WORLD HEALTH AND TREPONEMATOSES*

BY

THORSTEIN GUTHE and FRANK REYNOLDS

World Health Organization, Geneva, Switzerland

The Problem and its Approach

Hudson (1928, 1937, 1946) and, more recently, Hermans (1950) and Willcox (1950) have called for a world view of treponematoses rather than an approach by clinical entities based on signs, symptoms, and syndromes in syphilis, parasyphilitic diseases, pinta, and yaws. Differing opinions of a " unitarian " or " dualistic " concept of treponemal diseases have been expressed by many investigators (Butler and Peterson, 1927 ; Fox, 1938 ; Holcomb, 1945 ; Levaditi, 1930 ; Stannus, 1936 ; Turner, 1937), but it has, in any case, become necessary during the last few decades to re-examine our outlook on treponemal diseases and to recognize that, as a group, they affect a large proportion of the world's population—a larger proportion, perhaps, than are affected by the group of " venereal " diseases. Christian (1938) has rightly pointed out that regions in which yaws and other treponematoses are endemic must be considered as " so many reservoirs of world infection, exactly as foci of malaria and yellow fever ".

The rationale for a world view of treponematoses has been given practical support in recent years by new developments in the study of these diseases. First, it has been found that penicillin is a rapid and effective treponemicidal agent to which the *T. pallidum* of syphilis (sporadic and endemic types), *T. carateum* of pinta, and *T. pertenue* of yaws are vulnerable ; and it has been demonstrated that ambulatory treatment based on repository penicillin preparations is applicable to the control of treponemal diseases in large population groups. Secondly, the discovery of specific immobilizing treponemal antibodies in the serum of infected animals and individuals (Nelson and Mayer, 1949), and the observation that antigenic properties can be assessed on the basis of a close similarity of one single antigen in different strains of treponemes (Khan, 1950), make possible the study of fundamental relationships within the treponematoses group. Thirdly, the World Health Organization (WHO), acting on the advice of its Expert Committee on Venereal Infections and Treponematoses, has initiated an international comparative study of treponemal diseases, from both the clinical and the laboratory viewpoint, in an effort to find a more decisive approach to the control of these diseases.

Experience over the last several decades in Europe, North America, Australia, and limited areas elsewhere has shown that effective treatment of millions of infected persons has contributed to an accelerated decline in the incidence of syphilis. This downward trend has been particularly marked since the second world war. Today, five years after the war, it has been said in some European and North American university clinics that it is extremely difficult to find cases of early infectious syphilis for demonstration purposes.

From a global viewpoint, however, these regional achievements in syphilis control are limited in value. Less than a third of the world's total population of 2·3 billion lives in Europe (including the U.S.S.R.), North America, and Australia ; the greater part lives in the Middle East, Africa, the Pacific area, and South America, in areas which in many instances lag behind in social and economic development as these are understood in the West. In such regions, treponematoses control through extensive application of mass treatment schemes, systematic case-finding, and education has not been practicable. It is in these regions, therefore, that the great infectious reservoirs of syphilis and other treponematoses are found, to which it is logical that our attention should be directed in the future.

The toll taken by venereal and treponemal diseases has economic consequences. Public action to control them might well be initiated with the programmes for the economic development of under-developed areas which are being launched by national and international interests ; for example,

* Paper given by invitation before the Medical Society for the Study of Venereal Diseases, London, 24 November, 1950.

the United Kingdom Commonwealth Development Plan, the United States Point IV Technical Assistance Programme, and the United Nations Programme for Technical Assistance. As international intercourse is thus further stimulated, and communications by sea and air increase in volume and rapidity, the possibility of transferring venereal and treponemal diseases, particularly syphilis, from areas of high prevalence to areas of low prevalence are enhanced. This epidemiological problem may attract more attention from health workers than it has done in the past.

Today, syphilis is more often classed among the communicable diseases. It is no longer considered a " shameful " infection as it was a few decades ago in Europe, North America, Australia, and other areas, although some attention continues to be paid to the particular mode of transmission which gave rise in the West to the designation " venereal " disease. In many other areas, syphilitic disease has remained a " true " communicable disease, being also transmitted by non-sexual contact, through juvenile play, drinking vessels, common eating utensils, and, perhaps, insects. The *juvenile endemic syphilis* of Bosnia (Kogoj and Vuletic, 1939 ; Guthe, 1948) and Inner Mongolia (Jessner and Rossiansky, 1930), the *bejel* of Iraq and Syria (Akrawi, 1949 ; Hasselmann, 1938 ; Hudson, 1937), and the *njovera* of Rhodesia (Willcox, 1949, 1950) represent health problems as real today as the " sibbens " of Britain in the 17th century, the " radesyge " of Norway in the 18th century, and the " spyrocolon " of Greece and Russia in the 19th century. In Yugoslavia, there were, until quite recently, an estimated 100,000 cases of syphilis in the endemic syphilis area in Bosnia alone. In Iraq, approximately a million people are believed to be affected by bejel.

Non-venereal treponemal diseases in man include *yaws* and *pinta*. Approximately 75 per cent. of these infections are acquired in childhood and before the age of 18 is reached. *Pinta* is endemic in Mexico, Venezuela, Ecuador, Colombia, Brazil, and elsewhere in Central America (Fox, 1949 ; Malamos, 1949 ; Saenz and others, 1940 ; Triana, 1949 ; Varela and Avila, 1947 ; Weiss, 1947) where, it is estimated, more than a million cases exist. *Yaws* represents a significant health problem affecting further millions in the humid tropical areas of Central, East, and West Africa, in Middle and South America, in the Far East, and in the Western Pacific (Dwinelle, 1947 ; Gonzalez, 1949 ; LeFevre and others, 1944 ; Montel, 1949). While syphilis prevails as a disease of urban and semi-populated areas, yaws is an incapacitating disease affecting rural populations, reducing work efficiency in agriculture and retarding economic development.

Attempts to secure reliable information concerning the extent of the problem of treponemal diseases on a world-wide basis have revealed that the data available are quite limited. It is important for each area and country to be aware of its treponematoses problem, and all possible encouragement should be given to the inclusion of statistics on infectious syphilis and yaws in national demographic records, but it should be realized that this is not always practicable. Even an approximate estimate is sometimes not available to serve as a basis for planning control programmes. Morbidity and mortality reports and survey data are incomplete or non-existent ; syphilis is among notifiable diseases in only a limited number of countries ; information on yaws, pinta, and bejel is largely sporadic. The quality of data on incidence and mortality varies widely from area to area ; different indices are often applied in different areas ; the frequent absence of distinction between early infectious stages and latent or late manifestations of disease is particularly important ; prevalence often refers to selected population groups ; mortality rates give little information on current problems.

Yet another difficulty is the limitation of serology as applied in syphilis (Guthe and Hume, 1948) and the difficulty in interpreting sero-positivity in tropical and semi-tropical areas, so that false-positive reactions sometimes lead to an exaggerated estimate of its prevalence. The introduction of cardiolipin antigens has helped to increase the accuracy of serological determinations.

In spite of these statistical and serological difficulties, the ubiquity of syphilis is recognized ; the incidence is counted in millions of cases annually, to which should be added millions of cases from bejel, pinta, and yaws in tropical and semi-tropical regions.

Individual and Mass Control of Treponemal Diseases

To the individual patient complete cure not merely control of infectiousness is the *desideratum*. Indeed, it is a natural development that, in parts of the world where the incidence of infectious syphilis is reduced to a minimum, more and more emphasis is placed on the treatment of the individual and less on mass techniques. The addition of penicillin to the therapeutic armamentarium, has completely revolutionized the management of treponemal diseases since this antibiotic was, for the first time, successfully used in syphilis by Mahoney and others (1943), in yaws by Findlay and others (1944), and in bejel by Akrawi (1949). The rapid disappearance of treponemes from the early lesions of sporadic and endemic syphilis, yaws, bejel, and pinta has

been demonstrated repeatedly. Rapid healing of skin and mucous-membrane manifestations and reversal to sero-negativity occur in a great proportion of cases after the completion of penicillin treatment, with or without adjunct or consolidating therapy. To what extent the introduction of penicillin has contributed to the improvement of individual and mass control of treponemal disease is a public-health question widely discussed in those countries where penicillin has become available for general use.

SYPHILIS

Individual Control.—Seven years have now elapsed since Mahoney and others (1943) presented their first preliminary report on the effectiveness of penicillin in the control of early syphilis in the individual. In this comparatively brief period, an enormous amount of information has been accumulated regarding the usefulness of this form of therapy.

Four years ago, one of us (Reynolds, 1946) in an appraisal of this new therapeutic procedure stated :

> Penicillin is effective, but not always completely so. It is, in marked contrast to metal chemotherapy, non-toxic, approaching the ideal in this respect. It is relatively easy to administer, and therapeutically effective amounts can be given in a comparatively brief period of time.

The validity of this early appraisal remains the same today, although with the passage of time additional data which further delineate the proper place of penicillin in the treatment of syphilis have become available. In Table I, we have compared the preliminary results obtained with *amorphous penicillin* with previous methods of treatment; secondary syphilis has been selected in this and the subsequent evaluations since secondary syphilis is less amenable to therapy than sero-negative and sero-positive primary syphilis.

An " ideal " form of therapy from the point of view of effectiveness, toxicity, and convenience of administration has been compared to therapy with amorphous aqueous penicillin (2·4 million Oxford units); the 18-months' arsenic-and-bismuth standard continuous therapy (40 As and 40 Bi); and the 5-days' intravenous drip (1,200 mg. Mapharsen). The two latter have been chosen since they probably represent the extremes in metal chemotherapy in terms of toxicity as well as of convenience of administration. It will be seen that the results (2 years' observation or more) with amorphous penicillin in secondary syphilis are inferior in therapeutic effectiveness, though the convenience of administration is great and the " toxicity " rate extremely low. The therapeutic efficacy is greater with arsenicals, but at the expense of toxicity, the mortality being about 1:200 with the intravenous-drip method and 1:3,000 in the 18-months' therapy. The convenience of administration is considered high in the 5-days' drip treatment as well as with amorphous penicillin (hospitalization), since most patients complete treatment; in the 18-month schedule, some 50 per cent. of patients may complete treatment, with variations from 20 to 80 per cent. depending on the characteristics of the patient populations in different areas and countries and on the follow-up methods used.

