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On the Origin of the Human Treponematoses

(Pinta, Yaws, Endemic Syphilis and Venereal Syphilis)

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A close relationship between the four human treponematoses is suggested by their clinical and epidemiological characteristics and by such limited knowledge of the treponemes as there is at present. No treponeme of this group (except for that of the rabbit) is known other than in man, but the human treponemes probably arose long ago from an animal infection. The long period of infectiousness of pinta suggests that it may have been the earliest human treponematosis. It may have been spread throughout the world by about 15 000 B.C., being subsequently isolated in the Americas when the Bering Strait was flooded. About 10 000 B.C. in the Afro-Asian land mass environmental conditions might have favoured treponeme mutants leading to yaws; from these, about 7000 B.C., endemic syphilis perhaps developed, to give rise to venereal syphilis about 3000 B.C. in south-west Asia as big cities developed there. Towards the end of the fifteenth century A.D. a further mutation may have resulted in a more severe venereal syphilis in Europe which, with European exploration and geographical expansion, was subsequently carried throughout the then treponemally uncommitted world. These suggestions find some tentative support in climatic changes which might have influenced the selection of those treponemes which still survive in humid or arid climates. Venereal transmission would presumably remove the treponeme from the direct influence of climate. The author makes a plea for further investigation of many aspects of this subject while this is still possible.

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The human treponematoses comprise four closely-related infections: pinta (*mal del pinto*, *carate*), yaws (*pian*, *framboesia*, *bouba*), endemic syphilis (*bejel*), and venereal syphilis. More information is needed before their origins can be traced with confidence. However, consideration of this interesting question may indicate relevant studies to pursue.

The first four sections of this paper summarize various aspects of the problem and the fifth contains some suggestions based upon existing knowledge and reasonable assumptions.[1]

It is hoped that this brief survey will stimulate constructive action while this is still possible.

THE DISEASES

The human treponematoses

The four treponematoses in man are caused by organisms which are microscopically indistinguishable by present techniques. The appearance of the *Treponema pallidum*, which Schaudinn in 1905 described from the lesions of venereal syphilis, is typical of them.

These four human treponematoses[2] may be grouped according to the usual way they are transmitted, as follows:

(1) Non-venereal (often called endemic) treponematoses; transmitted mostly among children:

(*a*) Pinta

(*b*) { Yaws / Endemic syphilis[3] }

(2) Venereal (sometimes called sporadic) treponematosis; transmitted mostly among adolescents and adults:

Venereal or sporadic syphilis.

In the first group are two subgroups. One consists of pinta, which has different clinical manifestations, a long period of infectiousness and is geographically isolated in the Americas from the other treponematoses. Its causal organism, *Treponema carateum*, is the only one of the four treponemes with which animals have not yet been infected experimentally. These characteristics distinguish pinta from the other three treponematoses.

The other subgroup contains yaws and endemic syphilis. These, like pinta, are diseases of less-developed rural populations and are usually contracted in childhood. Between yaws and endemic syphilis are certain clinical and epidemiological differences. Typically, endemic syphillis occurs in warm, semi-arid and arid areas and yaws in warm countries with higher rainfall and more vegetation. As a rule, neither of them is endemic in urban populations nor do both occur in the same population (see page 12). In both, poor standards of hygiene are important.

There is little need here to describe the venereal disease of urban populations in any climate, syphilis. It was, until recently, a serious public health problem of advanced countries and caused much suffering and disability (see page 13). The severe late lesions of the heart, nervous system and eye appear to differentiate venereal syphilis from the non-venereal treponematoses (Table 1). However, the frequency of these lesions in venereal syphilis in Africa in the past was thought to be low, but Limbos (1957) comments upon the occurrence of central nervous system involvement in syphilis there.

The pattern of venereal disease in Africa may have changed in the last 15 years. Many of the present inhabitants of large African cities have come from the country, where they might have had yaws in childhood. The seroreactor rate in urban primiparae in several tropical African countries is about 20%, but congenital syphilis is often infrequent. This may be because childhood yaws protects against adult infection with venereal syphilis. However, in Dakar, which is just north of the yaws area, Senecal et al. (1962) have reported 10%-15% seroreactors among pregnant women and estimated 2% congenital syphilis among children. They also found that about 11% of children born of seroreactive mothers who were not treated during the pregnancy were also seroreactive with or without clinical signs.

Intra-uterine transmission in venereal syphilis and its absence in the endemic treponematoses are perhaps not important in the differentiation of those diseases because in venereal syphilis this transmission is also unusual when the mother has been infected

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[1] Much help has been received from the constructive criticism of many friends during the past four years.

[2] In this paper each of the four treponemes and the four diseases related to them are regarded as different entities. Hudson (1946, 1958) has, however, strongly contended that all the treponemal infections comprise one disease, treponematosis, which is caused by one treponeme, *T. pallidum*, " which presents different clinical patterns under different climatic and sociological conditions ".

[3] Since the name " endemic syphilis " still causes confusion because the significance of the " endemic " is often missed, another name for this disease is needed. Local names, such as *bejel*, are not suitable. In general, endemic syphilis is a treponematosis of arid areas and thus the name " treponaridosis " might be suggested because it is the treponematosis of arid countries. Were a new name needed for yaws, which it is not, the name " treponumidosis " might be proposed.

for more than five years. However, women with florid early infectious yaws have been reported to have borne healthy children (Baermann, 1911).

The unlikelihood of venereal syphilis occurring in populations infected in childhood with yaws or endemic syphilis casts doubt upon early reports of venereal syphilis in populations later found to have high prevalences of these diseases. This must be kept in mind in interpreting such reports in relation to historical medical geography. A growing problem for present public health workers and future medical historians is to know how soon venereal syphilis may enter such populations when the indigenous endemic treponematosis has been eradicated.

The differentiation of venereal syphilis and yaws has been discussed by Stannus (1926, 1936), Blacklock (1932a, 1932b), Turner (1937) and Turner & Hollander (1957). The solution of this problem must await the fuller study of the antigenic constitution of the treponemes.

Some clinical characteristics of these four infections are listed in Table 1.

TABLE 1
SOME CLINICAL CHARACTERS OF THE TREPONEMATOSES

Character	Pinta	Yaws	Endemic syphilis	Venereal syphilis
Usual source of treponemes	Skin anywhere	Skin anywhere	Buccal mucosa	Genital and mucosal lesions
Size of infectious area	Large	Large	Small	Small
Duration of:				
Infectiousness of individual lesions	Many years	A few months	A few months	A few months
Infectiousness of patients, including infectious relapses	Many years	3-5 years	3-5 years	3-5 years
Latency [a]	Absent	Characteristic	Characteristic	Characteristic
Lesions:				
Initial, site	Exposed skin	Skin of legs	Mouth ?	Genital
Initial, occurrence	Infrequent	Frequent	Unusual	Frequent
Generalized skin, extent	Extensive	Extensive	Limited	Moderate
Genital, occurrence	Unusual	Scanty	Scanty	Frequent
Buccal mucosal, occurrence	Absent	Scanty or absent	Moderate	Scanty
Palmar and plantar hyperkeratoses, occurrence	Absent [b]	Frequent	Scanty [c]	Scanty
Bone, occurrence	Absent	Moderate	Moderate	Scanty
Juxta-articular nodules, occurrence	Absent	Frequent	Scanty	Scanty
Heart, brain and other viscera, occurrence	Absent	Absent [d]	Scanty and mild, or absent	Moderate
Congenital transmission	Absent	Absent	Absent	Present
Age-group of most infections	Children	Children	Children	Adults

[a] Latency in a communicable disease is a stage in its course in which there is evidence of infection such as seroreactivity but no clinically detectable active lesions.

[b] Hyperkeratoses have been attributed to pinta in Cuba. However, there may have been confusion with hyperkeratoses of yaws.

[c] Many of the hyperkeratoses illustrated by Hudson (1936) and Murray et al. (1956) are not due to endemic syphilis (Hackett & Loewenthal, 1960).

[d] Weller (1937) reports lesions resembling those of venereal syphilis from supposed yaws cases in Haiti; he found no venereal syphilitic lesions of the brain in them.

The comparison of yaws or endemic syphilis with acquired sporadic syphilis contracted non-venereally by children from adults with infectious venereal syphilis would be more correct than the comparison of either with venereal syphilis contracted venereally by adults. Jeans & Cooke (1930), in a careful study of 34 cases, say that the manifestations of this " prepubescent syphilis " are those of acquired syphilis in adults, except that mucous membrane lesions and condylomata are more frequent and the Wassermann reaction more readily reversible. Other reports of juvenile syphilis (Eisenberg et al., 1949; Taylor, 1954; Rajam et al., 1955) support these findings. Grön (1928) does not clearly distinguish between endemic syphilis and non-venereally acquired sporadic syphilis of children. Many of the outbreaks to which he refers were clearly of the latter infection and some may have been of yaws.

Endemic syphilis is a non-venereal disease of rural children in warm, dry climates,[1] neither derived from, nor associated with, venereal syphilis in the community. The late cardiac and cerebral manifestations of venereal syphilis, which are typically severe in that disease, do not occur in endemic syphilis or are scanty and mild. This and its rural occurrence are perhaps distinguishing characters. Initial lesions are regarded as unusual. The early lesions are more frequent in children than in adults.

Non-venereally acquired sporadic syphilis in children is mainly an urban disease in any climate and originates from simple contact with infectious venereal syphilis in adults or through contaminated objects. Thus non-venereally acquired sporadic syphilis and venereal syphilis are present in the community and perhaps in the same family at the same time. Transmission among children may follow infection of children from adults and children may infect adults, but the epidemiological pattern is that of venereal syphilis with incidental infection of children. Initial lesions are infrequent (Eisenberg et al., 1949; Rajam et al., 1955). However, Tucker & Mulheim (1948) report that over a third of extra-genital chancres in children were in the buccal cavity. This non-venereally acquired sporadic syphilis in children gives rise to all the severe late manifestations of venereal syphilis. This and its urban and often familial incidence are perhaps distinguishing characters. Early lesions in adults are frequent and are usually due to venereal infections.

[1] Often the dryness may be modified by proximity of villages to marshes or rivers.

Fournier (1903) found that of 642 extra-genital chancres in venereal syphilis, 484 occurred on the head, and that of these, 435 occurred on or in the mouth (328 on the lips). He reports that probably about 10% of chancres were extra-genital.

Where endemic syphilis is reported out of its characteristic arid climatic range, as in Yugoslavia and Uganda, there is a possibility that it is, or has originated from, non-venereally acquired sporadic syphilis in children. However, the studies of Turner & Hollander (1957) on the treponemes do not support these suggestions because the Bosnian endemic syphilis treponemes differed from the treponemes of venereal syphilis.

Dr E. I. Grin, of Sarajevo, Yugoslavia, (personal communication, 1962) has observed among children small outbreaks of non-venereally acquired sporadic syphilis which had all the characteristics of endemic syphilis, arising from an adult with infectious venereal syphilis. However, he pointed out that the Bosnian endemic syphilis was probably brought from a long-standing focus in Anatolia during the Turkish occupation which commenced in the fifteenth century. Perhaps this present-day Bosnian treponematosis indicates an aspect of the pattern of the treponematoses before the last decade of the fifteenth century. Similar outbreaks of non-venereally acquired sporadic syphilis in childhood originating from infectious venereal syphilis in adults acquired in towns may occur in rural areas in other countries where the standards of personal hygiene are low.

A number of diseases such as *sivvens* and other so-called syphiloids occurred in Europe and elsewhere in the seventeenth and eighteenth centuries which are thought to be treponematoses (Swediaur, 1821). Attempts have been made to diagnose these conditions more accurately (Pollock, 1953). The possibility that they were non-venereally acquired sporadic syphilis should be considered.

Course of the human treponematoses

The course of venereal syphilis in man might be taken as typical of that of the treponematoses because in it may occur all the manifestations of endemic syphilis and yaws and because it has been intensively studied (Gjestland, 1955). The following description is a composite picture of the treponematoses.

The treponeme enters the body through the mucosa or through a break in the epidermis. Animal experiments indicate that this penetration may take only a few minutes but the longest time that may be

taken is not known, although such knowledge would have considerable practical value. Treponemes divide by transverse division about every 30 hours (Turner & Hollander, 1957).

Magnuson et al. (1956), from the results of the inoculation of known numbers of virulent *T. pallidum* into non-syphilitic male volunteers and into 12 rabbits, calculated that the 50% infectious dose was less than 57 treponemes. As few as 10 treponemes produced generalized infection with papular initial lesions but these developed more slowly than after larger doses which more often ulcerated. One thousand to 10 000 treponemes consistently produced lesions with an incubation of 19 days, which is about that of sexually acquired syphilis.

Infection in animals has followed the inoculation of two treponemes and of material in which treponemes were too few to be found microscopically (Schöbl, 1928; Magnuson et al., 1948; Turner & Hollander, 1957). Magnuson et al. (1948) also suggest that in man " one to two organisms may suffice to cause infection once they have passed through the epithelial layers of the skin or mucous membranes ". Gladstone & van Heyningen (1962) state that " *Treponema pallidum* is one of the most invasive organisms known ".[1]

Turner & Hollander (1957) found that the intradermal inoculation of 500 *T. pallidum* (Nichol's strain) in rabbits was followed by an incubation period of 17 days. Each tenfold increase or decrease in the number of treponemes shortened or lengthened the incubation period by four to five days. They estimated that a single treponeme would produce about 100 million organisms, which they believe are needed to produce a visible lesion, in 32 days. The number of treponemes involved in natural transmission in man needs further study.

Where the treponemes enter the skin they multiply and the dermal and epidermal tissues react by cellular proliferation and infiltration to produce the initial lesion. From infection to initial lesion is about three weeks, depending upon the criterion of size of the initial lesion. Initial lesions on healing leave little or no scar unless secondary bacterial infection has previously caused destruction.

While the initial lesion is developing, treponemes reach the neighbouring lymph glands, which become enlarged; some time later treponemes enter the blood-stream and are carried throughout the body, enter the skin and multiply there to produce the papillomata. In these lesions the treponemes continue to multiply until interrupted by the immune processes of the body or by some extraneous factor, such as treatment (Turner & Hollander, 1957). As the immune response increases the lesions heal but some treponemes persist through the latent stage that follows. Later, when treponemes again multiply, a relapse occurs. This migration occurs in experimental infections in animals (Eagle, 1948). The early generalized skin eruption appears some weeks after infection. Fenner (1950) showed that in ectromelia (a virus infection of mice) during a first blood infection, the virus enters the bone-marrow or other tissues where multiplication takes place. This is followed by another blood-stream infection by virus which gives rise to the generalized skin lesions. Schöbl (1928) believed, from his experimental yaws infections in monkeys, that generalized lesions were due to treponemes coming from the skin.

The initial lesions of yaws and pinta may appear on any exposed part of the skin but in yaws they are most frequent below the knee (Hackett, 1957b); in endemic syphilis they are said to be infrequent and have been thought not to occur, while in venereal syphilis they are usually genital (see page 10).

The characteristic early skin eruption of yaws (Hackett, 1957a) consists of numerous, usually discrete, proliferative papillomata, moist with exudate containing numerous infective treponemes. The early skin lesions of venereal syphilis are dry macules or papules as well as moist condylomata about the genitalia, axillae, etc. Yaws papillomata in these places, especially in adults, may resemble syphilitic condylomata. In endemic syphilis the early skin lesions are mucous papules, circinate papules and condylomata.

