THE RISE AND FALL OF THE TREPONEMATOSES*

II. ENDEMIC TREPONEMATOSES OF CHILDHOOD

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We have seen in Part I of the present study that information on venereal syphilis has been available for more than a hundred years and that some of the human ecological factors could be assessed in the rise and fall of this adult treponemal disease. In the endemic treponematoses of childhood—on the other hand—knowledge of human ecological factors influencing recrudescence and regression is limited and the morbidity reporting of early and late manifestations of yaws, pinta, and endemic non-venereal syphilis in the rural areas of developing countries is poor. Long-term trends and periodic recurrences can mainly be discerned through prevalence data obtained in campaigns and surveys over the last 40 to 50 years.

Trends in Endemic Treponematoses of Childhood

The concept in early endemic treponematoses campaigns was that introduced in Africa by Jamot in trypanosomiasis in 1918, namely clinical treatment surveys and re-surveys until it was believed that the disease was under control. This was the case after 1923 in yaws in Western Samoa (Buxton, 1928; Lambert, 1936) and in endemic syphilis in South Africa (McArthur, 1923), in Syria (Hudson, 1937), and in Yugoslavia (Kogoj and Vuletic, 1939; Grin, 1953). In these and similar programmes suppression of active lesions resulted, but repeated intramuscular or intravenous metal therapy was not practical, quite apart from toxic side-effects. The epidemiological concept that it was essential to treat symptomless contacts and latent cases as well as clinical cases, had as yet not evolved. Similarly, the population coverage could not be determined

at surveys and re-surveys in the absence of accurate census-taking—a quantitative aspect which has since become an efficiency index of importance in campaign evaluations. Finally, it is clear from the accounts of early campaigns that the disappearance of surface lesions was usually followed by the disappearance also of the interest of the public and of health administrators in further control measures. Failing such measures—particularly the installation or improvement of rural dispensaries and organization of home visits, etc.—endemic treponematoses recurred after all these early campaigns. Their effect was, therefore, of a transient palliative public health nature.

During the second world war standards of living and hygiene deteriorated in many developing countries, as did the available, often limited, stationary and mobile health services. In islands in the Pacific, holoendemic yaws prevalences were encountered after the allied reconquest (Jungalwalla, 1954; Rock, 1953). The increase in yaws was described in Africa (Hackett, 1953), South East Asia (Vachrotai, 1959), and the West Indies (Troupin, Reynolds, and Guthe, 1953). Endemic syphilis became more frequent in the Middle East (Luger, 1958) and the Balkans (Grin, 1953), and pinta in Central America (Rein, Kitchen, Marquez, and Vasela, 1952).

It is of interest to note that this rising trend in the endemic treponematoses of childhood during the second world war paralleled that taking place in the adult treponematosis—venereal syphilis—in the same context, but in entirely different ecological circumstances.

Penicillin Campaigns and Rapid Fall in Prevalence

The introduction of long-acting penicillin, notably POB, PAM, and later benzathine penicillin,

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which allowed effective single-session therapy to be used on clinical indication, and contact treatment to be applied on epidemiological indication, altered radically the possible scope of public health measures in combating the endemic treponematoses. The acceptance by the Second World Health Assembly in 1949 of this outlook and of a concept of treponematoses as a group because of their taxonomic and immunological relationships and their common response to therapy, set the scene for an international technical assistance programme which included strengthening of rural health services and long-term surveillance. In the next two decades large scale endemic treponematoses campaigns, particularly against yaws, were to go forward in 45 countries (Table I). Up to 1965 some 152 million people had been examined and some 46 million clinical cases, contacts, and latent cases treated with penicillin. The cost of these campaigns, including national and international contributions, was approximately 50 million dollars. The role of UNICEF is notable in regard to material support of these campaigns.

A remarkable fall in endemic treponematoses occurred after 1949-50, the international technical

assistance programme being kept under review by specially convened WHO Expert Committees (WHO, 1950; 1953; 1960), International Conferences (First International Symposium on Yaws Control, 1953; Report of Second International Symposium on Control of Yaws, 1956), Scientific Study Groups on research (WHO unpublished document, 1960), and on the Integration of Mass Campaigns into General Health Services (WHO, 1965).

Again it is of interest to note that the rapidly falling trend in the endemic treponematoses of childhood (yaws, endemic syphilis, and pinta) after 1949-50 coincided with the post-war decline in venereal syphilis. There can be little doubt that this fall in the frequency of all treponematoses as a group was attributable, to a major extent, to penicillin. On the one hand this drug was widely used in active venereal syphilis programmes in the post-war high incidence years and exerted, together with penicillin given fortuitously for other conditions, a certain mass effect in the population, whilst on the other hand in the endemic treponematoses of childhood direct application of penicillin to large populations in mass campaigns became possible.

TABLE I

ENDEMIC TREPONEMATOSES TREATMENT SURVEYS BY WHO REGIONS, 1965

Region	Persons examined at Initial Treatment Surveys	Examinations at All Surveys and Re-surveys	Cases, Contacts, and Latent Cases Treated
Africa	27,269,000	79,120,800	19,780,000
Americas	8,340,000	11,205,000	6,110,000
E. Mediterranean	758,000	1,860,100	324,500
Europe	145,000	883,500	52,500
S.E. Asia	115,515,000	269,971,000	19,850,000
W. Pacific			
Total	152,027,000	363,040,400	46,117,000

Clinical and Serological Patterns

Indonesia has the distinction of having maintained the largest anti-yaws campaign for the longest period of time. Table II suggests the extent in that country of high, medium, and low prevalence areas of yaws 15 years ago. A marked fall in yaws of all forms was observed between 1952 and 1962: on the first completed re-survey in consolidation, the infectious yaws residual amounted to a few cases per 10,000 rural population.

