

## SEROLOGICAL STUDY OF YAWS IN JAVA

HUAN-YING LI, M.D., M.P.H.  
*WHO Serologist,  
Treponematoses Control Project, Indonesia*

R. SOEBEKTI  
*Medical Analyst,  
Treponematoses Control Project, Indonesia*

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### SYNOPSIS

This report presents the results of serological analyses made by the laboratory of the Treponematoses Control Project, Indonesia, from its establishment in April 1951 until April 1953. All sera were tested quantitatively with the VDRL and Kline slide-tests or the Kahn test, or with all three.

A study of the mean reagin titre in untreated yaws cases showed that the percentage of seronegative reactors among clinically positive cases was low. Less seronegativity was observed among females than males.

Examination of decrease in mean reagin titre after treatment by clinical group showed maximum to minimum decrease in the following sequence: early contagious, early contagious plus hyperkeratosis, ulcerative plus osteo-articular, ulcerative, hyperkeratosis, and osteo-articular lesions. The decrease tended to be greater in females than males and in patients with high than with low titre; it also varied with the age of the patient. No significant variation in decrease was noted when four different PAM treatment schedules were tested comparatively. The percentage of serological cure and improvement with all schedules was highest in the cases with early lesions, and in the younger age-groups.

A study of patients requiring re-treatment at the time of re-survey showed no important difference in mean reagin titre between clinically cured and uncured patients suffering from palmar or plantar hyperkeratosis and ulcerative or osteo-articular lesions.

Serological testing of sera from clinically negative household contacts and non-contacts, with or without previous history of yaws, gave the following results: Among the household contacts, the number of seronegative reactors, while not affected by age-distribution, was significantly higher in the history-positive than in the history-negative groups. The percentage of seropositive reactors was in direct proportion to the prevalence of yaws, the seropositivity-rate being high in villages with a yaws incidence of 11%-30%.

The report also contains suggestions for improving the conduct of the anti-yaws campaign.

This article deals with the serological findings of the laboratory of the Treponematoses Control Project, Indonesia. The project—which has as its aim the elimination of yaws as a public-health problem from the archipelago—was established in May 1950 by the Indonesian Government with the technical assistance of the World Health Organization and the financial aid of the United Nations International Children's Emergency Fund (UNICEF, renamed in 1953 United Nations Children's Fund). Beginning with two target areas in the Residencies of Jakarta and Jogjakarta (Mid-Java), the operation has since been extended to West Java, Lesser Sunda Islands, North Sumatra, Kalimantan Barat (West Borneo), and Kalimantan Selatan (South Borneo). At the time of the preparation of this article (April 1953), the project had covered 5,315,982 persons, and 596,485 cases of yaws (11.2%) had been diagnosed and treated.

The laboratory, located at Jogjakarta, the headquarters of the project, began to function in April 1951. Working, in association with a field team of one doctor and nine "mantris",<sup>1</sup> in special control areas, the laboratory attempted to assist in the detection of latent yaws, the verification of clinical diagnoses, studies on the efficacy of treatment schedules with repository penicillin, and the solution of other problems of clinical and epidemiological interest.

#### *General description of region*

The Residency of Jogjakarta, located in the southern part of Mid-Java, comprises four regencies; the density of population and prevalence of yaws in each regency are given in table I. (See also fig. 1.)

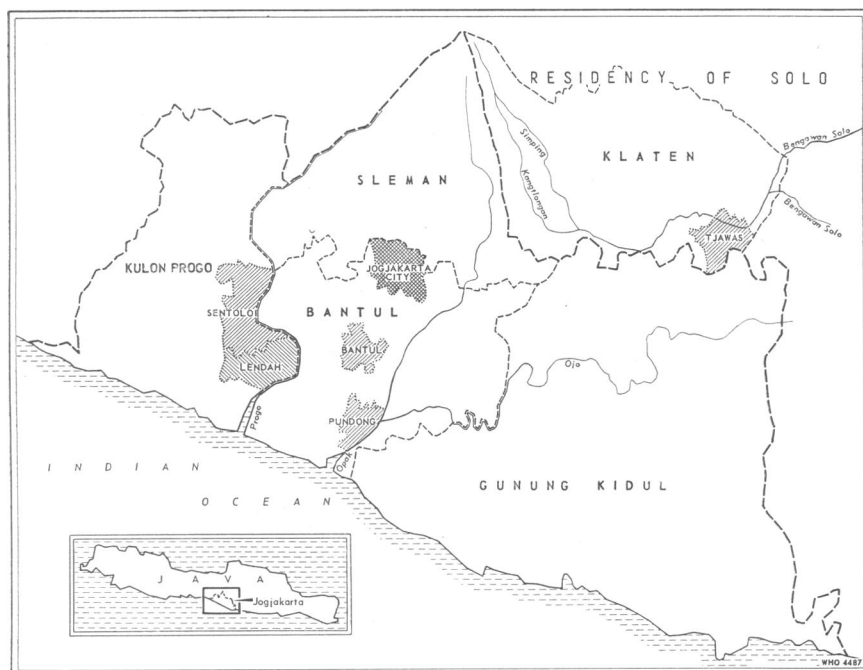
**TABLE I. POPULATION DENSITY AND YAWS PREVALENCE IN REGENCIES OF JOGJAKARTA, 1952**