The initial and early lesions of pinta are spreading, scaly plaques of various sizes to which are added after a few weeks bluish pigmentary changes elsewhere in the skin. Some years later these dyspigmented areas become depigmented, especially on the hands and feet, although both types of lesion can be present at the same time. The initial lesions are not frequently seen. The plaques usually, and the dyspigmentation sometimes, precede the development of seroreactivity. Condylomata and hyperkeratoses do not occur.

All these early generalized skin lesions start from treponemes reaching the surface of the body by the blood-stream. In endemic syphilis, yaws and venereal syphilis, the treponemes presumably reach the

[1] Burnet (1962) has said that in endemic diseases infection is most frequent in childhood and that the greater the ease of transmission the younger will be the age of transmission.

skin in the capillaries beneath the epidermis, are held up and escape through the capillary walls into the surrounding tissues. Their multiplication is accompanied by dermal and epidermal proliferation and by inflammatory cells which may be influenced by the temperature and condition of the skin.

At least in some countries in the humid geographical areas, in which yaws typically occurs, papillomata are more frequent in the rainy, humid but cool season than in the dry, warm season (Hackett, 1951). In the arid geographical areas of endemic syphilis, the skin is dry and the cellular proliferation of the lesions is less marked; the skin lesions of the later early (secondary) stage may extend as a thread-like, annular thickening which may enclose a large area of healthy skin (Luger, 1958; Murray et al., 1956). In these countries, while the summer is hot the winter is cold, but the former is longer. Nothing is known of the seasonal variations of prevalence of skin lesions in endemic syphilis.

Ramsay (1925, 1927) in Assam and Lopez-Rizal & Sellards (1926) in the Philippines have reported the anatomical restriction of generalized early yaws lesions (papillomata) to the mouth, nose and moist folds of the body (gluteal cleft, axilla, etc.) in mountain dwellers where the climate is cool and the wider anatomical dispersion of these lesions in yaws patients at lower, warmer altitudes. Ramsay observed this change in mountain-dwelling patients who moved down to the humid plains. He states " the cold weather lesions of yaws are indistinguishable from those of syphilis ". It would be interesting to confirm these observations. However, other factors may in part be responsible, especially nutritional deficiencies (Platt, 1958), and the influence of climate on the skin lesions needs further study.

The role of humid warmth in the transmission of yaws was shown in an outbreak among South African miners working 2000 m underground; the infection did not spread to contacts above ground (Hackett, 1953, p. 159).

Goundou [1] (Botreau-Roussel, 1925) is frequent in yaws patients in Africa and it responds well to treatment in its early stage. However, its extreme scarcity or absence in other yaws areas raises doubts that it is due to yaws despite its apparent response to neoarsphenamine (Hackett, 1951).

Hasselmann (1931) and Schöbl & Hasselmann (1932) have summarized the course of yaws in experimental infections and reinfections in Philippine monkeys which was reported in detail by Schöbl (1928). The initial lesion may heal and not be followed by any other lesions; it may be followed by an early eruption of papillomata with no subsequent late lesions; or it may persist for a long time and, without a papillomatous eruption, be followed by late ulcerated lesions. Schöbl (1928) showed that immunity to the treponeme of yaws was manifest in three ways; (*a*) resistance to superinfection, (*b*) resistance to the generalization of yaws lesions, and (*c*) modification of the yaws lesions that developed.

A characteristic of the *earliest* lesions of endemic syphilis is the relatively more frequent occurrence of papules on the buccal mucosa than in any other treponematosis (Hudson, 1937). Some of these lesions when they are single and associated with unilateral lymphadenitis may be initial lesions (Luger, 1958). Buccal mucosal lesions have been observed in Uganda in 6% of 150 yaws patients with papillomata (Hackett, 1939, 1946, 1951). However, careful observers in Java, Thailand and Brazil have unsuccessfully sought such lesions. The Lango district in Uganda, where these mucosal lesions were seen, consists of woodland savanna. The northern endemic syphilis zone of Africa (see Map 1) in Sudan is only about a hundred miles north of Lango. Grin (1961) reports on the occurrence of yaws and endemic syphilis in southern Sudan and speaks of the " mixture of endemic infections in one locality and even in one individual ". However, he does not define these diseases beyond indicating that the diagnosis of yaws depended upon " typical skin papillomata " and of endemic syphilis upon " oral mucous plaques and papules in the genital region ".

He refers to patients who, as he says, " pose a number of interesting clinical and epidemiological problems ":

> " One of the cases of endemic syphilis was a young girl who had on her neck a large papillomatous lesion which resembled a mother yaw. Furthermore, she had mucous oral plaques with swollen indurated submaxillary lymphnodes and papillomatous lesions of the genitalia (virgo intacta). "

The diagnosis of such patients must depend largely upon the criteria used. Perhaps, however, in this epidemiological fringe area there is a treponematosis with the characters of both yaws and endemic syphilis, or both diseases may be present in the same community, as Grin suggests.

[1] Goundou is a usually bilateral bony enlargement of the nasal processes of the maxilla.

Future study of treponemes may reveal the relationship between these Uganda and Sudanese *T. pertenue* of yaws and the *T. pallidum* of endemic syphilis. Treponemes from both these areas should be collected in readiness for improved methods of treponeme study.

It would be interesting to transport some children recently infected with endemic syphilis to a humid area and to move some others recently infected with yaws to a semi-arid or arid area and observe the courses of the diseases. Perhaps such infections, incidentally transported, have already been observed but not reported. It might be impracticable to observe experimental infections with each treponeme in volunteers in the geographical area of the other.

The differences in clinical manifestations of the various treponematoses are probably due to the treponeme strains themselves although Hudson (1946) does not accept this.

The lesions of the four treponematoses may be summarized as follows:

Pinta. Continuing activity of early lesions, either from extension of lesions or from blood-borne treponemes; the presence of treponemes in lesions for many years until the lesions become inactive and depigmented (Marquez et al., 1955); the absence of latency (Edmundson et al., 1953). The long period of, perhaps not great, infectiousness is unique among the treponematoses. Palmar or plantar lesions are absent and there are no bone lesions or late destructive lesions.

Endemic syphilis and yaws. Early stages: skin, palmar and plantar lesions; bone lesions. Late stages: destructive skin and bone lesions.

Venereal syphilis. Early stages: skin lesions; bone lesions not frequent. Late stages: destructive skin, bone and other tissue lesions, and lesions of heart and brain.

In the last three infections, treponemes are microscopically scanty or absent in lesions developing three to five years after infection, when early lesions are unusual; latency and relapses are characteristic of all stages.

Latency and relapses, occasionally some years after the original infection, may favour high prevalence and maintenance in small populations by the dispersal of apparently healthy individuals whose later infectious relapses disseminate the infection. Latency and relapses also occur in the late stage of these diseases but the late lesions are non-infectious compared with the early ones.

Luger & Schmid (1961), from their experience in Syria [1] and a review of the literature, believe that in endemic syphilis childhood infections and early repeated superinfections in childhood, with small numbers of treponemes which cause no lesion at the site of entry, result in a few years in the immunological protection of the heart and central nervous system. This is in contrast to adult infection and less frequent superinfection in venereal syphilis. In this way they account for the rarity, mildness (often only cerebrospinal fluid changes) or absence of late neurosyphilis and cardiovascular lesions in rural populations in whom endemic syphilis is prevalent. Grin (1953) had arrived at similar conclusions. On the other hand, early infection (Guthe & Luger, 1957; Grin, 1953) is said to produce a state of allergy, especially in the skin, to the treponemes so that later superinfection may be followed by destructive lesions such as gummata. These conclusions are not generally accepted. Symptomless superinfections have been observed in experimental infection in animals, but only as a stage in the development of more complete immunity (Magnuson & Rosenau, 1948; see also Magnuson et al., 1956; and page 11 above).

Akrawi (1949) reports two successful experimental infections in five volunteers under " natural " conditions of endemic syphilis, as indicated by the change from non-reactivity to reactivity to the Wassermann test in the serum. In them no initial lesions developed because, he inferred, very few treponemes were present in the inocula. When more treponemes were present initial lesions developed. These findings need confirmation.

Malaria infection in childhood followed by early and repeated superinfection certainly reduces the severity of *falciparum* malaria in adults in hyperendemic areas, but the early infections themselves are very severe. However, if the superinfection of the adults ceases, the protection decreases.

How many people infected with an endemic treponematosis (pinta excluded) suffer no serious disability is uncertain because where patients are not treated there are no competent observers. However, Gjestland (1955) from a study of untreated venereal syphilis of about 50 years' average duration assumed " that somewhere between 60 and 70, and probably closer to 60 than 70, out of every 100 un-

[1] In the same area Hudson (1958) started his studies on bejel in 1924.

treated syphilitics went through life with little or no inconvenience as a result of the disease ".[1]

In yaws and endemic syphilis perhaps about the same number also escape serious consequences.

Pathological characteristics of the human treponematoses

The organs characteristically affected in the treponematoses are indicated in Table 2.

TABLE 2
ORGANS CHARACTERISTICALLY AFFECTED IN THE TREPONEMATOSES

Pinta	Yaws	Endemic syphilis	Venereal syphilis
Skin	Skin	Skin	Skin
	Mucosa	Mucosa	Mucosa
			Central nervous system
	Bone [a]	Bone	Bone
			Heart and arteries

[a] Hasselmann (1931), because of the absence of bone lesions in experimental infections in animals, doubts this occurrence in man, except as an extension from skin lesions, as in gangosa.

All four treponemes almost certainly become blood-borne early in the infection and thus reach all the tissues of the body. However, the treponemes of syphilis cause lesions in tissues not known to be affected by the others. The work of Turner & Hollander (1957) suggests that different temperature preferences of treponemes may influence organ preferences. These may also be related to the occurrence of congenital infection in syphilis. Silverstein (1962) has suggested that the usual appearance of lesions of congenital syphilis at about the sixth month of pregnancy may be more related to the " maturation of foetal ability to respond to the stimulus with differentiation of immunologically active cells " than to the passage of the treponemes through the placenta.

[1] From the study of about a thousand patients untreated for the early manifestations of venereal syphilis contracted from 1891 to 1910, Gjestland (1955) found the following prevalences of subsequent manifestations: clinical secondary relapses, 23.6%; benign tertiary syphilis, 15.8%; neurosyphilis, 6.5%; cardiovascular syphilis, 10.4%. Syphilis was the primary cause of death in 10.8%.

The differences reported in the histopathological reactions to these treponemes appear to be more of quantity than of quality. The changes consist of perivascular infiltration by leucocytes, lymphocytes and plasma cells with or without endothelial proliferation. Ferris & Turner (1937, 1938) and Turner & Hollander (1957) conclude that " histologic criteria for the differentiation of the cutaneous and subcutaneous lesions of yaws and syphilis are in general unreliable ". In other words, the typical early lesions of yaws and syphilis may be distinguishable, but if they are not typical then distinction may be difficult. Differences in late lesions are more difficult to recognize than those in early lesions. However, Hallenberger (1916) maintained that the characteristic vascular changes of syphilis are absent in early and late yaws, but Furtado (1955) found these vascular changes in late yaws. Adequate comparable studies are needed. Hasselmann (1957) has written about " comparative studies on the histopathology of syphilis, yaws and pinta ". However, he deals mainly with the early skin lesions and he gives no indication of the number of lesions upon which his descriptions are based.

Prevalence of the human treponematoses

In most countries at present the endemic treponematoses (yaws: Hackett, 1959, 1960; endemic syphilis: Luger, 1958) and venereal syphilis are in recession compared with a generation ago, and their prevalences now are of little value in obtaining a picture of each disease in its " wild " state. From the information available the following prevalences of endemic treponematoses might be expected in populations where conditions favour their spread:

Seroreactors	60%-80%
Susceptibles	40%-20%
Total active clinical .	20%
Infectious lesions . .	2%-4%

In pinta the total prevalence of clinically active disease would approach that of the seroreactors, which might be as high as 80% because latency apparently does not occur (Marquez et al., 1955). In some villages in an endemic syphilis area in Senegal, Senecal et al. (1962) have reported prevalences of seroreactors of 92% and of clinically active cases of 4%. In venereal syphilis in favourable and primitive conditions seroreactor rates of 50%-60% and active lesion rates of 6%-10% of the population have been found. Although

some non-venereal transmission may occur under these conditions, it does not appear to be frequent because seroreactors among children may be few. However, among adults in developed countries seroreactor rates of 10%-30%, depending upon the sector of the community surveyed, were usual before the introduction of penicillin (McElligott, 1960; Hill & Mugge, 1954). The high infectiousness of the early lesions of the treponematoses is emphasized by these prevalences.

Geographical distribution of the human treponematoses

The general introduction of arsenical and bismuth preparations about 1920 (although mercury had been used at least as early as the fifteenth century) and of penicillin after 1945, together with improved standards of living, have greatly reduced the prevalence of the treponematoses during the past 20 years. The improvement in standards of living of the world's population up to the end of the nineteenth century was smaller and much less extensive than that which has occurred during the present century. Therefore, the geographical distribution of the treponematoses about 1900 might be of value in attempting to trace their origin.

The prevalence of early and late clinical manifestations and of seroreactors in different age-groups in a community provides reliable epidemiological information. Thus few or no clinical manifestations in the population and many seroreactors in adults are an indication of the recession of the infection during the previous generation. While early clinical manifestations of treponematoses are the result of recent infection, reactive sera in older people are due to more distant infection (Hackett, 1960). Thus such serological and clinical data indicate the recession or progress that may have occurred in the past generation.

When a map of the approximate distribution of the treponematoses at the beginning of this century (Map 1) [1] is scanned from west to east, several interesting points may be seen.

In the Americas a block of pinta extends from Mexico down to the upper Amazon basin (Guimarães & Roderigues, 1948), while yaws occurs in the Caribbean Islands and on the western and eastern coasts of South America south to Peru and Rio de Janeiro. Perhaps pinta survives only where there is a considerable Amerindian population. This distribution of yaws agrees with its importation with slaves from Africa during the sixteenth to nineteenth centuries, although Scott (1943) says that " yaws was probably autochthonous in Hispaniola, Brazil, Fiji, Samoa and West Africa, and imported into the West Indies by slaves ". However, he had earlier said (Scott, 1939) that " it can be affirmed almost with certainty that slaves introduced leprosy ... yaws... " into the Americas, where " they fell ready victims to diseases already present there notably tuberculosis and, next to that, syphilis ". Castellani (1908, p. 618), however, refers to authors in the second half of the seventeenth century who reported that yaws in the West Indies " occurs frequently among the natives (Caribs) who call it *pyans* or *yaya* ". This would not have been expected if they had originally been infected with pinta and had continued so (see page 19). However, nearly a century and a half of African slavery may by then have changed the pattern of disease. On the other hand, the statements that the populations were Carib may not have been ethnically correct because one of the original purposes of the importation of slaves from Africa was to replace the rapidly dying out indigenous population. Hume (1744) said that yaws was " endemical in Guinea and the hotter climates in Africa ". Nicholls (1899) made the interesting observation that Indians arriving in the West Indies were susceptible to yaws. *S. mansoni* bilharziasis probably arrived in the southern parts of the American continent with slaves but leprosy is thought to have arrived there earlier with Europeans (Scott, 1943).

Pinta is the ancient endemic treponematosis of the Americas (Guimarães & Roderigues, 1948; Sanchez et al., 1961). However, occasionally a not identical depigmentation of unknown origin (Hackett & Loewenthal, 1960) occurs in some yaws endemic areas in other parts of the world, but the pattern of depigmentation on the palms and wrists may resemble that of pinta (Castello & Castañedo, 1952; Herrejón, 1938).