These early findings with amorphous penicillin therapy in syphilis indicated a higher proportion of unfavourable results than is now known to be the case. Improvement in penicillin itself by the elimination of the relatively inactive *K* fraction and the subsequent development of *crystalline penicillin G*, the realization that foreshortened schedules of therapy not infrequently increase the number of reinfections (which is an indication of therapeutic success rather than failure), and a growing awareness of the fact that more than a few of the earlier cases were needlessly re-treated as " failures " on inadequate serologic grounds—all these have made penicillin therapy more effective than it first appeared (Moore, 1945, 1950; Rider, 1949). This develop-

TABLE I

COMPARISON OF VARIOUS FORMS OF THERAPY IN SECONDARY SYPHILIS

Therapy	" Ideal "	Arsenicals and Bismuth (Standard continuous 18-month course)	Arsenicals (Mapharsen, 1200 mg. 5-day intravenous drip)	Penicillin (Amorphous aqueous, 2·4 million units)
Therapeutic efficacy*	100·0	91·5	90·0	79·8
Toxicity†	0·0	0·033	0·5	0·001
Convenience of administration‡	100·0	50·0±	96·3	99·8

*Percentage apparent " cures " if full course is given. †Percentage deaths due to treatment. ‡Percentage patients completing full course prescribed.

ment is generally illustrated in Fig. 1, which, again, is based on data for secondary syphilis.

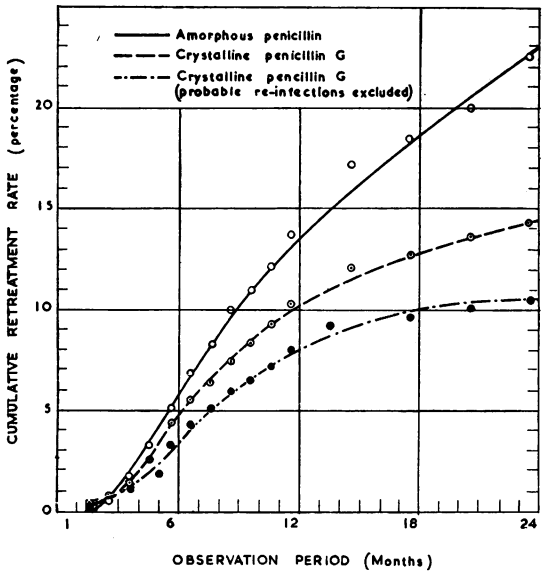

FIG. 1.—Cumulative retreatment rates of patients treated with penicillin (2·4 million U. or more) for secondary syphilis (U.S.P.H.S. data).

It will be seen that when crystalline penicillin G became available, the results improved considerably. The cumulative re-treatment rate was reduced from more than 20 to about 14 per cent. by the end of two years' observation. If the probable reinfections are excluded, the failure rate was approximately 11 per cent.

Because of rapid excretion of the antibiotic, penicillin therapy formerly required hospitalization for repeated injections at frequent intervals. With the development of absorption-delaying preparations, however, ambulatory therapy became feasible. Currently in widest use is a suspension of the slowly absorbed *procaine salt of crystalline penicillin G in oil gelled with 2 per cent. aluminium monostearate* (Buckwalter and Dickison, 1948). With this preparation, now internationally designated PAM, it has been repeatedly demonstrated (Boger and Flippin, 1949 ; Fairbrother and Daber, 1950 ; Kitchen and others, 1949 ; Robinson and others, 1948 ; Thomas and others, 1948 ; Young and others, 1949) that therapeutically effective serum concentrations of penicillin can be maintained for several days after a single injection of 300,000–600,000 units or more. Since there is evidence (Arnold and others, 1949 ; Rein, 1950 ; Thomas, 1949) that a high proportion of treponemal infections can be cured within that period of penicillin action, as judged by the clinical and serological picture more than two years after the therapy, the " one-shot " or " few-shot " form of therapy is rapidly coming within the horizon of practicability.

A great number of treatment schedules with single and multiple injections of PAM are being tried at the present time, and, as PAM is becoming more widely available, one gains the impression that increasing reliance is being placed on the use of this preparation in early syphilis. Preliminary, favourable results have recently been reported by investigators from many countries (Burckhardt, 1950 ; Coutts, 1949 ; Grin, 1950 ; Hellerstrøm, 1949 ; Hermans, 1949 ; Monacelli, 1950 ; Perdrup, 1950 ; Rajam, 1949), adding to the steadily increasing American experience. However, regardless of what type of penicillin preparation is used, the primary requisite is to maintain an effective serum (and tissue) concentration of penicillin for not less than 6 to 8 days. If this is achieved, should the patient not appear for further treatment, or should follow-up treatment not be practicable for other reasons, the physician can have the assurance that he has a 90 per cent. chance of rendering the patient non-infectious and " curing " the early syphilitic infection. This assurance can be obtained with PAM by applying a minimum initial dose of 1·2 million units in one, or 2·4 million units in two, depots (4 and 8 ml. PAM, respectively).

Penicillin crystals of approximately 5 microns in diameter appear to give serum concentrations of longer duration than do preparations of larger particle size (Chandler and others, 1948). This, and perhaps other variables in manufacturing techniques, may account for some dissimilarity in results among investigators who have employed seemingly similar preparations. In comparative studies of series of patients treated in different clinics, and especially in different countries, it is therefore important to define in detail the type of penicillin preparation used.

While it seems to be firmly established that PAM is the preparation of choice, there still remains considerable difference of opinion as to whether adjunct metal therapy should be given. The rationale for giving such concomitant therapy centres in the demonstration by Eagle and others (1946) and Magnuson and Rosenau (1948) of a synergistic action between penicillin and metal chemotherapy. What is seldom realized is that the synergism, as demonstrated in the experimental animal, is between *subcurative* amounts of the drugs, and that there is little evidence of synergism when " adequate " amounts of either preparation are used. The American and European experiences in humans indicate clearly that, when a limited number of injections of arsenic and bismuth are given con-

comitantly with penicillin, there is no evidence of increased therapeutic effectiveness (U.S. Public Health Service data, 1950; Paris Syphilis Seminar, 1950).

There is, in addition, the question of the advisability of "consolidating" penicillin therapy with subsequent metal chemotherapy, administered over a longer period of time. The so-called "double guarantee" thus afforded has been pointed out by several investigators, notably Gougerot and Degos (1950) in France, who prefer prolonged consolidation with bismuth. These investigators are also carrying out studies with PAM alone, as are other European syphilologists (Bolgert and others, 1950; Gaté, 1949; Huriez and Dujardin, 1949; Joulia, 1950; Lepinay, 1950; Pautrier, 1950; Sampaio, 1950; Tommasi, 1950). In the Scandinavian countries, penicillin plus metal chemotherapy has been the generally accepted regimen until the present time (Danbolt and Berdal, 1950; Gundersen, 1950; Hellerstrøm and Hagerman, 1948), although information on small series of patients treated with penicillin alone is also slowly accumulating in that area.

Jefferiss and others, (1950) have abandoned the use of arsenicals, but point to the case-holding value of follow-up courses of bismuth, in addition to its supposed consolidating effect. We have recently had the opportunity of obtaining information from the now considerable experience in England with this form of consolidation therapy. Data have kindly been furnished to us from Dr. McElligott's clinic at St. Mary's Hospital and from Dr. King's clinic at the London Hospital. We hope that this is only the beginning of a clinical, cooperative study among the major clinics in the United Kingdom, and that this development may lead to the establishment of an international clinical cooperative study which WHO may facilitate by obtaining similar material from several other interested countries. In a preliminary analysis, we have compared the data on secondary syphilis with some recent material on PAM from the United States Public Health Service, made available to us by courtesy of Dr. Bauer of the Venereal Disease Division (Table II). All observations are on the basis of a 24 months' follow-up of those who completed treatment.* The observation period is calculated from the time of commencement of the treatment.

It will be seen that the therapeutic efficacy appears to be higher with penicillin plus arsenic and bismuth (5·4 per cent.)† than with PAM with or without consolidating bismuth therapy, as judged on the basis of the cumulative retreatment rate by the end of 24 months. It is emphasized that this cumulative retreatment rate (which excludes re-infections) had risen to 15·5 per cent. by the end of 36 months, although this rate is based on comparatively small figures by the end of the period. At 24 months there is no significant difference in the cumulative rates with PAM alone (14·5 per cent.) and with PAM and bismuth (13·6 per cent.). The convenience of administration—in terms of patients completing treatment—is higher with PAM alone (96·8 per cent.), only 69·8 per cent. of the penicillin/arsenic/bismuth patients completing treatment. One cannot but be impressed by the high number of serious toxic reactions observed in the penicillin/arsenic/bismuth regimen (4·6 per cent.) which compare unfavourably with PAM alone (0·12 per cent.) or with PAM/bismuth (0·9 per cent.). Minor reactions have been excluded in the penicillin/arsenic/bismuth figures, as have 22 serious cases of hepatitis, which, if included, would bring the incidence of serious reactions from intravenous arsenicals to 9·55 per cent.

TABLE II

COMPARATIVE EVALUATION OF PENICILLIN (PAM) ALONE, PENICILLIN PLUS BISMUTH, AND PENICILLIN PLUS NEOARSPHENAMINE AND BISMUTH IN SECONDARY SYPHILIS
(Minimum of 2·4 million units Penicillin)

Therapy	PAM	Penicillin and Bismuth (10)	Penicillin, Neoarsphenamine (10), and Bismuth (10)
Therapeutic efficacy*	14·5	13·6	5·4
Toxicity†	·12	·91	4·67§
Convenience of administration‡	96·8	83·2	69·8

*Cumulative per cent. retreated at 24 months.
†Percentage Serious Reactions.
‡Percentage of Patients completing Course of Therapy.
§Excluding 22 cases of hepatitis. Were these included the percentage of serious reactions would be 9·55.

From this study it may once more be deduced that patients exposed to intravenous arsenic injections, with frequent and serious reactions, are much more apt to become defaulters or to disappear from treatment entirely. The possibly aggravated outcome in syphilis insufficiently treated with arsenicals would, therefore, appear to widen the indication for penicillin therapy in early syphilis.

The effectiveness of PAM is greatest in sero-negative primary syphilis, the apparent cure-rate at the end of two years being approximately 95 per cent.; in sero-positive primary syphilis the cure-rate

* Statistical analysis of this data is based on Iskrant, Bowman, and Donolines "Method No. 1" (Publ. Health Rep. No. 63, 970, 1948).

† This difference is not statistically significant (Swaroop).

is approximately 87 per cent. and in secondary syphilis it is about 85 per cent. with the treatment schedules so far employed.

However, the relative value of consolidation therapy with PAM alone or with PAM/bismuth, has not so far been adequately explored. In one of the first series of cases of secondary syphilis treated with 600,000 units twice weekly for 8 weeks (total dosage 9,600,000 units PAM), the cumulative re-treatment rate by the end of 18 months was approximately 7 per cent. ((U.S.P.H.S.).

