest to WHO.

The comments of the Executive Board on the report of the third session of the committee were noted. Full consideration was given to these comments throughout the meetings. Particular attention was paid to the

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1 The Executive Board, at its eleventh session, adopted the following resolution:

The Executive Board
1. NOTES the fourth report of the Expert Committee on Venereal Infections and Treponematoses;
2. THANKS the members of the committee for their work;
3. DURES the attention of governments to relevant recommendations contained in the report, and
4. AUTHORIZES its publication.


2 Off. Rec. World Hth Org. 25, 11

approval by the Board of the public-health outlook previously advocated by the committee, with emphasis on the maintenance of a balance between selective programmes and an overall programme of disease prevention, including the training of personnel for public-health, clinical, and laboratory purposes in regions where limited facilities exist.

Consideration was given to the committee's relationship with its Subcommittee on Serology and Laboratory Aspects, the report on the second session 4 of which had been approved by the members of the third session of the main committee after consultation by mail. The subcommittee's report was subsequently approved by the seventh session of the Executive Board. 5

The committee noted the resolution of the Executive Board at its seventh session with regard to the International Anti-Venereal-Disease Commission of the Rhine, 6 and that of the Third World Health Assembly 7 on the report of the first session of the Joint ILO/WHO Committee on the Hygiene of Seafarers, 8 as well as the resolution adopted by the ninth session of the Executive Board on the most effective utilization by WHO of short-term consultants. 9

The extensive preparatory documentation made available to the members of the committee (see Annex 1, page 41) was noted with satisfaction and carefully studied in relation to the agenda, the development and status of the WHO venereal-disease and treponematoses programme, including laboratory aspects, and the present and projected scope of the work.

In its deliberations, the committee placed major emphasis on technical orientation and epidemiological considerations relating to the large-scale programmes now being carried out by certain health administrations with international assistance. The general outlook of WHO in its approach to control programmes against venereal infections and treponematoses in the light of past experiences was considered, but as far as possible the still-valid considerations from previous sessions are not reiterated in the present report.

7 Resolution WHA3.31, Off. Rec. World Hlth Org. 28, 26
2. DEVELOPMENTS AND PERSPECTIVES

2.1 General Outlook

The rationale for an outlook by WHO on treponemal diseases—namely, syphilis, bejel, yaws, and pinta—as a group, was recognized by the third session of the committee in 1949\textsuperscript{10} and subsequently approved by the governing bodies of WHO. There is ample evidence that the diseases caused by treponemes have much in common: the causative agents are morphologically and immunologically related; there are comparable, if not always identical, responses to infection on the part of the human host; the outcome of effective therapy in all syndromes is prompt and favourable; and, finally, penicillin is unique in its applicability as a preventive, abortive, and curative weapon, and there continues to be an absence of penicillin resistance in the treponemes. These are the major elements which have contributed to the delineation of a more rational concept of, and approach to, the control of the treponematoses in individuals as well as in large population-groups. From the public-health viewpoint there are definite practical advantages in this overall view, as opposed to concepts based on the mode of transmission or on variations in resultant clinical syndromes.

Notwithstanding a substantial decline in the incidence of infectious venereal syphilis in Australia, Europe, North America, and limited areas elsewhere, since the second World War, important reservoirs remain in many other parts of the world. Furthermore, non-venereally-transmitted treponemal disease in children has been identified as an important health problem during the last several years. Examples of this are the "endemic syphilis" in Bosnia (Yugoslavia), Madras (India), Bechuanaland (South Africa), and Tahiti (South Pacific); "njovera" in Southern Rhodesia; and "bejel" in the Eastern Mediterranean region. In addition, pinta remains endemic in some areas in Central and South America. These are non-venereal treponematoses, in many ways clinically similar or identical to syphilis, but epidemiologically comparable to yaws. Yaws remains a serious social and economic burden of rural populations in tropical areas where lives a great proportion of the world's total population.

While it is recognized that, over the last few years, encouraging initial results have been obtained in national health programmes with or without WHO assistance, the committee wishes to emphasize the continuing need for the active encouragement of treponematosis-control measures in many

countries where organized programmes have not yet been initiated. Long-range planning is also necessary in areas where active programmes are under way and the reservoir of infection is being brought under control. Reorientation and further emphasis on case-finding by the use of new techniques may thus become desirable. This is now the case in many developed countries with regard to early venereal syphilis. More detailed attention to late manifestations of this and the other treponematoses has also, in some areas, become a desirable public-health objective. Without a flexible, long-term, purposeful programme which can meet the public-health needs as they arise, the progress in the control of treponemal diseases made in recent years might be placed in jeopardy.

With regard to venereal infections of non-treponemal origin—namely, gonorrhoea and non-gonococcal urethritis, chancreoid, lymphogranuloma venereum, and granuloma inguinale—the outlook remains essentially the same as that expressed in the committee's report on its third session. The committee wishes to repeat the views previously emphasized that special attention should be given to these diseases by WHO where particular geographical or other considerations pertain. Some further aspects relating to these disease entities are referred to in section 7, page 37, dealing with non-treponemal venereal infections.

Venereal infections, and non-venereal treponematoses and their sequelae, limit employability for work and result in chronic disability which reduces work-efficiency in industry and agriculture at the most productive period of life. On the basis of detailed information received during the last few years as a result of WHO-assisted control programmes in several regions, it is known that the prevalence of yaws in underdeveloped areas may be as high as 25%-30%, in large, rural populations. In the current yaws-control programme in Haiti it has been estimated that some 100,000 incapacitated people have been returned to work, thereby increasing the national production by several million dollars a year. Because of the economic consequences attributable to these diseases, health programmes directed against them are considered appropriate fields of activity under the United Nations Expanded Programme of Technical Assistance for the Economic Development of Underdeveloped Countries. The committee noted that this principle had been accepted by WHO and by the Technical Assistance Board (TAB); it also noted the manner in which technical assistance was rendered, as set forth by the TAB and as outlined by the Economic and Social Council at its ninth session.11 The committee also expressed the hope that co-operation between health administrations, the United Nations International Children's Emergency Fund (UNICEF), and WHO for the

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benefit of mothers and children would continue beyond the programmes actually being implemented against the treponemal diseases at the present time. In studying the selective public-health programmes embarked upon by WHO in support of national health-administrations which have requested assistance in the initiation, development, and follow-up of treponemal-disease-control programmes, including laboratory aspects, the committee noted the progress made in several countries which are Member States of WHO. An estimated total of five million people have been examined in such programmes over the last three years, and approximately two million people have been treated with penicillin. Data from six of the larger “mass” programmes are summarized in table I.

### TABLE I. NUMBER OF PERSONS EXAMINED AND TREATED IN SIX WHO/UNICEF TREPONEMAL-DISEASE-CONTROL PROGRAMMES

<table>
<thead>
<tr>
<th>Programme</th>
<th>Duration</th>
<th>Number examined</th>
<th>Number treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haiti (yaws)</td>
<td>July 1950 - April 1952</td>
<td>2,649,013</td>
<td>944,139</td>
</tr>
<tr>
<td>Indonesia (yaws)</td>
<td>May 1950 - July 1952</td>
<td>404,382</td>
<td></td>
</tr>
<tr>
<td>Iraq (bejel)</td>
<td>October 1950 - July 1952</td>
<td>394,281</td>
<td>14,980</td>
</tr>
<tr>
<td>Philippines (yaws)</td>
<td>August 1951 - July 1952</td>
<td>20,691</td>
<td></td>
</tr>
<tr>
<td>Thailand (yaws)</td>
<td>May 1950 - August 1952</td>
<td>1,016,807</td>
<td>205,858</td>
</tr>
<tr>
<td>Yugoslavia (endemic syphilis)</td>
<td>January 1949 - December 1951</td>
<td>941,063</td>
<td>91,988</td>
</tr>
</tbody>
</table>

In reviewing these programmes, the committee stressed the role of medical advances as “pacemakers” of social change and noted the preliminary report on the world social situation submitted by the Secretary-General of the United Nations to the United Nations Social Commission at its eighth session, which stated: “In the underdeveloped areas ... release of the resources of the countries from the tangled undergrowth of mass diseases is a prerequisite of development.”

Penicillin in mass diseases like syphilis and yaws is, indeed, an important pacemaker of this kind, and its impact on underdeveloped areas should be carefully studied. It is logical that the outlook of WHO should continue to be directed towards the less highly developed areas, where the attack-rates of the non-veneraeal treponematoses are high in the lower age-groups, where infantile syphilis and syphilis in pregnancy are prevalent, and where active control-work or further teaching, training, and laboratory facilities are required.

The committee reviewed the various elements in the selective public-health programmes of WHO against venereal infections and treponematoses, including demonstration and survey aspects, training and consultant

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activities, fellowships, symposia, special literature and exchange of scientific information, grants-in-aid, etc. With regard to these programme elements, the general outlook of WHO and its approach to health administrations remain essentially as outlined in previous reports of the committee. It was also emphasized that joint programmes with other health activities—maternal and child health, malaria, tuberculosis, health education, and others—are desirable whenever initial surveys and exploration of the health problems in an area show technical and administrative advantages. Single-phase or joint activities should, as soon as possible, serve as bridgeheads for wider, multiphasic, public-health activities, since isolated efforts directed towards specific health problems will have difficulty in surviving unless integrated into an overall programme. Control programmes against venereal infections and treponematoses would seem to be suitable bridgeheads for further health work, particularly the large-scale campaigns against treponemal diseases now under way in many areas. In reviewing the experiences of health administrations in such programmes, it was found desirable to consider in some detail the techniques by which treponemal diseases can now be effectively suppressed and perhaps ultimately eliminated as major health problems. One of the aims of WHO should be to assist health administrations in working towards the latter objective.

2.2 The Approach of WHO to Treponemal-Disease Control

It has been stated that "penicillin is not public health". Supplies alone will not assure success in a selective public-health programme against treponemal diseases. However, with its triple potential of (a) preventing infection on exposure, (b) aborting the infection in the incubation period, and (c) curing the established disease, penicillin is a powerful weapon in organized treponematosis-control work. Present knowledge indicates that mass diagnosis and treatment programmes, when carefully planned and systematically carried out, will result in a significant reduction in the incidence of infectious cases and in the general prevalence of the treponematosis (see table II); and, under favourable circumstances, infectivity can be completely eliminated (see table III and fig. 1).

The techniques of conducting control programmes with repository penicillin and by mass case-finding are still being perfected. In each programme it is essential to establish at least one controlled, local study-area with adequate laboratory facilities where detailed evaluation of various epidemiological methods, response to treatment schedules, etc., can be made. The knowledge acquired in such controlled, local study-areas ("pilot areas", "primary areas") will serve as a basis for the broader mass-programme as it develops. The selection and size of such controlled study-areas will depend upon a great many factors, several of which are
TABLE II. REDUCTION IN PREVALENCE OF YAWS (INFECTIOUS AND ALL FORMS) FOLLOWING MASS TREATMENT IN A CONTROLLED STUDY-AREA *

<table>
<thead>
<tr>
<th></th>
<th>Original survey and treatment, 1951</th>
<th>Control re-examination 5 months later, 1952</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,488</td>
<td>1,745</td>
</tr>
<tr>
<td>Number examined</td>
<td>1,325</td>
<td>1,574</td>
</tr>
<tr>
<td>Percentage examined</td>
<td>90.3</td>
<td>90.2</td>
</tr>
<tr>
<td><strong>Yaws, all forms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>308</td>
<td>248</td>
</tr>
<tr>
<td>Percentage of total population</td>
<td>21.0</td>
<td>14.2</td>
</tr>
<tr>
<td>Percentage of examined population</td>
<td>23.2</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>Infectious yaws</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of total population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of examined population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In percentage of yaws, all forms</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Bandjaran and Karangkan, Java, Indonesia

TABLE III. ENDEMIC SYPHILIS: EARLY INFECTIOUS LESIONS AND SEROPOSITIVITY OBSERVED IN FOUR SURVEYS IN MNO * SAPNA, BOSNIA, 1948-1952

<table>
<thead>
<tr>
<th>Area</th>
<th>Mean population**</th>
<th>Early infectious lesions</th>
<th>Seropositivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of cases</td>
<td>% of mean population</td>
<td>Number of cases</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>1. Kraljevici</td>
<td>418</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>2. Ramlci</td>
<td>310</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>3. Međedjla</td>
<td>356</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>4. Gdešl</td>
<td>354</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>5. Sapna</td>
<td>460</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>6. Andželci</td>
<td>273</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>7. Mehmatpāvlovič</td>
<td>225</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>8. Kravčević</td>
<td>307</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>9. M. Nežuk</td>
<td>416</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>10. Jusci</td>
<td>195</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>3,355</td>
<td>136</td>
<td>17</td>
</tr>
</tbody>
</table>

* " MNO " is a small administrative unit. The total area of MNO Sapna is 125 square kilometres (68 square miles).
** 94.5% of the mean total population was examined.
The four surveys were carried out on the following dates: I, 2 October 1948; II, 4 April 1950; III, 30 June 1951; IV, 10 January 1952. During each survey, the cases found were treated; in survey III, household contacts were also treated.
FIG. 1. DECREASING SEROPositIVITY-RATE FOLLOWING MASS-TREATMENT CAMPAIGN AGAINST ENDEMIC SYPHILIS IN BOSNIA

First Survey

Second Survey

Seropositivity-rate

- 0.4-10.1
- 23.3-58.6
- 59.6

- 11.5-19.8
- 31.1-32.9
FIG. 1. DECREASING SEROPOSITIVITY-RATE FOLLOWING MASS-TREATMENT CAMPAIGN AGAINST ENDEMIC SYPHILIS IN BOSNIA

Third Survey

Fourth Survey

Seropositivity-rate

- 0.4-10.1
- 11.8-19.8
- 23.3-28.6
- 31.1-32.9
- 59.6
indicated on pages 13 and 25. The study areas should be large enough to yield representative data but should include a limited number of communities only, so as to be manageable.

In the formula for a rational approach to treponemal-disease control on a large scale in less-highly-developed areas, five programme stages are held to be important:

(a) orientation and preliminary analysis of the problem;
(b) development of plan of operation;
(c) demonstration, training, and survey phase;
(d) expansion phase (“mass campaign”);
(e) consolidation of the programme.