Such depigmentations in Australian aborigines are said to be scanty or absent (Professor J. B. Cleland, Adelaide—personal communication, 1961), although Basedow (1932) writes that " white or pinkish patches appear which may increase in size and coalesce ". This occurred most frequently on the backs of the

[1] The maps attempt to show the distribution of pinta, yaws and endemic syphilis in the indigenous populations, except for yaws in the Americas. The distribution of venereal syphilis is that where other treponematoses are absent. No account is taken of syphilis in cities and towns and its extension therefrom into areas where another treponematosis might reasonably be expected to have been the earlier infection. The maps appear on pages 31 to 37.

hands but he says it was quite distinct from the depigmented patches in syphilis and leprosy. Cleland (1928) refers to a report of " mottling of the skin from extensive eczema of the palms and soles " in aborigines of the Northern Territory of Australia which was attributed to syphilis.

Venereal syphilis alone occurs in the Americas north and south of the two tropics but would, of course, be primarily a disease of urban populations in them.

In Africa an equatorial belt of yaws is bordered north and south by zones of endemic syphilis in semi-arid areas, while venereal syphilis predominates along the Mediterranean littoral and in the southern part of Africa. The last can be disregarded for the present purpose as three centuries of migration have confused the picture in the originally scanty population south of the Kalahari. In the Kalahari, endemic syphilis was the indigenous treponematosis until the present decade (Murray et al., 1956). Endemic syphilis has also been reported in East Africa (Davies, 1956). However, the disease in Buganda Province, Uganda, has become more definitely venereal syphilis during the present century, and this may raise some doubts about its true nature (see pages 10 and 29).

The populations of the Mediterranean littoral of Africa have undergone many centuries of migration and invasion and for all that time have been predominantly of races different from the rest of Africa. No evidence of venereal syphilis in the early Egyptian remains so far examined (Williams, 1932; Rowling, 1961) has been found, although gonococcal salpingitis has been reported.

In Europe, venereal syphilis is universal except for the anomaly of a non-venereally acquired endemic syphilis in parts of Yugoslavia—e.g., Bosnia, where it has been known for several centuries since the arrival of Ottoman invaders (Grin, 1953; and page 10). However, in the endemic treponematosis of Yugoslavia, occasional cardiovascular and central nervous system lesions, although mild, are reported; this is unusual in endemic syphilis elsewhere, except in Buganda.

In Asia, endemic syphilis is present in the rural areas of Syria, Saudi Arabia, Iraq and adjacent Iran and used to occur among the nomadic pastoral people of the Central Asian semi-arid steppes.

In India, yaws is an isolated remnant of a probably originally widely distributed disease and in Ceylon it is traditionally thought to have been introduced or perhaps reintroduced from Africa following European discovery (Spittel, 1923). From Assam, it extends south-east through Burma, Thailand, Malaya and Indonesia to New Guinea and the Philippines without interruption, and thence into the scattered Pacific islands, where it was present when the first European explorers arrived (Buxton, 1928). Lambert (1931) concludes that this was so for Renell and Bellona Islands in the southern Solomons. There are strong suspicions from the journals of Captain James Cook and other early explorers of this area that yaws was present in many Pacific islands in the mid eighteenth century. Its presence in New Zealand is uncertain; the Maoris are believed to have reached New Zealand from Polynesia about the middle of the fourteenth century and to have displaced the previous inhabitants. Yaws has, since 1950, been found endemic in the interior of West New Guinea where European exploration and administration had not previously extended (Kranendonk, 1958). The presence of yaws (Yu, 1957) in China (Kiangsu, north of latitude 30°N) is probably due to its repeated introduction by Chinese returning from southern lands where yaws was endemic (Maxwell, 1916). Yaws was also present in the aborigines in southern Taiwan (Takahashi, 1939).

In Australia the treponematosis pattern probably resembled that in Africa in the same southern latitudes. Bone lesions and serological reactions indicate that endemic treponematoses occurred among aborigines in Central Australia and further south (Hackett, 1936a).[1] While yaws was the infection in the tropical northern Australian coastal area, the recently increased knowledge about endemic syphilis suggests that possibly the treponematosis, *irkintja* (Hackett, 1936a), in semi-arid central and southern Australia might have been endemic syphilis. Professor J. B. Cleland of Adelaide (personal communication, 1962; and Black & Cleland, 1938) has long proposed that *irkintja* was a non-venereal treponematosis other than yaws. The aboriginal population and its cultural introductions came into Australia in several waves from the north and north-west (see page 26). The nearest endemic syphilis area lies far to the north-west; thus yaws coming into northern Australia from Asia may have been

[1] MacKay (1938) concludes that the pathological changes in aboriginal bones found near the River Murray in New South Wales are most likely due to venereal syphilis. He had excluded endemic syphilis, yaws and " some indigenous disease of which we have no medical knowledge, which also produces these striking pathological lesions in bone ". He said that at that time there was little evidence that bone lesions occurred in yaws. Cleland (1928) also refers to aboriginal bones with " osteitis and periostitis (possibly syphilitic) ".

the precursor of endemic syphilis in the semi-arid steppes of central Australia.[1]

The bone lesions of yaws (Hackett, 1951) and endemic syphilis (Rost, 1942) appear indistinguishable except that in the latter goundou (Botreau-Roussel, 1925) does not occur or is extremely rare. However, in yaws endemic areas out of Africa goundou does not occur or, again, is extremely rare (Botreau-Roussel, 1961).

Dr E. I. Grin of Sarajevo, Yugoslavia, (personal communication, 1962) has occasionally seen goundou in endemic syphilis in Bosnia, and it has been said not to be rare in Khuzistan (Iran).

Venereal syphilis on the map (Map 1) may be regarded as occupying the areas not previously " committed " to the endemic treponematoses.

From this information the geographical distribution of the treponematoses about the beginning of European explorations by sea (sixteenth century) (Map 2) may be *guessed* as follows:

Pinta : in Central America and South America, mainly in humid hilly or mountainous areas, absent elsewhere;

Yaws : in the tropical belt, but perhaps less extensive in India and absent in the Americas;

Endemic syphilis : in semi-arid steppes of northern and southern Africa, central Asia and probably central Australia; absent in the Americas;

Venereal syphilis : in Europe and the Mediterranean basin; absent elsewhere.

The introduction of venereal syphilis into Europe by Columbus from the Caribbean islands has often been debated with more heat than light. The history of venereal syphilis needs careful review (see page 28). Venereal syphilis in the tropics in the eighteenth and nineteenth centuries was probably often confused with yaws (Hackett, 1936b).

Reports of examinations of human bones of all periods, especially before 1500, from all parts of the world, in museums and elsewhere, should be reviewed for descriptions of lesions likely to have been caused by treponematoses, and bones not so reported should be carefully examined. Perhaps the first step in such a study should be to draw up diagnostic criteria for the diseases likely to be seen in such bones. Radiographic and microscopical examinations should be made. Descriptions of bone lesions in endemic syphilis (Rost, 1942) and in yaws (Hackett, 1936a, 1951) should be of value in these studies, as should be the publication on the bone lesions of leprosy by Møller-Christensen (1961). However, the possibility that some of the leprosy of pre-Columbian Europe might have been syphilis should be carefully considered. Williams (1932, 1936) has commenced this study and stressed the difficulties of the diagnosis of venereal syphilis in ancient bones and also the difficulty of dating them. Williams concludes that there is no certain evidence of venereal syphilis in pre-Columbian bones in Egypt or Europe but he accepts some of the osteological evidence of venereal syphilis in American Indians before Columbus's arrival. Holcomb (1940) comments on Williams's (1932) conclusions. However, all this needs reconsideration, especially since Hrdlička (1932; Lawrence, 1941) a leading anthropologist of the Amerindian, has stated that " from evidence of thousands of Indian skulls and skeletons predating the arrival of Columbus, there is, as yet, not a single instance of thoroughly authenticated pre-Columbian syphilis ".

In some pathological museums skulls with lesions labelled " syphilis " from burials in countries where endemic treponematoses, particularly yaws, have occurred have probably been wrongly diagnosed.

If effective treatment had not been discovered but present-day improvements in living standards had nevertheless occurred, endemic syphilis and yaws would probably be receding as they are now doing; however, chemotherapy has doubtless hastened this recession by a generation or more. The difference in severity of yaws in Africa and Indo-China commented upon by Botreau-Roussel (1962) was probably due to differences in the stage of recession (see page 20). Bancroft (1769) speaks of the very extensive eruptions of yaws in African slaves in Guiana. From the time that venereal syphilis in Europe first attracted attention at the end of the fifteenth century, it has extended into or been recognized in most countries in which yaws or endemic syphilis is not present. It is thought to have become less dermal and destructive and to involve the central nervous and cardiovascular systems more frequently now than then. Perhaps in the better-educated communities of modern highly developed countries, venereal syphilis would naturally have tended to

[1] In 1803 the explorer Mathew Flinders met a large fleet of a thousand Malay trepang fishermen on the Arnhem Land coast, north Australia; the trepang industry was, even then, long established. The dried and smoked molluscs were sold to Chinese traders in Timor. The epidemiological significance of this trade as regards the treponematoses is unknown, but is probably small. Earlier in the present century this trade was mainly in the hands of Japanese.

recede to its basic reservoir in the " submerged tenth ".

Animal treponematoses

The only treponeme in animals which is microscopically indistinguishable from the human *pallidum/pertenue* treponeme is *T. cuniculi*. This causes a natural venereal infection in rabbits. The organism was found by Bayon in 1913 and has not yet been cultivated. The rabbit is a European animal but this treponematosis may have arisen in Europe or elsewhere.

McLeod & Turner (1946) have reviewed the literature on this infection and described the clinical manifestations following intracutaneous and intratesticular inoculation. Natural infections start with a genital initial lesion after an incubation period of two to eight weeks. Metastatic skin lesions have followed intratesticular inoculation when there was no possibility for auto-inoculation, which shows that infection of the blood-stream must have occurred. These lesions differ from those of *T. pallidum* lesions in rabbits. Skin lesions start as erythematous papules which enlarge and become hypertrophic and crusted. Lymph-glands are also enlarged and treponemes can be demonstrated in them by animal inoculation. There are no lesions of bones or viscera. Festenstein & Bokkenheuser (1961) could not produce congenital infection. They thought the high body-temperature (39°C) of rabbits was unfavourable for the survival of the treponeme (see page 27), but the part possibly played by placental structure may need to be taken into account.

Turner & Hollander (1957) found considerable cross-protection between *T. cuniculi*, *T. pallidum* and *T. pertenue*, but the cross-protection between the last two was stronger than that between *T. cuniculi* and either of the others. Because of this close immunological relationship with the others, *T. cuniculi* may be a nearer descendant of the unknown forerunner in animals of the human pathogenic treponemes (see page 24). The sera of infected rabbits become reactive to the reagin and treponemal tests. The pathological changes consist of infiltration by lymphocytes and plasma cells much as in yaws and venereal syphilis. Perivascular infiltration is slight. Latency is frequent. The infection may last from several months to more than a year and cause death.

Infection rates in some stocks of rabbits may be nearly 40%. Man, apes and monkeys are reported to be insusceptible and inoculation of white mice and rats, guinea-pigs and hamsters gives rise to a latent infection (McLeod & Turner, 1946).

Although a number of spirochaetes have been observed from lesions in animals of many zoological orders no other treponeme closely resembling *T. pallidum* has been found. Careful serological search, using treponemal antigen, might reveal other such infections which might be of practical as well as theoretical interest.

THE CAUSAL ORGANISMS

The pallidum/pertenue *treponemes*

These microscopically identical treponemes are thin spiral organisms about 6-15μ in length and about 0.25μ thick. The spirals are remarkably uniform and measure about $1\mu \times 1\mu$. Their microscopical appearance and movements as seen under darkground illumination are characteristic.

The treponemes of the *pallidum/pertenue* group comprise three named species:

Treponema pallidum, Schaudinn (1905): venereal syphilis and endemic syphilis; [1]
Treponema pertenue, Castellani (1905): yaws;
Treponema carateum, Brumpt (1939): pinta.

None has been cultivated in artificial media; thus the knowledge of their characters and relationship to each other is incomplete. Further electron-microscopic studies of the morphology of these treponemes are needed (Swain, 1955), but important differences between them are unlikely to be found (Mölbert, 1956).

Experimental animal infections have shown fairly consistent differences in the lesions caused by the treponemes of yaws, endemic syphilis and venereal syphilis (Turner & Hollander, 1957). The greatest differences were between lesions caused by the treponemes of yaws and venereal syphilis, while those of the treponemes of endemic syphilis were usually intermediate. However, the differences observed in one animal—i.e., rabbits—did not always agree with those found in another—i.e., hamsters.

Workers in this field have stressed the unavoidable lack of precision and the relatively small numbers and small range of observations that have been made. Rabbits may not be very suitable animals for experimental work because of their higher body-temperature (39°C) (Festenstein & Bokkenheuser, 1961).

[1] If the treponeme of endemic syphilis is later differentiated from that of venereal syphilis, it might be named *T. trepenarida*.

In man yaws or syphilis of more than one year's duration probably renders the patient non-susceptible to superinfection with the same treponeme or infection with the other (Medina, 1954, 1959). However, the studies of Guimarães (1946) and the statements of Edmundson et al. (1953) [1] do not fully agree with this. Medina (1954) found that a few untreated pinta patients in the early or late stages could not be infected with virulent yaws treponemes. In the absence of attempts to infect pinta patients with syphilis treponemes, however, one might expect pinta patients to be resistant to syphilis. This would not favour the presence of venereal syphilis in the Amerindians when Columbus arrived. However, Medina refers to studies by Blanc in which patients in various stages of syphilis could be readily infected with the treponeme of pinta " as if there were no immunity of any kind ".

The experimental work in animals of Turner & Hollander (1957) showed that with adequate duration of infection there was complete cross-protection between different strains of venereal syphilis and endemic syphilis treponemes and between different strains of yaws treponemes; there was less between treponemes of venereal syphilis and those of yaws and least between those of venereal syphilis or yaws and *T. cuniculi*. This indicates the close relationship between the three human treponemes (see page 24). Smaller differences in cross-protection have, however, been demonstrated between the treponemes from different syphilis patients (Turner & Hollander, 1957). Turner & Hollander (1957) conclude that on the basis of limited evidence there is a fundamental difference between the various types of treponemes (excluding that of pinta). They also state that with rapid passage in rabbits there is a tendency for the selection from populations of yaws treponemes of those with characters of the syphilis treponeme.

It should be recalled that the treponemal antigens are components of the structure of the treponemes themselves and as such are genetically determined. Serological findings reveal no differences between the human treponemes and may be summarized as follows:

1. Sera from venereal syphilis, endemic syphilis, yaws and pinta react to the same antigens.

2. Serological cross-reactions with present treponemal antigens occur with sera from venereal syphilis, yaws and *T. cuniculi* infections.

[1] Edmundson et al. (1953) state that in some rural communities in Mexico in which pinta is " highly endemic ", syphilis is " considered relatively common ".

Little help in the differentiation of the treponemes is to be had from the response of their infections to chemotherapy. All treponemes are about equally susceptible to penicillin (Turner & Hollander, 1957). A single dose of 1.2 mega-units causes disappearance of the treponemes within 24 hours and is followed by rapid healing of early lesions.