Regency	Area		Population			Yaws	
	km <sup>2</sup>	square miles	number	per		diagnosed	prevalence (%)
				km <sup>2</sup>	square miles		
Kulon Progo	545	210	270,069	495	1,285	39,965	14.8
Bantul	471	182	414,448	880	2,275	44,462	10.7
Gunung Kidul	1,442	557	447,134	310	800	88,629	19.8
Sleman	506	195	447,396	885	2,295	5,404	1.2

The monsoon season prevails between November and March, with a monthly rainfall between 350 mm and 450 mm (12-18 inches); for the rest

<sup>1</sup> A "mantri" is an indigenous qualified male nurse.

FIG. 1. RESIDENCY OF JOGJAKARTA, INDONESIA



----- boundary of Residency    - - - - - boundaries of Regencies

of the year rainfall varies between 20 mm and 100 mm ( $\frac{3}{4}$ -4 inches). The annual rainfall is highest in the Regency of Sleman (2,100 mm—83 inches); in the other regencies it totals about 1,500 mm (59 inches).

Sleman, a fairly prosperous region situated on the southern slope of the volcano, Mount Merapi, has a good irrigation system and the highest rice production of the four regencies. Gunung Kidul is one of the poorest areas in Java, with barren hills of lime-stone along the coast, and is sparsely populated. According to surveys which have been made, the main food is cassava, which has very poor nutritional value. The general state of health of the people is poor, and it has been known for a long time that nutritional oedema is very common in this area.<sup>2</sup> The Kulon Progo and Bantul coastal regions consist mainly of sea alluvion and collovion, and, in the plains, river alluvion. In general, the soil in Kulon Progo is rather poor because of over-agriculture and soil erosion. The main agricultural products are corn, tapioca, and copra.

<sup>2</sup> Institute of Nutrition Research (1940) *Communication No. 5*, Batavia

## Classification and Methods

### *Classification of lesions*

Yaws is characterized by a variety of lesions, which have been described and classified into 30 different forms by Kodijat<sup>3</sup> (see also fig. 2). It is known that the different forms of lesion tend to occur in a certain sequence, and may overlap each other. For the sake of convenience in making comparative serological studies, the 30 different forms of lesion recorded in the field were grouped into four main categories. This classification basically agrees with that suggested by the participants at the First International Symposium on Yaws, held in Bangkok in 1952.<sup>4</sup>

1. *Early contagious.* Patients with early manifestations of the disease, in which treponemal lesions—such as initial lesion, generalized papilloma, recurrent papilloma including papilloma of the foot (so-called “wet crab”)—are readily demonstrable (fig. 2, I and II, 1-4, 6, and 10).

2. *Plantar and palmar hyperkeratosis.* Thickening, desquamation, deep fissuring of palms and soles (fig. 2, III, 9, and 11-14).

3. *Ulcerative.* Destructive superficial or deep ulcerations—the treponemes are not usually found in these secretions (fig. 2, IV, 16 and 17).

4. *Osteo-articular.* Subjective pain of joints and bones, periosteitis, dactylitis, ankylosis, and contracture (fig. 2, V, 18-25). Because of the relatively smaller number of patients involved in this group, no attempt was made to differentiate between early and late lesions.

Other lesions in the minority group—such as pian datre, macula, papule, tendovaginitis, bursitis, leucodermia, and juxta-articular nodules—were not included in the study since they are not sufficiently associated clinically with any of the four main categories or with each other. Furthermore, the number involved is very small. Active progressive gangosa is classified under ulcerative plus osteo-articular lesions.

The patients' history cards (fig. 2), designed for laboratory use, were filled in by the mantri at the time of examination in the field and were forwarded on the same day to the laboratory with the blood samples. The serological data were recorded and the cards were filed for later reference. During the re-survey, the cards were taken with the team to the field and the condition of each patient checked against the data recorded on his card. Follow-up examinations and serological results were also similarly registered.