The endemic-syphilis-control programme in Bosnia, Yugoslavia, is the first large-scale example of a selective public-health activity where such a pattern has been followed, and where the chain of infection has been rapidly interrupted. Within two years of the inception of the programme, the disease has been eliminated as a public-health problem in areas with approximately half a million people.\textsuperscript{13} The achievements of this programme are of international significance in view of the nature and extent of the problem and, particularly, of the failure in the past to control this non-venereal treponematosis with arsenic and bismuth. The committee therefore welcomed the publication by WHO of a monograph on the organization of this campaign and the results obtained.\textsuperscript{14}

The emphasis on the control of infectivity should not preclude treatment of disfiguring, deforming, and incapacitating late manifestations, nor the discovery and treatment of latent cases, since many late manifestations may subsequently become reactivated and infectious, and may serve as foci for further spread if untreated. Nor should the selective approach to treponemal-disease control preclude attention to the more obvious needs of the population for curative measures aiming at other conditions (e.g., scabies) when field teams work in an area and the opportunity to develop subsequently broader health services in rural areas arises.

Finally, the committee pointed to the fact that yaws and other non-venereal treponematoses are usually found to be endemic “at the end of the road”, roads being the symbol of socio-economic progress; general betterment of living standards and sanitation will, over a period, repress these infections. The presence of yaws in a community is an indication of low hygiene standards; the slow process of improved sanitation could

\textsuperscript{13} For comments on this work see Annex 2, page 43.

\textsuperscript{14} Grin, E. I. (1952) \textit{Bull. World Hith Org.} 7, 1. This study has also been published as \textit{World Health Organization: Monograph Series}, No. 11.
be expected eventually to rid a community of the disease. The approach through the medium of mass treatment does not necessarily produce more efficient permanent results. Mass treatment with penicillin is useful in the first assault on treponemal diseases through active, rapid suppression of infectiousness. Failure to consolidate the initial gains by further control measures will lead to the reappearance of the disease. The patchy distribution of endemic treponematoses in rural communities suggests that the lack of some simple hygienic measures may be responsible for the perpetuation of a high incidence of the disease. Investigations by WHO aiming at the definition of the factors concerned may point to cheaper and less complicated techniques for the control of non-venerereal treponematoses in the future.

2.2.1 Epidemiological considerations in mass campaigns

In its deliberations, the committee was mindful of the outlook emphasized at its third session three years ago. At that time, the rationale was established for the carrying-out of large-scale treponematoses-control programmes based on repository penicillin preparations and aimed at the eradication of treponemal disease in delimited geographical areas. The committee had recommended then that special consideration should be given by WHO to the study of measures for the prevention of reinfection and recurrence of disease, and that the findings should be carefully studied in view of the importance such new health techniques might have in endemic areas. For this reason the committee found it desirable to consider in some detail the epidemiological aspects of mass-treatment control programmes, and found the detailed data available from Indonesia and Yugoslavia particularly interesting.

The natural history of treponemal diseases is the result of multiple causes and effects which arise not only from the characteristics of the specific micro-organism, but also from the social, economic, and physical surroundings of the affected population and the habits and customs of the inhabitants. Socio-economic status, topography, population movements, educational and psychological factors, the sanitation level, the prevalence of the disease, its natural and seasonal cycles on the one hand, and the availability of a long-range plan of control, funds, personnel, facilities, supplies, transportation, popular opinion, accessibility of the patients on survey and re-examinations, and the completeness of coverage on such examinations on the other, are some of the many factors which are likely to differ in mass campaigns now being carried out in various regions against treponemal diseases. In reviewing the experience of field teams in the mass programmes conducted by the health administrations in Yugoslavia (endemic syphilis); Iraq (bejel); and Haiti, Indonesia, the
Philippine Islands, and Thailand (yaws), the committee considered, nevertheless, that several common considerations of epidemiological importance applied to mass programmes in non-venereal treponematoses, and made the following observations.

2.2.1.1 Completeness of population coverage

Every effort should be made to examine the entire population in the affected areas. Notwithstanding careful enumeration of the population, the ideal of complete coverage can seldom be obtained, although it was noted that, in areas of Indonesia, Thailand, and Yugoslavia, the initial survey and examination sometimes exceeded 95%. Also, on subsequent visits, an attempt must be made to apply control re-examinations to the entire population if maximum protection is to be offered, since by far the greater number of new infectious cases diagnosed during such follow-up activities are found in that part of the population which previously was not treated.

The merits of various methods of approach to communities through the use of stationary clinics, mobile clinics, "community calls" (following the ringing of a village bell for the gathering of the population), and house-to-house surveys must be taken into account. In a yaws-control programme, a house-to-house case-finding approach reached 91.9% of the population, whereas the mobile-clinic approach had yielded only 69.8%. The house-to-house method is, therefore, effective in reaching a large proportion of the population. A different approach (e.g., a "community call") may also provide sufficient coverage of the population; but, if other approaches fail to reach approximately 90% of the community, consideration should be given to the house-to-house method. The results of mass-treatment programmes are less effective, more time-consuming, and uneconomical when such a high percentage of the population is not examined.

2.2.1.2 The need for control re-examinations

In mass-treatment programmes recheck examinations are essential. There is ample evidence that the reservoir of infection will rebuild itself if adequate maintenance measures are not taken after the initial mass campaign. Having studied the various data available on the rapidity with which the reservoir may re-form in yaws and endemic syphilis when areas are left unattended, the committee considered that control re-examinations should take place within a period of approximately six months after the initial treatment programme. Some flexibility in the timing of such follow-up activities may be desirable, however, for climatic and other reasons. The actual need for one or several further control re-examinations will
vary with the completeness of the original population-coverage, the actual
number of infectious cases found during the surveys, the type of treatment,
and other factors referred to on page 13. Under no circumstances, how-
ever, should resurveys be deferred longer than 12 months.

The fact that repeated control of areas may be required in mass pro-
grammes does not signify that this approach is less successful than the
continued vaccination efforts necessary over a period in smallpox, or the
constantly maintained chlorination of water-supplies required for prevent-
ing recrudescence of enteric fevers.

Experience indicates that the foci of spread for new cases of treponemal
infections found on follow-up re-examinations are: (a) those persons who
escaped examination or treatment because of absence; (b) new cases
imported from other areas; (c) symptomless cases in the incubation period
at the time of the first examination and in whom infectious lesions sub-
sequently developed; (d) relapses from undiscovered latent cases (where
serological tests are not used routinely in mass campaigns), and in a small
percentage of cases arising from treatment failures.

2.2.1.3 Preventive treatment of contacts

From an epidemiological viewpoint, preventive treatment—also referred
to as "abortive" treatment—is an effective procedure when administered
during the incubation period to contacts of patients with infectious trepo-
nemal disease. Quantitative data show greater accomplishments when
all intra-household contacts of infectious cases found are treated. This
does not take into account potential cases from other households which
may have been in close contact with the infected patient elsewhere. Thus,
it may be necessary to provide treatment for known or suspected extra-
household contacts.

Unlike the situation in venereal syphilis, the "contacts" of cases of
non-venereal treponemal disease who may be incubating the disease are
difficult to define. For the purposes of mass control campaigns some
definition must nevertheless be developed, and it should depend on the
overall prevalence of infectious cases within the community. In areas
with a high prevalence of infectiousness there are many more opportunities
for the transmission of disease; and a broad segment of the population
at risk should receive preventive treatment—e.g., children, particularly
the toddlers and school-age groups, in which the attack-rate is high. In
areas with a somewhat lower prevalence of infectiousness, preventive
treatment may be restricted to more intimate contacts irrespective of age.
The development of the definition of contacts should be related to
quantitative data which show greater accomplishments when family mem-
bers, intra-household contacts, or extra-household contacts are treated
when an infectious case is found. In some areas with a low prevalence of infectiousness, the preventive treatment of contacts might be omitted provided that there are adequate health-facilities to assure discovery, prompt follow-up, and effective treatment of new cases, reinfections, and relapses.

2.2.1.4 Rapidity of coverage

From an epidemiological viewpoint it is essential that, in mass campaigns, the chain of infection be severed as rapidly as possible. Residual foci in areas being covered should not be allowed to give rise to further cases in adjacent, untreated districts. Conversely, the danger of reintroduction of the disease from untreated into treated areas should also be recognized. The wider the area cleaned up, the less likely may be such reintroduction of disease from the periphery. Geographically contiguous areas should therefore be covered as rapidly as is feasible.

2.2.1.5 Consolidation of the programme

A single mass-application of case-finding and treatment will not suffice to "control" endemic syphilis, bejel, or yaws. Repeated coverage of an affected area will, however, significantly reduce the incidence of infectious cases or eliminate the immediate infectious reservoir. Early results achieved with international assistance by means of mass treatment campaigns have been encouraging, but it is of paramount importance that such initial gains be consolidated, and that properly-oriented, local health-facilities be established and maintained so as to control the immediate and subsequent residual foci likely to arise. The specialized programme should serve as a bridgehead for the establishment of general health services, or should contribute to the further development of pre-existing services. Advantage should be taken of the progress already made: the citizens have been alerted, the population has been enumerated, personnel have been recruited, a basic record system is available, and community facilities are at hand in many areas. The further work cannot be expected to depend indefinitely on international assistance, but must devolve upon the national health services concerned.

The ultimate success of mass treatment campaigns will, in the long run, depend on the adequacy of permanent, local health-services. In general, yaws control serves as a nucleus around which to develop rural health work: auxiliary personnel, initially charged with treponematosis work, should gradually render other services, and a complete and integrated rural health programme should be developed as rapidly as possible. The planning of such local health services should begin at an early stage so that permanent facilities are at hand upon the conclusion of the mass campaign.
The Expert Committee on Venereal Infections and Treponematoses,

Noting the significant efforts made by several health administrations over the last three years in treponemal-disease control;

Expressing general agreement with regard to the approach developed in mass campaigns against the treponematoses by health administrations and WHO; and

Considering that current experiences with PAM 16 indicate that endemic syphilis and yaws are highly vulnerable to attack and can be eliminated as major public-health problems in large areas when:

(a) emphasis is put on epidemiological aspects and evaluation is made in terms of family units and communities rather than in terms of individuals alone;

(b) action is taken rapidly, simultaneously, and over a period in local areas as well as in adjacent districts, and systematic examination of the entire population is attempted;

(c) plans are established during the early phases aiming at the consolidation of the programme (provision of facilities for control re-examinations for reinfections, relapses, and reintroduced disease),

RECOMMENDS

(1) that, where treponemal diseases constitute a major public-health problem, contacts without overt signs of disease receive preventive (" abortive ") treatment with PAM;

(2) that control re-examinations of areas be undertaken at intervals of approximately six months, depending on seasonal and other factors;

(3) that national health-administrations take advantage of the opportunity offered by mass campaigns against non-venereal treponematoses to serve as a bridgehead for the development of wider, general, local health-services, that these campaigns be carefully planned and fully implemented, and that mass programmes be made part of a general development plan for the area whenever practicable;

(4) that WHO study further control techniques which may possibly be applicable in mass programmes, aiming at a definition of little-understood unhygienic factors which may facilitate the spread of the non-venereal treponematoses in rural communities.

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16 Procaine penicillin G in oil with 2% aluminium monostearate
3. DRUGS AND THERAPY

3.1 General

At previous sessions, the committee emphasized that the limited availability of penicillin was a major restricting factor in the control of syphilis and related diseases. The progress made by WHO in cooperation with the United Nations, other international organizations, and health administrations in increasing the availability of penicillin by the development of penicillin-production plants in Chile and India, and by the rehabilitation of plants in Austria and Yugoslavia, was therefore noted with satisfaction. The cooperation with the Expert Committee on Antibiotics and the establishment of a section on antibiotics within the structure of the WHO Secretariat was also noted.

The committee reviewed the progress made by WHO in regard to the inclusion of drugs and antibiotics used in venereal-disease therapy in the Pharmacopoea Internationalis (Ph.1.). It welcomed the decision of the Expert Committee on the International Pharmacopoeia to include a monograph on the minimum acceptable standards of procaine benzylpenicillin in oil with aluminium monostearate (PAM), as well as a description of the standard technique for biological assay of blood penicillin based on standard Sarcina lutea strain, in volume II of the Ph. 1. This is further referred to in section 3.2.4, page 22.

3.2 Antibiotic Treatment of Treponemal Diseases

3.2.1 General

Although aureomycin, chloramphenicol, and oxytetracycline have been demonstrated to have treponemical effect, present knowledge does not indicate that they will play an immediate role in the control of treponemal diseases. Nor was it considered likely that, at the present time, the use of peroral antibiotics, including penicillin, would cause a major realignment of health techniques used in treponematoses control. Penicillin has been demonstrated to be the most outstanding of the effective antibiotics in syphilis, bejel, yaws, and pinta; and, in reviewing available data on its usefulness, the committee found no evidence that true penicillin resistance had been observed in treponemes so far. However, constant vigilance should be exercised to detect the development of any such resistance.

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16 Oxytetracycline is the international non-proprietary name for terramycin (see Chron. World Hlth Org. 1953, 7, 41).
resistance in the future, and WHO should investigate any suspected evidence through the International Treponematoses Laboratory Center (see section 5.3, page 31) and other laboratory and clinical institutions.

Since the last session of the committee, three years ago, a significant further change in the attitude of the medical profession throughout the world has become apparent, the conclusion being reached that therapy with penicillin in early infectious syphilis (and other treponemal diseases) is preferable to treatment with arsenicals and bismuth when all factors—efficacy, toxicity, ease of administration, and cost—are considered. There is also a growing recognition that there is no advantage in supplementing the results obtainable with penicillin by concomitant or subsequent injections of "adjuvant" metal chemotherapy. The committee is basing this outlook on the views expressed in consultation between WHO and a number of recognized experts (members of the Expert Advisory Panel on Venereal Infections and Treponematoses) (see Annex 3, page 51) and on the opinions expressed in presentations before the Tenth International Congress of Dermatology as well as on the unanimous considerations of the members of the committee.