Small dosage is in general use in mass treatment campaigns against the endemic treponematoses—a single dose of 1.2 mega-units of procaine penicillin (Hackett & Guthe, 1956). This rapidly makes the patient non-infectious and probably prevents infectious relapses for some years. These are community measures and although some early infections may be cured, as judged by sero-reversal, others and late infections cannot be expected to be serologically cured but clinical relapses will be infrequent. The intention in mass campaigns is to stop the transmission of the disease in the community and the small dosage is justified by its effectiveness and reasonable cost and by the absence in yaws of severe late manifestations of the brain and heart. In venereal syphilis, treatment is of patients and with larger doses in longer courses—4.8 mega-units during one to two weeks in early venereal syphilis—because of the severe late lesions of this disease. Even in syphilis a number of early infections may be cured by the small doses used in mass campaigns against yaws but this would not justify their use in venereal syphilis.

A better understanding of the relationship of the treponemes to each other should follow the study of their antigenic characters when their cultivation is possible. Strains of *T. pallidum* that can at present be cultivated are regarded as non-pathogenic variants and in them other differences from the pathogenic treponemes from man have been found.

Site of entry and transmission of the treponemes

Three of the treponematoses have initial lesions at the site of entry of the infection. This is characteristically in venereal syphilis on the genitalia and in yaws on the skin elsewhere than the genitalia, most frequently on the leg below the knee. In pinta the initial lesion, although not frequently seen, may occur on any exposed part of the skin. The number of treponemes capable of transmitting infection may be small (see page 11); however, many treponemes may be expected to be inoculated in the natural transmission of yaws and of venereal syphilis and few in pinta and endemic syphilis. The larger numbers might be expected to favour the transmission of mutants more than the smaller numbers would.

In venereal syphilis transmission is most often by treponemes from genital condylomata or initial lesions; a few infections may come from buccal or anal mucous papules but these are not usual. The predominance of sexual contact in the transmission of venereal syphilis is probably also related to the fact that sexual contact is one of the closest direct physical contacts among adults.

In yaws infectious lesions are predominantly the papillomata of the early stages that may occur anywhere on the skin; early mucous papules and the relatively non-infectious palmar and plantar hyperkeratoses and late lesions are probably not important sources of infection. The frequency of initial yaws lesions on the lower part of the leg may be explained by the treponemes being passed from the fingers of a patient with moist papillomata to the fingers of a susceptible person, who, upon rubbing his leg in response to the irritation of a minor injury, implants the treponemes on a small abrasion (Hackett, 1957b).[1] Yasuyama (1928) found that *T. pertenue* in serum remained infectious at 28°C for up to two hours.

Powell (1923) in Assam, in what he says was a closely supervised population on tea plantations, failed to observe initial lesions in 20% of 205 patients who developed generalized early yaws 25-121 days after the presumed infection. The others developed lesions identical with the characteristic papillomata, except perhaps for being larger, 17-63 days after the presumed infection. This was a prospective study. No other similar data are known but initial lesions are probably at least as frequent as Powell reported.

In endemic syphilis initial lesions are so unusual that, for practical purposes, they are often regarded as not occurring. The source of infecting treponemes in endemic syphilis is usually thought to be the buccal mucosal papules and less importantly the less frequent condylomata. Where the treponemes enter the body is not known. Either the entry occurs without any cellular reaction or, what is more probable, the cellular response resembles the earliest recognizable lesion. In endemic syphilis, this might be the solitary papule on the buccal mucosa, especially if unilateral lymphadenitis were also present (Luger, 1958). Perhaps such small solitary papules are, in fact, initial lesions and, following later blood-borne dissemination, only those treponemes reaching the buccal mucosa cause lesions, except for an occasional implantation in the axilla or elsewhere which produces a condyloma or dry annular lesion.

In endemic syphilis Guthe & Luger (1957) suggest that, as in yaws, fingers might play an important part in transmission. Grin (1953) considers that the transmission of endemic syphilis in Yugoslavia was related to the indiscriminate use of drinking utensils and unhygienic village conditions. Perhaps the most important factor is defective personal hygiene in childhood.

In pinta the initial lesions are often not recognized, but they resemble the early ones. The source of infection must be the dry papular or pigmented lesions from which treponeme-containing serum can be expressed. The difficulty in understanding how treponemes get from these lesions to the skin of a susceptible person by contact has led to the suggestion that a biting insect, such as *Simulium*, might play a part (Sanchez et al., 1961). However, no close geographical association has been reported between pinta and onchocerciasis, which is transmitted by certain species of *Simulium*, but pinta may be transmitted mechanically by other species.

Again, it must be stressed that pinta, yaws and endemic syphilis are characteristically transmitted among children by non-venereal contact and that venereal syphilis is transmitted among adults through sexual contact.

In yaws, infectious lesions may be large, perhaps many square centimetres, and very infectious; in pinta they may be even larger but less infectious; and in endemic syphilis and venereal syphilis the area may be less, one or two square centimetres, and again very infectious. Infectious lesions may remain in yaws, endemic syphilis and venereal syphilis for several months and recur during three to five years; in pinta they may persist for many years (see Table 1 above).

Spreading circinate lesions may occur in endemic syphilis and less frequently as a variation of papillomata in the later part of the early stage of yaws.

In the recession of yaws (Hackett, 1959) transmission and severity of clinical manifestation are decreased, that is, as found at surveys early lesions are less numerous and drier and late destructive lesions are less frequent and less severe or absent. In the later stages of yaws eradication, isolated new cases occur which may be accounted for either by unusually prolonged latency or, as Dr F. N. Guimarães of Rio de Janeiro (personal communication, 1952) has found, by unexpected infectiousness of solitary hyperkeratosis of the palms and soles or of

[1] The role of flies in the transmission of yaws, although possible, is probably not important. It has been discussed by Barnard (1952).

late destructive lesions. Such possibilities are not readily apparent when the disease is rampant.

The essential factors that cause spontaneous recession cannot at present be more precisely defined than as " improved standards of living ". More complete knowledge about these might well be of value in the problem of the origin of the treponematoses as well as in the prevention of yaws. However, soap, through its direct effect on personal cleanliness, may aid the recession of yaws by reducing transmission. This would be related to the time taken for the treponeme to enter the body and its survival time on the surface of the skin. On the other hand, soap may merely be an indicator of prosperity and " improved standards of living ".

After the treatment of all patients who have active yaws with an adequate single dose of PAM [1] and the administration of single half-doses to the remainder of the population (total mass treatment; Hackett & Guthe, 1956), infectious lesions rapidly disappear and infectious relapses from early latency are mostly suppressed for some years. The re-establishment of infectious yaws after total mass treatment is slow and probably arises from the infrequent infectious relapses or from infectious cases entering the population (Hackett, 1960). There may well be little effective transmission in a yaws endemic community with high serological reactor prevalence (60%-80%). Harding (1949) in Sierra Leone demonstrated the high proportion of infectious yaws patients in such conditions that are relapses and the importance of relapses in transmission.

In the present low-prevalence phase of venereal syphilis recession in certain countries, the spread of syphilis in a series of small " epidemics " arising from individuals has clearly shown the epidemiological importance of the social activities of the individual (Hartmann, 1956; Olansky & Price, 1956). This also indicates the section of a community which is the infectious reservoir of syphilis and towards which public health measures should be directed.

Dr E. I. Grin (personal communication, 1962) found in Yugoslavia during the 1939-45 war that endemic syphilis extended beyond its usual geographical area. However, after 1945, with the general improvement of living conditions and the successful mass treatment campaign, the disease rapidly decreased. By 1960 endemic syphilis had been eradicated in Bosnia.

[1] Procaine penicillin G in oil with 2% aluminium monostearate.

At present, endemic syphilis and venereal syphilis are not the same disease and their treponemes, though closely related, do not appear identical.

Other treponemes in man and nature

A number of treponemes have been reported from man, such as *T. macrodentium* and *T. microdentium* in the mouth, *T. calligyrum* in smegma and *T. euygurata* in the intestine, but none is morphologically identical with *T. pallidum*, and none would be expected to have been its forerunner.

Veldkamp (1960) and de Bruijn (1961) report studies on a small, anaerobic, free-living organism whose morphological characters are intermediate between those of *Borellia* and *Treponema*. However, it was found to have the " group-specific protein antigen " of *T. pallidum* (Reiter). Veldkamp (1960) named it *T. zuelzerae*.

The present knowledge of the treponemes in animals and of saprophytic treponemes in the tropics is inadequate.

EVOLUTION OF THE TREPONEMATOSES

Origin of human infections

During the more than half a million years of man's existence most human infectious diseases, except those due to viruses, have probably arisen from:

(*a*) free-living or saprophytic organisms,

(*b*) commensals or infections of insects,

(*c*) infections of warm-blooded animals.

Some human infections are comparable to, if not identical with, certain existing animal infections. These range from malaria, various helminthiases and tuberculosis, to the animal infections that give rise to human infections, such as brucellosis, ornithosis, plague, rabies, Q fever and leptospirosis, in which man-to-man transmission is infrequent or absent.

In human infections for which no animal source is known, the original animal infection may have died out or may not have been discovered. However, such a human infection may have originated much later as a completely human possession from a saprophyte or commensal (Burnet, 1962).

No animal reservoir of the human treponemes is known although *T. cuniculi* infection in rabbits may be regarded as possibly having a common ancestor with them (see pages 18 and 24).

Infectious contacts in man

The transmission by contact of a communicable disease from an infectious to a susceptible person will be more likely the closer the physical contact and the less the personal cleanliness. Transmission by hand-to-hand contact is clearly shown by the transmission of bacillary dysentery and poliomyelitis where other opportunities are limited.

Only adolescents and adults are likely to have the necessary genital contacts for venereal transmission. However, transmission by indirect contact, through towels, occurs in gonococcal ophthalmia and vulvovaginitis, and non-venereal transmission of venereal syphilis to children can occur in unhygienic and crowded conditions (Eisenberg et al., 1949; Taylor, 1954).

Contact between children and adults, except between children and parents, is usually less frequent and less close than among children themselves. Probably contact between adults, except between marital partners, is the least close. This is also supported by findings in leprosy (Bechelli, 1954). Sosa-Martinez & Peralta (1961) report transmission of pinta between husband and wife as well as from parents to children, although other observers have not found this frequent.

The importance of any particular contact in the transmission of a communicable disease depends upon the ease or certainty of the passage of perhaps a *single* organism from an infectious patient to the susceptible person. Enormous numbers of organisms may be shed by an infectious patient but probably only a few (see page 11) are, of necessity, sufficient to infect a susceptible person. However, larger inocula may favour the transmission of mutants (see page 19).

In a community where adults are generally clothed, genital contact in coitus might have become the method of transmission in venereal disease because, although as an infectious contact it is relatively transient, it is as direct and as close as any contact among adults.

Because the gonococcus flourishes mainly in the genito-urinary tract, apart from the occasional transmission by hands, flies (ophthalmia) or intermediate inanimate objects, its transmission must be largely restricted to sexual contact.

In venereal syphilis, treponemes abound in the initial (genital) lesions, in condylomata (mainly genital) and buccal mucosal and early skin lesions—yet transmission is predominantly by genital contact. Such a transient and rather restricted contact may be effective because of the number of infective organisms involved and because of their invasiveness and may have become necessary because of their lack of survival away from the body and the anatomically restricted sites of effective infective lesions. However, not all sexual contacts with a patient with infectious syphilis result in transmission, but the proportion is not known. The transmission of venereal syphilis in adults would probably cease without sexual contact; it would not be expected to " revert " completely to some simpler contact transmission without deterioration of personal hygiene of the population. This stresses the closeness and perhaps transience of the infecting contact between children which is adequate for the transmission of endemic syphilis and yaws, because the treponemes of those infections are just as unable to survive away from the body as that of venereal syphilis. The types and closeness of skin contacts between children in rural endemic treponematoses areas should be carefully considered, in addition to the question of handling by older members of the family. They may be guessed at from the contacts among urban children.

Among the various devices which ensure the transmission and thus the survival of communicable diseases closeness of contact, long periods of infectiousness and latency with infectious relapses are important in the treponematoses.

Size of community needed to maintain infections

Each communicable disease needs a community of a certain size, otherwise it cannot maintain itself. A highly infectious disease of short duration with high mortality which produces lasting immunity in survivors would require a large population and the arrival, by birth, of many susceptibles. However, a communicable disease of lesser infectivity but of longer duration of infectiousness or having infectious relapses from latency during a number of years could maintain itself in a smaller population.

The treponematoses other than pinta have a potentially infectious period of between three and five years. This is not long enough to allow the transmission of endemic treponematosis from parents to children in a family but it is long enough in sufficiently large populations to ensure the transmission of infection from a relatively few infectious patients (4%; Hackett, 1960) to the uninfected susceptibles (40%) and its continuity in the community.

Endemic treponematosis in Australia was able to maintain itself in nomadic aboriginal family groups

which congregated into larger groups for only a few weeks each year, although there were probably a few other opportunities for limited contacts with occasional solitary visitors or visiting families.

Since venereal syphilis is transmitted almost entirely among adults, it will need a larger and denser total population than the endemic treponematoses. This doubtless influences its urban distribution.

On the other hand, with its larger area of skin involvement but similar duration of infectiousness (three to five years), yaws could be transmitted from child to child in large family groups such as occur with polygamy. This may have occurred in the nomadic, food-gathering aborigines of Northern Australia. However, children of sedentary populations are usually infected with yaws by children from outside their family.

The earliest human beings probably passed most of their time in family groups, the size of which depended upon the available food and water. These primitive human population groups, living as dispersed, nomadic food-gatherers, probably had specific group territories with water points, hunting grounds, vegetable food and firewood sources and perhaps extraterritorial salt sources. The family groups ranged over their own tribal areas, occasionally meeting other families of their own tribe, more rarely members of other tribes. Annually, or more or less frequently depending on the availability of food and water and upon the need, family groups gathered for communal purposes lasting a few days to a few weeks. These gatherings increased the effective size of the population, even if only for a few days, and would greatly assist the spread of communicable diseases.

The size of the group that can live as nomadic food-gatherers depends upon food supplies: the group might be large in fertile areas but would be small in savanna and even limited to a family in semi-arid steppes. Tindale (1960) estimates that the average tribal group in central Australia was fairly constantly about 500 and that the area of its tribal territory ranged from 50 to 3-5 or less square miles per person, depending upon the ability of the country to support the hunting and food-gathering way of life. Increase in size of a group is possible only when the food supply throughout the year is assured by the domestication of food plants and animals. Cook (1949), writing about the Australian aborigines, has pointed out that the sanitary habits that might be adequate for nomadic family groups can lead to fatal consequences when such people are suddenly settled. Under natural conditions such a tremendous change would be very gradual with the consequent adaptation of their infections to the people.

Burnet (1960) has pointed out that the persistence of herpes virus suggests that in such primitive conditions it would be an asset for an infection to remain infectious long enough for parents to infect their own children. Because treponemes can be obtained from pinta skin lesions of the same patient for long periods, pinta may be one of these early diseases (see also Sosa-Martinez & Peralta, 1961).

Only when man came to live in larger groups and thus to be, at least in part, more sedentary could communicable diseases of shorter infectious periods have arisen.

To summarize, the first human infections to become established probably had long infectious periods. Only in sedentary and especially in urban populations would those with short infectious periods evolve. However, the endemic treponematoses have maintained themselves among nomadic food-gatherers of the present century.