PREVALENCE OF YAWS AT INITIAL TREATMENT SURVEY (ITS), LAST RE-SURVEY (RSL), AND CONSOLIDATION SURVEY (CSL) IN 15 PROVINCES IN JAVA, INDONESIA

Initial Treatment Survey (ITS)			Survey Areas	Last Re-survey before Consolidation (RSL)		
Population a	Persons Examined b	Yaws Cases Found c		Population	Persons Examined	Yaws Cases Found d
29,813	21,632	245	I	—	—	—
2,480,491	2,022,802	80,268	II	2,507,163	2,037,808	24,697
3,144,366	2,541,228	216,738	III	3,172,449	2,640,438	36,877
4,137,401	3,402,121	444,475	IV	4,336,138	3,592,533	47,009
2,244,223	1,796,345	272,532	V	2,299,533	1,867,595	27,044
1,155,812	924,448	157,177	VI	1,292,835	1,009,176	13,475
645,775	477,252	86,641	VII	688,316	557,040	7,733
319,763	279,365	40,755	VIII	315,561	277,231	3,923
61,607	44,176	4,545	IX	56,062	44,875	764

Returns from Treponematoses Control Programme, Indonesia. Director: Dr I. Kodjaja.

Table III shows similar but more modest performance figures in the yaws programme for provinces in North-Eastern Thailand, 1952-60. Thailand had a medium-low prevalence of clinical yaws. The fall in prevalence to levels of total and infectious yaws similar to those in Indonesia can be observed for most areas. These and similar mass data from other campaigns illustrate grossly the public health benefits among children and adults obtained by the persistent work of national and international health workers, but they are unsuitable for detailed epidemiological studies of the regression process in endemic treponematoses. Studies of small populations, well examined and followed in pilot areas, are needed. Several reports on methodological and clinical aspects have appeared in this context (Hackett, 1955, 1959, 1960;

Hackett and Guthe, 1956; Guthe and Luger, 1960; Guthe, Reynolds, Krag, and Willcox, 1953; Grin, 1952, 1956; Hume and Facio, 1956; Samame, 1956), but representative epidemiological-serological data have been very limited. Available data were reviewed at the First (1953) and Second (1956) International Symposium on Yaws Control.

(i) Where endemic treponematoses have been introduced into a rural community and conditions have favoured their spread for some time, infectious lesions in children are followed by non-infectious active lesions also in adults, with inactive lesions and sequelae occurring in due course. Conversely, if endemic treponematoses are receding or are being eliminated, there will also—in due course—be no active lesions in children and, later, in adults.

TABLE III
PREVALENCE OF YAWS AT INITIAL TREATMENT SURVEY (ITS) AND LAST RE-SURVEY BEFORE CONSOLIDATION (RSL)* OR SCHOOL CHECKING SURVEY (Sch. RS)
Provinces in North-East Thailand, 1952-60

Initial Treatment Survey (ITS)			Survey Areas	Last Re-survey before Consolidation (RSL)			Percentages					
Population	Persons Examined	Yaws Cases		Pop-ulation	Persons Examined	Yaws Cases	Persons Examined		Yaws Cases			
							ITS	RSL or Sch. RS	ITS		RSL or Sch.RS	
									Total	In- fectious	Total	In- fectious
409,424	376,544	28,845	I	403,221	320,768	2,010	91.9	59.0	7.93	1.06	0.6	0.08
441,668	381,817	27,709	II	515,554	470,802	11,554	86.4	83.6	7.25	1.47	2.5	0.26
333,067	303,046	19,362	III	94,126	80,905	1,949	90.9	82.6	6.39	0.21	0.30	0.03
340,690	307,669	8,531	IV	37,272	26,946	9	90.3	72.3	2.77	0.31	0.03	0.01
636,830	573,379	33,123	V	190,761	173,192	1,880	90.0	90.8	5.78	0.04	1.08	0.03
135,044	123,027	1,731	VI	17,771	14,727	163	91.1	82.9	1.61	0.01	1.12	0.02
385,005	313,338	24,440	VII	402,752	353,796	9,907	81.4	89.7	7.8	1.20	1.41	0.01
319,268	295,250	7,120	VIII	—	—	—	92.5	—	2.41	0.03	—	—
153,126	136,411	4,989	IX	69,443	62,017	709	89.1	89.3	3.66	0.04	1.14	0.01
554,623	522,324	17,916	X	191,162	169,240	1,446	94.2	88.5	3.42	0.31	0.85	0.04
440,419	365,603	46,942	XI	326,133	236,745	2,712	83.0	46	8.8	1.34	1.15	0.11
289,264	264,143	3,269	XII	—	—	—	91.3	—	1.24	0.02	—	—
471,874	336,538	3,419	XIII	287,965	241,074	1,877	71.3	44	1.01	0.21	0.3	0.06
605,325	538,727	47,836	XIV	437,559	336,462	2,197	88.9	34	8.88	1.68	0.7	0.01
445,845	387,158	20,749	XV	266,412	244,812	2,828	86.8	91.9	5.61	0.47	1.16	0.01

Returns from Treponematoses Control Programme, TCP Thailand Director; Dr Somboon Vachrotai.

* There were several re-surveys between ITS and RSL.