The fate of penicillin in the host and its therapeutic effectiveness depend on many factors, including the distribution of penicillin in body fluids and organ tissues in relation to dosage, vehicle, and blood concentration. The latter does not necessarily picture directly the therapeutic effectiveness, tissue retention, or absorption, etc. Available knowledge indicates generally, however, that prolonged exposure of treponemes to the action of penicillin at a therapeutic level, as reflected in the tissue and blood concentrations over a period, is necessary. Such exposure can be obtained with repository preparations.

3.2.2 Minimal therapy for the individual clinic-patient with venereal syphilis

3.2.2.1 Early syphilis

Individual clinic-patients with primary syphilis should be treated with a minimum of 2.4 mega-units of repository PAM, and patients with secondary syphilis should be treated with a minimum of 4.8 mega-units. The committee considered that, in all cases, a large initial dose—no less than half the total minimal doses noted above—should be given to assure reasonably effective therapy since, in many areas, the patient may not return for further injections. With such a large initial "insurance" dose, a high proportion of cures will result. In view of the fact that the duration of an effective (blood) tissue penicillin-concentration is the most important single consideration in the treatment of treponemal infections, there is an advantage, in the case of the individual clinic-patient, in dividing the total dosage into several injections; this might permit the
utilization of various public-health techniques which are considered essential to good venereal-disease control (epidemiological investigations, education of the patient, clinical and serological follow-up).

3.2.2.2 Latent and late syphilis

Because of its demonstrated superiority over previously available forms of therapy, penicillin is the treatment of choice in other forms of syphilis also. Detailed optimum schedules of therapy could not be recommended, but in no case should less than 4.8 mega-units of PAM be given to patients with late or latent syphilis.

Although sufficient time has not elapsed to judge the insurance value of penicillin therapy in late latent syphilis vis-à-vis the known effectiveness of arsenicals and bismuth, the committee found no reason to believe that it will prove to be inferior, in view of the known efficacy of the antibiotic in neurosyphilis and so-called late benign syphilis.

3.2.2.3 Syphilis in pregnancy

At least one serological test for syphilis should be carried out during each pregnancy; whenever possible, a second test should be made in the last trimester. Treatment with penicillin alone should be given as soon as a diagnosis of syphilis in pregnancy is established; the amount should not be less than 4.8 mega-units of PAM. When facilities for clinical and quantitative serological examination plus assurance of adequate follow-up are not available, penicillin treatment might be repeated during each subsequent pregnancy.

3.2.2.4 Infantile congenital syphilis

In the light of increased experience with the use of penicillin in early congenital syphilis, and considering the generally increased availability of the antibiotic, minimal therapy in this condition should be 200,000 units of penicillin per kilogram of body-weight. Experience obtained with PAM in children over the last few years indicates that this preparation is a useful alternative to aqueous penicillin.

3.2.2.5 Late congenital syphilis

The treatment of late congenital syphilis should be as intensive as that used in late acquired syphilis, adjuvant therapy being given whenever indicated (e.g., cortisone locally for interstitial keratitis).

* * *

Specimen treatment-schedules for various forms of syphilis applicable in the case of the individual clinic-patient are given in Annex 4, page 54.
3.2.3 Minimal therapy in mass campaigns against treponemal diseases

While the actual treponemical concentration of penicillin in the tissues has not been accurately defined, the sensitivity of treponemes in vitro varies from 0.00075 to 0.003 units/ml fluid. The penicillin concentration in the circulating blood does not necessarily reflect directly the therapeutic effectiveness, but concentrations of 10 to 15 times the in vitro values, namely, 0.02 to 0.03 units/ml serum, are generally held to picture the “theoretically effective” blood-level in treponemal diseases. While in certain infections caused by bacteria and cocci intermittent high concentrations of penicillin are considered necessary, it is established that continued exposure of treponemes to penicillin concentrations over a period is required. With repository penicillin preparations, a high proportion of cures can be obtained in early infectious treponemal diseases if such concentrations are maintained from four to six days. Appropriate dosages of PAM will result in effective concentrations for at least the required length of time.

From the International Treponematosis Laboratory Center it is reported that, both in vivo and in vitro, the sensitivity to penicillin of the treponemes of venereal syphilis, endemic non-venereal syphilis, bejel, and yaws is of the same order of magnitude, suggesting the rationale for translating data derived from large-scale studies in the treatment of venereal syphilis into the treatment of the other treponemal diseases.

On the basis of experimental work and information available from clinical and laboratory investigations in non-venereal syphilis, bejel, yaws, and pinta, the important question of minimal therapy in mass campaigns was considered by the committee, with particular reference to single versus multiple injections, total dosage, and preventive contact dosage.

(1) It was recognized that, in mass campaigns, penicillin must be conserved in so far as is compatible with effective public-health results. There is, however, a limit below which the total dosage of penicillin does not give effective results in a sufficiently high percentage of cases of early infectious treponemal disease. When given in a single injection, there is clear evidence that, by increasing the dose from 300,000 to 600,000 units, and further to 1.2 and 2.4 mega-units of PAM, the resulting further prolongation of the blood concentration is not proportionate to the dosage increase, or to the concomitant doubling of the cost of the antibiotic. This pattern, or “law of diminishing returns”, also appears to apply in terms of the resulting percentage of successful clinical outcome. As penicillin remains proportionately one of the most expensive immediate outlays to be budgeted for in mass campaigns in underdeveloped areas (on a patient-cost basis), the decision on dosage must be a “calculated risk”—a compromise between maximum efficacy and practical economy. It is
considered that, in mass campaigns, the total dosage in adults should be no less than 1.2 mega-units of PAM, and proportionately less in children.

(2) Recent information indicates that, when PAM is used, the advantage of dividing the total dose into two injections is very small in terms of prolonging the blood penicillin concentration, as well as in terms of clinical results in secondary syphilis. With the administrative and practical advantages of a "one-shot" treatment schedule in mass campaigns, it is considered that this procedure is preferable and that at least the minimum total dose should be given in one injection.

(3) There is some evidence from laboratory experiments and from field studies in syphilis and yaws that the amount of penicillin required to abort preclinical infections may be related to the size of the inoculum and to the duration of the infection, and that the dosage of PAM required to prevent (abort) treponemal infections in exposed contacts is less than that required to cure the established disease. In mass campaigns there is no way at present of determining the size of the inoculum or the actual length of time since any possible contact was effected.

Taking into account the various technical aspects of this question and its recommendation of frequent control re-examination of areas (see page 14), the committee considers it feasible to treat contacts without overt signs or history of treponemal diseases with smaller amounts of PAM than the amounts used to treat the established infection. The preventive dose in adults should not be less than half the total dose used in early infectious lesions in mass campaigns and proportionately less in children, provided that PAM of minimum standard is used (see section 3.2.4).

The committee noted with interest the recent development of new insoluble amine penicillin salts which would maintain effective blood-levels of penicillin for a considerably longer time than an identical dose of PAM. This offers promise for the future in the treatment of venereal syphilis and the non-venereal treponematoses, particularly in mass campaigns. The members of the committee agreed to undertake clinical trials with such penicillin salts in syphilis, under an agreed plan co-ordinated by WHO, with a view to establishing suitable dosage schedules. Co-ordinated investigations as to the potential value of these salts in mass-treatment campaigns in the other treponematoses might also be undertaken by WHO.

3.2.4 Quality of PAM preparations

In mass campaigns based on simplified schedules of treatment, it is necessary to use preparations of PAM that consistently maintain effective blood-concentrations for several days following a standard test dose. The
recommendations of the committee, both in this report and in the report on its third session, are predicated on the use of such preparations of a minimum standard. The recent experience of WHO indicates that, unfortunately, great differences exist among PAM preparations of different origin (see fig. 2).

These findings are of importance to health administrations, since the success of the mass-treatment programmes depends upon the efficacy of the therapy administered. The committee noted with satisfaction the steps taken to assure the use of uniform PAM preparations of proved characteristics suitable for tropical climates, and the minimum requirements for PAM preparations established in co-operation with the Expert Committee on the International Pharmacopoeia (see Annex 5, page 55). The committee noted the necessity for adopting a standard assay technique and the use of a standard test organism in biological assays of blood penicillin, and welcomed the inclusion in volume II of the Ph.I. of a description of such a technique based on *Sarcina lutea* as the test organism (see page 56). The details of this technique might be further considered by the Subcommittee on Serology and Laboratory Aspects.

The Expert Committee on Venereal Infections and Treponematoses,

Noting the increasing availability and use of penicillin in treponemal disease-control work and the increasing experience with PAM therapy in clinical patients and in mass-treatment programmes;

Recognizing that economical and effective results depend upon reasonably uniform characteristics of PAM preparations and the exposure of the infectious agents in syphilis, bejel, yaws, and pinta to penicillin in the body tissues and fluids over a period; and

Approving the steps taken by the WHO Expert Committee on the International Pharmacopoeia for the establishment of minimum requirements for the PAM procured by WHO and other international organizations,

RECOMMENDS

(1) that, for the individual clinic-patient with early infectious venereal syphilis, a large initial dose of PAM ("insurance dose") be given on the day of diagnosis to assure reasonably effective therapy should the patient not reappear for further treatment;

(2) that, in mass campaigns against non venereal treponematoses, the minimal total dosage for early infectious lesions in adults be no less than 1.2 mega-units of PAM and proportionately less for children; that this dose be given in one injection; and that the preventive (or "abortive") dose for contacts be no less than half that used in the early infectious stages of the established disease;
Spread and mean arithmetic value of observations based on 10 ambulant persons injected intramuscularly with 300,000 units of PAM. Plasma concentrations were determined by the Sar-cina lutea technique at the time-Intervals indicated.

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(3) that WHO bring to the attention of health administrations the minimum PAM requirements established in volume II of the *Pharmacopoea Internationalis*, and that these minimum requirements be used as a guide in national procurement; and

(4) that WHO encourage the establishment of facilities for determining penicillin blood duration levels in major treponemal-disease-control programmes and in laboratories used by major clinics so that additional studies in ambulatory patients under different local conditions can be made.

4. SERODIAGNOSIS AND OTHER LABORATORY ASPECTS OF VENEREAL INFECTIONS AND TREPONEMATOSES

The outstanding single problem in the field of serology is the lack of a simple, practical, serological screening-test for ambulatory testing, which is sufficiently sensitive, specific, and reliable for the diagnosis of treponemal disease in field programmes. Further studies should be encouraged, and WHO should watch for possible new developments in this regard. This problem should be studied by the Subcommittee on Serology and Laboratory Aspects with a view to recommending a practical procedure and suitable methods.

It has been pointed out that a well-equipped laboratory capable of carrying out several serological tests with modern methods is necessary as an integral part both of limited demonstrations and, in the controlled study-areas, of mass programmes against treponemal diseases. In the latter case, laboratories should be associated with the local, controlled study-areas on a long-term basis to (a) evaluate the efficacy of treatment schedules; (b) verify doubtful clinical diagnoses; (c) find latent cases; and (d) study special epidemiological, clinical, and other problems connected with the particular area and population concerned. Such laboratories should also be used for training purposes during the demonstration and survey phase of the programme. The functions of these laboratories could gradually be broadened into general public-health laboratories to meet the requirements of the area as general health services are developed.

Not only is the venereal-disease-control programme dependent to a major degree on the efficient conduct of serological tests for syphilis, but the close immunological relationship between syphilis and the other treponemal diseases, and the similar serological response in syphilis, bejel, yaws, or pinta also justify a definition of specificity of serological tests in terms of these infections, non-specific and biologically false reactions being, conversely, represented by any other condition in the human host
giving rise to positive serum tests within the normal range of accuracy of present laboratory methods. The rationale for this view has been further emphasized by the development of a treponeme-immobilizing technique (TPI) which, at the time of the third session of the committee, was a recent scientific development. Experience gained over the last three years, initially in North America and later in Europe, has added to our knowledge of immunology in syphilis as well as in the other treponemalediseases. The important preliminary work of the International Treponematosis Laboratory Center in this connexion was noted by the committee. The techniques necessary to obtain reliable results are still complicated. It is likely that, for some time to come, only major laboratories will be in a position to use the TPI test. WHO might consider co-ordinating an inter-laboratory study of the TPI technique among a limited number of laboratories in different countries. Should other techniques become available, permitting further investigations of immunological phenomena in treponematous diseases, similar studies might be undertaken.

The committee approved the general views of the Subcommittee on Serology and Laboratory Aspects as presented in the report on its second session 17 and noted with satisfaction the active co-operation and participation of many national laboratories and of the members of the WHO Expert Advisory Panel. The co-operation with the Expert Committee on Biological Standardization was welcomed, particularly the depositing by the latter committee of international reference preparations of cardiolipin and lecithin in the International Standards Department of the Statens Serum Institut, Copenhagen. This, the publication by WHO of an extensive monograph on cardiolipin and its control, 18 and the inclusion in volume II of the Ph.I. of a standard description of these products—as recommended by the Expert Committee on the International Pharmacopoeia at its tenth session 19—represent significant steps which have been taken to ensure that comparable antigen components are available to different laboratories. Controlled by these principles, further standardization of testing methods based on cardiolipin antigens has thereby been made possible throughout the world. Further work towards standardization of antigens and uniformity of testing procedures is required, however, and the services of WHO should continue to be made available to national health laboratories and other producers in order to secure uniform reactivity and purity of cardiolipin and lecithin. The actual production of cardiolipin and lecithin has been started in the European Region, and

19 Unpublished working document WHO/Pharm/220, p. 7
detailed plans for similar production, supported by WHO and other agencies, are now under way in the South-East Asia Region and the southern part of the Region for the Americas.

An important pilot-study on freeze-dried sera of different levels of seroreactivity has been carried out by co-operating laboratories in Denmark, India, Israel, Norway, the United Kingdom of Great Britain and Northern Ireland, and the USA. The final recommendation of this study-group was to the effect that “further studies on freeze-dried sera would be of real value, and [the participants] are in favour of a continuation of this work according to the plans originally agreed on by the subcommittee and presented in its report, i.e., the establishment of a large collection of such sera for international reference purposes” (Annex 6, page 62). This development forecasts that international reference standards of freeze-dried sera might become a reality. It was noted that the further evaluation studies on a larger number of such sera, prepared in laboratories in several regions, was already under way, and that control sera for both sensitivity and specificity were envisaged. The committee emphasized the importance of standard freeze-dried reference-sera ultimately being made available by WHO to national laboratories for national serodiagnostic standardization purposes.