The overall chances for control of early syphilis in the individual may thus be slightly less with PAM alone with the schedules so far used, than with some amount of consolidating arsenic/bismuth therapy, because of the slightly higher risk of endogenous reactivation (that is, clinical and serological relapse) and of more frequent re-infections, but the overall chance of cure and control of the disease in the mass of patients is greater since more patients will complete the therapy. There is, in addition, the amenability of failures to re-treatment with penicillin, in the absence of important evidence of penicillin resistance in the treponemes. The problem posed is, therefore, not an absolute one, but is rather a question of the extent to which the physician wishes to expose the patient to the risk of frequent, and sometimes fatal, toxic effects of metal therapy on the one hand (Möller, 1950), or to the slightly higher re-treatment risk with a harmless antibiotic on the other.

One of the features of penicillin therapy has been the marked reduction in numbers of relapses other than those manifested in the skin and mucous membranes. Ocular, hepatic, and early osseous relapses are now rarely observed, and neuro-recurrences are also very rare. The absence of any clinical and laboratory evidence of nervous-system involvement in Mahoney's original patients seven years after penicillin therapy has repeatedly been referred to in the literature. Recently Altshuler and others (1949) re-examined 5,590 out of a series of 30,927 patients (14·8 per cent.) treated for early syphilis with amorphous penicillin alone, during the recent war, and found spinal-fluid abnormalities in less than 0·4 per cent. Johnson (1950) recently reported a comparable percentage in a similar group; and King (1950) found no spinal-fluid evidence of neurosyphilis in a series of cases treated with penicillin and examined at various periods from 6 months to several years after treatment. Thomas and Landy (1950) examined the spinal fluids of 291 out of 689 patients (40·8 per cent.) successfully *re-treated*, for relapse or re-infection, with penicillin alone. None had abnormal spinal-fluid findings when re-examined a year later. Although such initial observations are favourable, considerably longer periods will be required to evaluate the long-term ability of penicillin to prevent central nervous system involvement or cardiovascular damage after adequate or inadequate penicillin therapy.

Finally, a word about prenatal and infantile syphilis. Complete suppression of the disease by treatment of the syphilitic woman was a cherished dream of many investigators as far back as the early 19th century (Mahon and Lamauve, 1804). This dream was brought into the realm of possibility with the introduction of arsenicals and bismuth; with the use of penicillin, it is now a distinct probability. Evidence from several countries indicates that treatment of the syphilitic pregnant woman with penicillin will result in a syphilis-free infant in approximately 95 per cent. of cases (Bundesen and others, 1950; Cross and others, 1949; Emery and others, 1949; Goodwin, 1950; Ingraham, 1951; Morgan, 1949); and there appears also to be general agreement as to the advantages of employing this antibiotic, with or without adjunct therapy, in the treatment of congenital syphilis (Batchelor, 1949; Debré, 1949; Enkvist, 1948, 1950; Nabarro 1949). It has been predicted that congenital syphilis will gradually cease to be a serious medical and public health problem as mother and child health programmes are established. It will continue to be a threat, however, so long as early syphilis remains prevalent among the adult population and systematic sero-examination of pregnant women is not generally applied.

National Control Programmes.—The question has been asked if—or to what extent—the introduction of penicillin has contributed to the decline of syphilis in Europe, North America, and elsewhere since the end of World War II. It is recognized by all investigators that wherever some reliable measure of trends has been available, there has been a decline in the incidence of syphilis, after every major war, with a return to normal economic and social conditions and with the stabilization of the population. This "natural" decline in the incidence of the disease may be accelerated by systematic case-finding and educational efforts and through adequate facilities for treatment.

Fairly reliable data are available in the Scandinavian countries for periods covering both world wars, and it may therefore be of interest to consider the syphilis epidemics which occurred there during those periods.

Fig. 2 (opposite) shows that in the second world war the incidence of early syphilis per 10,000 population did not reach the level of the first. After 1919 there was a sharp initial drop, followed by a

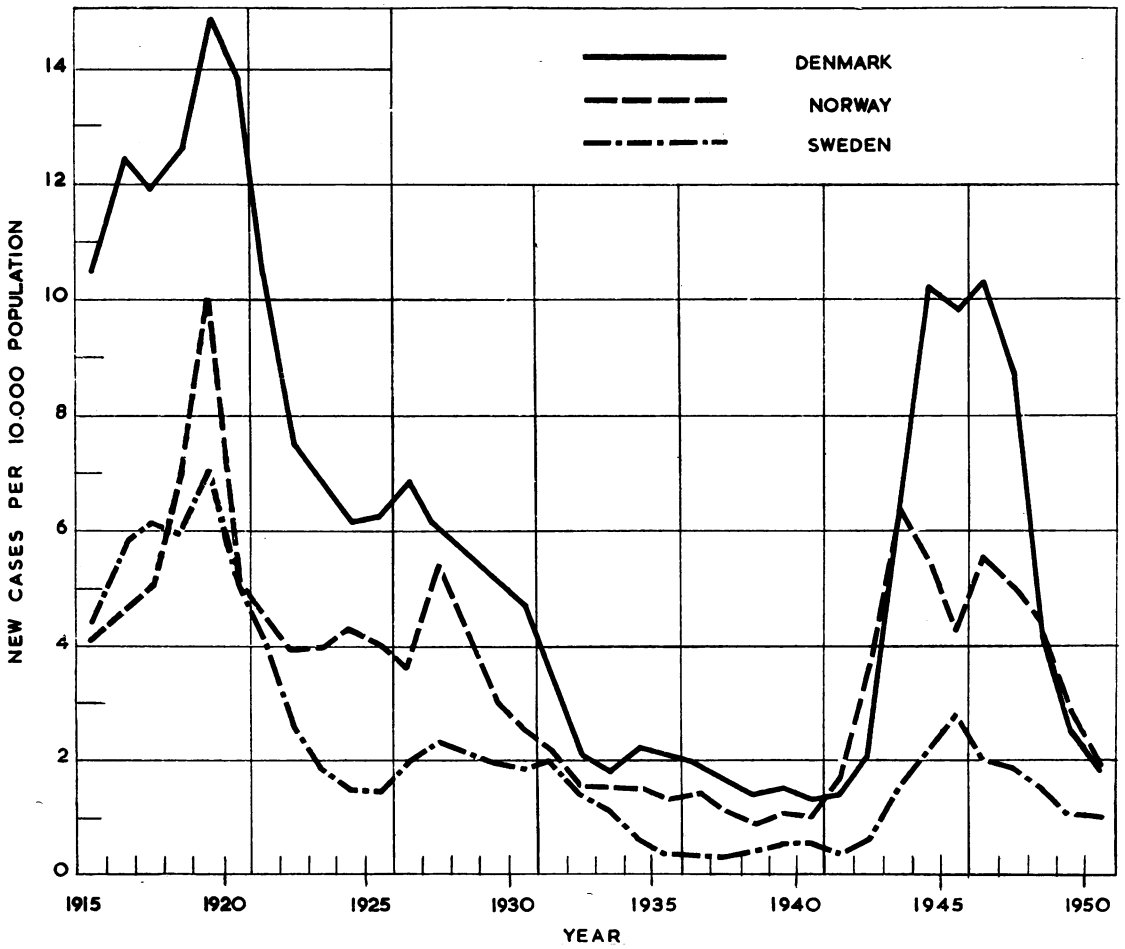

FIG. 2.—New cases of acquired syphilis, 1915–1950. Rates per 10,000 population, annual basis: Denmark, Norway, Sweden.

slow intermittent secondary downward trend, the lowest incidence being reached in the years 1938 to 1939. The entire process extended over a period of 15 to 20 years. During the second world war, there was an acute outbreak of syphilis in occupied Denmark and Norway and a marked upward trend in neutral Sweden. Secondary post-war peaks, probably resulting from return of military personnel, civilians, and displaced persons were observed in Denmark and Norway. Later the same initial acute drop in incidence was observed in Denmark and Norway as that which followed the first world war. However, this drop persists and continues down towards pre-war levels without the slow secondary drawn-out process which formerly took almost two decades. There has been a *rapid* decline almost to pre-war levels over a period of four to five years.

Penicillin was not available for syphilis treatment in the Scandinavian countries to any appreciable extent before 1947-1948, but has been applied since then on an increasing scale as *traitement d'attaque*.

In Poland, syphilis was epidemic during the second world war. A large-scale venereal-disease control programme was initiated in 1947, when the incidence of early syphilis, as determined by fairly reliable mass surveys, was approximately 14 per 10,000 population. This programme included all known techniques such as mass serological examination of a great part of the people, epidemiological contact work, case-holding enforced by legislation, and rehabilitation of prostitutes in prophylactoria similar to those of the U.S.S.R. Treatment was based on penicillin initially with some adjunct therapy. The incidence declined rapidly and, by the end of 1949, was estimated to be at about the same level as that of the Scandinavian countries.

The outstanding feature of the Polish campaign was the rapidity with which early syphilis was brought under control.

In post-war Germany, where military occupation and population instability might have tended to maintain the incidence of venereal diseases at a relatively high level for some time, a continued decrease in early syphilis has been experienced after a maximum incidence in 1947 in all three Western occupied zones (Guthe, 1949). In Western Germany, penicillin was not available for the treatment of venereal diseases in the civilian population before early 1949. The downward trend already noted before this has continued rapidly, with little other change in the trend characteristics.

Similar rapid declines in the incidence of early syphilis have also been observed in Finland, France, Italy, and Greece.

In 1949, the World Health Organization established an International Syphilis Study Commission to investigate recent methods of syphilis control in the U.S.A. where a continuing decline in the incidence of early infections has taken place since 1947. The Commission concluded that the anti-syphilis drug on which control programmes relied was not a decisive factor, that availability of adequate treatment and particularly active case-finding were more important. The Commission pointed out, however, that the establishment of a practical degree of venereal-disease control was facilitated by rapid and effective therapy; herein probably lies the great value of penicillin from a public health point of view.

Some investigators have considered penicillin to be a major and decisive factor in controlling infectious syphilis in certain areas of the U.S.A. A point which may deserve attention in this connexion is the increasing practice in the U.S.A. of giving abortive penicillin treatment to symptomless contacts who have been exposed to infectious lesions. The epidemiological advantages of this procedure have been clearly established by Alexander and others (1949), who demonstrated that almost 100 per cent. protection was afforded in a large series of recognized contacts thus treated, whereas 62 per cent. of untreated contacts in a control series developed lesions. In some areas the prophylactic administration of PAM to persons habitually exposed to venereal contagion has given interesting results (Samame, 1950). Finally, there is the increasing use and misuse of oral penicillin for all sorts of minor or major ailments, with or without the physician's blessing, and the possible effect which this may have on incubating syphilis, preventing the disease or modifying its course. Whether such practices are good from a medical and public health view-point is a question still under discussion.