ORIGIN OF THE HUMAN TREPONEMATOSES

The probable distribution of the treponematoses at the beginning of the present century may be used as a starting-point for a discussion of their origin. The distribution in Map 1 is, within broad limits, probably moderately accurate.[1] It is based upon reports from about 1900 with the omission of statements that can now be reasonably regarded as errors of diagnosis or interpretation. Until the present century " disgusting " or " revolting " disease manifestations were often reported as syphilis by explorers and even by doctors (Hackett, 1936b). The *Treponema pallidum* of venereal syphilis was then unknown, and diagnosis depended upon clinical examination. That yaws was not well known is clear from descriptions of the time (Charlouis, 1897; Manson, 1898) and also by the fact that the late destructive changes were not generally accepted until the 1920s (van Nitsen, 1944), despite the able descriptions by Rat (1891) and others of the " tertiary period " in yaws. Although Moseley (1800) said that yaws " ends in shocking nodes and destruction of the bones ", Nicholls (1899) thought that " the sequels of yaws " and " the tertiary symptoms " resulted from treatment with mercury. There was much confusion

[1] See footnote on page 15.

between yaws and venereal syphilis in tropical countries. Endemic syphilis as seen in arid lands was not clearly recognized until the third decade of this century (Lacapère, 1923). Pinta was regarded as a mycosis until after 1930 and many were the " causative " fungi described from it.

The geographical distribution of the treponematoses in Columbus's day would be of great assistance in considering their origin and Map 2 is an attempt to provide this (see page 17).

The mixture of ignorance and error, and sometimes even emotion, in writings and discussions of the origin of the treponematoses, may be due in part to the fact that few workers have had adequate personal experience of all of them.

In putting together the rather inadequate evidence on the origin of the treponematoses, account should be taken of the behaviour of other infections both in the field and in the laboratory. The temptation should be avoided to deal with " awkward cases " by making exceptions or special situations.

An initial problem is the interrelations of the treponemes themselves. The close relation of the treponemes of yaws, endemic syphilis and venereal syphilis is obvious and the intermediate position of endemic syphilis to the others is stressed by Turner & Hollander (1957). The treponeme of pinta, although microscopically identical with the other treponemes, has never been transmitted to animals, although such transmission is relatively easy with the other treponemes. Moreover, pinta remains infectious for many years, which is quite uncharacteristic of the other treponematoses.

Professor S. Adler of Jerusalem (personal communication, 1962) has called attention to the need to define more precisely the relationship of the treponeme of pinta to those of the other human treponematoses. The closer this relationship, the more likely it is that the four human treponemes are a consecutive series starting with that of pinta (see hypothesis A in the accompanying diagram). The less close this relationship, the more likely it is that the treponeme of pinta is an earlier and independent branch from the treponeme of an ancestral animal infection (see hypothesis B in the diagram). He favours the latter possibility. However, in this paper the former has been proposed because of the occurrence of somewhat similar depigmentation in pinta and in the other treponematoses. For this reason an independent origin for pinta in the Americas and another for the other human treponematoses in the Euro-Afro-Asian land mass has not been proposed. However, such an alternative independent origin of pinta would not change the main proposals in this paper.

Professor Adler has also stressed how minute biological differences in morphologically identical treponemes may cause major epidemiological differences, as is also seen in *Leishmania* and *Borellia*.

Although no thorough search has been made, no natural animal infection with a treponeme resembling those of the syphilis/yaws group is known except that with *T. cuniculi* in rabbits. This is a disease of a European animal (see page 18), but, because of the resemblance of its treponeme to those of the human treponematoses, it would appear to be related to some forerunner of the human infections which probably started in a part of the world with a warmer climate than Europe ever had. This would strongly suggest that the human pathogenic treponemes arose more directly from an ancient animal infection than from a saprophyte or commensal.

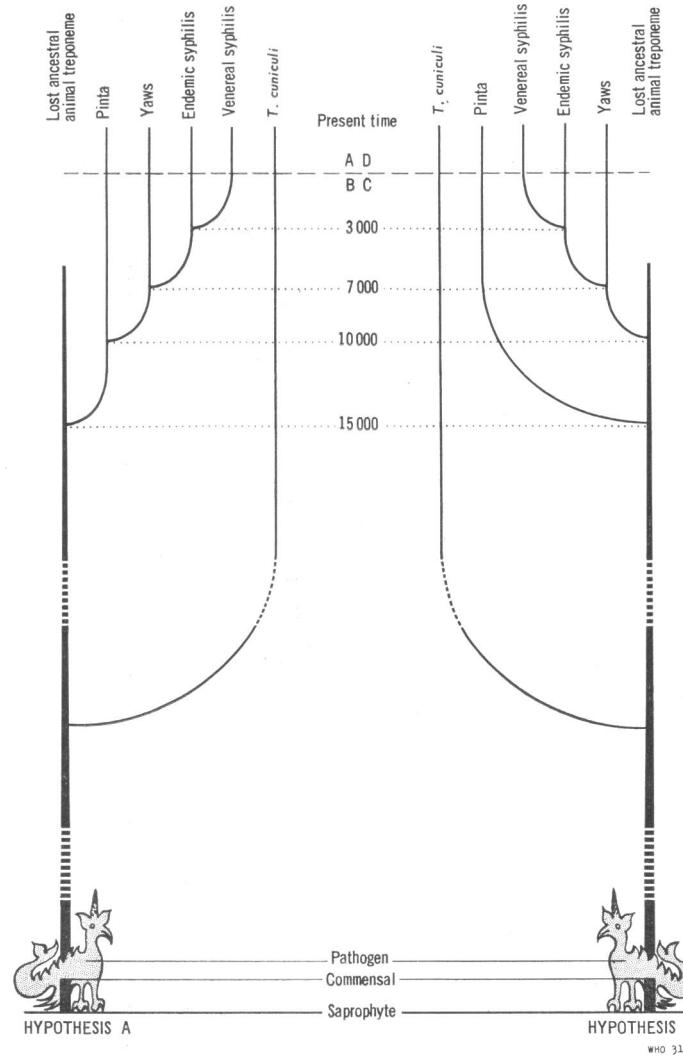
The curative effect of an induced attack of malaria in late syphilitic lesions of the central nervous system has been demonstrated in the present century. Thus the influence of highly endemic malaria on the course of venereal syphilis and of other treponematoses in tropical countries needs review and further careful study, although relatively little high fever may be experienced by adults under these conditions. This study, however, may not be possible until more is known of the role of auto-immune phenomena in the clinical manifestations of the treponematoses.

Step 1—Pinta (Map 3)

As already mentioned, pinta has many characteristics of a primitive infection, such as lack of invasion of deeper tissues than the skin and a long duration of infectiousness which would maintain it in small population groups, even in families. These suggest that it is an early human treponematosis. Another characteristic that must be taken into account in considering its origin is its present isolation in the Amerindian populations in humid areas of the Americas (Map 1).

The proposed original treponematosis, pinta, might have extended throughout Africa and Asia and into the Americas with the migration of man and other animals over the ice-free Bering Strait land bridge which probably last existed about 15 000 to 10 000 B.C. (Zeuner, 1958). This would have been during the last part of the last (Wisconsin) glaciation before the ocean levels had risen from the melting of the polar ice-caps (Haag, 1962). Willett (1953)

TWO HYPOTHESES AS TO THE POSSIBLE EVOLUTION OF THE SYPHILIS-YAWS TREPONEMES



says that the end of this glaciation " is usually placed at approximately 6500 B.C.", but it is now more generally regarded as being about 8000 B.C. It can be confidently assumed that little came out of the Americas after the last glaciation until Columbus's discovery in the late fifteenth century.

Had pinta—like the primitive marsupials now isolated in the Americas and Australia (Mathew, 1939)—been world-wide, one would expect to find pockets of it in isolated and especially peripheral communities such as the Australian aborigines (see also Darlington, 1957). An Indonesian corridor to Australia would have had water crossings of 20 miles or more thousands of years before man's first entry into Australia. Except for the dingo, which probably accompanied man in his boat, and rats and bats, the indigenous mammals of Australia and Tasmania were all marsupials or monotremes of more ancient ancestry; thus Australia, from a zoological point of view, must have been isolated from the Euro-Afro-Asian land mass much earlier than were the Americas.

Pinta might have been expected to have survived, had it ever been present, among isolated communities such as the pygmies and negritos in remote mountain fastnesses, but no report of this is known.

Although all the pigmentary changes characteristic of pinta are not seen in yaws areas, loss of pigment frequently occurs in many such areas on the hands and wrists which closely resembles some of the changes reported in pinta and has sometimes caused confusion (see page 15). Some of these pigmentary losses are associated with the plantar hyperkeratosis of the later stages of yaws (Hackett, 1957a, 1960). Other pigmentary losses occurring in yaws areas do not appear to be due to a treponematosis and do not respond to arsenical or penicillin therapy.

In attempting to date the spread of an infection from the Euro-Afro-Asian land mass to the peripheral Americas and Australia it had been thought that the absence of genes for the blood groups A and B from the Indians of South America and of that for B from the Australian aborigines (Mourant, 1958) would be useful. Recently, however, these blood groups have been found in certain apes, thus their dating value has diminished.

After taking the above points into consideration, it is here proposed that pinta arose from an animal infection in the Euro-Afro-Asian land mass, perhaps before about 20 000 B.C. and had spread through the then accessible world by about 15 000 B.C. (Map 3).

This leaves unexplained the lack of evidence of survival of mutants of pinta treponemes in the Americas as it is proposed below happened elsewhere. If the differences of colours of the pinta lesions reported from different South American countries are real, these may be due to mutants; perhaps the environment may have been too constant to favour mutants. The Americas differ from the other continents in that desert zones are much less extensive because both North and South America are so narrow in the latitudes concerned. A study of yaws in Africa in environments resembling those in which pinta is endemic might be instructive.

Step 2—Yaws (Map 4)

Pinta is assumed to have spread originally throughout the world by about 15 000 B.C. and to have been cut off in the Americas from the main land masses after about this time. Maps 1 and 2 indicate the more recent patterns of yaws, endemic syphilis and venereal syphilis.

With the exception of the small areas of endemic syphilis in southern Africa and possibly in central Australia, the most peripheral infection of the three remaining infections is yaws. This may mean (Mathew, 1939) that it was the first of the three to develop. It is therefore proposed that in Afro-Asia a humid, warm environment favoured mutants of the pinta treponemes which were more invasive and destructive of tissue and which caused yaws. This might have occurred about 10 000 B.C. Yaws then spread through the Afro-Asian area, but did not reach the Bering Strait before it was again flooded. The last glaciation was extensive and many of the now arid geographical areas probably enjoyed good rainfall and a more uniformly warm climate. Thus yaws might have appeared anywhere in Africa and southern Asia where the environment was favourable and spread widely to reach Australia and the Pacific islands if or when they were inhabited, but not America.

Of mutation among the treponemes little is known and little may be learnt before they can be cultivated. Because drug resistance has not yet developed in treponemes, mutation affecting other characters is not excluded. The treponemes would be expected to undergo mutation at a rate comparable to that found in other micro-organisms, but only those mutants would survive which changing climatic, social or other conditions favoured.

Only *T. pallidum* of venereal syphilis flourishes in a wide range of climates; the others appear rather strictly limited to warm climates either humid (yaws and pinta) or arid (endemic syphilis).

Mr N. B. Tindale of the Department of Anthropology, South Australian Museum, Adelaide (personal communication, 1962) says that man was almost certainly in Australia for part of the last half of the last glaciation, perhaps before 20 000 B.C. and that three separate racial groups came into Australia from Asia. The earliest known were negritos, who were short in stature, dark-skinned with crisp, curly hair and of a different race from later arrivals who displaced them. Their most obvious survivors were the Tasmanians (Tindale, 1960). No pathological changes suggesting treponematoses have been described in the few Tasmanian bones that have survived.

The extension of yaws across the Bering Strait would have been checked by the rising of the sea levels due to the melting of the glacial polar caps about 15 000 B.C., although Lamb (1963) states that present sea levels were probably not reached until later—about 4000 B.C.

In the Pacific islands yaws was apparently present when the first Europeans arrived. Stewart & Spoehr (1952), by radiocarbon dating, placed some skulls from the Mariana Islands with lesions probably due to treponematoses at the mid ninth century A.D.

There is also considerable evidence of yaws in Hawaii (Samwell, 1786), although mistaken for " the venereal disease ", and also in Australia (Hackett, 1936b) before the arrival of Europeans (see page 16).

In India, yaws has survived in Orissa, Madhya Pradesh and Hyderabad in rather isolated aboriginal tribes in inaccessible localities.

Kynsey (1881) and Spittel (1923) state that yaws was introduced into Ceylon, where it was known as *parangi*, meaning " the foreign disease ", by slaves brought by the Portuguese from Africa. Such a means of introduction may also explain the focus of *S. haematobium* bilharziasis in Gimvi near Bombay.

In Africa, yaws has so flourished that some observers have thought that it was the cradle of the disease. The prevalence and severity of yaws in tropical Africa during the first 30 years of this century were probably much greater than anywhere else (Botreau-Roussel, 1962). More than one observer regarded yaws then as a bigger burden to some African populations than all other infections put together (van Nitsen, 1944).

Thus yaws had the capacity in suitable conditions to become a widely spread, non-killing disease affecting most of the population by adult life.

To summarize, somewhere in Afro-Asia by about 10 000 B.C. conditions favoured certain mutants of the pinta treponeme that gave rise to yaws which then spread throughout the world except the Americas, which were by then isolated by the reappearance of the Bering Strait.

Step 3—Endemic syphillis (Map 5)

On Map 2 an uninterrupted block of endemic syphilis extends from Africa through western into central Asia, comprising deserts and semi-deserts, often with nomadic populations. There were two smaller but perhaps epidemiologically no less important areas of endemic syphillis in similar but southern latitudes, in Bechuanaland until recently (Murray et al., 1956) and perhaps in central Australia in the past (Hackett, 1936a, 1936b). How endemic syphilis could have occurred in Bechuanaland is difficult to understand if it did not evolve from yaws. Since endemic syphilis is at present mostly restricted to arid, warm climates these may be assumed to favour the selection of mutants that gave rise to it. Such conditions would have developed in the present geographical distribution of endemic syphilis following the end of the last glaciation about 8000 B.C. and have been maintained, with some variations, ever since.

The small area of endemic syphilis in East Africa (Map 1) in the Buganda Province of Uganda (Davies, 1956) may have been venereal syphilis with non-venereally acquired sporadic transmission, rather than endemic syphilis (see page 29), and this may have arrived there much more recently.

Reference has already been made (see page 12) to the effects of climate on the skin lesions of yaws as reported by Lopez-Rizal & Sellards (1926), by Ramsay (1927) and also by Fitzgerald & Dey (1931). One of these was the frequency of buccal mucosal papules in cooler climates; such mucosal lesions are characteristic of endemic syphilis. In arid, intra-continental climates, the summers are hot and the winters cold but on the average the climate is warm. Turner & Hollander (1957) have shown that maintaining rabbits inoculated with treponemes at cool air temperatures resulted in higher infection rates, shorter incubation periods and more severe lesions than did maintaining them at higher air temperatures. The optimal temperature for treponemes is about 35°-37°C and the body temperature of the rabbit is about 39°C; above 40°C treponemes are destroyed. Turner & Hollander speculate about the effects of " environmental temperature on the treponematoses in human beings ".