The Statens Seruminstitut in Copenhagen has undertaken to serve as an international reference laboratory for many of the activities in which WHO has an interest, and this co-operation has proved of great value. There continues to be a need for further centres in other regions, and it was noted that a similar centre in the South-East Asia Region might co-operate with WHO in the near future.

The committee fully approved the work done over the last three years to implement the WHO programme on serology and laboratory aspects of venereal infections and treponematoses (see Annex 6, page 59) and observed that, in view of the steps that had been taken and the progress made, the need for the holding of an international serological conference, as originally planned, might be obviated. The Subcommittee on Serology and Laboratory Aspects should consider this matter further at its third session early in 1953.

The Expert Committee on Venereal Infections and Treponematoses,

Noting the substantial progress made by WHO to implement the programme on serological and other laboratory aspects of venereal infections and treponematoses in regard to WHO-assisted field programmes, as well as on standardization of antigens and laboratory methods;
Approving fully the outlook and the work of the Subcommittee on Serology and Laboratory Aspects and the co-operative inter-laboratory activities in several countries; and

Considering the continued need for close association between epidemiological and clinical activities in small or large programmes and for purposeful laboratory studies and services,

RECOMMENDS

1. that WHO continue its activities aiming at further standardization of laboratory reagents and methods in the diagnosis of venereal infections and treponematoses and, in so doing,

   (a) brings to the attention of health administrations, national laboratories, and other interested institutions and workers the establishment of an international reference preparation of cardiolipin and lecithin, the inclusion of a standard description of these components in volume II of the *Pharmacopoea Internationalis* (Ph.I.) and the publication by WHO of an extensive monograph on the subject;

   (b) encourages further the work aiming at the early establishment of international reference standards of freeze-dried sera on different levels of seroreactivity;

   (c) considers co-ordinating an inter-laboratory study in several countries on the treponeme-immobilizing, or related, tests, and continues other comparative inter-laboratory evaluation studies already under way, including an analysis by the subcommittee of material collected on cardiolipin and lecithin;

2. that full opportunity be taken by health administrations and WHO in field programmes, particularly mass campaigns, to:

   (a) use laboratory facilities for training purposes and develop them gradually into general public-health laboratories as local health services are being broadened;

   (b) utilize the local laboratory services in the study and evaluation of special epidemiological, clinical, and other problems connected with the particular area;

   (c) co-operate further with the International Treponematoses Laboratory Center for a wider sampling of strains of treponemata for local and central study.
5. OTHER PROGRAMME ELEMENTS

5.1 Training of Personnel

5.1.1 Professional personnel

The committee noted that, since its last meeting, more than a hundred WHO fellowships had been awarded in many parts of the world for advanced study of venereal infections and treponematoses, and considered that the WHO fellowship programme is making a significant contribution to the training of professional personnel.

The proper selection of personnel for WHO fellowships was held to be of primary importance, and two additional points were stressed: (a) that every effort should be made to assure that professional personnel who receive advanced specialized training have a specific post to fill in the same field of work upon return to their own areas; and (b) that fellowships should be granted for study at the International Treponematosis Laboratory Center and similar institutions.

In the training programme stress should continue to be laid on personnel from underdeveloped areas. On the other hand, there is now an increasing need for professional personnel—especially teachers in medical schools—from countries where venereal infections and non-venereal treponematoses are becoming infrequent to study these diseases in areas where they are highly prevalent.

5.1.2 Auxiliary personnel

In view of the overall magnitude of the treponemal-disease problem and the fact that the largest reservoirs are in the underdeveloped rural areas of the tropics, the fullest utilization should be made of auxiliary personnel engaged in treponemal-disease-control work (sanitarians, male nurses, technicians, etc.). Multipurpose training of permanent auxiliary personnel is preferable to unilateral training of temporary personnel, but is not always practicable. Specialized training in treponemal-disease control may, however, be a useful starting-point for further and more general training. The emphasis should be on practical, on-the-job work, and the committee suggested that field activities in WHO-assisted programmes are suitable places for such training.

The proper selection of personnel is of paramount importance. Medical supervision of auxiliary personnel should be carried out whenever possible. With proper supervision, auxiliary personnel can carry out a wide variety
of functions in venereal-disease-and treponemal-disease-control work. When such supervision of auxiliary personnel is not possible as, for example, on board merchant ships, the committee considered that the required training courses should be as complete as possible.

More favourable conditions of employment in terms of salary, tenure, etc. than those offered at present would perhaps help to attract the best available types of persons.

5.2 Exchange of Scientific Information

The committee stressed the role of WHO in the exchange of information among venereal-disease and treponematoses workers. The technical documents prepared at WHO Headquarters from data collected from many parts of the world were held to be exceedingly valuable, and should be distributed as widely as possible to health administrations, interested institutions, and workers in the field.

The First International Symposium on Yaws Control, held by WHO in Bangkok in March 1952, in co-operation with the Thai health administration and UNICEF, was a successful undertaking. In its deliberations, the committee took the views expressed at that symposium fully into account, and considered that the symposium had had a forceful impact on the planning, approach, and evaluation in yaws-control programmes in many parts of the world, as well as on the promotion of exchange of scientific information, understanding, and international relationships. A second international inter-regional symposium would be useful but should preferably not be held before 1955. The subject matter might then be broadened to include also treponemal infections other than yaws in less highly developed areas in view of the importance of treponematoses activities under the Technical Assistance Programme. The number of participants might be somewhat smaller than in 1952. It was suggested that the symposium be held in the African Region, where is known to exist an extensive and important reservoir of treponemal disease.

WHO might also consider the possibility of co-operating in the organization of a section on tropical treponematoses during future International Congresses on Tropical Medicine.

The regional syphilis symposia held in Helsinki and Paris in 1950 have contributed in a major way to the reorientation in European syphilology after the war—as was pointed out during the Tenth International Congress of Dermatology—and the committee considered that similar regional symposia in other regions during the next five-year-period could serve an extremely useful purpose.
5.3 Co-ordination of Research

The committee noted with approval the willingness of the Johns Hopkins University School of Hygiene and Public Health to function as the International Treponematosis Laboratory Center, as was recommended in the report on its third session.\(^{20}\) The work of the Center to date, presented in a series of useful technical reports,\(^{21}\) was reviewed. This work has covered: (a) studies on the isolation of strains of treponemata from WHO-assisted projects in many parts of the world; (b) comparative studies of treponemal-disease phenomena in animals; (c) comparative histopathological studies; (d) comparative serological studies; (e) studies in immunity and cross-reactions in the treponeme-immobilization test developed at the Center, and studies of patients' sera for immobilizing antibody content; and (f) comparative studies on penicillin sensitivity of old and freshly isolated strains of treponemes from patients with different clinical syndromes of treponematoses. The preliminary results have added to present knowledge on the biological relationship of the treponematoses in an important manner, and co-ordination of research being carried out at the Center should remain an important leadership function of WHO. Considering the inherently long-term nature of the work, the International Treponematosis Laboratory Center should continue to be encouraged by WHO; other well-equipped laboratories capable of conducting similar or related research should also be encouraged in the future. The importance of the Center as a look-out establishment for possible penicillin resistance arising in treponemes in the future has already been pointed out (page 19).

The committee noted the progress report on the outcome of untreated syphilis in the analysis of the Boeck-Brusgaard material at the University Clinic of Oslo, Norway. Expressing the view that this unique material will be of great interest and value to syphiliologists throughout the world since it provides a "natural" base-line for comparative study, the committee considers that the widest possible circulation should be given to the final report on this investigation.

The committee also noted the progress of the international clinical co-operative study of antisyphilitic treatment, as recommended by the third session,\(^{22}\) and expressed interest in the continuation of this and similar studies. The contributions already made by Australia, Denmark, India, Norway, and the United Kingdom of Great Britain and Northern Ireland were noted.

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The need for the development of a simple, inexpensive, and acceptable serodiagnostic test for screening purposes which can be performed with minimal amounts of blood remains one of the outstanding needs for the control of syphilis and non-venereal treponemal diseases. This was referred to in section 4, page 25. WHO should co-operate in every way possible with laboratories endeavouring to develop such a test.

The committee recognizes the need for further studies on the "minor" venereal diseases (particularly lymphogranuloma venereum and non-gonococcal urethritis) and suggests that WHO should encourage and co-ordinate such studies in national research institutions.

Although not the primary function of field teams in WHO-assisted programmes, studies on various clinical, laboratory, and epidemiological aspects of treponemal-disease control are considered to be a useful and necessary function; the opportunity should be taken to encourage and utilize as fully as possible the pathological material available in the controlled study-areas as well as in the mass programmes.

5.4 Nomenclature

5.4.1 Definition of early latent and late latent syphilis

The terms "early latent" and "late latent" syphilis have various connotations in different countries, and sometimes even among workers within the same country. Among clinicians, two, three, or four years are used as the distinguishing line, while in public-health literature the two-year period is sometimes found, the reason for the latter being that some 85% of infectious relapses in syphilis occur within that period. The International Statistical Classification of Diseases, Injuries, and Causes of Death (Sixth Revision, 1948) classifies the infection on the basis of a duration of four years, after which it is classified as late latent syphilis.23

In their discussion, the members of the committee were unable to reach a common view on this question, which was deferred, and it was considered that the attention of WHO should be drawn to the desirability of arranging for appropriate consultations with expert groups of venereologists in Member States of WHO before the matter is considered further and revision of the classification takes place.

5.4.2 Yaws nomenclature

There are wide variations in the nomenclature used in yaws in different countries. This is evidenced by the literature as well as in the recent discussions on this subject at the First International Symposium on Yaws

Control, held in Bangkok, Thailand, where the nomenclature practice in Africa, the Americas, south-east Asia, and the western Pacific area was reviewed. In regard to the clinical and scientific classification required for detailed study and research, the committee was of the opinion that considerable study will be required to establish a suitable classification acceptable to all investigators in different parts of the world. However, such a study might well be undertaken by WHO through an appropriate corresponding study-group composed of several competent experts, whose report could be presented at a subsequent session of the committee. Such a study-group may wish to consider as a basis for its work the publications by Hermans, Hill, Kodijat, and others. While there is need on the one hand for this accurate scientific classification of lesions and syndromes for clinical and research purposes, there is, on the other hand, a more acute need for a simple, practical, standard classification of yaws lesions in broad groups for use in field programmes where lesions are recorded by sanitarians and auxiliary personnel with limited training. In regard to such a classification for field use, the committee approved generally the recommendations made by the participants in the Yaws Symposium, and was of the opinion that the following grouping should be adopted:

1. Initial lesions
2. Multiple papillomata
3. “Wet crab” yaws
4. Other early skin lesions
5. Hyperkeratosis
6a Gummata and ulcers
6b Gangosa (rhinopharyngitis mutilans)
7. Bone and joint lesions
8. Latent yaws
9. Other manifestations

For illustrations of these stages of yaws, see Annex 7, page 67.

The Expert Committee on Venereal Infections and Treponematoses, Noting the various activities of WHO in regard to the training of professional and auxiliary personnel, exchange of scientific information, co-ordination of research, and standardization of nomenclature in syphilis and yaws,

RECOMMENDS

(1) that full utilization be made of national auxiliary personnel engaged and trained for treponematoses-control programmes so that such

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24 Eighteen of the papers presented at this symposium, together with summaries of the discussions, have been published in World Health Organization: Monograph Series, No. 15.
training can be a starting-point for subsequent general training as local health services are broadened in less highly developed areas, and that consideration be given by health administrations to more favourable conditions of employment;

(2) that efforts be continued by WHO for the widest possible exchange of scientific information, that a symposium on treponematoses in the tropics be held in the African Region in 1955, and that WHO might co-operate with future International Congresses on Tropical Medicine in the organization of a study section on the same subject;

(3) that the studies of the biological and immunological relationships of the treponematoses carried out by the International Treponematoses Laboratory Center continue to be encouraged and supported by WHO in view of the fundamental character of these studies and their inter-regional character, and

(4) that WHO take steps to establish through a corresponding study-group suitable standard nomenclature applicable for clinical and scientific purposes in the study of yaws, and that the classification of lesions, etc., proposed by the First International Symposium on Yaws Control for use by auxiliary personnel in field programmes, be applied in control programmes assisted by WHO.

6. MARITIME ASPECTS OF VENEREAL-DISEASE CONTROL

Venereal infections remain a major health-problem in many ports, particularly in southern Europe, South America, south-east Asia, and the Far East; and the decrease in diagnosed cases of venereal infections observed in recent years in inland areas of Europe and North America has not always been accompanied by a concomitant reduction in seaports.

Venereal infections interfere with the employability and working capacity of maritime and industrial populations, and the committee noted the interest shown by the International Labour Organisation (ILO) in maritime hygiene. From a review of the previous reports of the committee, the first session of the Joint ILO/WHO Committee on the Hygiene of Seafarers,25 and other data, it appeared that there is a need for international co-operative undertakings in this field for many years to come. ILO might collect valuable information on the conditions in ports relating to the welfare of seafarers. Studies of health aspects in ports might with advantage be carried out simultaneously by WHO as a basis for joint action by the two organizations.

The committee noted the interim report on the progress made in the co-operative undertaking between the Netherlands Government and WHO to establish a port demonstration project in Rotterdam to serve as an international centre for the training of various categories of personnel, for the collection of information on the organization of treatment centres in international ports, and for the study of certain aspects of venereal-disease epidemiology, therapy, and serology as they relate to seafarers. Based on the findings of the study-groups associated with this project, an overall report of various aspects of maritime venereal-disease control might be prepared by WHO.

The Brussels Agreement of 1924 remains the principal international instrument for venereal-disease control. In the last three years two more maritime nations have adhered to this agreement in response to the recommendation of the WHO Executive Board, at its fifth session, that more countries adhere to this instrument. WHO had recommended previously that a revision of the Brussels Agreement be undertaken as soon as the International Sanitary Regulations had been finalized. The committee noted that the latter have now been established by decision of the Fourth World Health Assembly. However, in view of the special study of the Brussels Agreement now going forward as a part of the activities of the Rotterdam Port Demonstration Project, and since the outcome of this study might have a bearing on the proposed revision of the Brussels Agreement, the committee favoured deferment of the establishment of a final draft text for a revised Brussels Agreement. Before the international legal aspects are taken up, the draft text would eventually be transmitted to Member States and to the ILO for consideration.