Mass Campaigns.—Those based on penicillin therapy concentrate effort on reducing the reservoir of infectious syphilis to a minimum within a short period. An example of interest is the campaign against endemic syphilis now being conducted in Yugoslavia. It will be recalled that the particular problem of endemic syphilis in Bosnia-Herzegovina attracted international interest even before 1930, as did the endemic syphilis of the Burgas area in Bulgaria. Considerable academic argument then ensued between two different schools of thought in syphilology. One (Glück, 1922) was of the opinion that the endemic syphilis found in the geographically, religiously, socially, and economically delimited area of Bosnia-Herzegovina, comprising a population of about two million Moslems, differed from "sporadic" syphilis in not exhibiting primary lesions and not giving rise to late systemic manifestations, including neurosyphilis; the other (Kogoj and Vuletic, 1939) contended that there was no difference in the selection of the organs attacked, that primary lesions occurred, and that cardio-vascular and other systemic manifestations existed. The Public Health Institute in Zagreb, in co-operation with the Rockefeller Foundation, investigated this problem through a field team of internationally recognized experts. It was shown that endemic syphilis only differed from ordinary sporadic syphilis in its mode of spread. Besides being congenitally acquired, the disease was, in the great majority of cases, transmitted by non-sexual contact in infants and children, and spread in and between families as an ordinary communicable disease. Primary lesions occurred in the oral region, and all systemic manifestations were observed in a large sample of the population examined. Efforts to control the disease were not successful with the prolonged treatment, based on arsenicals and bismuth.

After the second world war, sample surveys of the area indicated that the total number of persons infected might be approximately 120,000 (about 6 per cent. of the population). Prevalence varied from 1·3 to 30·7 per cent.; in small compact settlements (villages) sero-positivity was sometimes found to be much higher. The typical age distribution of sero-positivity was as follows:

Age Groups	Positive Meinicke & Kahn %
0–5	0·6
6–10	6·0
11–15	8·9
16–18	13·4

In 1948, a long-term plan for the control of endemic syphilis and for its elimination as a health

problem in Bosnia-Herzegovina was instituted; this was followed by a similar plan for Serbia, where syphilis is also highly prevalent. The plans extend over a period of five years. The programme started late in 1948 and gained momentum throughout 1949, during which time 292,000 persons were examined; an additional 800,000 are to be examined in 1950 and 1951. Field laboratories were established, and early in 1950 more than fifty mobile field-treatment teams were in action. Approximately 10 per cent. (30,404 cases) of those examined were diagnosed as syphilitic and were treated. The treatment schedule employed was 4·8 million units of PAM, with bismuth given as adjunct therapy in some areas.

In addition to the systematic examinations, special epidemiological studies have been undertaken, with emphasis on uniformity of procedure and quantitation of serological technique with cardiolipin antigens. One such study merits particular mention:

An isolated village with little or no migration had a prevalence of syphilis of 67 per cent. of the population, of which about half the cases were in the secondary or early latent stages. There were one or more infected persons in half of the families. The population was divided into two groups, one of which received 600,000 units of PAM at 2-day intervals, with a total of 3,600,000 units, while the other half received the same amount of PAM plus 10 ml. 10 per cent. bismuth subsalicylate. Re-examination of the entire village population at the end of 10 months revealed no significant difference between the two groups. The results of the re-examination are shown in Table III, which shows that, after all cases of syphilis in this village had been treated, 13 per cent. were sero-negative by the end of two, and 68·3 per cent. by the end of 10 months' observation; 71·5 per cent. of the early cases were sero-negative at the end of 10 months.

The medical officer in charge of the programme (Grin, 1950), an authority on endemic syphilis, comments as follows:

Although the results obtained do not allow at this moment any definite conclusions in regard to the cure of syphilis, nevertheless the clinical and serological results are very satisfactory and allow two significant epidemiological statements.

(*a*) In the described village we have been able to examine 100 per cent. of the population and to treat without exception all infected cases. In this way it was possible to eliminate the local reservoirs of infection and in view of a very low migration of the population in this area, the opportunity to contract syphilis from other foci in the region was of no importance. With regard to such circumstances the epidemiological effect was evident; the control examination of the healthy members of infected families showed that still ten months after treatment of their relatives in no case occurred a new genital or extra-genital infection and that also all non-infected families remained so.

(*b*) The second very important conclusion is the fact that in our described village now, ten months after treatment, not one failure (relapse or re-infection) was observed.

TABLE III

ENDEMIC SYPHILIS CAMPAIGN, BOSNIA, YUGOSLAVIA, 1950

I. Serological outcome in village after two and ten months' observation*

Findings	Observation Period			
	Two months		Ten months	
	Cases	%	Cases	%
Sero-negative	29	13	151	68·3
Serological improvement	93	42	70	31·7
No significant serological change	99	45	0	—
Clinical or serological relapse	0	—	0	—

II. Serological outcome according to stage of disease at ten months' observation

Findings	Early Syphilis		Late Syphilis	
	Cases	%	Cases	%
Sero-negative	158	71·5	108	48·8
Marked reduction in titre	63	28·5	—	—
Serological improvement	—	—	113	51·2

*Village population 330 (all examined). Syphilis cases diagnosed 221.

These results emphasize the practicability of the approach and the immediate contribution which can be made to public health by syphilis-control programmes based on penicillin therapy, if such programmes are well planned and executed. The long-term results of the Yugoslav action are awaited with interest in several countries. The WHO Expert Committee on Venereal Infections and Treponematoses (World Health Organization: Technical Report Series, No. 13, 1950), and WHO Technical Advisers (Clark, 1950; Guthe, 1948), who have made several field studies at the request of the Yugoslav Health Administration, have pointed out the international as well as the national importance of the programme now in progress.

BEJEL AND NJOVERA

Since Hudson (1928) originally described bejel, much interest has been attached to the epidemiology and symptomatology of this treponemal disease. Akrawi (1949), in addition to his recent review of the state of our knowledge of the disease, showed

that " primary " lesions could be produced experimentally by inoculation to the human lip. (However, the " natural " early manifestations observed in bejel are oral mucous membrane lesions of a secondary type ; and the late destructive manifestations in bejel are similar to syphilitic gumma.) It has also been demonstrated (Akrawi 1949) that in previous sero-negative individuals the sole response of the human host could be sero-positivity resulting from the contact by oral mucous membranes with infectious bejel material suspended in water. This sub-clinical manifestation is of collateral interest in view of current discussions on the occurrence of asymptomatic re-infections in syphilis. In bejel the existence of congenital and late systemic manifestations have been described, but further detailed information would be desirable.

Descriptions almost identical to the " usual " manifestations of bejel have been given of " njovera" (Willcox, 1949) ; this investigator studied njovera in Rhodesia, as well as bejel in Iraq. He is of the opinion that these conditions are the same—extravenereally acquired syphilis—and points out that similar clinical conditions are also found in the Zambesi Valley and in Bechuanaland.

Akrawi (1949) demonstrated the susceptibility of the *T. pallidum* of bejel to penicillin. In an initial series of early bejel patients in Baghdad, treponemes disappeared in less than 48 hours. Lesions also disappeared rapidly, as in early syphilis and yaws. Early bejel cases observed for three months showed progressive decline in serological titre (Kahn, Rein-Bossack, cardiolipin), and complete reversal to negative resulted in several cases at the end of this observation period. The treatment schedule employed was one single injection of PAM 1,200,000 U. Other schedules are being investigated.

Bejel is widespread in Iraq, particularly among the nomadic and semi-nomadic tribes of the Euphrates and Tigris area. About four-fifths of the persons with infectious lesions are under 18 years or are women of child-bearing age. The Iraq Health Administration, in cooperation with the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF), has recently launched a large-scale programme against the disease, aiming at the control of the infectious reservoir through a mass case-finding and treatment campaign. During the first period (1950–51) this programme is scheduled to reach some 75,000 infectious cases. Activities will be carried out under difficult desert or semi-desert conditions, by self-supporting field units. After the initial attack, the Iraq Health Administration aims to expand its present facilities for follow-up and future control of the disease.

YAWS

Early in 1944 the susceptibility of the *T. pertenue* to penicillin was reported by a number of investigators (Da Cunha and others, 1944 ; Findlay and others, 1944 ; Lofgren, 1944 ; Whitehill and Austrian, 1944). Rapid healing of the acute lesions in primary and secondary yaws within 8 to 10 days was observed. These early clinical observations have been subsequently confirmed in large series of patients (Dwinelle and others, 1946 ; Hill and others, 1946 ; Rein and others, 1949) in pilot studies in Haiti. Rein and others (1949) compared several treatment schedules in a series of 787 patients, of whom 65·5 per cent. were re-examined clinically and serologically at the end of one year. The results of the penicillin treatment were excellent, 95 to 98 per cent. of the patients being clinically

TABLE IV

SEROLOGIC OUTCOME IN 787 PATIENTS WITH EARLY YAWS TREATED WITH PENICILLIN, ONE YEAR'S OBSERVATION
(Quantitative Kahn Technique)

Treatment Schedule Penicillin in beeswax oil	Serologic Outcome								Total Number
	Cure		Improvement		Cure and improvement	Fastness	Relapse	Fastness plus Relapse	
	Cases	%	Cases	%	Total %	Cases	Cases	Total %	
1·2 mill/Units in 4 days	115	36·8	173	55·4	92·2	21	3	7·7	312
1·2 mill/Units in 2 days	122	38·9	163	51·9	90·8	26	3	9·3	314
2·4 mill/Units in 4 days	79	49·0	73	45·3	94·3	8	1	5·6	161
Total	316	—	409	—	—	55	7	—	787

TABLE IVA

REGROUPING OF OBSERVATIONS IN SAME PATIENTS

Total Cases	Serologic Cure		Serologic improvement, Fastness, or Relapse	
	Cases	%	Cases	%
787	316	40·1	471	59·9

" cured " or improved, and these results were better than those previously obtained with arsenic and bismuth. Furthermore, penicillin could be administered without any fear of serious untoward reactions.

In the past there has been considerable uncertainty as to the nature of sero-reactions in yaws. It has been stated that sero-reactions are, at the most, a guide to treatment rather than a test of permanent cure. It appears that true quantitation of serological techniques has not been employed in most of the yaws studies so far carried out. Apted and others (1948) used a standard qualitative Kahn reaction in Sierre Leone and found it difficult to interpret the results. Hill and others (1946) did not use quantitative serological techniques in West Africa in one of the early penicillin experiences in yaws. The Jamaica Yaws Commission (1933–1936) found that the Wassermann reaction reversed to negative in more than 50 per cent. of cases over a period of two and a half years. Da Cunha and others (1944), on the other hand, observed a rapid reversal of the Wassermann reaction in only a limited number of cases.