<sup>3</sup> Kodijat, R. (1939) *Geneesk. T. Ned.-Ind.* 79, 3018

<sup>4</sup> World Health Organization (1953) *First International Symposium on Yaws Control, Bangkok, 1952*, Geneva, p. 255 (*World Health Organization: Monograph Series*, No. 15)

The approximate occurrence of different forms of lesions can be seen in fig. 3, in which the serological titres of a random group of patients have been analysed. Hyperkeratosis of palms or soles, or both, (palms, 1; palms plus soles, 3; soles, 10) constitute about half of all cases; early contagious lesions plus hyperkeratosis of palms or soles, 23%; early contagious lesions, 14%; and ulcerative and osteo-articular lesions—the remainder—13%.

Since a large number of patients presented a combination of symptoms at the time of survey, it was felt that they represented a special phase of the disease and should be analysed separately. This was particularly true in the case of early contagious plus hyperkeratosis, and ulcerative plus osteo-articular, lesions.

#### *Laboratory methods*

The data presented in this study represent serological results obtained from sera collected in the control villages of the Regencies of Bantul and Kulon Progo (Residency of Jogjakarta) and Klaten (Residency of Solo), all situated within 50 km (about 30 miles) of the laboratory (fig. 1). The samples, which were collected in vacutainer tubes, usually reached the laboratory on the afternoon of the day of collection. They were stored in the refrigerator (4°-6°C) and tested within 2-4 days.

All sera were tested quantitatively with two cardiolipin slide-tests—namely, the VDRL (Venereal Disease Research Laboratory, Chamblee, Ga., USA) slide-test, and the Kline slide-test using LaMotte antigen—or with the Kahn test using Difco beef-heart-extract antigen, or with all three. A sample of sera was also tested by a complement-fixation test (Kolmer method, cardiolipin antigen).

It was very important to maintain a uniform level of sensitivity for some length of time to permit the comparison of decrease in the reagin titre in various types of lesion, following a particular dosage of penicillin. This was assured by carefully checking each batch of antigen with known control serum of definite titre which had been used over a period of months. Except at the beginning, when expired antigen from leaking bottles was used, VDRL antigen, provided in 0.5-ml ampoules, produced a high level of uniform sensitivity.

As a check on the reliability of the laboratory methods a special experiment was conducted under ordinary working conditions. A collection of 175 sera was split and tested twice at one-day intervals with quantitative VDRL and Kline tests over a period of four weeks. The difference in the two consecutive tests never exceeded two dilutions, and the correlation between the two tests (0.919 for VDRL and 0.910 for Kline) was high. Half of the sera showed twice the same value of the titre, and 4% showed a discrepancy of two dilutions.

The VDRL test employing antigen of known chemical composition, with its high degree of sensitivity and specificity, is becoming more and more

FIG. 2. PATIENT'S HISTORY CARD

**TREPONEMATOSES CONTROL PROJECT INDONESIA.**  
**LABORATORY**

Key to Sympt. No. of Yaws lesions (Dr Kodjat):

<ol style="list-style-type: none"> <li>1. Papilloma</li> <li>2. Ulcus</li> <li>3. Papilloma (generalized)</li> <li>4. Condyloma</li> <li>5. Pian dartre (Keratosis pilaris)</li> <li>6. Ringworm yaws</li> <li>7. Roseola, Macula</li> <li>8. Papula</li> <li>9. Psoriatic framb. (early)</li> <li>10. Papilloma (palm &amp; sole)</li> <li>11. Keratodermis</li> <li>12. Psoriatic framb. (late)</li> <li>13. Rhagades</li> <li>14. Keratoeczidiz</li> <li>15. Pigmentary changes</li> <li>16. Ulcera, serpiginous (shallow)</li> <li>17. Ulcera, crateriform (deep)</li> <li>18. Arthralgia</li> <li>19. Hydrarthrosis</li> <li>20. Arthritis</li> <li>21. Ankylosis &amp; Contracture</li> <li>22. Ostealgia</li> <li>23. Polydactylitis</li> <li>24. Ostitis</li> <li>25. Periostitis</li> <li>26. Tendovaginitis</li> <li>27. Bursitis</li> <li>28. Rhinopharyngitis mutilans</li> <li>29. Nodositas juxta-articularis</li> <li>30. Goundou</li> </ol>	<p>REMARKS:</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>Date: ..... Signed: .....</p> <p>.....</p> <p>.....</p> <p>Date: ..... Signed: .....</p> <p>.....</p> <p>Date: ..... Signed: .....</p> <p>.....</p> <p>Date: ..... Signed: .....</p>
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<b>TCP. LABORATORY</b>			
Inter-pretation	Type of Test	Lab. No.	Date: .....
			weeks
	VDRL		Date: .....
			months
	Kline		Date: .....
			months
	Kahn (units)		Date: .....
			months
	C'-fix		Date: .....
			months
	VDRL		Date: .....
			months
	Kline		Date: .....
			months
	Kahn (units)		Date: .....
			months
	C'-fix		Date: .....
			months
Cure	VDRL		Date: .....
			months
Improvement	Kline		Date: .....
			months
Fastness	Kahn (units)		Date: .....
			months
Relapse	C'-fix		Date: .....
			months
Cure	VDRL		Date: .....
			months
Improvement	Kline		Date: .....
			months
Fastness	Kahn (units)		Date: .....
			months
Relapse	C'-fix		Date: .....
			months