The committee noted with satisfaction that a revised edition of the International List of Venereal-Disease Treatment Centres and the Personal Treatment Booklet—as part of WHO's obligations under the Brussels Agreement—had appeared in 1951 and that several thousand copies of the list had been made available to health administrations, port health-offices, and to ships' captains. Nevertheless, it was felt that if this publication is to be of maximum practical value, it should become an obligatory part of ships' medical chests. This would assure its availability to seafarers when in foreign ports. This question might be considered further by the Joint ILO/WHO Committee on the Hygiene of Seafarers.

The committee noted the work of the International Anti-Venereal-Disease Commission of the Rhine, established by the Executive Board at

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26 Off. Rec. World Hlth Org. 25, 11
27 Resolution WHA4.75, Off. Rec. World Hlth Org. 35, 50
28 World Health Organization (1951) International list of venereal-disease treatment centres at ports, Geneva. The Personal Treatment Booklet is reproduced on page 199 of the same publication.
its seventh session. The pattern of this regional inter-governmental commission could be of value to other regions with international river areas. On the Rhine, the incidence of venereal infections has now fallen to a relatively small number of cases among the river boatmen coming for treatment to the centres along the Rhine. Consideration might be given by WHO and the Regional Committee for Europe to the possibility of integrating this specialized activity into a broader, general health-commission for the area in co-operation with the ILO and in accordance with the principles of the Agreement (1950) concerning the social security of Rhine boatmen.

As a result of investigations carried out on foreshortened treatment schedules with penicillin in syphilis and gonorrhoea, the treatment of seafarers with penicillin has reduced the period of disability ashore and has increased employability in an important manner. The introduction of PAM represents, therefore, a direct economic gain for seafarers, ship-owners, and governments. The acceptance by major maritime nations of the principle of carrying penicillin as part of the ship’s medical chest and the treatment of gonorrhoea aboard ship have contributed in the same direction. The committee noted that the practice of permitting the treatment of penile ulcers with penicillin aboard ship varied among the different maritime nations. Patients exhibiting penile sores or symptoms of gonorrhoea aboard ship should, under any circumstances, be instructed to consult a venereal-disease treatment centre or a qualified physician at the next port of call. The committee was not in favour of indiscriminate preventive use of penicillin—either peroral or by injection—among seafarers.

No convincing data have been published indicating that the masking of syphilis is of any quantitative importance in the treatment of diagnosed gonorrhoea when syphilis has been acquired concomitantly; the evidence rather shows a prolonged incubation period as a result of sub-curative dosages of penicillin given in the preclinical stage of syphilis.

Active case-finding in ports needs to be further encouraged, and epidemiological investigations should be carried out to a larger extent and more accurately among seafarers, both on the national and international level.

There is a need for a specially trained individual aboard ships not carrying a doctor to be responsible for medical treatment. The type of training required might be further considered by the Joint ILO/WHO Committee on the Hygiene of Seafarers.

29 Resolution EB7.R34, Off. Rec. World Hlth Org. 32, 7
The Expert Committee on Venereal Infections and Treponematoses,

RECOMMENDS

(1) that health administrations in all WHO regions take advantage of
the facilities of the International Port Demonstration Project at Rot-
tterdam and of the training courses to be organized in 1953 and 1954
and for which fellowships might be awarded by WHO;

(2) that a report on the epidemiology, therapy, laboratory, and other
aspects of venereal-disease control among seafarers be prepared for
consideration by a subsequent session of the committee—or by a
special study-group called by WHO for this purpose—and by the Joint
ILO/WHO Committee on the Hygiene of Seafarers.

7. NON-TREPONEMAL VENEREAL INFECTIONS

The situation outlined in previous reports of the committee in regard
to gonorrhoea and the "minor" venereal diseases remains essentially the
same. WHO should continue to pay attention to these diseases whenever
special geographic or other considerations pertain, and to their spread
from one country to another.

7.1 Gonorrhoea

It was noted with interest that there appears to be a trend in some
areas to administer larger amounts of penicillin to gonorrhoea patients
for the purpose of aborting concomitantly acquired syphilis. The com-
mittee considered PAM as the treatment of choice and 300,000 units to
be adequate dosage in uncomplicated acute cases in both males and females.
Treatment of patients with various complications should be individualized.

7.2 Non-gonococcal Urethritis

Non-gonococcal urethritis is being increasingly recognized as a public-
health problem in many areas. In some countries its incidence actually
exceeds that of gonorrhoea, and the condition has to be reported by treat-
ment centres and practitioners to health administrations for statistical
purposes. The condition, notoriously resistant to treatment, may be
accompanied by complications of some importance. There are many gaps
in present knowledge on the etiology, communicability, clinical course,
therapy, and control of this condition, and basic research bearing on these
points should be encouraged. WHO might collect further information
on this condition, particularly on the extent of the problem.
7.3 Lymphogranuloma Venereum (Nicolas Favre)

Lymphogranuloma venereum is not considered a "minor" venereal disease in some areas, both because of its actual general prevalence and because of the nature of serious incapacitating sequelae in infected individuals. WHO might consider collecting data on the nature and the extent of the problem.

7.4 Chancroid

Chancroid appears to have a relatively high prevalence in seaports throughout the world, particularly in the Far East. In view of their known efficacy and low cost, sulfonamides are considered practical therapy for this condition. Certain of the newer antibiotics, e.g., streptomycin, aureomycin, chloramphenicol, and oxytetracycline, are also active in this disease. Further experience with these antibiotics is desirable.

7.5 Granuloma Inguinale (Donovan)

With regard to granuloma inguinale, the committee observed that there was evidence indicating an increased resistance to therapy with streptomycin. The disease responds favourably to treatment with certain of the newer antibiotics, and streptomycin-resistant cases respond favourably to aureomycin, chloramphenicol, and oxytetracycline.

8. RELATIONSHIPS WITH OTHER INTERNATIONAL ORGANIZATIONS AND WITH COMMITTEES WITHIN THE STRUCTURE OF WHO

The committee noted the co-operation of WHO with UNICEF and considered that the continued co-operative support by WHO and UNICEF of mass campaigns against treponemal diseases in less-developed areas was highly desirable. The combined maternal and child health and venereal-disease programmes supported by WHO and UNICEF were also noted. Reference to such programmes has been made more specifically elsewhere in the report (page 7).

The committee noted the continued interest of ILO in maritime aspects of venereal-disease control, and the co-operation between WHO and ILO in regard to the International Anti-Venereal-Disease Commission of the Rhine.

The hope was expressed that the International Union against Venereal Diseases would continue to study anti-venereal-disease projects and
activities suitable for international action, and that health education and basic social problems relating to venereal-disease control would be emphasized in the various programmes.

Within the framework of WHO, several recommendations by other expert committees were noted, particularly those of the Expert Committees on Biological Standardization, the International Pharmacopoeia, Mental Health, Professional and Technical Education of Medical and Auxiliary Personnel, and the Joint ILO/WHO Committee on the Hygiene of Seafarers. These recommendations were taken into account during the deliberations of the committee. Some problems of common interest to these committees, as well as to the Subcommittee on Serology and Laboratory Aspects, have been specifically referred to in various sections of the present report.

9. SUMMARY OF RECOMMENDATIONS TO HEALTH ADMINISTRATIONS

In accordance with the resolution of the Executive Board at its eleventh session, the recommendations of particular interest to governments are summarized below.

Mass treponemal-disease-control campaigns (page 17)

1. Where treponemal disease constitutes a major public-health problem, contacts without overt signs of disease should receive preventive ("abortive") treatment with PAM.

2. Control re-examinations of areas should be undertaken at intervals of approximately six months, depending on seasonal and other factors.

3. National health-administrations should take advantage of the opportunity offered by mass campaigns against non-venereal treponematoses to serve as a bridgehead for the development of wider, general, local health-services; these campaigns should be carefully planned and fully implemented and should be made part of a general development plan for the area whenever practicable.

Therapy (page 23)

1. For the individual clinic-patient with early infectious venereal syphilis, a large initial dose of PAM ("insurance dose") should be given on the day of diagnosis to assure reasonably effective therapy should the patient not reappear for further treatment.

21 In the resolution (EB11.R15) concerning this report (see footnote 1, p. 3), the Executive Board "draws the attention of governments to relevant recommendations contained in the report..."
2. In mass campaigns against non-venereal treponematoses, the minimal total dosage for early infectious lesions in adults should be no less than 1-2 mega-units of PAM and proportionately less for children; this dose should be given in one injection; and the preventive (or "abortive") dose for contacts should be no less than half that used in the early infectious stages of the established disease.

3. The attention of health administrations is drawn to the minimum PAM requirements established in volume II of the Pharmacopoea Internationalis; and it is recommended that these minimum requirements be used as a guide in the national procurement of this penicillin preparation.

Serological aspects (page 28)

Full opportunity should be taken by health administrations in field programmes, particularly mass campaigns, to:

(a) use laboratory facilities for training purposes and develop them gradually into general public-health laboratories as local health services are broadened;

(b) utilize the local laboratory services in the study and evaluation of special epidemiological, clinical, and other problems connected with the particular area;

(c) co-operate further with the International Treponematosis Laboratory Center for a wider sampling of strains of treponemata for local and central study.

Auxiliary personnel (page 29)

Full utilization should be made of national auxiliary personnel engaged and trained for treponematosi-control programmes so that such training can be a starting-point for subsequent general training as local health services are broadened in less highly developed areas. Consideration should be given by health administrations to more favourable conditions of employment for such personnel.

Maritime aspects (page 37)

Health administrations in all WHO regions should take advantage of the facilities of the International Port Demonstration Project at Rotterdam and of the training courses to be organized in 1953 and 1954.
Annex 1

LIST OF SUPPORTING DOCUMENTS

(This paper has been published also in World Health Organization: Monograph Series, No. 11)

Myrdal, G. (1952) "Economic aspects of health", Chron. World Hlth Org. 6, 203


Winslow, C.-E. A. (1952) "The economic values of preventive medicine", Chron. World Hlth Org. 6, 191

World Health Organization (1952) "Report of technical discussions on the methodology of health protection in local areas", Chron. World Hlth Org. 6, 219

World Health Organization (1953) First International Symposium on Yaws Control, Geneva (World Health Organization: Monograph Series, No. 15)

Unpublished Working Documents


WHO/VD/72 Minimum penicillin therapy in the treatment of treponemal infections by WHO/UNICEF field teams

WHO/VD/74 World health and treponematoses

WHO/VD/77 Repository penicillin therapy of pinta in the Mexican peasant: a clinical and serological survey

WHO/VD/79 A study of acquired infectious syphilis in childhood

WHO/VD/80 Treponemal-disease control in underdeveloped countries: experiences in mass therapy

WHO/VD/81 Past experience and present outlook in WHO treponemal-disease control programmes in the Eastern Mediterranean Region: advisability of various types of projects

WHO/VD/82 Minimal PAM therapy in mass campaigns

WHO/VD/83 Mass treatment of treponemal diseases with particular reference to syphilis and yaws

WHO/VD/84 Non-specific urethritis: classification and diagnosis of non-gonococcal urethritis

WHO/VD/85 Treatment schedules that lend themselves to out-patient therapy
WHO/VD/86 Variations in the stability of sexual relations as explanation of differences in the spread of syphilis and gonorrhoea

WHO/VD/87 Lymphogranuloma venereum

WHO/VD/88 Report of a resurvey of two villages in the first “TCP Simplified” Area, Drijordjo, Indonesia

WHO/VD/89 The approach of WHO to treponemal-disease control

WHO/VD/90 Epidemiological considerations in mass campaigns

WHO/VD/91 The nomenclature of yaws

WHO/VD/92 Integration of yaws campaigns into existing public-health services

WHO/VD/93 Maritime aspects of venereal-disease control: Rotterdam Port Demonstration Project

WHO/VD/94 The definition of early and late latent syphilis

WHO/VD/95 Serology and laboratory aspects of the WHO programme in the field of venereal disease and treponematoses

WHO/VD/96 The work of the International Treponematosis Laboratory Center (including report of activities, 1 July 1951 - 30 June 1952)

WHO/VD/97 The need for intensified research work in the mass treatment of yaws

WHO/VD/98 The approach of WHO to treponemal-disease control—co-ordination of research

WHO/VD/99 Past experience and present outlook in WHO treponemal-disease-control programmes in the Americas

WHO/VD/100 Blood testing for syphilis in an island population

WHO/VD/101 Non-gonococcal urethritis

WHO/VD/102 Mass eradication treatment of treponemal diseases with penicillin. Laboratory and clinical basis for selection of effective schedules
Annex 2

NOTES ON THE ENDEMIC-SYPHILIS-CONTROL CAMPAIGN IN BOSNIA

The foreword to Dr. E. I. Grin’s paper clearly states the underlying principles and objectives of this outstanding public-health experience. This is more than a control programme devoted to the widespread treatment of a health hazard of great magnitude. It is an epidemiological investigation as well and, as such, is a distinct contribution to internationally important epidemiological principles and is a bridgehead to nationally important public-health programmes.

That these developments are not incidental or accidental is quite clear from the statement of objectives made at the very outset of the mass campaign. They are the result of co-operative planning and the generally accepted premise that the endemic-syphilis-control programme was a means rather than an end in itself. Indeed, the support of WHO and UNICEF was predicated upon this far-sighted principle, which was outlined in July 1948 as follows: “It becomes evident that a campaign against endemic syphilis must include measures for improvement of educational and health standards. This means that the campaign has to become a part of a general plan for improvement of cultural, educational, economic and health conditions of these areas.”