Table IV (opposite) shows the observations made by Rein and others (1949) in Haiti in 787 patients, re-examined with quantitative serological technique by the end of one year, after penicillin therapy using three different schedules.

Serologic " cure " or improvement was observed in from 90·8 to 94·3 per cent. of cases. If only negativization of sero tests is used as the criterion for evaluating the serological effectiveness of a treponemocidal agent in studies of this kind, the " outcome " might appear somewhat different. This is illustrated in Table IVA by presenting the same material in a different way. Here it appears that in only 40·1 per cent. of the cases will a favourable serologic outcome be indicated if negativity solely is recorded, the results thus being open to the interpretation that the serological response to penicillin treatment in yaws is extremely slow.

It will be recalled that, while the initial lesions in yaws are roughly analogous to those in syphilis, stages and time relationships in yaws are not so sharply delimited. The generalized secondary " framboeside " of the skin and the lesions of the joints and bones (which have been particularly studied by Hackett, 1946) may appear a few weeks after the initial lesion and can persist for years in the absence of treatment with intermittent and relapsing periods. Tissue destruction takes place earlier and is a more constant feature in yaws than in syphilis.

The immediate and alleviating effect of penicillin (PAM) in early yaws is better illustrated in pictures than by figures. Some cases of early yaws before and after treatment with PAM are shown in Figs 3 to 10.

The first effort made to carry out a community-wide yaws control programme based on penicillin therapy apparently was made by Hill and others (1946) in West Africa. In two small villages no

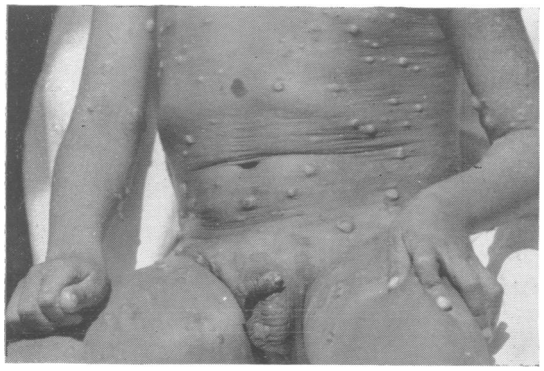

FIG. 3.—Six-year-old male. Initial lesion one year ago, now scar on ankle. Papillomatous framboesides over neck, condylomatous and papular framboesides over trunk and limbs.

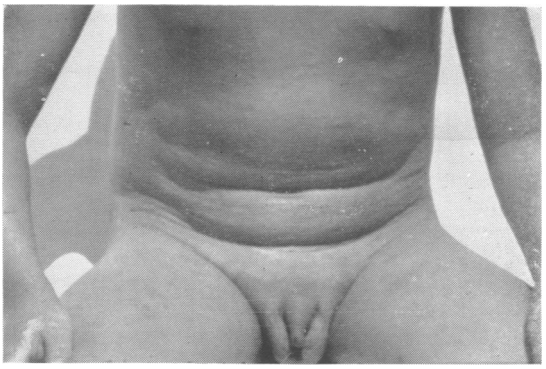

FIG. 4.—Same patient three weeks after first injection. Lesions disappeared. Follow-up after three months showed no clinical signs of disease. Sustained cure, no sign of relapse.

Treatment: 600,000 units PAM × 2, at one week's interval. Total dosage 1,200,000 units PAM i.m.

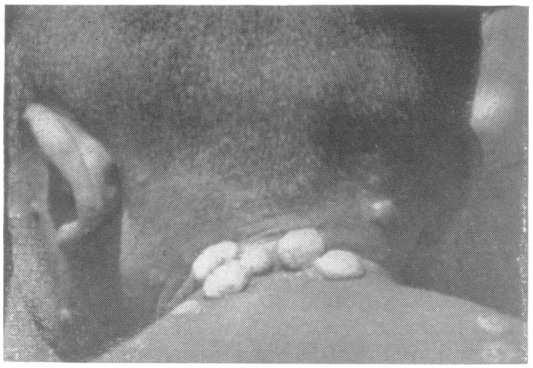

FIG. 5.—Papillomatous framboesides of neck of same patient as shown in Figs. 3 and 4, before treatment.

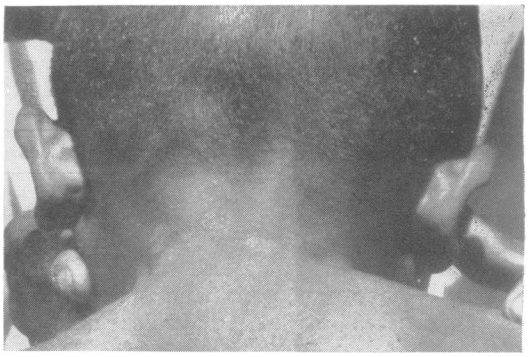

FIG. 6.—Same patient 3 weeks after first injection. Sustained cure, no signs of relapse 3 months later.

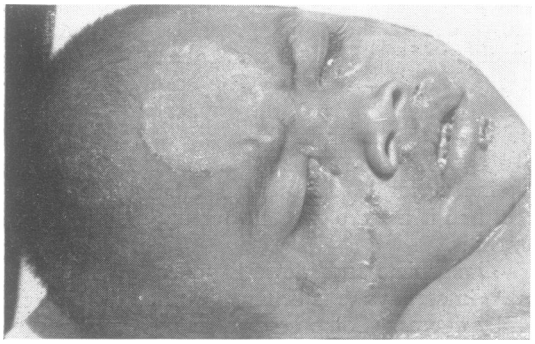

FIG. 7.—Seven-year-old male. Initial framboeside on ankle 3 months ago. Circinate framboeside on face; desquamative and papular framboeside on back and bilateral ulcerative plantar lesions. Face shows circinate areas surrounded by a confluence of papules.

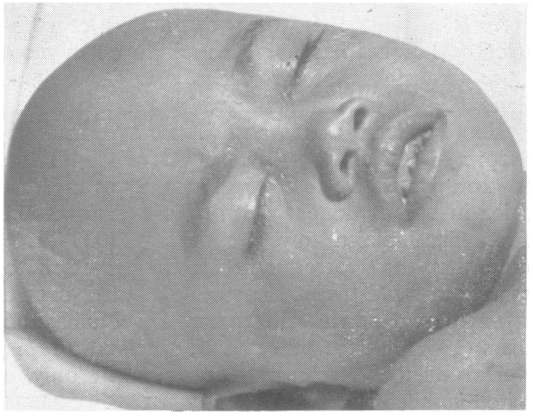

FIG. 8.—Same patient two weeks after first injection. Follow-up after 3 months.

Treatment: 600,000 units of PAM × 2, at one week's interval. Total dosage 1,200,000 units of PAM, i.m.

case of primary or secondary yaws appeared during a 5-month follow-up period after all early infective cases had been promptly treated. The use of penicillin as a public health measure for the control of yaws has also been demonstrated in the Pacific Island groups of Truk (Arje, 1947).

Having studied the various experiences in treponematoses control in different parts of the world, the WHO Expert Committee on Venereal Infections and Treponematoses recommended late in 1949 (World Health Organization: Technical Report Series No. 13, 1950) that a mass campaign against yaws in the island of Haiti would be of the greatest interest, since available techniques would need to be tried on a large scale. In so doing the Committee was no doubt mindful of the efforts of the past, and of the experience with arsenicals and bismuth in the yaws programme in Jamaica in 1933–1936 (Jamaica Yaws Commission, 1936) and in the campaigns in the Dutch East Indies. In these previous efforts, initially encouraging gains were lost for lack of adequate follow-up measures and long-term control. The results of a similar treponematoses campaign relying on bismuth and acetarsol administered intramuscularly carried out by Harding (1949) in a peasant population of 276,000 in Eastern Sierre Leone are illustrated in Table V, from which some extremely important conclusions can be drawn. First, that there was a considerable reduction in infectious yaws after the initial mass diagnosis and treatment. Secondly, that when this was followed by the establishment of permanent treatment facilities, the incidence fell from about 6 to 1·8 per cent. over a period of several years (1942–1945). Thirdly, that when home-visiting was added, no infectious cases of yaws were found in several

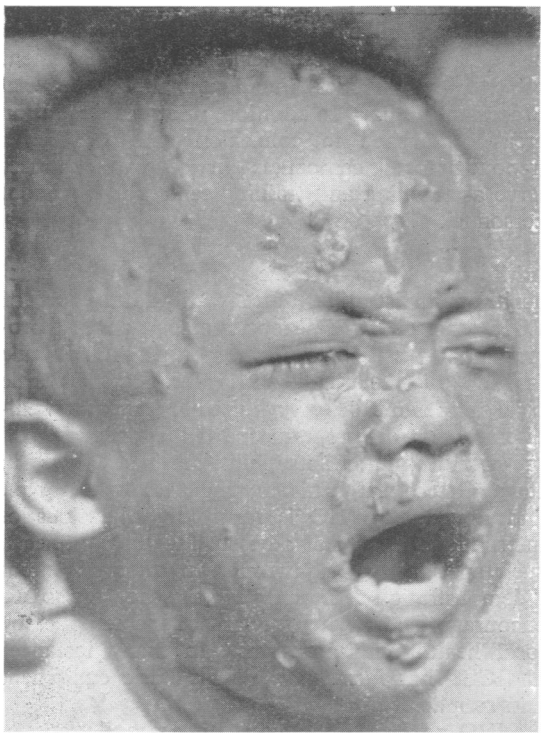

FIG. 9.—Two-year-old male. Initial lesion on ankle two months ago. Generalized papillomatous, circinate, and ulcerative plantar lesions. Face shows papillomatous and circinate framboeside.