<b>SEROLOGIC FOLLOW UP</b>			
Date of Exam: .....			
VI	Others:	5	7
V	Lesions of joints	18	19
	Lesions of bones	22	23
IV	Ulcerative lesion	16	17
III	Keratoderma of palms	9	11
	Keratoderma of soles	9	11
II	Generalized lesion	3	4
		6	10
I	Initial lesion	1	2
Hamlet: ..... Village: ..... Subdistrict: ..... Regency: .....			
I	Leprosy Type: .....		
II	Malaria acute .....		
	chronic .....		
III	Smallpox Vacc. .... Date .....		
IV	Acute Respiratory Disease & Fever .....		
V	Syphilis Type: .....		
VI	Others: .....		
<b>Serologic Follow UP</b>			
Date: ..... months			
Lab. No. ....			
C'-fix	VDRL	Cure	
	Kline	Improvement	
	Kahn (units)	Fastness	
	C'-fix	Relapse	
<b>Darfield Exam. (record only pos.)</b>			
Date	Sympt. No.	P. N.	
Date	Sympt. No.	P. N.	
Date	Sympt. No.	P. N.	
Date	Sympt. No.	P. N.	
<b>Clinical Follow UP</b>			
Date: .....			
Sympt. No. of new lesions: .....			

widely used. In order to facilitate intra- and inter-laboratory comparisons, only results obtained with the VDRL test are reported in this article, with the exception of tables II, III, and IX, in which the results of Kline and Kahn tests are also given, to serve as supplementary data.

### Reagin Titre in Untreated Yaws

The results of the serological testing of clinically diagnosed yaws cases from the villages surveyed were analysed according to the classification mentioned earlier. The data on initial and generalized papillomata tend to be limited to patients of over 3-4 years of age, although initial and generalized lesions were observed fairly frequently in infants. Blood was taken at random before the administration of penicillin, no attempt being made to select any particular type of case.

#### *Reagin titre of patients with initial lesions only*

The percentage of seronegative patients from 30 cases with initial lesions is 37 (table II), as compared with 6 in the remainder (522 cases) of the early contagious group (fig. 3). The sense of time of village people may not be very accurate, but more than half of the seronegative results originated from patients with a stated duration of illness of two weeks or less. It is difficult to understand why patients with early yaws of three months' duration should remain seronegative. Table II shows four patients with an initial lesion of three months' duration who reacted negatively to the serological test. Two of these cases had lesion 2 (ulcer)—a fact which, unfortunately, remained unconfirmed by darkfield microscopy. It is possible that these patients had developed a non-specific (non-treponemal) lesion, which had persisted for 4-8 weeks before they became contaminated with *Treponema pertenue*, so that, in fact, they had had yaws infection only 2-3 weeks instead of 2-3 months. It may also be noted from table II that the frequency of lesion 2 increases with the increase in the duration of the illness ( $\leq$  one month, only lesion 1 ; 2-3 months, 5 lesion 1 out of 12).

Table III illustrates the case-history of a male patient of 45 years, who, at the first examination, showed a papilloma on the right thigh of about 10 days' duration. He was admitted to hospital at headquarters, and the course of the development of clinical symptoms and reagin titres was studied before treatment was given. During the period of observation, generalized lesions developed (see fig. 4-7), accompanied by an increase in titre, which rose still further immediately after therapy ( $2 \times 1.2$  mega units of procaine penicillin G in oil with 2% aluminium monostearate (PAM) at intervals of one week). The initial ulcer healed and the papular lesions disappeared, followed by a gradual decline in titre, but in ten months the patient had not reverted completely to seronegativity.



**TABLE II. SEROLOGICAL TESTS IN 30 PATIENTS WITH INITIAL LESIONS**

Patients				Serological tests *		
age (years)	sex	lesion 1 or 2	duration of illness	VDRL	Kline	Kahn
45	M	1	10 days	—	—	—
2	F	1	½ month	—	—	—
5	F	1	½ "	—	—	—
8	M	1	½ "	—	—	—
14	M	1	½ "	—	—	—
30	F	1	½ "	—	—	—
1	M	1	½ "	32	32	
1	M	1	½ "	128	128	16
10	F	1	½ "	256	128	
1	M	1	1 "	2	1	
1	F	1	1 "	2	1	
10	M	1	1 "	4	4	
6	M	1	1 "	32	16	8
10	F	1	1 "	32		4
3	M	1	1 "	64		8
8	F	1	1 "	512	256	
12	M	1	2 "	—	—	
2	M	2	2 "	32	32	
2	F	1	2 "	128	32	
5	M	2	2 "	256	128	
6	M	2	3 "	—	—	—
7	M	1	3 "	—	—	—
8	F	2	3 "	—	—	—
43	F	1	3 "	—	—	—
14	M	1	3 "	8	8	4
1	M	2	3 "	32		4
5	M	2	3 "	32	32	8
11	M	2	3 "	128	64	
3	M	2	12 "	16	16	
3	M	2	12 "	16		4