), AND COMPLETED RE-SURVEYS IN CONSOLIDATION (RCI)
1962

Completed First Re-survey in Consolidation (RCI)				Percentages of							
Population	Persons Examined	Yaws Cases Found		Persons Examined			Yaws Cases				
		Total	Inf.	ITS	RSL	RCI	ITS	RSL	RCI		
									Total	Inf.	
26,875	20,722	60	0	72.56	—	77.11	1.13	—	0.29	0	
61,426	2,151,727	11,958	399	81.55	81.28	80.85	3.97	1.21	0.56	0.02	
56,609	2,682,913	19,900	1,506	80.82	83.23	77.62	8.53	1.40	0.74	0.06	
22,247	3,825,923	29,314	2,009	82.23	82.85	81.02	13.06	1.31	0.77	0.05	
30,779	2,041,799	15,878	1,523	80.04	81.22	84.94	15.17	1.45	0.78	0.07	
26,067	1,091,420	7,224	736	79.98	78.06	82.31	17.0	1.34	0.66	0.07	
74,864	653,087	5,484	870	73.90	80.93	84.28	18.15	1.39	0.84	0.13	
56,364	319,758	2,633	107	87.37	87.85	89.73	5.59	1.42	0.82	0.03	
68,641	56,536	592	72	71.71	80.05	82.36	10.29	1.70	1.05	0.13	

* There were several re-surveys between the ITS and the RSL.

Between these extremes a number of clinical patterns are possible, as experienced in endemic syphilis (Grin, 1953), in yaws (Wang, 1966; Kranendonk, 1958; Klokke, 1956; Van der Hoff, 1956), and in pinta (Langagne, 1964; Edmundson, Rico, and Olansky, 1953).

In Table IV are grouped four clinical patterns

of active yaws in children and adults in hyperendemic, mesoendemic, hypoendemic, and feeble prevalence areas of yaws, as observed in pilot studies at Initial Treatment Surveys before mass penicillin application. Experience in these WHO projects (Fig. 1) has shown that to break an endemic level established in the rural community,

TABLE IV
CLINICAL AGE PATTERNS OF ACTIVE YAWS IN WHO STUDY AREAS OF DIFFERENT ENDEMICITY

Endemicity Level	Pilot Areas	No. Examined	Active Yaws					
			- 15 years		+ 15 years		Total	
			Infectious Per cent.	Non-Infectious Per cent.	Infectious Per cent.	Non-Infectious Per cent.	No.	Per cent.
Hyper-endemic (>10 Per cent.) (Active Yaws)	New Hebrides	868	12.9	1.4	6.2	6.3	229	26.4
	Western Samoa	4,309	3.7	6.9	0.7	11.4	977	22.7
	Former Netherlands N. Guinea	731	1.9	1.8	1.5	17.0	163	22.3
	British Solomon Islands	3,623	3.8	3.2	1.6	11.8	738	20.4
	Upper Volta	1,193	1.8	3.1	0.9	12.9	223	18.7
	Total	10,724	4.1	4.4	1.5	11.6	2,330	21.7
Meso-endemic (5-10 Per cent. Active Yaws)	Cambodia I	6,638	1.2	0.8	0.1	6.2	551	8.3
	Thailand	9,292	1.0	1.24	0.05	3.0	491	5.3
	Total	15,930	1.1	1.1	0.07	4.3	1,042	6.5
Hypo-endemic (1-5 Per cent. Active Yaws)	Sierra Leone	6,501	0.18	0.45	0.08	3.54	275	4.2
	Cambodia II	4,699	0.08	0.08	0.02	2.10	106	2.3
	Tonga	5,199	0.06	0.13	0.02	1.80	106	2.0
	Total	16,399	0.21	0.23	0.04	2.6	487	3.0
Feeble Prevalence (<1 Per cent. Active yaws)	Malaya	7,068	0.4	0.20	0	0.01	43	0.6
	S. Thailand	7,320	0.16	0.04	0.01	0.05	18	0.26
	Togo	5,019	0	0	0	0.02	1	0
	Total	19,407	0.10	0.08	0.005	0.003	62	0.32

FIG. 1.—Clinical age patterns of active yaws in WHO Study Areas of different endemicity.

mass penicillin treatment provides the momentum under which a very rapid transition from one clinical pattern to another may take place, say from hyperendemicity to hypoendemicity or further; active yaws can be reduced to negligible proportions within 1 to 2 years, resulting in near-interruption of transmission depending on the adequacy of the campaign. On the other hand, the rapid clinical effect will not be detectable for some considerable time in the serological response of the rural community. Residual non-infectious cases, the so-called "last cases" of indigenous or imported origin, "sero-resistant" infections of long duration, etc., will give rise to a discrepancy between the clinical and serological community status, a phenomenon which could be called an *epidemiological paradox*.

(ii) Information of total sero-prevalence rates in a rural community is of limited value in the study of the fall—or rise—of endemic treponematoses. Careful consideration is necessary of serological age profiles in untreated study areas or surveys statistically representative of the population. Such age profiles for different levels of endemicity are shown in Fig. 2. The hyperendemic patterns of former Netherlands New Guinea, Western Samoa, and New Hebrides, etc., indicate the rapid age "saturation" with sero-reactors from early childhood, while an increasingly delayed saturation is evident in the mesoendemic Cambodian area and the

FIG. 2.—Serological patterns of yaws in WHO Study Areas, showing sero-prevalence (VDRL), by age.

hypoendemic Tonga Islands. The exponential, catalytic shape of these age-prevalence curves contrasts with the sigmoid curve type, with relatively low sero-reactor rates in children in the *treated* study areas in Eastern Nigeria and Thailand. The last three profiles are taken from epidemiological-serological studies approximately 10 years after Initial Treatment Surveys.