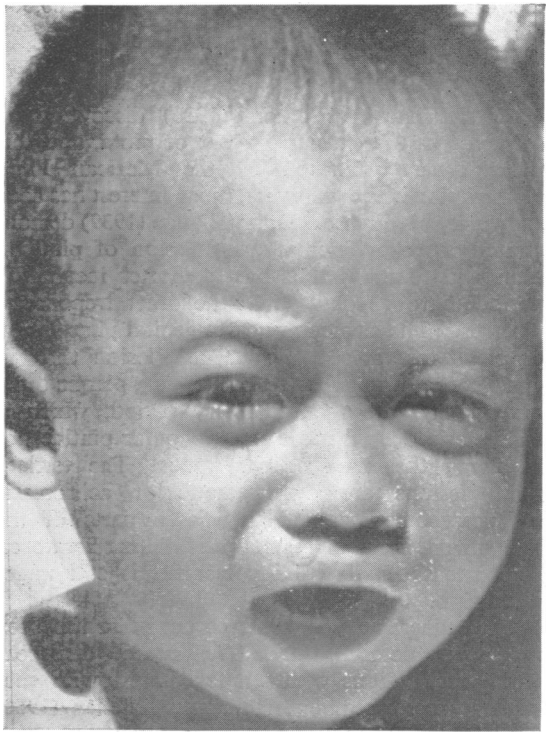

FIG. 10.—Same patient one month after first injection. Follow-up after 3 months showed sustained cure, no sign of relapse.

Treatment: 600,000 units of PAM at one week's interval. Total dosage 1,200,000 units PAM.

population samples of 1,500 to 1,700 people. Fourthly, that when treatment facilities were withdrawn (1943), the incidence of yaws rose (1945) to half its original level. From this experience the necessity for establishing adequate, permanent, control machinery to consolidate gains becomes clear.

TABLE V

OUTCOME* OF YAWS CAMPAIGNS IN SIERRA LEONE, 1941–46
(From Harding, 1949)

Method	1941	1942	1943	1944	1945	1946
Mass treatment only ..	13·7	5·8	—	7·5	—	—
Mass treatment plus permanent treatment facilities	—	5·8	—	3·0	1·8	—
Mass treatment and permanent facilities plus home visits	—	—	—	3·4	0·6	0

*All rates are expressed as percentage prevalence of infectious yaws among sample population groups.

The Haiti programme was initiated in July, 1950. In a total population of some 3,000,000 people, the prevalence of yaws was estimated at about 17 per cent., corresponding to about 500,000 cases, the prevalence ranging from 0·5 per cent. or lower in semi-urban areas to 60 per cent. or more in the Marbial Valley district. Up to the end of October, in the 336 communities so far screened, a total of 111,557 persons had been treated, of which 57,598 had infectious yaws.

A similar large-scale campaign has been launched in Indonesia, with the combined efforts of the Indonesian Health Administration, WHO, and UNICEF; programmes have been started in the areas of Djakarta and Jogjakarta. Surveys carried out in 1935–1940 showed a prevalence of yaws of 6 per cent. in half a million people examined, but present studies indicate a higher percentage. The immediate target in this programme is some three million people, with expansion over the next three and a half years. Ten mobile teams are at present at work in the initial areas. Since the inception of

the campaign in June, 1950, more than 60,000 persons have been examined.

PINTA

Since Saenz and others (1938) discovered *T. carateum* as the causative agent of pinta, and this finding was confirmed by the Mexican Pinta Commission in the same year, much interest has been shown in this disease. Leon y Blanco (1939) demonstrated the experimental transmission of pinta in man and found that it has a shorter incubation period (5 to 12 days) than the other treponemal diseases. The elementary extra-genital pinta lesion develops fast into a chancre-like lesion through coalescence of papules. The resulting plaque often persists far into the secondary period, which is characterized by a roseolar or papular pintide not involving the mucous membranes. The tertiary pinta lesions are dyschromatic or achromatic plaques, sometimes affecting large parts of the integument, including plantar and palmar keratoses. The extent of visceral involvement is still under discussion.

The vulnerability of pinta to penicillin has been repeatedly demonstrated. Treponemes disappear from early lesions within a few hours, with subsequent rapid healing. Rein and Kitchen (1950) have recently completed a one-year follow-up examination in 665 pinta patients treated with PAM by different schedules. These excellent clinical and serological results have not yet been published.

Role of the World Health Organization

One of the objectives laid down in the Constitution of the World Health Organization is to :

> stimulate and advance work for the control of epidemic, endemic, and other diseases.

The World Health Organization selected venereal infections and treponematoses as one of several priority activities within its health programme, largely because of the technical advancements in this field over the last few years. Some of the methods by which WHO has had the privilege of " stimulating and advancing " health activities relating to these diseases are summarized below.

Professional Training and Education.—Fellowships for post-graduate studies and travel grants for advanced studies abroad have been awarded by WHO to nationals of many countries. In 1949 and 1950 a total of 446 fellowships was awarded, of which 63 were in the field of venereal and treponemal infections including the laboratory aspects of these diseases. Many fellow-physicians have been received in this country under the auspices of the Ministry of Health in Great Britain.

In recognizing the great need for training facilities, particularly in less developed areas, WHO has encouraged the establishment or development of training facilities in Guatemala, Venezuela, Brazil, and India. In addition, pilot demonstration areas established in connexion with the larger treponematoses campaigns in several countries serve as teaching and training centres for national personnel.

Advisory Services.—At the request of the national health administrations, and with the support of WHO and UNICEF, treponematosis-control programmes have been established on a national scale in Indonesia, Thailand, and Haiti. A large-scale bejel campaign is being organized in Iraq. Venereal-disease control programmes, with emphasis on pre-natal and infantile syphilis, are being set up in Italy, Greece, Afghanistan, India, Burma, Egypt, and Ecuador. WHO is furnishing a nucleus of international technical advisers for these projects, such specialists being withdrawn after an initial " demonstration " period of a year or so to encourage the carrying forward of the activities by local health administrations. In many instances UNICEF has furnished valuable basic equipment and supplies.

WHO advisers in venereal disease and treponematoses are attached to the WHO Regional Offices for Europe, the Eastern Mediterranean, South-East Asia and the Americas, to ensure co-ordination of the work. Temporary expert consultants of many nationalities are called upon for field studies.

Plans are under consideration in India and elsewhere for the establishment, with the international support of UNICEF and WHO, of penicillin and cardiolipin production facilities in South-East Asia and the Eastern Mediterranean.

The administration of the International Brussels Agreement relating to the venereal-disease treatment of seafarers also comes within the province of the advisory services. On the basis of a decision of the First World Health Assembly, a revised international list of venereal-disease treatment centres has recently been published, and the new international treatment booklet for seafarers is now available.

WHO Expert Committees and Research.—To advise the World Health Organization on its anti-venereal disease activities, an Expert Committee on Venereal Infections and Treponematoses has been established, in addition to a panel of specialists drawn from all member countries. A special advisory group on serology and laboratory aspects has also been appointed. The reports of these

committees have guided the development of the WHO programme.

In 1950 to facilitate the exchange of scientific information on particular questions, WHO organized as part of its European programme, two international symposia on recent advances in syphilis—one in Helsinki and one in Paris—in which experts from nineteen countries participated.

Recent scientific advances, notably the identification of treponemal antibodies by the immobilization technique, have given WHO the opportunity of stimulating basic research into the biological and immunological relationships among the causative agents of syphilis, yaws, bejel, and pinta in man and animals (WHO document VD/23, 1949). Several treponematoses projects supported by WHO in different parts of the world now contribute strains of different treponemes for comparative investigation, to a central international treponematoses reference centre, Department of Bacteriology, Johns Hopkins University, under Dr. T. Turner, where all strains are studied. Such fundamental research could contribute to our present limited understanding of the immunology and other factors in treponemal diseases—individually and collectively. This international treponematoses study was started in 1950 under the guidance of the expert committee.

Other laboratory activities for the evaluation of sero-test performance and standardization in syphilis are under way, including the possible organization of an international serological laboratory conference, patterned on the laboratory conferences of the Health Section of the League of Nations. The selection of a limited number of outstanding laboratories in different regions as antigen- and sera-control reference-centres is envisaged. It is also expected that international standards for cardiolipin and purified lecithin will be established in 1951.

It is hoped that these remarks may contribute to a further understanding of the WHO activities as they relate to venereal and treponemal diseases, an account of which has recently been published in the British Medical Press (Biraud, 1950; Chisholm, 1950; Eliot, 1950; Howard-Jones, 1950; Stocks, 1950).

Discussion

Several significant technical advances over the past few years indicate the need for a revaluation of the principles and methods of individual and mass control of treponemal diseases. The advent of penicillin-therapy, the introduction of cardiolipin-lecithin antigens in serodiagnosis, and the demonstration of treponemal immobilizing antibodies are the main developments in our ability to cope with the problem of treponematoses.

The common vulnerability of *T. pallidum*, *T. pertenue*, and *T. carateum* to the action of penicillin, and the availability of long-acting repository preparations, will enable us to break the infectious cycle of treponemal diseases in the individual as well as in mass-treatment projects. To the individual, the effectiveness of penicillin, its freedom from serious by-effects, and the ease of its administration represent a significant advance over previous methods of treatment. In mass-treatment activities, penicillin therapy brings brighter prospects for a reduction of the reservoir of infection and, ultimately perhaps, the elimination of major foci.

Harrison (1949) has admirably described the development from "chaos to order" in the management of syphilis and other venereal infections in "half a life time". He points out that these diseases have become the most "manageable of all serious diseases" and forecasts that, with the availability of penicillin therapy, they will become a minor public health problem in times of peace. Moore, (1950) on the other hand, believes that the control of syphilis is not yet in sight in any country, or on an international scale, and that the prospects for it are dim with present scientific methods. He suggests that "mass immunization, if this can be developed through further medical research, is a more promising approach" once the *T. pallidum* has been successfully grown on artificial media. While fundamental research into immunity factors should be encouraged, it is difficult to envisage the practical machinery whereby immunization could be applied on a mass scale in a world where available immunization against some of the more fatal diseases, like smallpox or cholera, has not yet reached a similar level.

The impracticability of seeking a vaccine which would be effective has also been pointed out by Thomas (1949) and by Rein and Kostant (1949). As judged from the immunity obtained in acquired infections, 6 months to 2 years may be required to effect adequate protection in humans. If and when protection is established, only partial immunity may result, i.e. chancre immunity may be established which may be insufficient to prevent asymptomatic re-infection. Again, if the degree of immunity were to be judged on the basis of skin tests or serologic reactions, the resulting problems in indications for syphilotherapy might indeed be complex. Moralistic arguments against syphilis vaccination would undoubtedly arise in some countries, rendering a universal acceptance of artificial immunization against syphilis extremely difficult.

Therefore, until immunization is within our practical and administrative grasp, it would seem pertinent to foster the widest possible application of

present knowledge in each country and internationally, so as to obtain in the individual and in the mass of patients a practical degree of syphilis control. With obvious modifications, similar considerations apply to the other treponemal diseases of bejel, yaws, and pinta : in the absence of important evidence of penicillin resistance in treponemes, the widest possible use of present methods could contribute towards the reduction—and perhaps in some areas to the elimination—of important reservoirs of treponemal infections.