Lesion 1 = papilloma; lesion 2 = ulcer

\* All results are given in dilts.

It is to be expected that negative serological reactions will occur in the very early stage of the disease. In yaws, as in syphilis, reagin may appear after the initial lesion has developed, and the time required to develop reagin above the detectable level of the serological test employed varies with the immunological response of the patient. Those with negative serological reactions invariably remained negative at follow-ups of one week, one month, and longer intervals, after penicillin treatment.

For the detection of reagin in the very early stage of yaws, one type of test seems to possess no special advantage over another. It is claimed that Kahn antigen, being made of crude beef-heart and therefore not being of high purity, tends to give positive results sooner than cardiolipin antigen. It may be mentioned here that, in order to conserve time and antigen, only

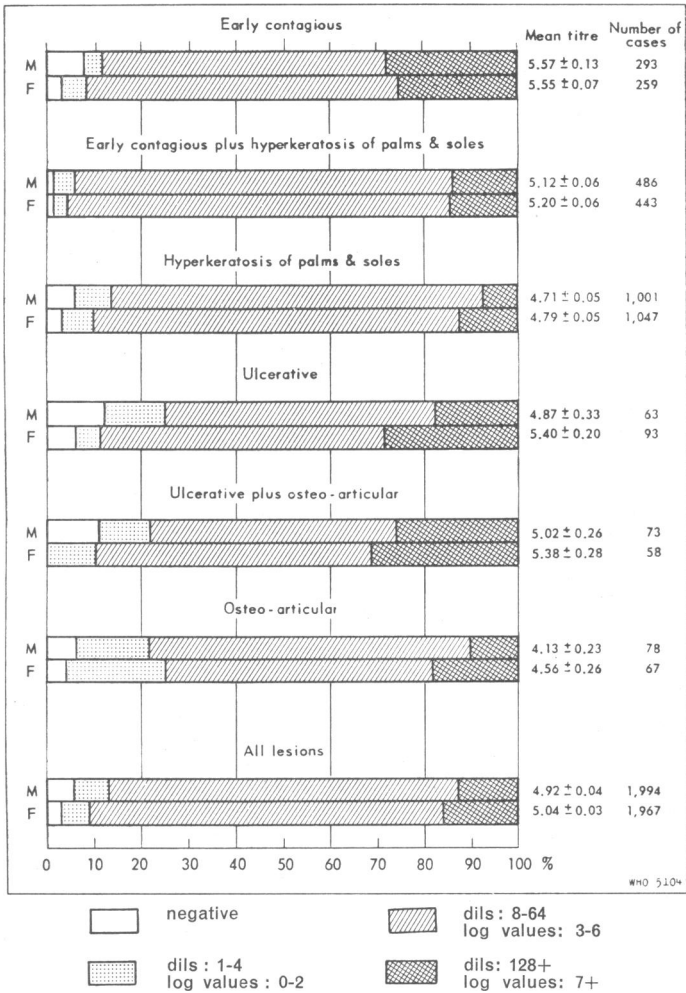
**TABLE III. SEROLOGICAL OBSERVATION  
OF TITRE OF CASE \* WITH SERONEGATIVE INITIAL LESION**

No. of days after appearance of lesion	Serological tests **			
	VDRL	Kline	Kahn	darkfield
10 (first seen in clinic)	—	—	—	positive
12	1	2	—	
14	1	1	—	
16	2	2	—	
18	2	2	—	
20	4	4	1	
22	4	4	1	
24	8	8	1	
33	16	16	2	positive
49	16	16	4	
59	32	16	8	
67	treatment	4 ml	PAM	
74	"	4 ml	"	
81	128	64	32	
89	64	64	32	
105	4	8	4	
197	2	2	—	
298	—	1	—	
375	2	2	—	

\* Case No. 1: age, 45; male; lesion—primary papilloma on right thigh, of 10 days' duration

\*\* All results are given in dils.

**FIG. 3.**  
**DISTRIBUTION OF REAGIN TITRE BY LESION (SAMPLES**  
**FROM BANTUL AND TWAJAS)**



the Kahn quantitative method was used instead of examining first by the three-tube standard method. It is possible that by using the standard test more positives might have been detected.