The significant epidemiological feature of this campaign has been an attempt to define the characteristics of the causative agent, human host, and environment which contribute to the natural history of endemic syphilis. Success in prevention and control depends upon knowledge of natural history, defined as the process of the disease, beginning with the first forces that inaugurate it in the environment or elsewhere, through the resulting changes in form and function which result. Thus, natural history includes both a prepathogenesis period before man is involved as well as the origin and development of the disease in man himself. Such a natural history is the result of multiple causes and effects. Dr. Grin has established beyond doubt that the causes of this disease are multiple and that they are active before the disorder involves the subject. These

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1 Submitted by Dr. E. Gurney Clark, Professor of Epidemiology, School of Public Health, Columbia University, New York, USA; WHO Consultant to Yugoslavia.
causes are to be found in the social, economic, and physical surroundings of the affected population and in the habits and customs of the inhabitants, not just in the characteristics of the specific micro-organism itself.

The success of the present control programme lies in the recognition of the following principles:

(1) Action should be taken simultaneously and continuously throughout the infected areas.

(2) Systematic examination of the entire population should be attempted.

(3) Major emphasis should be on the epidemiological rather than on the clinical and pathological aspects of the disorder.

(4) Advantage should be taken of the most effective schedules of treatment with antibiotics.

(5) Improvement of social and economic standards must go hand in hand with the treatment programme.

Careful study on an individual, family, and community basis has confirmed the concept of endemic syphilis outlined in 1948 as follows:

"The main characteristics of the endemic syphilis as it appears in our country are: (1) extragenital infection (as a rule not connected with the sexual sphere); (2) spreading of infection regardless of sex but mostly among children; (3) low educational and hygienic standard.

"Without these conditions, syphilis cannot develop to an endemic disease. Taking into consideration the above basic factors, we are of the opinion that the correct definition of endemic syphilis would be as follows: 'Endemic syphilis is syphilis appearing in small or large numbers in a community or family regardless of age or sex and is prevalently transmitted extra-genitally due to low health and economic standards'."^4

It has been found that this disease is not homogeneously distributed in an endemic area. In local areas, relatively free and highly infected villages may adjoin. Some households in highly infected areas are not affected. This has led to the conclusion that all households and all members of families must be examined for effective control action.

This campaign has directed its attention to these characteristics and to the principles of simultaneous, systematic, and continuous examination and re-examination, always striving to consolidate gains for long-term progress in public health.

The uneven distribution of endemic syphilis in local areas—which is similar to that found in the case of yaws—will require more detailed study of social and family customs as well as other environmental factors before

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a satisfactory explanation is forthcoming. Certain observations, and questions related to them, seem pertinent to the point:

(a) There is a direct relationship between the size of the community and crowding and infection: the smaller the community, the more crowding, the higher the rate. (Is there a similar relationship in household crowding?)

(b) The more active the focus, the greater is the proportion of children affected. (Is there a correlation with the size of family and age distribution in families and communities, and is this related to previous experience with endemic syphilis in the area?)

(c) This is a family disease and, once it has gained access to a family, follows certain patterns, irrespective of whether it originates from a child infected non-venerally in the neighbourhood, or from a parent or older sibling infected venereally. (Is the proportion of sexually active persons in the family related to the variable occurrence in involved areas?)

Family studies in this programme give pertinent facts pointing to answers to these questions. Dr. Grin’s monograph does not answer them conclusively but indicates the means by which answers may be obtained.

These investigations demonstrate the need for extensive study of the affected and the non-affected, the sick and the well, the young and the old, in order to establish the essential features of the course of a disease in man. The earlier impressions of the benign nature of this disease were first questioned in the studies made in 1934-5, and it remained for the present studies to confirm and explain these impressions. Apart from the scarcity of primary lesions and the method of transmission, there appears to be little or no difference between this and conventional syphilis that cannot be explained on the basis of age of acquisition, frequency of exposure, and environmental circumstances. There may be some question as to what happens following frequent exposure to small numbers of organisms, particularly those taken in by the mouth. In the first place, does infection take place through the gastro-intestinal tract (shown by Akrawi in jejel)? In the second place, what is the effect of multiple exposures once infection has taken place? Is the second, or third, or later inoculum lost on an already infected host, or does superinfection (symptomatic or asymptomatic) take place? Experimental evidence is conclusive that, within certain limits, the size of the inoculum dictates in large measure the incubation period and the symptomatology (the severity or complete absence of initial lesions).

4 Vuletić, A., ed. (1939) Endemijski stjilis u Bosni i Hercegovini, Zagreb
There is further experimental evidence that symptomatic superinfection manifests lesions characteristic of the stage of the first infection. These observations have been borne out in the present investigations. A few cases are presented which seem to show early lesions superimposed upon early latency entirely compatible with superinfection rather than with relapse. In addition, there is abundant evidence that benign late lesions of the skin and mucous membranes result from exogenous sources of treponemes in persons with untreated, or inadequately treated, late latent syphilis. Not only is there a direct correlation in the community between the incidence of early and late skin-lesions to substantiate this, but also there are numerous family case-studies which support it. This observation is not new, but more quantitative support is presented for it than exists elsewhere in the literature on syphilis. It may be possible, under more or less similar epidemiological circumstances, that the prevalence of active benign late lesions of the skin and mucous membranes provides an accurate epidemiological index to "freshness" and activity of an endemic focus.

The low discovery-rate of congenital syphilis in endemic areas is amply explained by two basic facts: (1) the age of acquiring endemic syphilis as related to the age of child-bearing; and (2) the high neonatal and infant mortality-rates which prevail in the low economic areas conducive to the spread of endemic syphilis.

Nothing but the highest praise can be offered for the organization of this mass campaign and the special investigations arising from it. My own impressions have been stated in considerable detail in my reports to WHO following visits to these areas and can be summarized as they were in these reports: "As can be readily gathered from this report, my impres-sions of the accomplishments in the control of endemic syphilis sponsored by UNICEF and WHO in Yugoslavia are very favourable. The quantitative reports of accomplishments are impressive indeed, but one must observe the field conditions under which this progress was made in order to appreciate fully what has been and is being done. I have never seen public health funds spent to greater advantage." Particular emphasis should be given to the expertly trained teams, the official and citizen cooperation, the population enumeration, the excellent field laboratories, the record system, and especially the enthusiasm and energy of the workers.

The endemic-syphilis-control programme in Bosnia has contributed materially to the formulation of certain epidemiological principles valuable in mass-treatment programmes against treponemal disease. These principles have been outlined in papers presented at the Annual Venereal Disease Symposium 7 and at the Tenth International Congress of Derma-

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7 Reynolds, F. W. & Guthe, T. (1952) *Amer. J. Syph.* 36, 424
tology, London. They are clearly expounded in Dr. Grin’s monograph, as follows.

1. *Every effort should be made to examine the entire population in the affected areas.* In Bosnia, the best and quickest results were obtained when this was done and when the infectious cases and family contacts were treated simultaneously. In spite of careful enumeration of the population, complete examination was not possible in all instances, but it seems clear, from this and other experiences, that a 90% examination is the critical level. At the beginning of the programme, it was believed that the potential sources of subsequent infections would lie in the treatment failures, i.e., infectious relapses. The high degree of success with penicillin alone, together with investigations of new infectious cases, soon proved that the important sources of infection were: (a) those infected persons who escaped examination or treatment because of absence; (b) new cases of syphilis imported from other areas; and (c) symptomless cases in the incubation period at the time of examination in whom infectious lesions subsequently developed.

Examination of the entire available population and concentrated attempts to find the absent persons provided measures to combat (a) above. New cases from other areas, i.e., (b), proved a most baffling problem, and would probably be solved best by leaving one or more health workers in the areas between control examinations. The solution of the infectious-source problem, i.e., (c), led to the adoption of the next principle, below.

2. *It is essential that abortive treatment be given to contacts.* For the purpose of mass control campaigns, some practical definition of “contact” must be established. This is being done in Bosnia. The development of such a definition is related to quantitative data which show greater accomplishments when all members of a household are treated when one infectious case is found. This does not take into account potential cases from other households which may have been in close contact with the infected patients elsewhere. Thus, for greater accomplishment, it may be necessary to provide treatment for known or suspected extra-household contacts. Studies are now in progress to determine just how extensive abortive treatment of contacts should be in mass control campaigns.

3. *In areas of actively expanding foci and numerous and fresh infections, the first control-examination should preferably be carried out three to four months after the initial survey.* This period depends upon: (a) the precision and completeness with which the original systematic examination and treatment of the population were carried out; (b) the extent of the

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8 Unpublished working document WHO/VD/83
reservoir of infectiousness at the beginning of the campaign; and (c) the extent of population movement in and out of the area. In any event, the interval should be no longer than one year, preferably no longer than six months. There is ample evidence in Dr. Grin’s monograph to support the contention that a single mass application of case-finding and treatment will not suffice to “control” this disease. There is outstanding evidence, however, that repeated coverage of an affected area will reduce the incidence of infectious cases to the point where properly oriented local health-facilities will serve to control the residual foci. How many surveys are required in any particular instance will depend upon factors (a), (b), and (c) above.

4. Control re-examinations must be applied to the entire population if maximum protection is to be offered. For example, in the re-examination of the total population of a village of 573 persons 22 months after the original examination, only 5 cases of infectious syphilis were found among the 29 persons previously treated. Among the remainder of the population, 24 new cases were found. These would have been missed had the re-examinations been limited to a follow-up of treated cases.

For the purpose of this discussion, only a few points need to be made in respect of the contributions of these investigations to the generally accepted ideas about penicillin treatment in mass programmes of this kind as set forth by Rein & Kitchen ⁹ and by Guthe et al. ¹⁰ Schedules of treatment were in conformity with the recommendations of the WHO Expert Committee on Venereal Infections and Treponematoses. ¹¹ During the initial stages of the campaign (1948 and early 1949), some patient-groups were treated with PAM combined with bismuth; but, when subsequent control studies showed that no advantage had been gained with this combination, it was abandoned and penicillin alone was used. The basic schedule has been 3.6 to 4.2 million units in six to seven injections of 600,000 units each, but other schedules of shorter duration have been explored. These investigations have prompted Dr. Grin to make such statements as the following: ¹²

"It was noted during the campaign that, with a total dosage of 3,600,000 to 4,200,000 units, no differences occurred whether the dose was given in single injections, in three injections of 1,200,000 units each on the first, second, and fifth days, or in six or seven injections of 600,000 units daily or every second day."

"The experience gained in the Bosnian programme supports the view that larger doses of repository penicillin should be given over a short period rather than smaller doses over a longer period."

⁹ Unpublished working document WHO/VD/102
¹⁰ Unpublished working document WHO/VD/83
¹¹ See unpublished working document WHO/VD/72
"No case of endemic syphilis in the early clinical stage was encountered which did not respond favourably to treatment."

"The Bosnian programme has afforded only limited experience in the use of single injections of PAM; yet, although it is too soon to draw any definite conclusions, the results observed so far are not inferior to those obtained after two years with a larger number of injections, even when the total dosage is reduced to 1,500,000 units of PAM."

The illustrations in numerous families and communities presented in support of these statements seem to be sound. Indeed, the major contribution of this study to the principles of mass control campaigns lies in the fact that epidemiological, clinical, and serological evaluations have been made in terms of family, household, and community units, rather than in terms of the individual.

Epidemiological evidence gathered throughout the campaign has contributed significantly to the ideas about relapse, reinfection, and sero-resistance in this disease. Of particular importance was the repeated and almost universal observation that what might appear to be clinical or sero-relapse generally occurred in those families in which new cases of early syphilis were found, usually before "relapses" were diagnosed. Similarly, "seroresistance" had an uncanny way of appearing in members of families in which a new case had appeared previously. Furthermore, in isolated geographical areas with no immigration, the phenomenon of relapse was not observed when all cases and contacts were treated at the time of the initial survey. "It was found that relapse or reinfection did not occur in families all of whose members had been treated so long as a fresh infection was not introduced from outside." These are very important observations in reference to the evaluation of penicillin therapy and add support to the statements about treatment made by Dr. Grin. Many impressive illustrations are given in support of these observations. Another significant fact in this connexion is that 50% of the so-called "relapses" after completing PAM treatment were in children under ten years of age. This is at variance with the observations of "sexual" syphilis where treatment failure in young children is rare. This would seem to be additional support to the effectiveness of penicillin treatment and to the thesis that a majority of the so-called "failures" are indeed not failures of treatment per se, but failures to remove the foci of infection which led to the reinfection of those in the same "epidemiological" circles.

In addition to the clinical, laboratory, and epidemiological information supplied by this campaign against endemic syphilis in Bosnia, there are other contributions of signal importance. Not the least of these is the demonstration of the effectiveness of specially trained non-medical

personnel in mass programmes of this sort, not only in the phase of action, but also in that of consolidation. Consolidation is used here not only in terms of maintaining gains against the specific disease, but also in terms of progress toward generalized public-health programmes.