(iii) How clinical patterns and serological age profiles are changing with time as a result of mass penicillin campaigns in a given area is illustrated in detail in Western Samoa. Table V (overleaf) shows the very rapid regression of active clinical yaws in six subsequent mass surveys and resurveys (with a coverage generally over 90 per cent.), in a special survey of children (26 per cent.), and in a statistical random survey of children and adults (9.1 per cent. sampling fraction), all within a period of 10 years in a population of some 100,000 people. The clinical community effect of the wide therapy used is obvious. The serological age pattern (Fig. 3) by

Age Group	1955/56		1965/66				
	VDRL		VDRL			FTA ₂₀₀	
	No Examined	Percentage Reactive	No Examined	Percentage Reactive	≥ 16 dil.	No Examined	Percentage Reactive
Children	2,559	53.1	1,992	7.1	0.6	3,320	1.7
Adults	3,563	82.1	796	39.1	1.6	915	37.3
All Ages	6,122	69.9	2,788	16.2	0.9	4,245	9.1

FIG. 3.—Serological age patterns in yaws in W. Samoa at Initial Treatment Survey and 10 years later. (WHO Project Laboratory, W. Samoa: Drs W. Frolich, and P. N. Wang.)

TABLE V
YAWS CONTROL IN THE WHO W. PACIFIC REGION, 1955-66
Western Samoa, 1965-66

Type of Survey		ITS	IRS	IIRS	IIIRS	IVRS	VRS	VIRS (a)	ESRS (b)
Year		1955/56	1956	1957	1958	1959	1960	1961	1965/66
Estimated Population		96,969	96,969	100,174	102,180	103,000	108,750	110,000	113,000
Population Examined	No.	93,767	59,761	99,736	97,000	98,470	100,446	28,820	10,220
	Per cent.	96.7	61.9	99.6	95.0	95.6	92.4	26.1	9.1
Yaws	Active	No.	10,356	38	36	12	11	5	1
		Per cent.	11.04	0.06	0.04	0.01	0.01	0.005	0.01
	Infectious	No.	2,767	13	28	12	11	5	0
		Per cent.	2.95	0.03	0.02	0.01	0.01	0.005	0.00
	Non-Infectious	No.	7,589	25	8	0	0	0	1
		Per cent.	8.09	0.04	0.01	0.00	0.00	0.00	0.01

ITS: Initial Treatment Survey; IRS: First Re-survey; IIRS: Second Re-survey, etc. Serologist: Dr P. N. Wang.
(a) Only children under 15 years examined (VIRS). (b) Epidemiological-serological (ESRS) random sampling survey.

VDRL testing in 1955-56 corresponds to the hyperendemic clinical pattern at the time of the Initial Treatment Survey; 10 years later, in 1965-66, the sigmoid age curve indicates a fall from a maximum of some 80 per cent. to approximately 50 per cent. sero-reactors among adults in the community. The new child generation now shows a very low sero-prevalence indeed. We have here introduced immunofluorescent testing (FTA) in rural random studies of yaws. A systematically lower community prevalence of FTA reactors than VDRL reactors is seen in most age groups. Accepting FTA testing as reference procedure, the findings indicate that transmission has almost ceased in the child age groups previously at maximum risk of infection.

Also, in endemic syphilis of children, a similar pattern evolves in the regression of the infection when exposed to community-wide preventive and clinical penicillin treatment. This has been demonstrated in Bosnia-Herzegovina in longitudinal studies by Grin, 1948-1958 (Grin, 1959). Data from a small administrative rural unit in Bosnia

with an initial high prevalence of clinical disease and sero-reactivity are shown in Table VI.

In pinta, epidemiological-serological investigations of this nature have so far not been made, although exploratory community surveys were undertaken as part of the penicillin campaigns in Mexico (Langagne, 1964; Edmundson and others, 1953; Sosa-Martinez, and Peralta, 1961), and Venezuela (Medina, 1965). The epidemiological patterns encountered in pinta leave traits similar to those in the other endemic treponematoses.

Epidemiological-serological Sampling Surveys

In the foregoing we chose small, relatively isolated areas to illustrate clinical regression and serological recession after mass campaigns in endemic treponematoses. It was emphasized that age-specific serological prevalences were needed to evaluate campaign results and to appraise levels of transmission. In large areas or continents, *e.g.* Indonesia and Africa, it is obvious that millions of serological tests cannot be undertaken where laboratory services are often in their inception stages. In order to evaluate the effect of mass campaigns and to obtain information on the prevalence of infection until such laboratory services have been established, WHO has, in its treponematoses programme, created three international epidemiological-research teams to record clinical data and obtain serum collections based on stratified random survey designs, the sampling units being villages and households, with adults and children being examined in groups representative of the population. Some fifty to sixty sample points may be covered over 2 to 3 years in each project area. In

TABLE VI
ENDEMIC SYPHILIS: INFECTIOUS LESIONS AND SERO-REACTOR RATES
Srez Zvornik, Bosnia Herzegovina, 1949-1953

Year	Surveys	Estimated Population at Risk	Examined Population		Infectious Lesions		Sero-reactors	
			No.	Per cent.	No.	Per cent.	No.	Per cent.
1949	Initial	3,689	3,159	82.9	158	5.00	829	26.2
1950	2nd	3,742	2,875	76.8	20	0.62	454	15.8
1951	3rd	3,851	2,594	67.3	19	0.73	172	6.6
1952	4th	3,923	2,668	68.0	4	0.11	81	3.0
1953	5th	4,164	3,655	87.7	2	0.05	91	2.5
1958	6th	4,983	3,386	67.9	0	0.00	44	1.3

collaborative studies between such teams, WHO/HQ and WHO Reference laboratories overseas, computerized data are emerging of considerable interest for the study of the epidemiology of disappearing disease, based on reagin, fluorescent, and immobilizing antibody determinations. Such evaluation and research projects undertaken by our group from 1960 are summarized in Table VII (overleaf, pp. 42 and 43), for which survey designs (WHO INT/VDT/165; INT/VDT/196 Rev. 1; INT/VDT/209; INT/VDT/206; INT/VDT/169; INT/VDT/201; INT/VDT/212) and preliminary reports in some instances (WHO INT/VDT/200; INT/VDT/211; WHO 1964) have appeared.