*Distribution of reagin titre by types of lesion*

The reagin titres of 3,961 clinically diagnosed yaws cases from Bantul and Tjawas were analysed by type of lesion. For the quantitative test, the twofold serial dilution method was used, in which results are expressed in logarithms to the base two of the dilution; for example, titre 5 is equivalent

to positive up to 1/32 dilution, titre 6 is equivalent to 1/64 dilution, and titre 5.5 is in between the two (1/48). The mean titre is calculated on the basis of seropositive reactors only, as it was not possible, either with the laboratory facilities available at the time, or with clinical examinations in each clinical group, to determine who the true yaws sufferers were among the seronegative patients.

*Seronegatives.* The percentage of seronegatives among the clinically positive cases is low—an over-all percentage of 4.5. Studies have proved that cardiolipin antigen is highly sensitive and specific in syphilis; its high diagnostic value in yaws is supported by the fact that the percentage of negative serological reactions is especially low (1.6%) in patients with the combination of early contagious plus plantar or palmar hyperkeratosis or both. It is evident that cases with several types of lesion were more easily recognized as yaws cases than were those with, for instance, only an atypical ulcer.

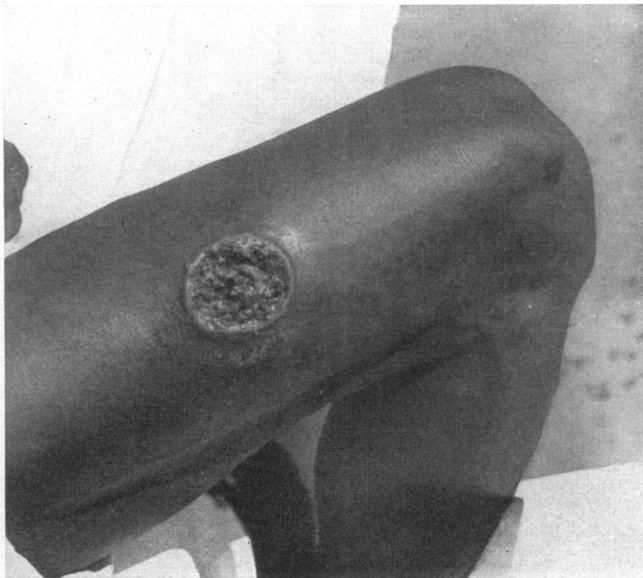
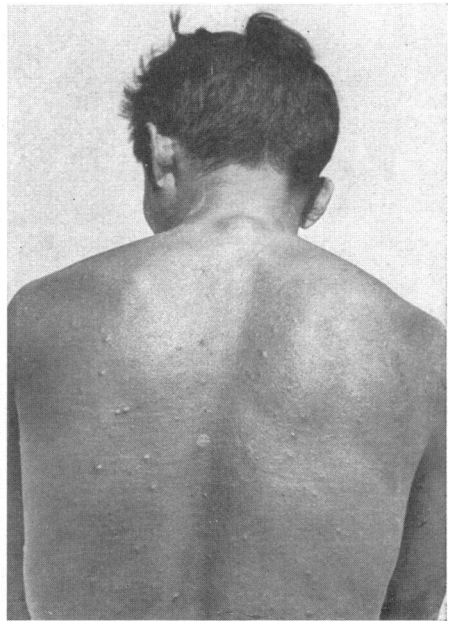
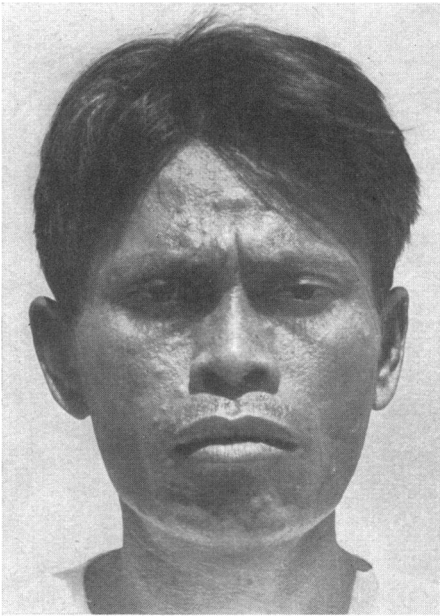
There is no doubt that a certain fraction of the negative reactions was due to technical errors, such as mislabelling, over-inactivation (over 62°-63°C for three minutes), etc., but this is considered to be negligible because of the smallness in number of the seronegative reactors among all the samples collected. In addition, the ability of the technicians was checked periodically by providing them with duplicate samples (once with triplicate serum samples); the results obtained agreed very well. Zone reactions were carefully avoided by performing quantitative tests on all clinically diagnosed cases regardless of the results of the qualitative test. Other diseases prevalent in the tropics which may be mistaken for yaws—namely, tropical ulcer, scabies, scrofuloderma, a number of fungus infections, and traumatic plantar and palmar hyperkeratosis—may produce negative serological results.