Some observers have reported a higher prevalence of yaws in the cooler rainy season than in the hot dry season (Harding, 1949). However, the temperatures at the cool season in tropical climates would be much higher than those of the cool season in semi-arid, intra-continental ones, which at night may fall below 0°C. Fitzgerald & Dey (1931), however, reported the scarcity of papillomata in Assam during the winter.

Marshall (1959) found that resistance of rabbits to invasion by myxomatosis virus of only moderate virulence was increased at higher temperatures and reduced at lower ones, and Lwoff (1959) found that higher temperatures checked the development of poliovirus of low virulence. Raised temperatures did not influence the course of virulent virus strains.

Turner & Hollander (1957) also report changes in behaviour in experimental animals of a few strains of the yaws treponeme towards that of venereal syphilis, especially when they were kept under favourable cool air conditions (18°-21°C). Further such studies are needed.

It is proposed here that mutants of the yaws treponeme were selected by arid, warm climates resulting from the retreat of the last glaciation and that by about 7000 B.C. yaws in such areas had changed into endemic syphilis, while in humid warm climates yaws has continued unchanged.

Step 4—Venereal syphilis (Maps 6 and 7)

In Map 2, venereal syphilis is shown as occurring in Europe and the Mediterranean countries. Of the origin of venereal syphilis in Europe as in Persia (Elgood, 1951), India (Reddy, 1936), China (Wong, 1918; Eckstein, 1928) and Japan, there are two main explanations.

One is that venereal syphilis appeared within about ten years before or after the year A.D. 1500. Thus Bloch (1908), Hutchinson (1908), Capper (1925), Power (1934), Hamlyn (1939) and Harrison (1959) attribute venereal syphilis in Europe to its introduction by the crews of Columbus's ships returning in 1493 from the discovery of America; they cite the writings of the sixteenth century to support their contention. Their main points are the absence of references in writings before the end of the fifteenth century to a disease like venereal syphilis as known at present, statements that it was then a new disease, the absence from Europe of pre-Columbian bones with lesions resembling those of venereal syphilis and the alleged presence of such bones in America. However, diagnosis in some references to " pre-Columbian syphilis in America " such as " most likely due to syphilis ", " almost certain evidence of luetic infection ", " changes regarded as pathognomonic of syphilis " and " changes consistent with, although not diagnostic of, syphilis " (Cole et al., 1955) leave much to be desired.

References by early writers, in the other countries mentioned above, to syphilis have been thought to have been mistaken; venereal syphilis in these countries was believed to have been recent and to have appeared about the time of its supposed introduction into Europe by Columbus's crews. Venereal syphilis was often known by such names as *phirangi roja* (India), indicating its foreign origin. The opinion of Elgood (1951; personal communication, 1962) that syphilis first appeared in Persia at the beginning of the sixteenth century is based upon wide personal examination of original texts. However, as far as syphilis in Europe is concerned, the evidence for its origin in America is neither impressive nor precise. The history of venereal syphilis in Asia needs further study.

The other explanation (Buret, 1895; Sudhoff, 1925; Holcomb, 1940; Castiglione, 1947; Campbell, 1954; Singer & Underwood, 1962) is that venereal syphilis was present in Europe but was not identified from among a number of diseases, including some epidemic diseases, referred to *en masse* as " leprosy ". They speak of the alleged venereal transmission of this " leprosy " which disappeared from writings after the identification of syphilis in the sixteenth century and its naming by Fracastorius in 1530. They also refer to writings and edicts (Sudhoff, 1925) relating to the avoidance of venereal diseases of wider clinical range than gonorrhoea, either before the return of Columbus or within the following decades. Harrison (1959), after careful study, has called attention to the misdating of the earliest Paris edict relating to *grosse vérole* (Holcomb, 1934) as 25 March 1493, whereas the correct date is 6 March 1497. Singer & Underwood (1962) however, suggest that perhaps a new strain of *T. pallidum* was brought to Europe from America, which changed the character of syphilis completely during the closing years of the fifteenth century.

Lancereaux (1868) believed that most of the manifestations now known as syphilis were known in Europe long before the Naples " epidemic ". Only after that outbreak were many lesions of the various stages of the disease related to each other to give the picture of venereally transmitted syphilis. Previously some had been separately described and others were confused with other diseases.

Hirsch (1885) stated that there was little doubt that venereal syphilis occurred in antiquity in Greece and Rome and in the Middle Ages in Europe. He also stated that syphilis occurred before the end of the fifteenth century in other parts of the world such as India, China and Japan, but that it was taken to America and the Pacific islands by Europeans. European contact with Japan, however, was very restricted until about a century ago.

Cole et al. (1955) state: " Syphilis is a disease of antiquity. It was undoubtedly present from the earliest times among the Arabians, Greeks, and Romans in the Dark Ages, and it probably came from China, Japan and India."

A leading article in the *British Medical Journal* (1962) typifies the confusion and lack of precision. It states that " syphilis continues to be the most controversial disease of all, there still being inadequate material to prove conclusively whether it originated in the New World or the Old ". Later it is suggested that " there is, in fact, no good reason why both continents should not have been affected during pre-Columbian times ",[1] but no good reason is given why they should.

[1] The possibility that venereal syphilis was brought to Europe by invaders from Asia in the thirteenth century needs investigation. Rat (1891) says that if syphilis did not originate in Europe, it might have been brought to Spain from Africa by the Moors. The last Moorish kingdom in Spain (Granada) did not surrender until 1492.

Bones with allegedly venereal syphilitic changes have been found in cemeteries near former leprosy institutions. The question has also been raised why mercury, one of the first effective substances used in the treatment of venereal syphilis, was of such high repute in Europe during the first fifteen centuries of the Christian era, if there were no venereal syphilis. The significance of the apparent absence of syphilitic bone lesions in Europe during this period still remains to be understood.

Some writers think that the epidemic of Naples in 1493, like others before it, was not due to venereal syphilis but to an outbreak of one of the epidemic communicable diseases that are known today. Others have pointed out that the American origin of the " Naples epidemic " was not raised until 25 years after Columbus's return.

In considering the absence of clear descriptions of syphilis before the early years of the sixteenth century one should remember that syphilis and gonorrhoea were not generally recognized as separate diseases until the second half of the eighteenth century (Bell in 1793). Even such an able investigator as John Hunter (1728-1793) did not accept this and carried out an experiment upon himself by which he erroneously satisfied himself that they were the same disease. Locomotor ataxia (tabes dorsalis) was not clearly described in the medical literature (Duchenne in 1858) nor its syphilitic origin recognized (Fournier in 1876) until the nineteenth century, although in its later stages it can be readily diagnosed at a distance by the gait of the sufferer. McGeoch (1960) reports that no reference to neurosyphilis has been recognized in the writings of Shakespeare (1564-1616). Therefore, before and for some time after the fifteenth century the diagnosis of syphilis doubtless included many conditions, for example, some forms of leprosy and some skin diseases now known not to be syphilitic. Something similar happened a generation ago with " influenza ", which was a generic rather than a specific diagnosis before laboratory methods for diagnosis were developed.

This third and last suggested step in the evolution of the treponematoses would involve the change from a non-venereal disease (endemic syphilis) of rural children to a venereal disease (venereal syphilis) of urban adults. This might begin with the decrease of childhood infections because venereal transmission would not be expected in a population infected and immunized in childhood. If endemic syphilis from childhood infection decreased more adults would be susceptible and a few " last cases " of delayed condylomatous relapses might provide the opportunity for venereal transmission to uninfected and susceptible partners. Guthe & Luger (1957) suggest this change in Syria. Denser settlement, more clothing and increasing sexual laxity as well as decreasing endemic syphilis might well have assisted climatic change in the selection of mutants towards venereal syphilis treponemes.

Davies (1956) has suggested that venereal syphilis was introduced into the lake areas of Uganda in the last half of the nineteenth century and since the turn of the century has replaced an already existing endemic syphilis. The increase in the amount of clothing worn in these districts during the present century may have hastened this. However, the change, which would accompany the improvement of standards of living, might rather have been the reduction of non-venereally transmitted venereal syphilis. The affected population made up an organized kingdom in contrast to the organizational disorder of their relatively naked neighbours among whom yaws was highly endemic (Hackett, 1947). It has been pointed out already that the climate of the affected province, Buganda, is not arid or semi-arid but humid.

If endemic syphilis was in Buganda, how it came is unknown. There is the same problem of venereal syphilis in Ethiopia, where it may have been introduced by visitors, slavers or other traders.

The change to venereal transmission might have occurred with the growth of big cities, together with increased clothing, in the now arid countries of the eastern Mediterranean and south-western Asia (Map 6). This might have been about 3000 B.C. during the post-glacial climatic optimum which culminated between 5000 B.C. and 2500 B.C., when the climatic zones were displaced towards the higher latitudes and temporarily the equatorial/monsoon belts were widened and the desert zones less severe. However, from about 3000 B.C. desiccation of the previously arid areas returned and has remained ever since (Brooks, 1949; Lamb, 1963) and was probably maximal during the twentieth century. Venereal syphilis was probably carried to the Mediterranean littoral by shipping and later throughout Europe, which was a treponemally uncommitted area, especially after the first century B.C. with the Roman conquests. In rural populations in Syria, Saudi Arabia, Iran and Iraq the indigenous treponematosis is still endemic syphilis. In rural Syria (Hudson, 1946) venereal syphilis was known as *franji*, meaning " foreigner ". This is also reported of parts of India (Reddy, 1936). The absence of

lesions resembling those of venereal syphilis in bones in Europe before the end of the fifteenth century and in early Egyptian burials (Rowling, 1961) needs careful consideration. However, the disease which, it is here suggested, evolved from endemic syphilis about 3000 B.C., may have still been a " mild " one, until a mutant appeared at the end of the fifteenth century in Europe which caused a more grave disease (Shrewsbury, quoted by Harrison, 1959; and *Med. J. Aust.*, 1961).

The social conditions, customs and habits of the congested urban populations of Europe in the fifteenth and sixteenth centuries (Taylor, 1953) would have assisted in spreading venereal syphilis both non-venereally and venereally. Venereal syphilis in Europe is generally supposed to have become less destructive since its first recognition at the end of the fifteenth century. At present venereal syphilis is regarded as being more gummatous in patients of African descent (in America) and more neuropathogenic in patients of European stock. However, *T. pallidum* of venereal syphilis appears to be a fairly uniform species. Any variations in its clinical manifestations might have been due to other than treponemal factors.

One of Hudson's (1958) conclusions is that yaws arose in Africa from a saprophytic treponeme several hundred thousand years ago and spread eastwards to India and Oceania about 100 000 years ago. He also thinks yaws extended into America. As yaws left the tropics and entered cooler climates it became, he says, endemic syphilis and about 10 000 years ago in towns and cities on the Nile and Mesopotamia it became venereal syphilis.

Hudson (1962) at the end of an assessment of *las buvas* of Villalobos (1472-1556) states:

> " It is more likely that in the latter decades of the fifteenth century the venereal form of syphilis was coming to be recognized as it emerged from a widely disseminated non-venereal endemic form of the disease in Europe. The process of transition in the epidemiology of syphilis from non-venereal to venereal, and endemic to sporadic, had been going on in that continent for many years before 1493. Columbus could have had nothing to do with it ".

Cockburn (1961) presents ideas of a " philosophical nature " about the characteristics and origin of the treponematoses, and Willcox (1960) stresses environmental factors in the " evolutionary cycle of the treponematoses ".

Since venereal syphilis is geographically and pathologically more closely related to endemic syphilis than to yaws its origin from the former seems likely. Probably yaws was not present in the Americas when Columbus arrived; pinta is the ancient American endemic treponematosis. Venereal syphilis was said to have been unknown in North Canadian Indians before European contacts (Holcomb, 1940) and the limited studies of Medina (1954) of the resistance of pinta patients to the yaws treponeme would suggest possible resistance to syphilis. This in turn is further though weak support for the absence of syphilis in the Americas.

As stated above, it is suggested here that in cities, perhaps in the eastern Mediterranean or south-west Asia, conditions developed which favoured treponeme mutants tending towards venereal syphilis. This resulted in the replacement of endemic syphilis by venereal syphilis in urban populations, and later Europe became gradually but finally generally infected. Thence it or a further mutant causing a grave disease was probably carried during and after the sixteenth century to the Americas, southern Africa (Sax, 1952), India, south Asian countries, China and Australia (Map 7) (see page 28).

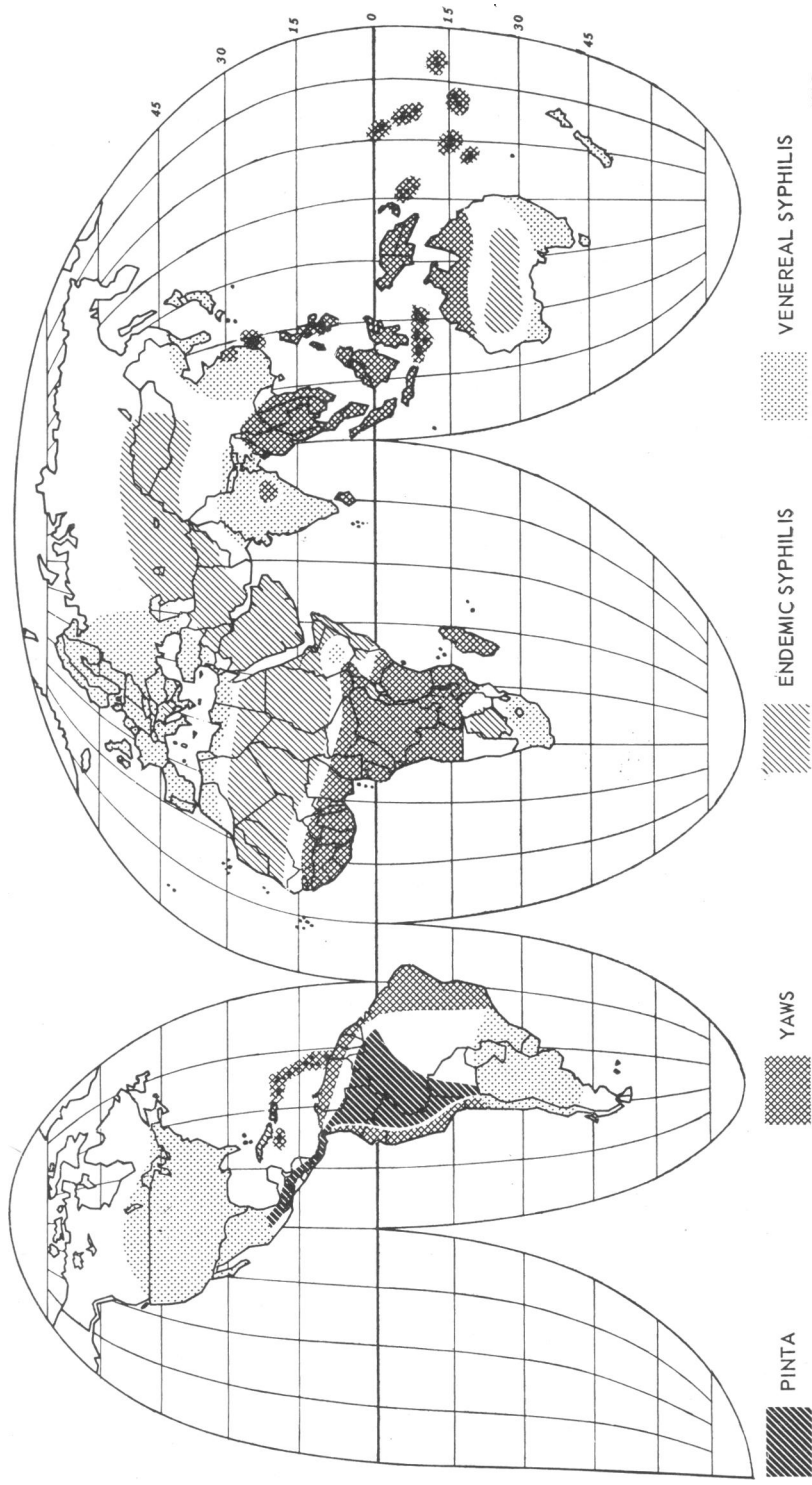
Dr H. H. Lamb of the Meteorological Office, Bracknell, Berks., England (personal communication, 1962) has pointed out that in Europe during the fifteenth century the climate was deteriorating (cooling)—in some decades, particularly in the 1430s and 1490s, deteriorating sharply—though it temporarily recovered somewhat between 1500 and 1550. The fifteenth century was one of considerable difficulty for the rural people, particularly of northern Europe, because of the worsening of the climate and the grave results of the Black Death.