The present control programme will serve as a bridgehead for the development of general public-health services provided it is possible to take advantage of the progress to date: the citizens have been alerted, the population has been enumerated, personnel have been recruited, a basic record system is available, and community facilities are at hand in many areas. The time for transition is “now”, and the endemic-syphilis-control programme of Bosnia is indeed an opportunity for promoting rural health-services.\(^{14}\)

Annex 3

PRESENT STATUS OF TREATMENT OF EARLY SYPHILIS

Summary of Discussions of a Group of Members of the WHO Expert Advisory Panel on Venereal Infections and Treponematoses

A meeting of the following members of the Expert Advisory Panel on Venereal Infections and Treponematoses of the World Health Organization took place at Bedford College, London, on 26 July 1952:

Dr. W. Burckhardt, Professeur de Dermatologie et de Syphiligraphie à l’Université de Zurich, Suisse
Dr. H. T. Chaglassian, Professor of Dermatology and Syphilology, American University, Beirut, Lebanon
Dr. N. Danbolt, Professor of Dermatology and Syphilology, University of Oslo, Norway
Dr. J. Martins de Barros, Chief of the Service of Syphilis, Social Service of Industry, São Paulo, Brazil
Dr. A. Dostrovsky, Dean, University Medical School, Jerusalem, Israel
Dr. C. Doucas, Associate Clinical Professor of Dermatology and Syphilology, Chief, Skin and Venereal Diseases Department, Evangelismos Hospital, Athens, Greece
Dr. H. Gudmundsson, Skin and Venereal Disease Department, State Hospital, Reykjavik, Iceland
Dr. S. Hellerström, Professor of Dermato-syphilology, University of Stockholm, Sweden
Dr. E. H. Hermans, Director, Rotterdam Port Demonstration Project, Netherlands
Dr. I. Katzenellenbogen, Chief, Department of Skin and Venereal Diseases, Jerusalem, Israel
Dr. S. Lapière, Professeur de Dermatologie et de Syphiligraphie, Clinique de l’Université, Liège, Belgium
Dr. G. L. M. McElligott, Director, Venereal Disease Department, St. Mary’s Hospital; Adviser in Venereal Diseases, Ministry of Health, London, England
Dr. P. Marcussen, Chief, Dermatology Department, Finsen Institute, Copenhagen, Denmark
Dr. A. Musger, Professor of Dermatology and Venereology, University Clinic of Dermatology, Graz, Austria
Dr. J. Gay Prieto, Professor of Dermatology and Venereology, University of Madrid; Member, Royal National Academy of Medicine, Madrid, Spain
Dr. R. V. Rajam, Professor of Venereology, Government General Hospital, Madras, India
Dr. C. Rein, Associate Professor of Clinical Dermatology and Syphilology, New York University Postgraduate Medical School, New York, USA
Venereal Infections and Treponematoses

Dr. I. M. Sabry, Professor of Venereal Diseases, Faculty of Medicine, University of Alexandria, Egypt

Dr. A. de Carvalho Sampaio, Professor of Bacteriology, Director, Laboratory of Bacteriology, Lisbon, Portugal

Dr. M. Soetopo, Professor of Dermato-syphilology, Director, Venereal Disease Research Institute in Indonesia, Sourabaya, Java, Indonesia

The purpose of the meeting was to have an informal discussion among the members of the panel on the present status of treatment of early syphilis. As a result of the discussions which took place, the following resolution was approved for submission to the fourth session of the Expert Committee on Venereal Infections and Treponematoses:

The concensus of opinion of the members of the WHO Expert Advisory Panel on Venereal Infections and Treponematoses here present is that:

1. Repository penicillin preparations are currently the treatment of choice in syphilis and, at the present time, PAM (procaine penicillin G in oil with 2% aluminium monostearate) is the most useful of these preparations, provided it meets the minimum specifications of the World Health Organization as described in volume II of the Pharmacopeia Internationalis.

2. Therapy with penicillin in cases of infectious syphilis is preferable to therapy with arsenicals and bismuth when all factors—efficacy, toxicity, ease of administration, and cost—are considered. A majority of the group considers that there is no advantage in supplementing the results obtainable with penicillin therapy by subsequent injections of metal-chemotherapy.

The group is agreed that the early results of therapy with penicillin have been excellent, but most of its members have, to a greater or lesser degree, certain reservations regarding the long-term outlook, especially in so far as the possible development of cardiovascular syphilis is concerned.

Patients treated for early syphilis should receive careful follow-up, both clinical and serological, the latter with quantitative serological tests.

3. The group unanimously considers that, for the treatment of early syphilis, the concept of a large initial ("epidemiological") dose is one that should be recommended by the World Health Organization. At the present time, the initial injection should be 1.2 to 2.4 million units of PAM; in the case of secondary syphilis, the larger amount should preferably be given.
4. Examination of the cerebrospinal fluid should be carried out routinely in all persons treated for early syphilis. If only one such examination is feasible, it should preferably be made some time between one and two years after treatment is given.
Annex 4

SPECIMEN SYPHILIS-TREATMENT SCHEDULES—
WITH PROCAINE PENICILLIN G IN OIL
WITH 2% ALUMINIUM MONOSTEARATE (PAM)—
FOR THE INDIVIDUAL CLINIC-PATIENT

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Annex 5

MONOGRAPH ON
OILY INJECTION OF PROCAINE BENZYL-PENICILLIN

Oily injection of procaine benzylpenicillin is a sterile suspension of procaine benzylpenicillin in a suitable oil containing 2% w/v of aluminium monostearate. It contains not less than 90% of the number of International Units of penicillin stated on the label.

*Consistency.* Passes readily through a hypodermic needle of internal diameter 0.895-0.905 mm at 25°C.

*Particle size.* The diameter of not less than 65% of the particles does not exceed 5 μ.

*Stability.* When shaken by hand it forms a suspension which is stable for 48 hours at 37°C; if any separation takes place during this time, the thickness of the oily layer should not be greater than 3 mm.

*Water.* Not more than 1.4%.

*Sterility.* After the addition of a quantity of solution of penicillinase R or other suitable inactivating agent adequate to ensure complete inactivation of the penicillin present, complies with the tests for sterility.

*Blood-level duration.* When determined as described in the Appendix, a quantity equivalent to 300,000 International Units of penicillin produces blood-serum levels at 72 hours of not less than 0.03 International Unit per ml in not less than half the number of subjects used.

*Other requirements.* Complies with the requirements stated under "Injections".

*Assay.* The potency is determined by the method required by the law of the country concerned; a suitable method is included in the Appendix.

*Storage.* Oily injection of procaine benzylpenicillin should be stored in a cool place, but not in a refrigerator.

*Labelling.* The label on the container must state: (1) the name of the injection; (2) the number of International Units in 1 ml; (3) "For intramuscular use only".

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1 Prepared for possible inclusion—with amendments if necessary—in volume II of the *Pharmacopoea Internationalis* (Ph. I.) at the eleventh session of the Expert Committee on the International Pharmacopoeia (unpublished document WHO/Pharm./250, p. 4).

The letters "TS" (test solution) and "R" (reagent) refer to the solutions and reagents listed in the Ph. I.
When oily injection of procaine benzylpenicillin is prescribed, no strength being stated, oily injection of procaine benzylpenicillin containing 300,000 International Units per ml shall be dispensed.

Appendix

BLOOD-LEVEL DURATION TEST

1. The Test

Ten or more persons in good health and weighing between 60 and 90 kg who have not taken penicillin or similar antibiotics in any form during the previous seven days are selected as test subjects. Each subject is injected with a quantity of the oily injection of procaine benzylpenicillin under test equivalent to 300,000 International Units of penicillin. A 5-ml sample of venous blood is withdrawn 72 hours after the injection, and, if desirable, at other times during the test period; the subject should receive no other antibiotic during this period. The blood is allowed to clot, and the serum is separated by centrifuging and transferred immediately to a sterile tube. If it is not to be tested on the same day, the serum is frozen at −20°C or below and stored frozen. The penicillin content of the samples of serum is determined as described below.

2. The Blood-Serum Assay ("Sarcina lutea" Method)

The antibiotic potency of a sample of serum presumed to contain penicillin is determined by comparing the volumes of it required to inhibit the growth of a standard strain of Sarcina lutea with the quantities of a standard preparation of penicillin required to produce the same degrees of inhibition.

International Standard Preparation and Unit

Working standard solution

To about 0.015 g of the International Standard Preparation of penicillin, accurately weighed in an atmosphere of 50% relative humidity or less, sterile 1% phosphate buffer, pH 6.0, is added to make a stock solution containing 0.6 mg per ml (1,000 International Units per ml). This solution is kept at a temperature of about 10°C and used for two days only. On the day of the assay, this stock solution is diluted to 1.0 International Unit per ml, using the above-mentioned buffer. Working dilutions of the latter solution are prepared, using as the diluent bovine albumin TS which, before use, has been filtered through a bacteria-proof filter and tested on plates for inhibition of Sarcina lutea under the conditions outlined below. Bovine albumin TS which shows inhibition under these conditions should not be used.

Preparation of serum samples

Serum samples expected to contain not more than 0.4 International Unit per ml need not be diluted. Samples expected to have a potency greater than 0.4 International Unit per ml should be diluted to about 0.1 International Unit per ml with bovine albumin TS known to have no antibiotic activity.

Suggested method

The general procedure described under "Biological Assay of Penicillin" is applied with the specific changes set forth below.

* May be defined in volume II of the Ph. I.
Media

Nutrient agar for the base layer and for carrying the test organism is prepared as follows:

- Peptone ........................................... 6.0 g
- Pancreatic casein digest ......................... 4.0 g
- Yeast extract .................................... 3.0 g
- Beef extract ..................................... 1.5 g
- Glucose R ......................................... 1.0 g
- Agar R ............................................ 15.0 g
- Water, sufficient to produce ................. 1,000 ml

The reaction is adjusted so that the pH is 6.5 to 6.6 after autoclaving at 121°C for 20 minutes.

Agar for the inoculated layer is prepared as above, but omitting the pancreatic digest of casein and adjusting the reaction so that the pH is 6.5 to 6.6 after autoclaving.

Nutrient broth for preparing an inoculum of the test organism is prepared as follows:

- Peptone ........................................... 5.0 g
- Yeast extract .................................... 1.5 g
- Beef extract ..................................... 1.5 g
- Sodium chloride R ............................... 3.5 g
- Glucose R ......................................... 1.0 g
- Dibasic potassium phosphate R ............ 3.68 g
- Monobasic potassium phosphate R ......... 1.32 g
- Water, sufficient to produce ................. 1,000 ml

The reaction is adjusted so that the pH is 6.9 to 7.0 after autoclaving.

Instead of preparing the media from the individual ingredients specified, they may be prepared from a dehydrated mixture which, when reconstituted with water, has the specified composition. Minor modifications of the individual ingredients specified are permissible if the resulting media possess growth-promoting properties at least equal to the media described.

Preparation of bulk culture suspension

The test organism is *Sarcina lutea* (P.C.I. 1001 and American Type Culture Collection 9341). The test organism is maintained on slants of nutrient agar as described for the base layer and transferred to a fresh agar-slant once a week. A suspension of the test organism is prepared as follows. An agar slant is streaked heavily with the test organism and incubated for 24 hours at 26°C. The growth is washed off with 3.0 ml of nutrient broth. The suspension so obtained is used to inoculate the surface of a Roux bottle containing 300 ml of this nutrient agar. The suspension is spread over the entire surface with the aid of sterile glass-beads. The bottle is incubated for 24 hours at 26°C. Growth is washed from the agar surface with 15 ml of nutrient broth prepared as described. The density of organisms in this bulk suspension is tested by diluting 1 part with 9 parts of nutrient broth, and measuring the light transmission at about 650 nm in a suitable photoelectric colorimeter. If the light transmission is about 10% of that of sterile nutrient broth, similarly treated, the bulk suspension is satisfactory for use. Otherwise, the bulk suspension is adjusted by dilution so that a 10% dilution of the adjusted suspension gives about 10% light transmission. The bulk suspension, adjusted by dilution if necessary, may be used for at least two weeks.

Preparation of plates

On the day of the assay, 10 ml of base layer agar-medium is added to Petri plates (20 mm x 100 mm). The agar is distributed evenly in the plates and allowed to harden.
0.4 ml of bulk culture suspension is added to 100 ml of the agar prepared for the inoculated layer, previously melted and cooled to 48°C. The culture and agar are thoroughly mixed and 4 ml are added to each of the plates containing the 10 ml of the hardened uninoculated agar. The inoculated agar is spread evenly over the surface by tilting the plates back and forth. The plates are covered with porcelain covers, glazed on the outside.

Standard curve and assay procedure

Six cylinders are placed on the inoculated agar surface so that they are at approximately 60° intervals on a 2.8-cm radius. One plate is used for each sample. Three cylinders on each plate are filled with the 0.1 International Unit per ml dilution of the International Standard Preparation, and three cylinders with the serum sample under test, alternating standard and sample. The plates are incubated for 16 to 18 hours at 26°C and the diameter of each zone of inhibition is measured. At the same time, a standard curve is prepared, using concentrations of 0.03, 0.05, 0.10, 0.20, 0.30, and 0.40 International Units per ml of the International Standard Preparation in bovine albumin T5. Three plates are used for the determination of each point on the curve, making a total of 15 plates. On each of three plates, three cylinders are filled with the 0.1 International Unit per ml dilution of the International Standard Preparation, and the other three are filled with one of the five other diluted solutions of the International Standard Preparation. After the plates have been incubated, the diameters of the zones of inhibition are read. Thus, there will be 45 determinations at 0.1 International Unit and nine determinations at each of the other points on the curve. The readings of 0.1 International Unit per ml concentration and the readings of the point tested for each set of three plates are averaged and also all 45 readings of the 0.1 International Unit per ml concentration. The average of the 45 readings of the 0.1 International Unit per ml concentration is the correction point for the curve. The average value obtained for each point is corrected to the figure it would be if the 0.1 International Unit per ml reading for that set of three plates were the same as the correction point. Thus, if the average of all 45 readings of the 0.1 International Unit concentration is 20.0 mm, and the average of the 0.1 International Unit concentration of a given set of three plates is 19.8 mm, the correction is +0.2 mm. If the average reading of the 0.05 International Unit concentration of these same three plates is 17.0 mm, the corrected value becomes 17.2 mm. The corrected values, including the average of the 0.1 International Unit per ml concentration, are plotted on 2-cycle semi-logarithmic graph paper, using the concentration in International Units per ml as the ordinate (the logarithmic scale) and the diameter of the zone of inhibition as the abscissa. The standard curve is drawn through these points. To estimate the concentration of penicillin in the sample, the zone readings of the International Standard and the zone readings of the sample on the 1 plate used are averaged. If the sample gives a larger average zone-size than the average of the International Standard, the difference between the two averages is added to the 0.1 International Unit zone on the standard curve. If the average sample value is lower than the standard value, the difference between the averages is subtracted from the 0.1 International Unit value on the curve. From the curve are read the concentrations of penicillin, in International Units per ml, corresponding to these corrected average zone-sizes.
Annex 6

SEROLOGY AND LABORATORY ASPECTS
OF THE WHO PROGRAMME ON VENEREAL DISEASES
AND TREPONEMATOSES

1. Introduction

The following is an account of activities which have been carried out
on the basis of the recommendations of the first and second sessions of
the Subcommittee on Serology and Laboratory Aspects of the WHO
Expert Committee on Venereal Infections and Treponematoses.\(^1\) It repre-
sents a summary of developments and work done by laboratories co-
operating with WHO in this field in which members of the subcommittee
have taken part.