The original coverage in ITS is epidemiologically unsatisfactory except in Western Samoa, Northern Nigeria, and Bosnia. The regression of clinical infectious yaws is evident in all studies, but seroprevalence by VDRL is variable and has remained high in some areas of initial low prevalence of infectious yaws, *e.g.* N.E. Thailand. It will also be noted that the serum collections have been utilized for multi-subject exploitation; the conditions investigated and collaborating laboratories have been indicated in the right hand part of the Table. Some of these results have become available (Voller and Schindler, 1967; Guthe and de Vries, 1966; WHO GES/SR, 66.3; Yale Arbovirus Research Unit).

Long-distance shipments of large serum collections have in the past bedevilled serological surveys in the tropics. Uncertainty has often prevailed in regard to the nature, extent, and influence on antibody reactivity of temperature variation, denaturation of proteins, haemolysis, and secondary infection of specimens. In treponematoses, reagins are particularly sensitive to temperature changes, as shown *inter alia* by Orpwood Price (1956). Recently, significant differences in medium-range temperature tolerances of reagins, immunofluorescent, and immobilizing antibodies have been demonstrated by Hederstedt (1966) and by Vaisman (1966). However, like most biological material, reagins and treponemal antibodies remain unchanged by ultra-rapid freezing to extreme temperatures, such as is obtainable by the use of liquid helium or nitrogen. We have adapted bull sperm preservation techniques in liquid nitrogen at -200°C . to the freezing and shipment of sera. The physical considerations and the equipment now available for this purpose have recently been described (Guthe, 1965, 1966). This technique has been used in the Western Nigerian WHO survey undertaken in co-operation between the VDRL, London, and WHO.

Also in the context of the WHO research and development programme a simple technique has

been developed, using dried finger-prick blood, absorbed by blotting-paper disks or "rondelles", for FTA testing of the eluent. Within defined limits this procedure as established by Vaisman, Hamelin, and Guthe (1963) has been most useful in children and other individuals where venepuncture has been difficult to achieve. The technique is being used as a supplementary measure in all sero-epidemiological studies following mass yaws campaigns (Guthe, 1966b).

Some preliminary findings from the first stage of this project in the Mid-West Region of Nigeria are shown in Fig. 4, which pictures the prevalence curves for sero-reactors in the two villages which were tested by the TPI test as well as the VDRL and FTA. The fit of the age-prevalence profiles of FTA₂₀₀ and TPI₁₈ suggests the closeness of the reactivity patterns in the community in these tests.

FIG. 4.—Epidemiological serological random survey of two villages (Igolo and Error), Mid-Western Region, Nigeria, 1966-67 (population 1,508).

VDRL, FTA₂₀₀, and TPI testing some 10 years after Initial Treatment Survey of mass campaign when infectious yaws prevalence was 9.1 and 6.4 per cent.

The findings in Eastern Nigeria, completed some time ago, are shown in Fig. 5 (overleaf, p. 44). The infectious yaws range at ITS 10 years ago is indicated for each stratum from 0.21 to 3.48 per cent. At the recent epidemiological-serological evaluation survey it was low, namely 0.07 per cent., for all three strata together, with most of the infectious clinical cases in the previous high-level stratum. Considering first the FTA age profiles and accepting again this treponemal test as near specific for yaws, the

WHO EPIDEMIOLOGICAL-SEROLOGICAL EVALUATION AND RESEARCH SURVEYS
Stratified Random Designs, Multiple

Country	Mass Campaigns								
	Year ITS (a)	Rural Census Pop- ulation (millions)	Examined at ITS (a)		Infectious Yaws (Per cent.)	Year	Infectious Yaws (Per cent.)	No. Examined	
			Millions	Per cent.				Clinical	Sero- logical
Togo (Yaws)	1956- 1961	1.5	0.6	40.0	4.1	1961- 1965	0.11	16,171	7,617
W. Samoa (Yaws)	1955- 1956	0.10	0.09	93	3.0	1965- 1966	0	7,839	2,788
Northern Nigeria (Yaws)	1954- 1956	2.5	2.2	88.9	2.7	1965- 1966	(c)	8,500	5,000
E. Nigeria (Yaws)	1954- 1955	6.8	3.6	54.4	1.9	1963- 1964	0.07	8,824	4,201
Western and Mid- West Nigeria (Yaws)	1953- 1955	4.2			1.8	1966- 1967	0.2 (b)	2,991 (b)	1,329 (b)
S. Thailand (Yaws)	1953- 1955	3.0	2.1	70.0	0.13	1961- 1962	0.06	15,538	7,320
Philippines (Yaws)	1952- 1954	2.4	0.8	33.3	0.10	1962- 1963	0.04	16,024	8,001
N. E. Thailand (Yaws)	1952- 1954	8.4	4.2	50.0	0.7	1960- 1961	0.11	22,744	11,935
Bosnia (Endemic Syphilis)	1948- 1951	1.1	0.96	87.2	2.3	1968- 1969	(c)	15,000	10,000

(a) ITS = Initial Treatment Surveys.

(b) Midwest Region only.

(c) Data processing not completed; material not exploited; or project in planning stage.