There is a tendency for females to give fewer seronegative results than males. Although this difference is generally small, the fact that this is so in all the forms of yaws considered means that it cannot be ignored. In the same way, among seropositive cases one always finds a higher mean titre in females than in males, even when eliminating the effect of different age-distribution.

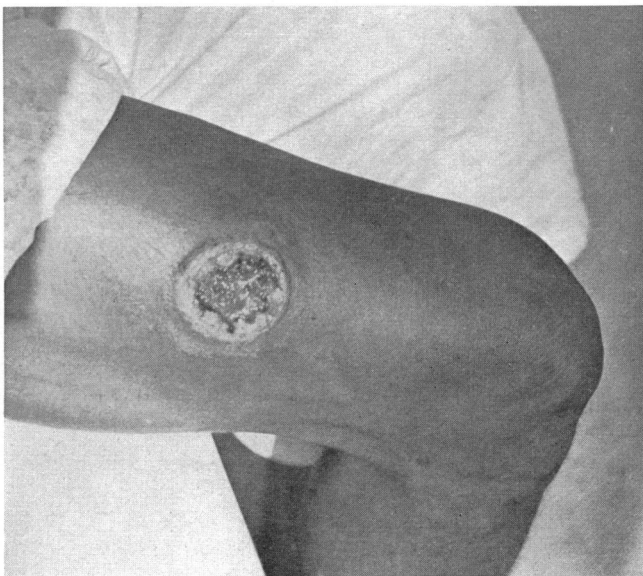
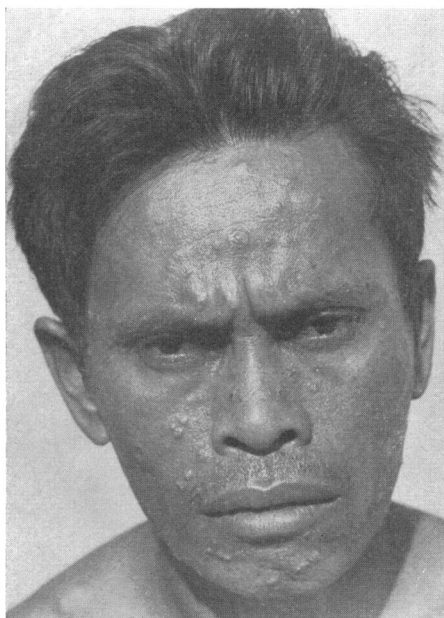
The patients with low titres seem to be associated more with ulcerative and osteo-articular lesions—just as in syphilis negative serological reactions and low reagin titre may occur more frequently in patients in the late phase of the disease.

*Seropositives.* Although individuals vary in their ability to produce reagin under the same stimulus, the high titres are to be found more among patients suffering from early contagious and ulcerative forms of yaws. Of the 3,961 patients examined, only four cases had a titre of 1/1,024; three were female patients with early contagious yaws, and one was a male with

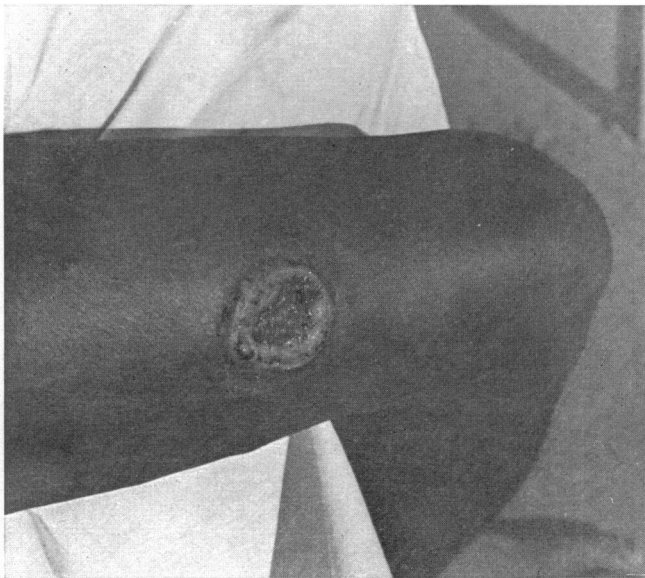
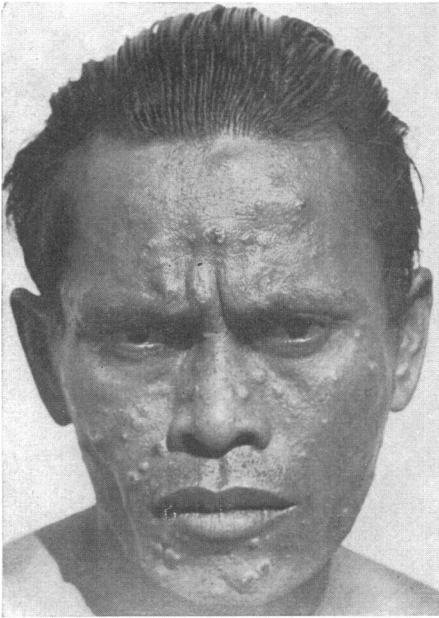
**FIG. 4. CASE No. 1 : 54 DAYS AFTER APPEARANCE OF INITIAL LESION**