2. Stability of Blood Samples in Postal Transmission\(^2\)

The following laboratories participated in this experiment, which was
started on 6 November 1950 and completed on 18 February 1951:

Pan American Sanitary Bureau supported Laboratory, Guatemala
School of Tropical Medicine, Calcutta, India
Municipal and Beilinson Hospitals, Tel Aviv, Israel
Gade's Institute, University of Bergen, Norway
Venereal Diseases Reference Laboratory, St. Peter's Hospital,
London, United Kingdom of Great Britain and Northern
Ireland
Venereal Disease Research Laboratory, Communicable Disease
Center, Chamblee, Ga., USA

The donors from whom the samples were taken were syphilis patients with
seroreactions of different strengths. Four samples were taken from each
donor. One of the samples was immediately examined in the collecting
laboratory, two were sent by post to an address from which they were
returned without delay and examined on re-arrival in the collecting labora-
tory. The total transit-time for these two samples varied from 2 to 27
days. The fourth sample was stored at 4°C in the collecting laboratory
and examined at the same time as the two samples mentioned above.

The results were reported to the Secretary of the subcommittee on special forms. The reports, all of which were received by the end of April 1951, disclosed the following information:

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of donors</th>
<th>Number of methods of testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergen</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td>Chambly</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Guatemala</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>London</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Tel Aviv</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

The reports from Calcutta showed that 11 samples had been delayed in transit for more than two weeks and were found to be unsuitable for testing when eventually received. It was decided that the Calcutta laboratory should discontinue participation in the experiment, as the interlaboratory test evaluation experiment in which they were distributing samples to five laboratories had by that time started.

Altogether some 4,000 results were produced. Evaluation of these has so far shown that 70% of the samples in transit for from 5 to 11 days gave the same titre as those stored at 4°C during the same period. Almost all the samples which were in transit for a longer period showed a reduced titre. This reduction was never more than one dilution step, but some samples were found on arrival to be unsuitable for serological examination.

The percentage of samples showing a reduced titre was higher among those transported at 18°C than among those transported at 30°C.

The percentage of samples arriving in a haemolysed condition increased with the length of time they had been in transit, and all samples which had been in transit more than a week were found to be haemolysed.

3. Inter-Laboratory Test Evaluation

Twenty-nine laboratories (comprising laboratories of the members of the panel, the Guatemala laboratory, and two WHO field-laboratories) took part in an experiment on the exchange of blood samples. Vacutainers received as a gift from an American firm were distributed to participants—30 to 60 vacutainers to each laboratory. In several cases the vacutainers were used only for collecting blood from which serum was prepared for distribution.

In order that there should be one common antigen for the comparison, Kahn antigen was supplied to most of the participating laboratories, while some laboratories received antigen for the Meinicke test, or for the Harrison-Wyler test.

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The experiment started on 12 February 1951 and finished in the middle of May 1951. Each laboratory distributed weekly three or four samples of blood or serum to each of three other laboratories, keeping an additional sample for from 3 to 5 days at room temperature in their own laboratories and afterwards testing it.

Results were reported to the Secretary of the subcommittee by donor and receiver laboratories on special forms which had been previously distributed.

The whole experiment covered the examination of samples from some 1,300 donors. Each sample was examined in four laboratories with from 2 to 6 serological tests.

The reports from the laboratories came in rather slowly. Some were lost in transit and duplicate reports had to be requested, while the information given in many of the reports was incomplete. This entailed a somewhat protracted correspondence with certain laboratories.

For evaluation purposes, the results were transferred to specially designed punch-cards—one for each donor; the cards were then coded and punched. Work on the transfer of results to the punch-cards was completed on 10 July 1952.

4. Pilot Study of Freeze-Dried Sera of Different Levels of Sensitivity

4.1 Pilot experiment

This experiment, which was planned by the subcommittee in collaboration with one of the members of the Expert Committee on Biological Standardization, entailed the collection of serum from 14 donors—namely, 3 seronegative cases, 10 syphilitics with various degrees of seroreactivity, and one with a false-positive seroreaction. These sera were collected and freeze-dried by the WHO International Serological Reference Laboratory at the Statens Serum Institut, Copenhagen, and some 80 ampoules, each containing 2 ml of freeze-dried serum, were prepared from each of the 14 sera. These ampoules were distributed by the WHO International Serological Reference Laboratory on 13 and 14 December 1950 to five of the panel laboratories—Bergen, Calcutta, Chambly, London, and Tel Aviv—the Reference Laboratory in Copenhagen retaining one set of 168 ampoules for its own part in the experiment.

The six laboratories tested three ampoules of the freeze-dried sera during the last part of December 1951; three months later the remaining nine ampoules of sera were tested after having been stored at temperatures of $-10^\circ\text{C}$, $-20^\circ\text{C}$, $-37^\circ\text{C}$.

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The purpose of the experiment was to evaluate the usefulness and keeping quality of freeze-dried sera with a view to using such sera as a basis for comparison between different serological tests.

The results of the pilot experiment were reported to the Secretary of the subcommittee on specially prepared forms previously distributed to the participating laboratories. Some 4,000 results were produced for evaluation.

After interpretation of readings and titres had been discussed by letter with the participants, the different types of readings were transferred to a common logarithmic titre. A draft report, which included extensive tables, was prepared, mimeographed in September 1951, and distributed to the laboratories which had taken part in the experiment. Each participant signed the following draft statement:

Having taken active part in the pilot experiment in which 14 freeze-dried sera were used for serological tests for syphilis, the members of the Subcommittee on Serology and Laboratory Aspects and the Chief of the WHO International Serological Reference Laboratory in Copenhagen expressed the following opinion.

The pilot experiment on freeze-dried sera prepared in the WHO International Serological Reference Laboratory in Copenhagen has shown that:

1. Ampoules arrived in good condition (no breakage or leakage).
2. Sera were, as a rule, free from bacteriological contamination. (Less than 3% of about 300 culture experiments showed growth.)
3. It was possible to reconstitute sera without any great difficulty.
4. Redissolved sera were, to some extent, turbid and contained microscopic or macroscopic particles, but serological examination was not thereby disturbed.
5. Experienced technicians were easily able to distinguish between such particles and the precipitation occurring during testing with antigen suspension.
6. Freeze-drying and reconstitution together caused only a slight reduction in reactivity.
7. Storage under unfavourable conditions (+20°C and +37°C) during three months caused a slight reduction in reactivity, especially at +37°C, but even sera thus stored gave typical reactions.
8. Zone phenomena occurred only rarely; they were not specifically associated with storage at 37°C.
9. The various tests employed showed agreement and disagreement in proportion to that usually encountered in the testing of fresh sera.
10. The various tests showed different degrees of variability in titre from ampoule to ampoule of the same serum.
11. The various tests showed different degrees of sensitivity, and the one presumably false positive serum showed great discrepancy in results obtained with different tests.

The participants in the pilot experiment consider that further studies on freeze-dried sera would be of real value, and are in favour of a continuation of this work according to the plans originally agreed on by the subcommittee and presented in its report, i.e., the establishment of a large collection of such sera for international reference purposes.
The participants are willing to assist in such work and recommend that the necessary steps be taken by WHO to organize it.

The participants are aware that such a project cannot be fully realized within a few months, but express their confidence in WHO's ability to find the necessary funds for the work.

Finally, the participants agree that the value of freeze-dried sera for evaluation of serological testing methods should be fully explored before discussion is re-opened on the holding of an International Serological Laboratory Conference.

4.2 Continuation of the experiment

In October 1951, 15 laboratories in different parts of the world were approached on the freeze-drying of serum from 80 selected donors. Funds were made available by the Organization to cover a grant to each laboratory selected to undertake the freeze-drying. It was decided that nine laboratories should take part in the experiment, and agreements with seven of these were signed before the end of 1951. The eighth laboratory is the WHO International Serological Reference Laboratory in Copenhagen, while negotiations with two other laboratories are still being conducted with a view to selecting the ninth.

Each of the nine laboratories will prepare from 300 to 500 ampoules, each containing 0.5 ml serum taken from each of from 6 to 12 donors.

Six of the nine laboratories received ampoules and other equipment as part of their grant.

Each laboratory received detailed instructions on the selection of donors, and on the preparation of sera, in order that a representative collection of good quality sera might be made.

Subcommittee members and some of the members of the expert advisory panel were consulted as to the type of donors to be used, and the following broad categories were finally decided upon:

- Non-seroreactive non-syphilis . . . 9
- Falsely seropositive non-syphilis . . . 57
- Syphilis with different seroreactions . . 14

The selection of donors in each area is being made by one or two clinicians in collaboration with the laboratory performing the freeze-drying.

The WHO International Serological Reference Laboratory has already prepared serum from seven donors, and most of the other laboratories started work on the freeze-drying a short time ago.

The total collection will comprise some 25,000 ampoules which will be stored in the WHO International Serological Reference Laboratory and later distributed by them. It is planned that the 80 sera shall be tested in the laboratories of several members of the panel before the next meeting.
of the subcommittee in order that the latter may be able to advise on the ultimate use of these sera for evaluation of serological tests.

The draft report on the pilot experiment and the plans for the collection of the 80 sera were discussed by the members of the Expert Committee on Biological Standardization at their meeting in December 1951.5

5. Serodiagnostic Methods Used in Different Parts of the World 6

Information on serological methods used in laboratories throughout the world has continued to be collected since the last meeting of the subcommittee. In March 1951 a further letter was sent to those Member States which had not at that time complied with the original request for information, and as additional States became Members of the Organization the original request letter was sent to them.

Supplementary information had to be requested from a certain number of laboratories.

During 1951 the information available on laboratories in the European, Eastern Mediterranean, and South-East Asia regions was collated, and work on the remainder is still in progress.

6. WHO International Serological Reference Laboratory, Copenhagen

On 14 November 1950 an agreement was signed between the Organization and the Statens Seruminstitut, Copenhagen, to set up the WHO International Serological Reference Laboratory.

Since its establishment, this laboratory has undertaken the following work for the Organization:

(1) Testing of antigens—mostly preparations which have been found by field teams to be unsatisfactory in use.

(2) Testing of freeze-dried sera produced by Cannefax, and of sera used in the laboratories of the United Nations Relief and Works Agency for Palestine Refugees from the Near East.

(3) Freeze-drying of sera for the pilot experiment and its continuation.

(4) Participating as key laboratory in the inter-laboratory test evaluation, sending samples to six other laboratories.

(5) Making chemical analyses of cardiolipin and lecithin at the request of a member of the Expert Committee on the International Pharmacopoeia.

(6) Co-operating with the Division of Laboratories and Research, New York State Department of Health, Albany, N.Y., USA, on the improvement of methods for the control of cardiolipin and lecithin.

(7) Receiving and instructing WHO Fellows.

7. Cardiolipin

7.1 *Monograph on cardiolipin*

At its 1950 meeting, the subcommittee recommended the production of a monograph on the preparation of, and methods of control for, cardiolipin and lecithin. The paper was written by Dr. Mary C. Pangborn and other members of the staff of the Division of Laboratories and Research, New York State Department of Health, Albany, and was published by WHO.8

7.2 *Specificity of cardiolipin antigens*

Five laboratories are undertaking a study on the influence of the type of lecithin used in cardiolipin antigens—beef-heart lecithin compared with egg lecithin. International reference preparations of cardiolipin and lecithin are being used in this study.

8. Co-operation with Other Expert Committees

8.1 *Expert Committee on the International Pharmacopoeia*

During its meetings held in November 1950, April 1951, October 1951, and April 1952,9 the Expert Committee on the International Pharmacopoeia considered the subcommittee’s recommendation that descriptions of cardiolipin and lecithin should be included in volume II of the *Pharmacopoeia Internationalis*.

The chemical methods for the control of these two substances were examined by some members of the Expert Committee on the International Pharmacopoeia, and it was finally agreed that a text prepared jointly by members of that committee, of the Expert Committee on Biological Standardization, and of the Subcommittee on Serology and Laboratory Aspects should be included.

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8.2 Expert Committee on Biological Standardization

At its meetings in November 1950 and December 1951, the Expert Committee on Biological Standardization found that definite standards of cardiolipin and lecithin could not be established at the time, but arranged for international reference preparations of these two substances to be deposited in the Standards Department of the Statens Seruminstitut, Copenhagen, where they are available on request to laboratories controlling national production of cardiolipin and lecithin.

9. Expert Advisory Panel on Serology and Laboratory Aspects

This panel, which was established during the summer of 1950, has increased in membership. Most of the members took part in the inter-laboratory test evaluation experiment. Some members of the panel have, either directly or through the agency of the Secretary of the subcommittee, disseminated technical and scientific information to other panel members.

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Annex 7

YAWS LESIONS *

* The 19 figures which follow illustrate the different types of lesions within each of the classification groups indicated in the body of the report (see page 33), which may be encountered in the field. Latent yaws is that stage of the infection during which there are no detectable clinical manifestations, and hence this stage is not illustrated. The diagnosis is established by the clinical history and/or a positive serological test.

Fig. 1, 2, 3, 4, 9, 11, 12, 14, 15, 16, and 17 were kindly provided by Dr. C. J. Hackett, Director of the Wellcome Museum of Medical Science, London, and fig. 5, 6, 7, 8, 10, 13, 18, and 19 by Dr. K. R. Hill, Professor of Pathology, University College of the West Indies, Jamaica.
FIG. 2. MULTIPLE PAPILLOMATA
FIG. 3. WET CRAB YAWS

FIG. 4. OTHER EARLY SKIN LESIONS: I
FIG. 5. OTHER EARLY SKIN LESIONS: II
FIG. 6. OTHER EARLY SKIN LESIONS: III
FIG. 7. OTHER EARLY SKIN LESIONS: IV
FIG. 8. OTHER EARLY SKIN LESIONS: V
FIG. 11. GUMMATA AND ULCERS: I
FIG. 12. GUMMATA AND ULCERS: II
FIG. 13. GANGOSA
FIG. 14. BONE AND JOINT LESIONS:
FIG. 15. BONE AND JOINT LESIONS: II
FIG. 17. OTHER MANIFESTATIONS: II
FIG. 18. OTHER MANIFESTATIONS: III

FIG. 19. OTHER MANIFESTATIONS: IV