5 CAMPAIGNS AGAINST ENDEMIC TREPONEMATOSES OF CHILDHOOD, 1960-67
itation of Serum Collections

Epidemiological Serological Survey and Investigations						
Sampling Fraction Points		Efficiency Coverage (Per cent.)	Treponematoses		Multisubject Exploitation of Material	
Per cent.	No.		WHO Laboratory	WHO Reference Centre	Other Conditions	Co-operating Laboratories
1·24	22	96·3	Field Laboratory	Institut Fournier, Paris	Pertussis Parapertussis Poliomyelitis Measles Rubella	Institute of Epidemiology and Microbiology, Prague National Institutes of Health, Bethesda Institut Pasteur, Dakar
6·35	32	97·3	Field Laboratory	Laboratoires de Biologie Médicale, Paris	Helminthiasis Mycosis Eye Conditions	—
0·34	56	(c)	Field Laboratory	Institut Fournier, Paris	Arbovirus Malaria Immuno-haematology Others	Yale Arbovirus Laboratory, Newhaven Nuffield Institute of Medical Research, London International Haemaglobin Centre, London Centre de Transf. Sanguine, Rouen
0·14	56	91·9	Field Laboratory	State Serum Institute, Copenhagen	Pertussis Parapertussis Poliomyelitis Measles Rubella	Institute of Epidemiology and Microbiology, Prague National Institutes of Health, Bethesda
0·34	15 (b)	92·4 (b)	Field Laboratory	VD Reference Laboratory, London	Malaria Arbovirus Others	Institute of Epidemiology and Microbiology, Prague Nuffield Institute of Medical Research, London Hospital for Tropical Diseases, London Institut Pasteur, Dakar
0·49	16	87·3	Field Laboratory	State Serum Institute, Copenhagen	Pertussis Parapertussis Poliomyelitis Measles Rubella	Institute of Epidemiology and Microbiology, Prague National Institutes of Health, Bethesda
0·67	37	90·2	Field Laboratory	State Serum Institute, Copenhagen	Rubella Measles Mumps Poliomyelitis Amoebiasis Bilharzia Vaccinia Arbovirus	Yale Arbovirus Laboratory, Newhaven National Institutes of Health, Bethesda
0·25	24	91·4	Field Laboratory	State Serum Institute, Copenhagen	Pertussis Parapertussis Poliomyelitis Measles Rubella	Institute of Epidemiology and Microbiology, Prague National Institutes of Health, Bethesda
1·30	60	(c)	Inst. Milocevic Laboratory, Sarajevo	State Serum Institute, Copenhagen	Q Fever Typhus Immuno-haematology Arbovirus Tetanus	Gamelia Institute, Moscow Institute of Hygiene, Medical Faculty, Sarajevo Institute of Hygiene, Zagreb Nuffield Institute, London Centre de Transf. Sanguine, Rouen

FIG. 5.—Epidemiological serological sample survey in Eastern Nigeria, 1965-66.

Age-specific sero-reactor rates by VDRL and FTA₂₀₀ testing in representative samples of the population in previous areas of low (Stratum I), medium (Stratum II), and high (Stratum III) prevalence of yaws at Initial Treatment Survey.

Reference Laboratory: WHO Serological Reference Centre, State Serum Institute, Copenhagen. Director: Dr Aa Nielsen.

slack sigmoid curve characteristic of low prevalence is noted in Stratum I, with few sero-reactors in the age groups under 10 years and an increasing—but low—residuum in the older age groups. In Stratum II the sigmoid curve also prevails but with a more steeply rising prevalence slope for adults. These aspects are further accentuated in Stratum III, where yaws was previously hyperendemic. If we recall the FTA age profile from Western Samoa—also previously a hyperendemic area—the difference is striking: in the present curve we find prevalences of up to 25 per cent. sero-reactivity by FTA in children under 15 years of age, as against 1.7 per cent. in Western Samoa. That transmission therefore continues in this stratum in Eastern Nigeria is confirmed by the finding of several infectious cases as well as a relatively large proportion of high-titre sera at

some sampling points. A probable explanation lies in the coverage, which was 54.4 per cent. at the initial survey and less in subsequent resurveys, while it was generally better than 90 per cent. in the annual resurveys in Western Samoa over a period of 10 years. By and large the FTA₂₀₀ community prevalence curve shows a 2 to 3 per cent. closeness of fit to the TPI curve. The fine aspects of this problem need further research and are currently being investigated in London at the VD Reference Laboratory. Quantitative FTA and FTA absorption techniques are being applied in addition to TPI testing in the Western Nigerian survey.

In a further epidemiological research project now being prepared in Bosnia, Yugoslavia, for 1968-1970, the haemagglutination inhibition test recently introduced by Rathlev (1967) at the WHO Serological Reference Centre in Copenhagen—and claimed to be as sensitive as FTA and as specific as TPI—may be utilized.

Public Health Implications of Mass Campaign Evaluations

We have seen in the epidemiological-serological surveillance and research activities undertaken some 10 years after mass campaigns that penicillin has had—and is having—a significant impact on the *clinical regression* of yaws and endemic syphilis and that near interruption of transmission can be rapidly achieved in large areas. But sporadic cases of infectious yaws continue to occur. The serological recession is slow and transmission in children continues at a low level in most large areas, depending on population coverage in the mass campaigns, the extent of community treatment, the strength of post-campaign surveillance, and the possibility of integrating these activities into growing health services. In smaller, more isolated, areas—e.g. Western Samoa and Bosnia—there is evidence that transmission has nearly or completely ceased, but in no large area or country has a similar situation been attained.