CONCLUSION

A brief review of the causal organisms, clinical course, epidemiology, estimated geographical distribution at the beginning of the present (Map 1) and of the sixteenth centuries (Map 2) and several other aspects relevant to the origin of the four human treponematoses shows that much more knowledge is needed before a definitive statement about this can be made. However, indications can be given as to where steps should be taken or investigations made, before it is too late, which will assist in the ultimate solution of these interesting and not unimportant questions.

MAP 1

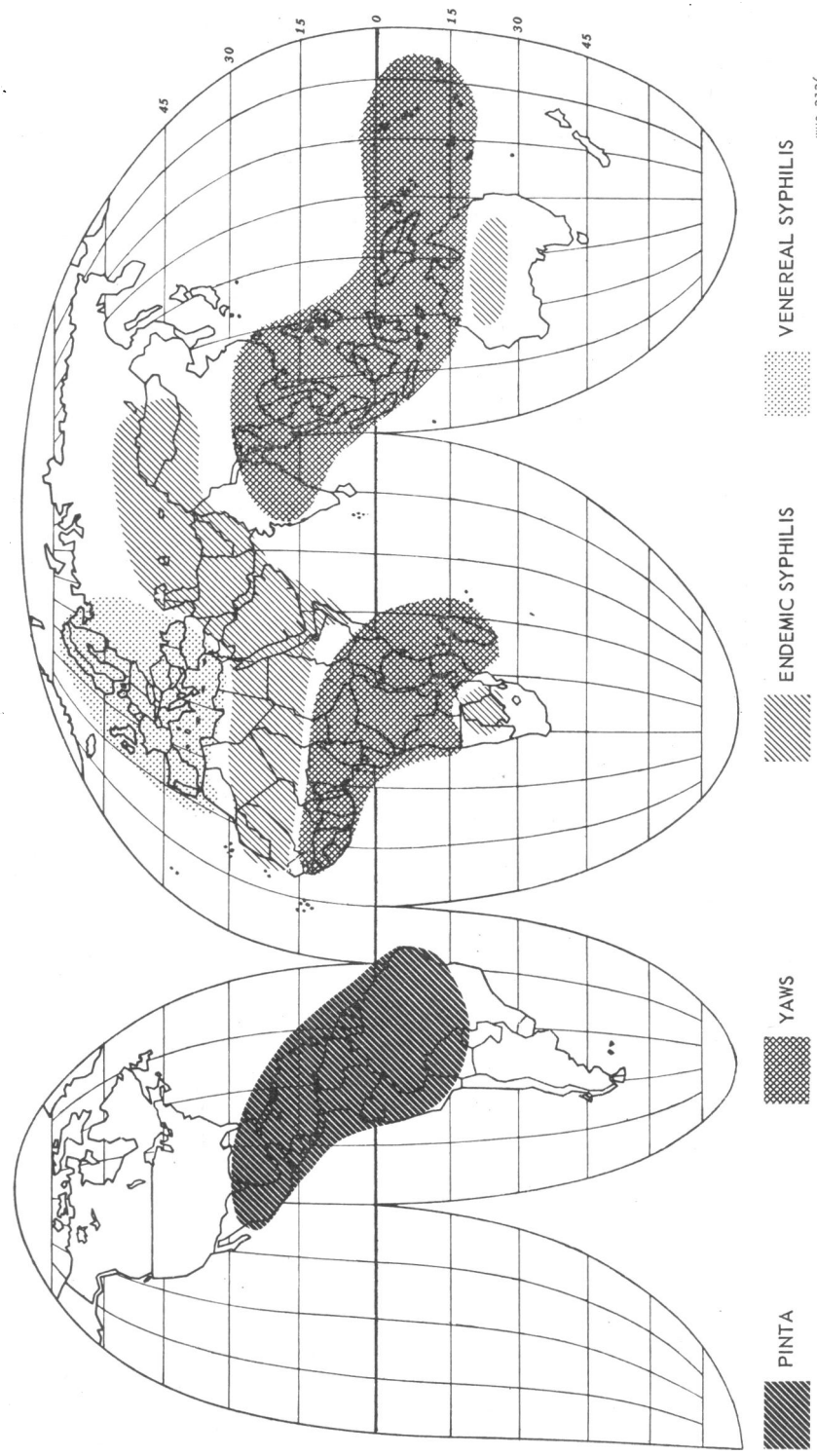
PROBABLE GEOGRAPHICAL DISTRIBUTION OF THE TREPONEMATOSES ABOUT A.D. 1900 [a]



[a] See pages 15, 17 and 23 and footnote on page 15.

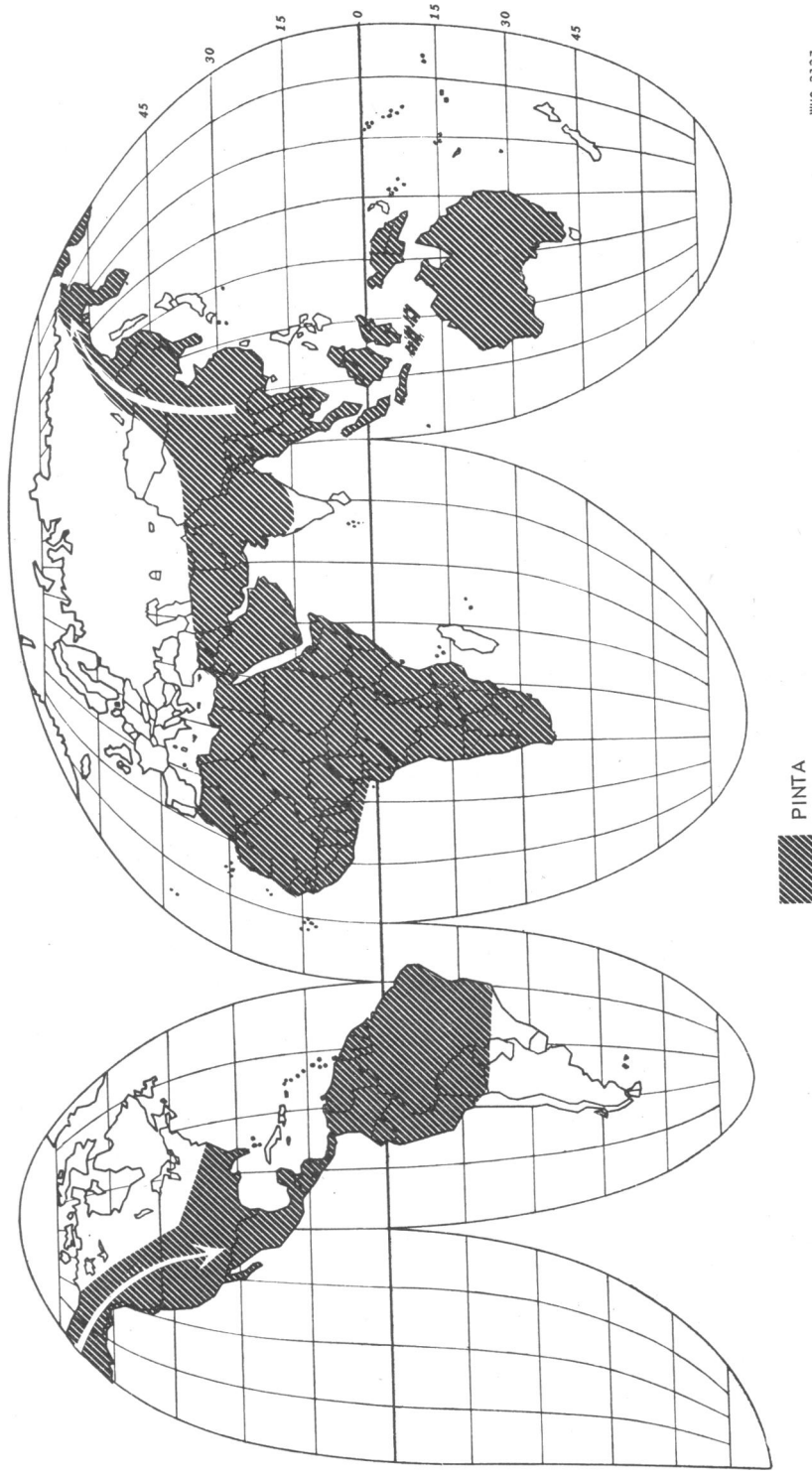
MAP 2

PROBABLE GEOGRAPHICAL PATTERN OF THE TREPONEMATOSES AT ABOUT THE TIME OF EUROPEAN EXPANSION IN THE 16TH CENTURY A.D.[a]



[a] See pages 17 and 24 and footnote on page 15.

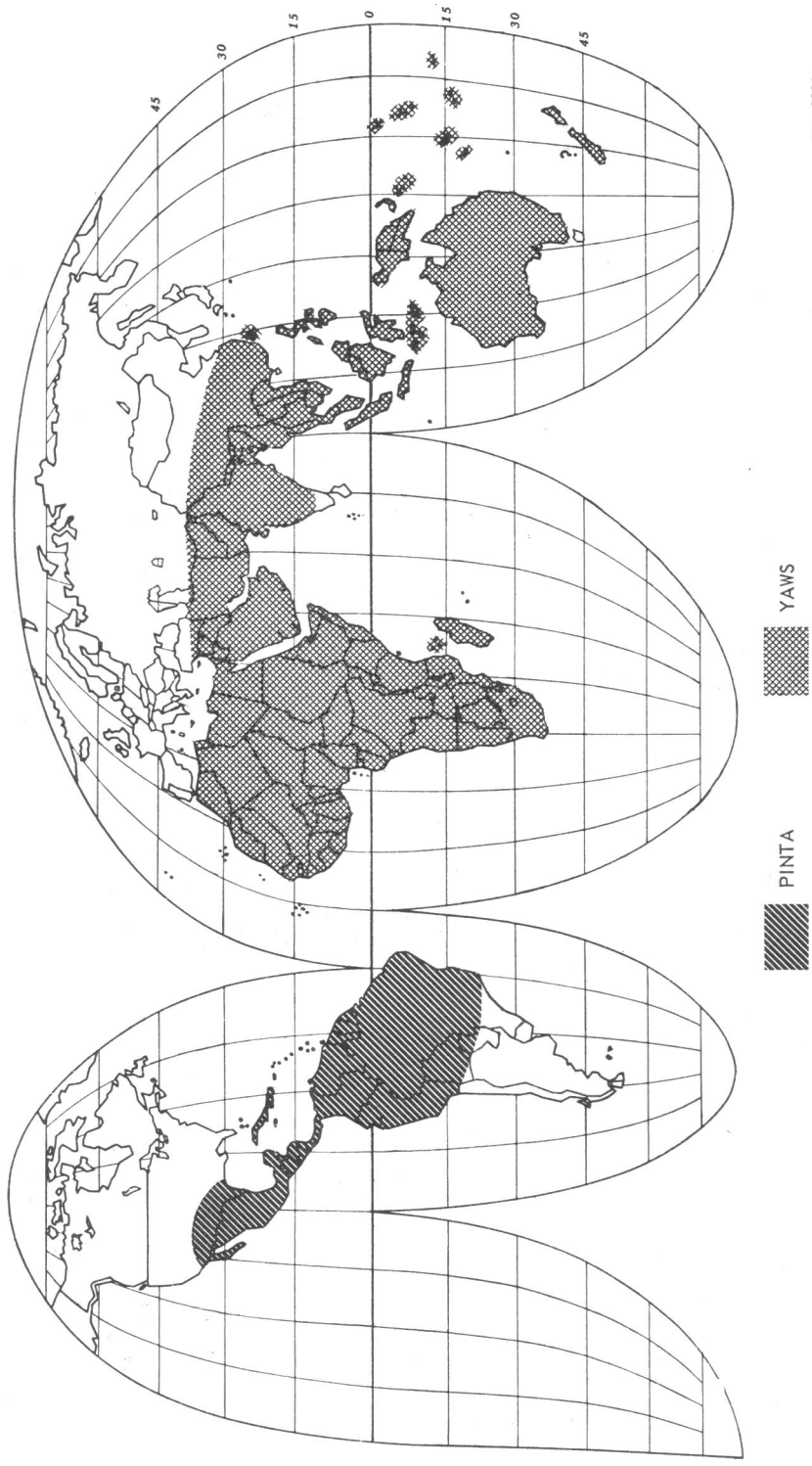
MAP 3
PROBABLE EXTENT OF PINTA ABOUT 15 000 B.C.[a]



[a] See page 24 and footnote on page 15.