The simplification of therapy of treponemal diseases has quite outstripped the availability of diagnostic and treatment facilities in the less developed areas of the world, where the larger reservoirs of these diseases, as well as of ill-classified and non-defined tropical lesions, are found. Rather than deny the benefit of treatment to these masses pending the refinement of diagnostic methods, modern treatment might be applied in advance of such aids through mobile teams and trained auxiliary personnel in well-organized, large-scale campaigns. " Single-shot " or " few-shot " treatment with PAM has been suggested as a practical basis for this approach in Africa (Willcox, 1950), in South America (Levitan, 1950), in the Western Pacific (Hill and others, 1950), and in South-East Asia (Huggins, 1950). This statement should not prejudice the application of additional penicillin and other therapy as local circumstances and administrative and other considerations may dictate.

Practical experience shows that the primary goal in mass campaigns should be the reduction to a minimum, or, if possible, the elimination, of infectious cases, with subsequent establishment and maintenance of treatment facilities and of secondary measures aiming at the control of relapses, re-infections, and re-introduction of the disease. It has been shown that these measures are most effective when they include health education and home visits by special attendants, nurses, etc., to seek out patients and their contacts and to direct them to treatment. The value and importance of such consolidation in a mass programme—without which the initial effort will have been in vain—has been admirably stressed by Harding (1949) in yaws campaigns.

These experiences must, however, be viewed in the light of results obtained in previous decades when such an approach to control of yaws or syphilis was impracticable. In highly organized areas such as the United States or the Scandinavian and other European countries, the reduction of infectious syphilis to its current low level, for example, has taken place by gradual steps over a period of over 20 to 30 years, and has accompanied general social and economic progress ; the decline was accelerated by the emphasis placed on the disease in the general health programme, mainly through the availability of free treatment and through case-finding and educational efforts. This downward trend of syphilis was interrupted by a sharp increase in infections during two major world wars ; but, over a long period, a practical degree of syphilis control has been achieved.

The acute reduction or elimination of infectious cases of treponemal disease in sizeable areas may involve certain dangers. Thus Harding (1949) points to the increased susceptibility to syphilis in population groups where yaws was prevalent before a mass control programme.

The health education aspects of the mass penicillin treatment of yaws and syphilis in hyper-endemic areas may have far-reaching implications. On the one hand, there is the immediate and impressive alleviation of symptoms and incapacity ; on the other hand, there might develop a general demand for further health and other measures which could not be met at once in the less developed areas, and this, in turn, might create new problems. Limitations of economy, training facilities, and other considerations will therefore make it necessary to discriminate in the selection of health projects and to confine them, at least initially, to those in which the greatest benefits can be obtained in productivity and work efficiency ; in this regard, syphilis and yaws have been considered to be of distinct economic consequence in the general development of highly affected areas.

It remains to be seen whether it is practicable with present methods to proceed from a low incidence of yaws or syphilis, attained in some areas, through mass campaigns to the elimination of infectious cases in large population groups ; whether integration of specific control measures into the general preventive and curative health services, with continued emphasis on treponemal diseases, particularly in mothers and children, will result in their ultimate extinction ; and whether their actual eradication, including the late and latent stages, will be possible, and how far it will depend on extraordinary measures. So far, medical history has no example of an infectious disease having been actually treated out of existence.

Summary

(1) The introduction of penicillin in syphilotherapy, with its recognized epidemiological advantages, may have contributed to the rapidity with which syphilis was brought under control in certain European countries, North America and

elsewhere after the second, as compared with the first world war. Though, for example, 20 to 25 years were required in the Scandinavian countries after the first world war for the incidence to reach its lowest level, almost the same level has been reached in only 5 years since the second world war.

From a global viewpoint, the achievements in syphilis control during the last few years in certain European countries, North America, Australia, and other areas are of a limited value, since large reservoirs of syphilis and extra-venereally acquired forms of other treponemal diseases remain in temperate, semi-tropical, and tropical areas throughout the world.

(2) The broadest possible view of treponemal diseases is called for, since millions of people are incapacitated by " endemic " and other syphilitic diseases—bejel, yaws, and pinta—in different parts of the world where this is of economic consequence, and since the common vulnerability of *T. pallidum*, *T. pertenue*, and *T. carateum* to penicillin has demonstrated the applicability of repository penicillin preparations in the control of treponemal diseases.

In the absence of important evidence of penicillin resistance in the treponemes, the introduction of procaine penicillin G in oil with 2 per cent. aluminium monostearate (PAM)—which is capable of maintaining an effective blood level over several days with appropriate " one-shot " or " few-shot " treatment—has made a convenient, safe, and inexpensive therapy available for individual and mass control of treponemal disease. This development offers opportunities for the future ; defensive health measures are being abandoned in favour of a more aggressive approach and, particularly in less developed areas with a high prevalence of disease, mass-treatment control programmes are now practicable.

The study of the fundamental biological and immunological relationships among the treponemal diseases should be encouraged, and further research aiming at the development of methods for artificial immunization in syphilis (and other treponemal diseases) should be stimulated—once the *T. pallidum* has been successfully grown on artificial media—and the fullest application of our present knowledge and control methods should be made in each country, and internationally, so as to obtain a practical degree of treponematoses control.

(3) The reduction of reservoirs of treponemal infection to a relatively low incidence appears, fundamentally, to be attainable through two different mechanisms : *one*, the general socio-economic evolution over a long period during which general health services are developed, with some accent on specific disease programmes as required ; and the *other*, the mass effort, which can be superimposed on the first at any stage—depending on the magnitude of the problem—and which requires a concentrated technical, administrative, and financial effort over a limited period, aiming at the maintenance of secondary supervisory measures for the control of relapses, re-infections, and re-introduction of disease.

The complete elimination of reservoirs of syphilis infection has been demonstrated in limited areas in communities in Bosnia (Yugoslavia), and that of yaws in Pacific islands and African villages. Mass campaigns against syphilis and yaws covering areas with several million people (Bosnia, Indonesia, Thailand, Haiti) show encouraging results. However, the lasting value of such campaigns, after the initial effort, depends on the establishment of permanent treatment facilities and on other secondary measures.

(4) National Health administrations may request technical and financial assistance from such international bodies as the World Health Organization and the United Nations International Children's Emergency Fund for venereal disease, treponematoses, and other health programmes. These organizations are at present cooperating with health administrations in several countries in mass campaigns against bejel, yaws, and rural syphilis (Haiti, Indonesia, Iraq, Thailand), while limited venereal-disease control projects, with emphasis on pre-natal and infantile syphilis have been encouraged in others (Italy, Afghanistan, Egypt, India). Specific reference is made in the text to some of these projects, including some of the preliminary observations made.

Other activities of the World Health Organization in relation to fellowships, travel grants, advisory services, and research are briefly reviewed in connexion with the role that the Organization can play in venereal-disease and treponematoses control.

References

Akrawi, F. (1949). *British Journal of Venereal Diseases*, **25**, 115.

Alexander, L. J., Schoch, A. G., and Mantooth, W. B. (1949). *Amer. J. Syph.*, **33**, 429.

Altshuler, L., Karpinos, B. D., Leifer, W., and Ozog, J. J. (1949). *Ibid.*, **33**, 126.

Apted, I., Harding, R. D., and Gosden, M. (1948). *Trans. roy. Soc. trop. Med. Hyg.*, **42**, 55.

Arje, S. L. (1947). *Nav. Med. Bull., Wash.*, **47**, 965.

Arnold, R. C., Mahoney, J. F., Nicholson, T. P., and Wright, R. D. (1949). *J. vener. Dis. Inform.*, **30**, 125.

Batchelor, R. C. L. (1949). *Practitioner*, **162**, 369.

Biraud, Y. (1950). *Brit. med. J.*, **1**, 1046.

Boger, W. P., and Flippin, H. F. (1949). *J. Amer. med. Ass.*, **139**, 1131.