It is evident that primitive standards of living and economic conditions, physiographic and meteorological factors in backward rural areas, and—above all—poor personal, household, and environmental hygiene play essential roles in maintaining transmission. An essential epidemiological element is the role of soap and water for cleansing, since yaws is transmitted by direct bodily contact which includes the hands of children—the most active human instruments of early life and easily contaminated from highly infectious papillomata, as indicated by Hackett (1959). Grin (1953) has implicated drinking utensils in endemic syphilis, taking into

account the infectiousness of the early oral lesions. Guthe and Luger (1957) have pointed to the likely additional role of the hands also in these endemic treponematoses, in view of frequent finger-sucking by children, and child to child contact through moist hands. It is unlikely that *Hippelates* or other insects play a role in transmission of yaws, endemic syphilis, or pinta.

The late Dr Fraisse reported several years ago to WHO that certain naked tribes in Northern Nigeria had a high prevalence of yaws, while the condition was almost absent in the Moslems who were well clothed from an early age. Christiansen (WHO/INT/VDT 212) found a great difference in hygiene and standards of living between Moslems and Buddhists in Southern Thailand and could demonstrate this quantitatively by their age/sero-prevalence (Fig. 6).

FIG. 6.—Comparison between Moslem and Buddhist sero-reactor rates, by age group, in South Thailand in a random sample of 6,166 persons examined clinically and 3,695 (60 per cent.) examined serologically by VDRL in comparable numbers in the two Community groups.

Grin, Swaroop, and Guthe (1959) recorded similar observations in regard to endemic syphilis among households in Moslem and Orthodox populations in Bosnia (Fig. 7). Obviously, religious beliefs and social customs represent in these groups only a common denominator for practices which facilitate maintenance of the ecological balance more in favour of the treponeme than the host—as compared with other more fortunate groups.

FIG. 7.—Comparison between Moslem and Orthodox sero-reactor rates, by age and sex, at Initial Treatment Survey of endemic syphilis in the province of Zvornik, Bosnia-Hertzevovina, Yugoslavia, examined in comparable numbers in the two community groups.

The factors concerned in the spread as well as the control of endemic treponematoses with particular reference to yaws and the points of attack in the ultimate surveillance programme are illustrated in Fig. 8 (overleaf, p. 46).

The need for general improvement in the environment applies equally or even more to communicable diseases other than endemic treponematoses and is among the obstacles to global malaria eradication. In such contexts we may perhaps ask:

(i) When will the economic growth of developing countries permit the advancement of living standards necessary to improve hygiene and install facilities needed for integration of special programmes into the general health services?

(ii) How long after mass campaigns will it be before systematic surveillance is assimilated into growing local health services in an epidemiologically significant way?

(iii) Can the interest of the public be held in the meantime by health education and can budgetary provisions be maintained by the health administration when morbidity declines conspicuously and the cost of the "last cases" mounts exponentially?

As far as endemic treponematoses of childhood are concerned, it is believed that the public health prognosis should not be too optimistic, having regard to the results of epidemiological-serological studies in several countries since the conclusion of mass campaigns.

There is also the public health implication of the fact demonstrated in the epidemiological-

FIG. 8.—Yaws control: surveillance phase.

serological investigations described that, after penicillin mass campaigns against yaws, the number of sero-reactors among millions of people in rural tropical areas has decreased substantially in the last 10 to 15 years. In such areas syphilis has been exceedingly rare, but the relative cross-immunity from yaws possessed by the previous generation against venereal syphilis is now much lower at puberty in the new generation. It is, however, too early to appraise how far this new immunological situation may—in conjunction with other ecological changes favouring the spread of syphilis—set the scene for a large-scale public health problem which will require our intensified attention in the cycle of fall—and rise—of the treponematoses.

Summary

In Part I of the present study (Idsøe and Guthe, 1967) published in a previous issue of this Journal, the evolutionary aspects of the treponematoses, the ecological background changes, and the long-term rise and fall of syphilis, yaws, and pinta were appraised. The importance was suggested of recent scientific discoveries: commensal *T. pertenuis* in certain cynocephalus monkeys, the persistence of *T. pallidum* in human lymph glands of treated late

syphilitics, and the role of reagins as autologous auto-immune antibodies. Changing ecological factors in relation to long-term international incidence trends in venereal syphilis were reviewed, documented, and assessed in some detail.

In the present study (Part II) recent international trends in the endemic treponematoses of childhood are evaluated with reference to results in mass campaigns undertaken since 1950 by health administrations in 45 different countries in co-operation with the World Health Organization. In these campaigns against yaws, pinta, and endemic non-venereal syphilis, some 150 million people were examined and some 46 million clinical cases, latent cases, and contacts were treated with long-acting penicillin (PAM) or benzathine penicillin (DBED). Illustrations are given of the rapidly changing clinical patterns in yaws and endemic syphilis under the impact of community-wide application of penicillin. With disappearing surface lesions epidemiological-serological evaluations are needed. The surveillance methodology developed by the World Health Organization in this field based on statistically valid random surveys in rural tropical populations is outlined. New techniques and equipment are described suitable for preservation of (a) serum

collections frozen at -200°C . under tropical field conditions for transport of specimens in inert form to distant laboratories for reagin (VDRL) and treponemal (FTA and TPI) testing, and (b) finger-prick blood specimens dried on absorbent paper (rondelles) for mailing to remote laboratories for FTA testing.