MAP 4

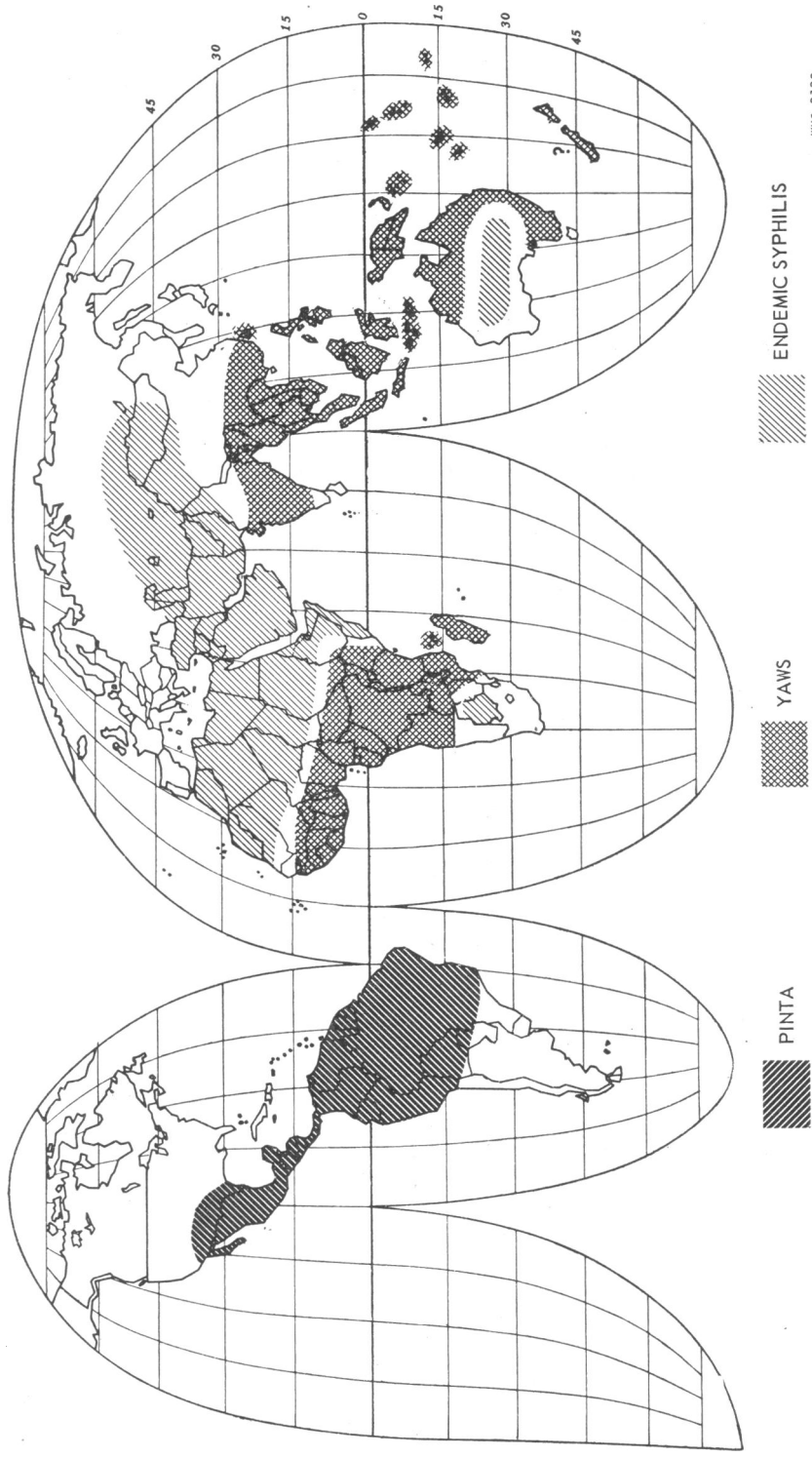
PROBABLE EXTENT OF PINTA AND YAWS ABOUT 10 000 B.C.[a]



[a] See page 26 and footnote on page 15.

MAP 5

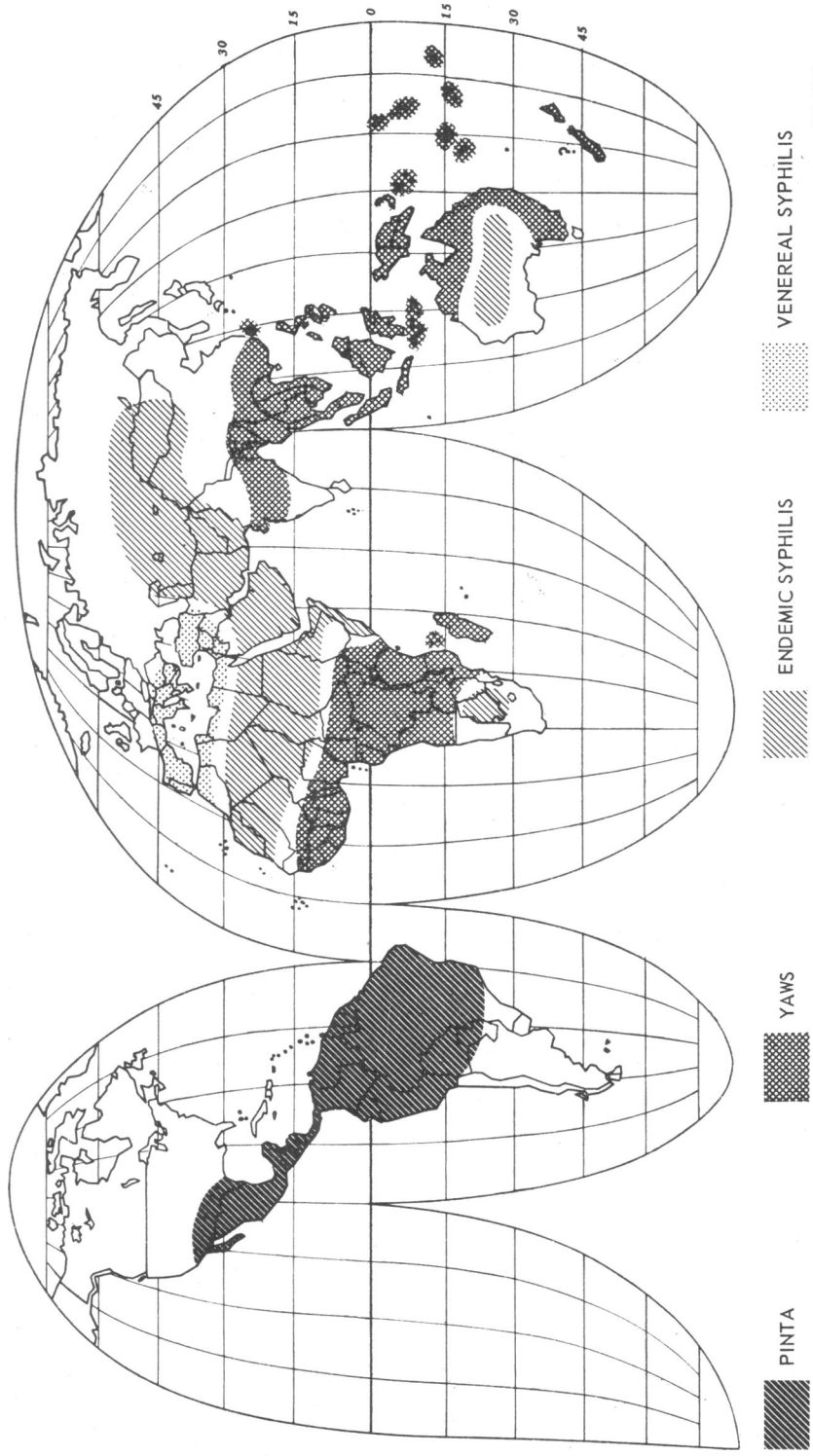
PROBABLE EXTENT OF PINTA, YAWS AND ENDEMIC SYPHILIS ABOUT 7000 B.C.[a]



[a] See page 27 and footnote on page 15.

MAP 6

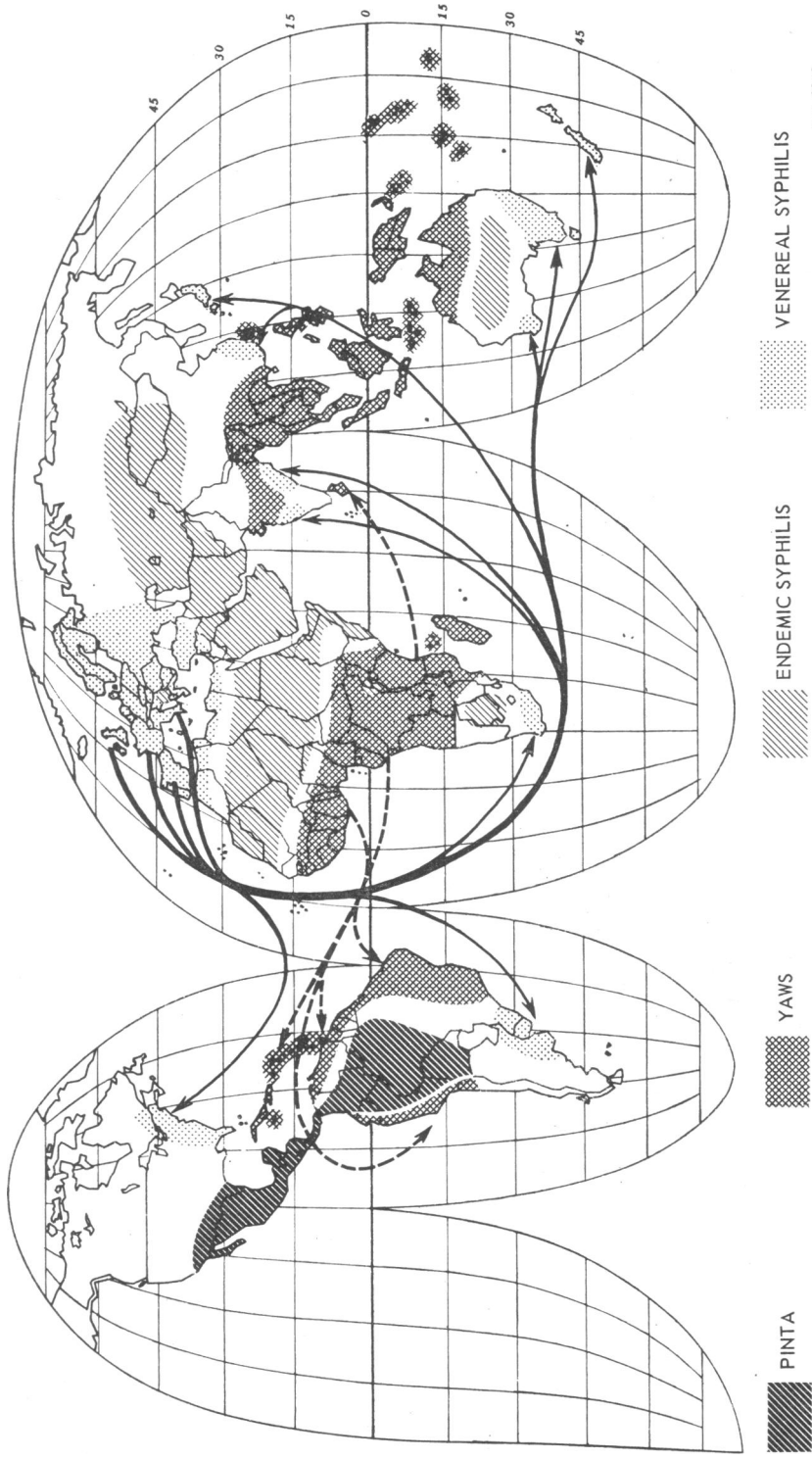
PROBABLE EXTENT OF PINTA, YAWS, ENDEMIC SYPHILIS AND VENEREAL SYPHILIS FROM ABOUT 3000 B.C. TO THE 1ST CENTURY B.C.[a]



[a] See page 28 and footnote on page 15.

MAP 7

SPREAD OF VENEREAL SYPHILIS THROUGHOUT EUROPE AT ABOUT THE 1ST CENTURY A.D. AND SPREAD OF VENEREAL SYPHILIS THROUGH THE WORLD AND OF YAWS TO THE AMERICAS AND CEYLON FROM THE 16TH CENTURY A.D.[a]



[a] See pages 28 and 30 and footnote on page 15.

It is suggested that:

1. Pinta probably arose in the Afro-Asian land mass from an animal infection and by about 15 000 B.C. had spread throughout the world (Map 3). It later became isolated in the Americas.

2. Yaws arose in the Afro-Asian land mass from mutants of the pinta treponeme and by about 10 000 B.C. had spread throughout the world, but did not reach the Americas, which were then isolated by the flooding of the Bering Strait with the melting of the polar ice-caps towards the end of the last glaciation (Map 4).

3. Endemic syphilis arose from yaws about 7000 B.C. when arid climates following the retreat of the last glaciation favoured the selection of suitable treponemes (Map 5).

4. Venereal syphilis evolved from endemic syphilis about 3000 B.C., when big cities developed in south-western Asia during the post-glacial climatic optimum which produced conditions favouring the selection of suitable mutants (Map 6); later (after the first century B.C.) it spread throughout Europe. This was probably a " mild " disease until a mutation towards the end of the fifteenth century A.D. may have given rise in Europe to the syphilis of the present.

5. Venereal syphilis was carried to the treponemally uncommitted populations of the world with the European expansion of the sixteenth and subsequent centuries (Map 7).

The proposed order of the events is more probable and important than the dates suggested. However, with more knowledge both may be changed. This is not the occasion to consider the changing conditions of the present which might favour further treponeme mutants nor to hazard what characters they might possess.

Much more information is needed. One of the most obvious and urgent needs is the collection of an adequate and carefully selected representative series of treponemal strains in readiness for the time when full antigenic studies of treponemes can be made. Already it may be too late to do this for the Australian endemic treponematoses. In a very few years it may well be too late to attempt to make a useful collection of such strains elsewhere. Then not only will an important contribution to the study and history of human disease be lost but so will information about the migrations of man long ago. The elucidation of the origin of the treponematoses might be of importance in the eradication of venereal syphilis.

A careful study is needed of bones from accurately dated burials throughout the world before the end of the fifteenth century. This must start with an attempt to define the criteria for the recognition of changes due to treponematoses and other diseases likely to have been present in ancient times. The possibility of finding antibodies to treponemes in pre-Columbian material might be studied (Durel, quoted by Harrison, 1959). To know if syphilitic, or rather treponemal, lesions occur in pre-Columbian bones in Europe or America—or in both or in neither—would be of great interest. There are already suspicions that some of the lesions of European bones of long ago may result more from excessive treatment with mercury than from infectious disease.

A search for further animal treponematoses by the examination of sera for antibodies might be combined with other studies on wild animals which are going on in various tropical countries.

RÉSUMÉ

L'origine des tréponématoses, que l'auteur tente de retracer, reste en grande partie conjecturale. Ce que l'on sait de l'évolution clinique, de la répartition géographique et épidémiologique des quatre tréponématoses humaines (syphilis vénérienne, syphilis endémique, pian et pinta) qui semblent étroitement apparentées, montre la nécessité d'études plus poussées, dans le présent et le passé, pour préciser leur développement.

Les connaissances actuelles, pour imparfaites qu'elles soient, peuvent donner lieu aux hypothèses suivantes:

1. Vers 15 000 av. J.-C., la pinta, d'origine probablement animale, s'est répandue à travers le monde, mais à la suite du creusement du détroit de Behring à la fin de la dernière période glaciaire, s'est trouvée cantonnée sur le continent américain.

2. Vers 10 000 av. J.-C., des conditions de milieu ont peut-être favorisé des mutations du tréponème, mutations responsables du pian, largement répandu à travers l'Asie et l'Afrique.

3. Vers 7000 av. J.-C., le climat aride ayant succédé à la dernière grande glaciation a favorisé les mutations qui ont, secondairement, déterminé l'éclosion de la syphilis endémique.

4. Vers 3000 av. J.-C. la naissance, dans l'Asie du Sud-Ouest, de grandes villes sous le meilleur climat post-glaciaire a produit des conditions favorables à la sélection

de mutants responsables de la syphilis vénérienne; c'est après le 1er siècle de notre ère que la maladie s'est étendue à toute l'Europe.

5. A la fin du XVe siècle une nouvelle mutation peut avoir fait de la syphilis vénérienne la maladie grave que nous connaissons maintenant.

6. Pendant le XVIe siècle et depuis lors la maladie a été transportée du fait des explorations et de l'expansion géographique aux contrées indemnes de tréponématoses.

On devrait recueillir, pendant qu'il en est encore temps, des tréponèmes provenant de parties du monde délibérément choisies; on devrait également rechercher soigneusement d'autres tréponématoses de l'animal (en plus de celle du lapin, déjà connue), cela en attendant d'avoir de meilleures méthodes d'études. Il faut avoir des connaissances plus étendues et plus précises sur la fréquence et la distribution géographique des lésions tréponémateuses des os trouvés dans les tombeaux précolombiens des Amériques ainsi que dans plusieurs autres parties du monde. Des confusions entre syphilis vénérienne et pian, faites par les premiers explorateurs dans leurs journaux de voyage, se retrouvent dans les musées.

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