Bolgert, M., Lévy, G., Desvignes, P., and Caramanian, M. (1950). *Bull. Soc. méd. Hôp. Paris*, 21–22, 1131.
Buckwalter, F. H., and Dickison, H. L. (1948). *J. Amer. pharm. Ass., Sci. ed.*, **37**, 472.
Bundesen, H. N., Rodriquez, J., Aron, H. C. S., and Korman, B. F. (1950). *Arch. Derm. Syph., Chicago*, **62**, 230.
Burckhardt, W. (1951). *Proph. antivénér.* In the press.
Butler, C. S., and Peterson, E. (1927). *J. Lab. clin. Med.*, **12**, 670.
Chandler, V. L., Romansky, M. J., Welch, H., Robinson, J. A., Zeller, W. W., Dowling, H. F., and Hirsh, H. L. (1948). *J. Amer. pharm. Ass., Sci. ed.*, **37**, 21.
Chisholm, B., (1950). *Brit. med. J.*, **1**, 1021.
Christian, H. A. (1938). "Osler's Principles and Practice of Medicine", 13th ed. Ed. H. A. Christian: Appleton-Century, New York. *Quoted in* E. H. Hudson, (1946). "Treponematosis", p. 116. Oxford University Press: New York.
Clark, E. G. (1950). World Health Organization unpublished document. VD/36, 1 September, 1950.
Coutts, W. (1949). *Ibid.*, VD/46 Rev. 1.
Cross, J. B., McCain, J. R., and Heyman, A. (1949). *Amer. J. Obstet. Gynec.*, **57**, 461.
Cunha, A. M. da, Guimarães, F. N., Arêa Leão, A. E., and Cardoso, H. T. (1944). *Mem. Inst. Osw. Cruz*, **41**, 247.
——, Arêa Leão, A. E., Guimarães, F. N., and Cardoso, H. T. (1944). *Ibid.*, **40**, 195.
Danbolt, N., and Berdal, T. (1950). *Acta derm.-venereol., Stockh.*, **30**, 354.
Debré, R. (1949). *Sem. Hôp. Paris*, **25**, 357.
Dwinelle, J. H. (1947). *Trop. Dis. Bull.*, **44**, **907**.
——, Rein, C. H., Sternberg, T. H., and Sheldon, A. J. (1946). *Amer. J. trop. Med.*, **26**, 311.
Eagle, H., Magnuson, H. J., and Fleischman, R. (1946). *J. vener. Dis. Inform.*, **27**, 3.
Eliot, M. M. (1950). *Brit. med. J.*, **1**, 1027.
Emery, J. L., Rose, L. M., Stewart, S. M., and Wayne, E. J. (1949). *Ibid.*, **1**, 1110.
Enkvist, O. (1948). *Acta derm.-venereol., Stockh.*, **28**, 104.
——(1950). *Ibid.*, **30**, 445.
Fairbrother, R. W., and Daber, K. S. (1950). *Brit. med. J.*, **1**, 1098.
Findlay, G. M., Hill, K., and Macpherson, A. (1944). *Nature, Lond.*, **154**, 795.
Fox, H. (1938). "Syphilis and Yaws: Different Diseases." Science Press.
——(1949). *Arch. Derm. Syph., Chicago*, **59**, 127.
Gaté, J. (1949). *J. Méd. Lyon*, **30**, 139.
Glück, A. (1922). *Arch. Derm. Syph., Wien*, **138**, 214.
Gonzalez, C. L. (1949). *Unid. sanit.*, **3**, 259.
Goodwin, M. S. (1950). *J. vener. Dis. Inform.*, **31**, 178.
Gougerot, H., and Degos, R. (1950). *Proph. antivénér.*, **22**, 389.
Grin, E. I. (1950). World Health Organization unpublished document VD/36, September 1950.
Guimarães, F. N. (1951). *J. invest. Derm.*, **16**, 77.
Gundersen, H. (1950). *Acta derm.-venereol., Stockh.*, **30**, 442.
Guthe, T. (1948). World Health Organization unpublished document IC/217, Add. 1, 1–6.
——(1949). *Epidem. vital Statist. Rep.*, **2**, 1.
——, and Hume, J. (1948). *J. soc. Hyg.*, **34**, 51.
Hackett, C. J. (1946). *Trop. Dis. Bull.*, **43**, 1091.
Harding, R. D. (1949). *Trans. roy. Soc. trop. Med. Hyg.*, **42**, 347.
Harrison, L. W. (1949). *Med. illustr. Lond.*, **3**, 318.
Hasselmann, C. M. (1938). *Arch. Derm. Syph., Chicago*, **38**, 837.
Hellerström, S. (1949). Statement to the Third Session of the World Health Organization Expert Committee on Venereal Infections. Unpublished.
——, and Hagerman, G. (1948). *Acta derm.-venereol., Stockh.*, **28**, 81.
Hermans, E. (1949). World Health Organization, unpublished working document VD/52.
——(1950). *Ned. Tijdschr. Geneesk.*, **94**, 1810.
Hill, K. R., Findlay, G. M., and Macpherson, A. (1946). *Lancet*, **2**, 522.
——, Kodijat, R., and Hasselmann, C. M. (1950). World Health Organization, unpublished reports of WHO/UNICEF/Indonesian Health Administration Treponematoses Campaign, 1950.
Holcomb, R. C. (1945). Centaur of Alpha Kappa Kappa, p. 99. *Quoted in* E. H. Hudson, "Treponematosis".
Howard-Jones, N. (1950). *Brit. med. J.*, **1**, 1032.
Hudson, E. H. (1928). *Nav. Med. Bull., Wash.*, **26**, 817.
——(1937). *Trans. roy. Soc. trop. Med. Hyg.*, **31**, 9.
——(1938). "The Significance of Bejel", Syphilis, Science Press.
——(1946). "Treponematosis." Oxford University Press, New York.
Huggins, D. R. (1950). World Health Organization, unpublished reports of WHO/UNICEF/Thai Health Administration Treponematosis Campaign, 1950.
Huriez, C., and Dujardin, J. (1949). *Pr. méd.*, **57**, 1.
Ingraham, N. R., Jr. (1951). *Acta derm.-venereol., Stockh.* In the press.
Jamaica Yaws Commission (1933–1936). Reports of Jamaica Yaws Commission, 1933–1936. Government Printing Office, Kingston, Jamaica.
Jefferiss, F. J. G., Willcox, R. R., and McElligott, G. L. M. (1951). *Lancet*, **1**, 83.
Jessner, M., and Rossiansky, N. (1930). *Arch. Derm. Syph., Wien*, **160**, 224.
Johnson, B., Jr. (1950). Personal communication to the authors.
Joulia, P. C. (1951). *Proph. antivénér.* In the press.
Khan, A. S. (1950). "On the Behaviour of Various Strains of Spirochaeta Pallida, Pertenue and Cuniculi towards Homologous and Heterologous Immobilizing Antibody." Thesis, Johns Hopkins University School of Public Health and Hygiene, Baltimore, Maryland, U.S.A.
King, A. J. (1948). "The Prognosis of Syphilis". *In* "British Encyclopedia of Medical Practice", Interim Supplement 70, p. 12–13. Butterworth, London.
——(1950). Personal communication to the authors, 23 October.
Kitchen, D. K., Thomas, E. W., and Rein, C. R. (1949). *J. invest. Derm.*, **12**, 111.
Kogoj, J., and Vuletic, A. (1939). Naklada Skole Narodnog Zdravla U Zagreb, Zagreb 1939.
LeFevre, I. D., Jr., McDermott, K. F., and Venner, R. B. (1944). *Nav. Med. Bull., Wash.*, **43**, 739.
Leon y Blanco, F. (1939). *Medicina Mex.*, **19**, 17.
Lepinay, E. (1950). *Maroc Médical*, **29**, 124.
Levaditi, C. (1930). *C. R. Soc. Biol., Paris*, **104**, 477.
Levitan, S. (1950). World Health Organization, unpublished reports of WHO/UNICEF/Haitian Health Administration Rural Syphilis/Yaws Campaign, 1950.
Lofgren, R. C. (1944). *Nav. Med. Bull., Wash.*, **43**, 1025.
Magnuson, H. J., and Rosenau, B. J. (1948). *Amer. J. Syph.*, **32**, 203.
Mahon, P. A. O., and Lamauve, L. (1804). "Histoire de la Médecine clinique, et Recherches importantes

sur l'Existence, la Nature et la Communication des Maladies syphilitiques dans les Femmes enceintes, etc." Buisson, Gabon, Mequignon, Lenormand, Paris.
Mahoney, J. F., Arnold, R. C., and Harris, A. (1943). *J. vener. Dis. Inform.*, **24,** 355.
Malamos, B. (1949). *Trans. roy. Soc. trop. Med. Hyg.*, **43,** 11.
McElligott, G. L. M., Jefferiss, F. J. G., and Willcox, R. R. (1948). *British Journal of Venereal Diseases*, **24,** 45.
Midana, A. (1949). *Bull. Soc. franç. Derm. Syph.*, **56,** 398.
Möller, P. (1951). *Acta derm.-venereol., Stockh.* In the press.
Monacelli, M. (1950). *Proph. antivénér.*, **22,** 490.
Montel, L. R. (1949). *Bull. Soc. Path. exot.*, **42,** 210.
Moore, J. E. (1945). *Amer. J. Syph.*, **29,** 474.
——(1951). " An Evaluation of Public Health Measures for the Control of Syphilis. An Epidemiologic Study." To be published.
Morgan, E. A. (1949). *Canad. med. Ass. J.*, **61,** 275.
Nabarro, D. (1949). *British Journal of Venereal Diseases*, **25,** 133.
Nelson, R. A., and Mayer, M. M. (1949). *J. exp. Med.*, **89,** 369.
Nilzén, A. (1950). *Acta. derm.-venereol., Stockh.*, **30,** 1.
Pautrier, L. M. (1951). *Proph. antivénér.* In the press.
Perdrup, A. (1951). *Acta derm.-venereol., Stockh.* In the press.
Rajam, R. V. (1949). Statement to the Third Session of the World Health Organization Expert Committee on Venereal Infections and Treponematoses. Unpublished.
Rein, C. R. (1947). *N. Y. St. J. Med.*, **47,** 2450.
——(1951). *Acta derm.-venereol., Stockh.* In the press.
——, and Kitchen, D. K. (1950). Personal communication to the authors.
——, ——, and Petrus, E. A. (1949). Address before the 10th Annual Meeting of the Society for Investigative Dermatology, Atlantic City, N.J., U.S.A., 11 June 1949.
——, and Kostant, G. H. (1949). Address before the 8th Annual Meeting of the American Academy of Dermatology and Syphilology, Chicago, Ill., U.S.A., 6 December 1949.
Reynolds, F. W. (1946). *Amer. J. Med.*, **1,** 661.
——(1948). " Oxford Medicine ", Ch. 28. Oxford University Press, London.
Rider, R. V. (1949). *Amer. J. Syph.*, **33,** 19.
Robinson, J. A., Hirsh, H. L., Milloff, B., and Dowling, H. F. (1948). *J. Lab. clin. Med.*, **33,** 1232.
Saenz, B., Triana, J. Grau, and Alfonso, J. (1938). *Arch. de Med. Int.*, **4,** 116. (Habana).
——, ——, and Armenteros, J. A. (1940). *Arch. Derm. Syph., Chicago*, **41,** 463.
Samame, G. (1950). Address before the 3rd Central American Congress of Venereology, El Salvador, 4 May 1950.
Sampaio, E. (1951). *Proph. antivénér.* In the press.
Sokhey, S. (1950). *Brit. med. J.*, **1,** 1037.
Spillmann A. (1949). World Health Organization. Unpublished working document VD/42.
Stannus, H. S. (1936). *In* " Empire Social Hygiene Year-Book ". 3rd ann. ed., p. 577. Allen and Unwin, London.
Stocks, P. (1950). *Brit. med. J.*, **1,** 1044.
Thomas, E. W. (1949). " Syphilis : Its Course and Management ", p. 41. Macmillan, New York.
——, and Landy, S. (1950). *Amer. J. Syph.*, **34,** 126.
——, Lyons, R. H., Romansky, M. J., Rein, C. R., and Kitchen, D. K. (1948). *J. Amer. Med. Ass.*, **137,** 1517.
Tommasi, E. (1951). *Proph. antivénér.* In the press.
Triana, J. Grau (1949). *Ann. Derm. Syph., Paris*, 8 sér, **9,** 276.
Turner, T. B. (1937). *Amer. J. Hyg.*, **25,** 477.
Varela, G., and Avila, C. (1947). *Amer. J. trop. Med.*, **27,** 663.
Weiss, P. (1947). *Rev. Med. exp., Lima*, **6,** 1.
Whitehill, R., and Austrian, R. (1944). *Bull. Johns Hopk. Hosp.*, **75,** 232.
Willcox, R. R. (1949). " A Venereal Disease Survey of the African in Southern Rhodesia." A report to the Secretary of Health, October 1949.
——(1950). *J. vener. Dis. Inform.*, **31,** 254.
World Health Organization (1949). Unpublished document VD/23, August 1949.
——(1950). " Report on the Third Session of the Expert Committee on Venereal Infections ". Tech. Rep. Ser. No. 13.
Young, M. Y., Andrews, G. W. S., and Montgomery D. M. (1949). *Lancet*, **1,** 863.