The findings in epidemiological-serological evaluations undertaken in the surveillance of previously holoendemic, mesoendemic, hypoendemic, or low-prevalence areas of yaws and endemic syphilis are illustrated by examples from W. Samoa, Nigeria, Yugoslavia, and other countries. Initial rapid regression of clinical lesions has been followed by very slow serological recession. In no large area (except Bosnia in Yugoslavia) have endemic treponematoses of childhood been eliminated. Isolated clinical cases occur or residual foci persist. FTA and TPI sero-reactor rates in the children indicate that low level transmission continues in many areas 10 to 15 years after the penicillin mass campaigns, regardless of the number of surveys and re-surveys. High titre sero-reactivity in a good proportion of child sero-reactors suggests a further recrudescence potential. Continued active epidemiological surveillance of endemic treponematoses is therefore required after mass campaigns and the integration of such activities into the growing basic health services will be needed to maintain control of the endemic treponematoses, but general improvements in the environment and hygienic and economic standards are by themselves essential epidemiological elements which could contribute essentially to the interruption of transmission of endemic treponematoses.

Following mass campaigns against endemic treponematoses, the children of the new generation are now attaining puberty without the relative cross-immunity from yaws possessed by the previous generation against venereal syphilis. The increasing number of susceptibles to this adult treponematoses may thus represent an epidemiological factor of some importance, which will have to be taken into account in conjunction with the other ecological changes described in Part I of this study and may favour the national and international spread of venereal syphilis.

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L'augmentation et la diminution des tréponématoses

II. Les tréponématoses endémiques de l'enfance

RÉSUMÉ

Dans la première partie de cette étude (Idsøe et Guthe, 1967) déjà publiée dans ce journal les aspects de l'évolution des tréponématoses, les causes des changements écologiques et l'augmentation et la diminution à long terme de la syphilis, du pian, et du pinta ont été évalués. L'importance des récentes découvertes scientifiques a été suggérée: le *T. pertenue* commensal chez certains singes cynocéphales, la persistance du *T. pallidum* dans les ganglions humains des cas de syphilis tardive traités, et le rôle des réagines comme anticorps auto-immuns et autologues. Les facteurs écologiques changeants en relation des tendances internationales à long terme de la syphilis vénérienne ont été passés en revue, ils ont été aussi documentés et évalués en quelque détail dans la première partie de ce travail.

Dans la deuxième partie de cette étude les récentes tendances internationales concernant les tréponématoses endémiques de l'enfance sont évaluées en se référant aux résultats obtenus des campagnes massives entreprises depuis 1950 par les services de santé publique de 45 pays différents en coopération avec l'Organisation Mondiale de la Santé. Dans ces campagnes contre le pian, le pinta, et la syphilis non-vénérienne endémique, à peu près 150

millions de personnes ont été examinées et à peu près 50 millions de cas, de cas latents et de contacts ont été traités avec de la pénicilline à action prolongée (PAM) ou avec de la benzathine pénicilline (DBED). Des exemples sont donnés des changements cliniques qui ont eu lieu rapidement dans le pian et la syphilis endémique sous le coup de l'usage étendu de la pénicilline. Avec la disparition des lésions de surface des évaluations sérologiques épidémiologiques sont nécessaires. La méthodologie développée par l'Organisation Mondiale de la Santé dans ce domaine, basée sur des relevés faits au hasard mais valides chez des populations rurales et tropicales est esquissée, les nouvelles techniques et l'équipement nécessaire sont décrites pour la préservation des (a) prélèvements de sérum gelé à -200° C. sur le terrain sous des conditions tropicales et le transport des spécimens sous une forme inerte aux laboratoires éloignés pour le test à la réagine (VDRL) et le test pour les tréponèmes (FTA et TPI) et (b) spécimens de sang pris des doigts et séché sur du papier absorbant ("rondelles") et envoyés par la poste aux laboratoires distants pour le test FTA.

Les constatations des évaluations sérologiques et épidémiologiques entreprises dans la surveillance des régions holoendémiques, mesoendémiques, hypoendémiques ou des régions de basse fréquence de pian et de syphilis endémique sont illustrées par des exemples pris de la Samoa Occidentale, de la Nigérie, de la Yougoslavie et d'autres pays. La régression initiale et rapide des lésions cliniques a été suivie par une récession sérologique très lente. Les tréponématoses endémiques de l'enfance n'ont pas été éliminées dans aucune grande région excepté la Bosnie en Yougoslavie. Des cas cliniques isolés ou des foyers résiduels continuent à paraître. Les taux séro-réacteurs FTA et TPI chez les enfants indiquent qu'une transmission à basse échelle continue dans plusieurs régions 10 à 15 ans après les campagnes massives de pénicilline, malgré le nombre des relevés et relevés répétés. Les hauts titres de séroactivité chez une bonne proportion qui réagit suggèrent de nouveau une recrudescence potentielle. La surveillance épidémiologique active et continue des tréponématoses endémiques est donc nécessaire après les campagnes massives, et l'intégration des ces résultats aux services publiques de santé qui prennent de l'extension serait nécessaire pour maintenir le contrôle des tréponématoses endémiques, mais les améliorations d'ordre général dans le milieu, le niveau économique et celui de l'hygiène restent par elles-mêmes les éléments épidémiologiques essentiels qui pourraient contribuer à l'interruption de la transmission des tréponématoses endémiques.

Après les campagnes massives contre les tréponématoses endémiques, les enfants de la nouvelle génération atteignent maintenant la puberté sans l'immunité croisée relative donnée par le pian que la génération précédente possédait contre la syphilis vénérienne. Le nombre croissant des personnes susceptibles à cette tréponématose adulte pourrait ainsi représenter un facteur épidémiologique de quelque importance qui devrait être pris en considération de concert avec les autres changements écologiques décrits dans la première partie de cette étude et qui pourrait favoriser la propagation nationale et internationale de la syphilis vénérienne.