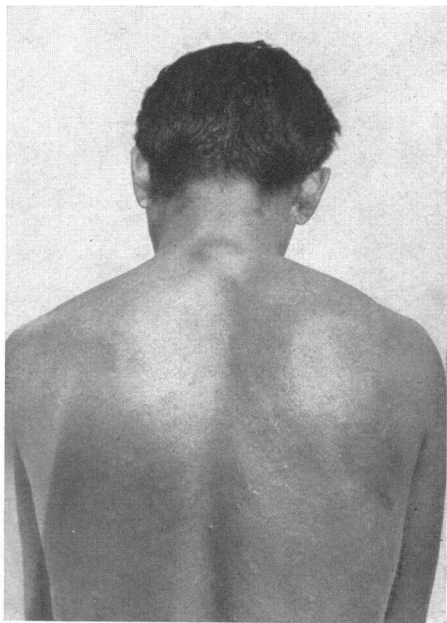
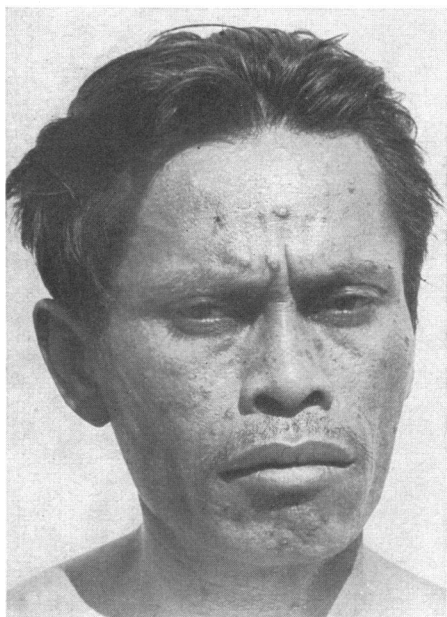
**FIG. 5. CASE No. 1 : 63 DAYS AFTER APPEARANCE OF INITIAL LESION**



**FIG. 6. CASE No. 1 : 67 DAYS AFTER APPEARANCE OF INITIAL LESION**



**FIG. 7. CASE No. 1 : 76 DAYS AFTER APPEARANCE OF INITIAL LESION,  
9 DAYS AFTER FIRST INJECTION OF 4 ml OF PAM**





ulcerative lesions plus lesions of joints and bones. Sixteen cases had a titre of 1/512 (11 of the 16 were females, and 6 of the 11 were early contagious). The majority of the patients had titres between 1/8 and 1/64.

The mean reagin titres of the different forms of yaws rank in the following order, from highest value to lowest value : Early contagious, early contagious plus hyperkeratosis, ulcerative plus osteo-articular, ulcerative, hyperkeratosis, and osteo-articular. Fig. 3 also shows for each mean titre the conventional standard error; for example, "males, early contagious,  $5.57 \pm 0.13$ ".

The mean titre in yaws appears, in general, to be of lower level than in syphilis of relatively the same stage.<sup>5</sup>

#### *Distribution of reagin titre by age and sex*

The tendency for females to have a higher titre is more clearly shown in fig. 8, in which the mean value of each age-group is compared in three forms of yaws. The difference of titre in children is less than in adults.

There is a tendency for the titre to be somewhat lower in the age-group 20-49 years for the early contagious cases and in the age-group 20-39 for the hyperkeratosis cases. For the cases with ulcerative or osteo-articular lesions or both, the males show a gradual decrease in titre and the females no change in titre.

In the early contagious and hyperkeratosis groups, the age-distribution is the same for males and females, but the ulcerative or osteo-articular group contains a relatively large number of young males.

Ulcerative lesion in females differs from the same lesion in males in the percentage of seronegatives (male 12.7%, female 6.4%, see fig. 3); in the number of patients with high titres (male 17.5%, female 28.0%, see fig. 3); in the age-distribution (affecting females more in the advanced age-groups, see fig. 8); and the morbidity-rate (male 2, female 3). Except in the percentage of persons with high titres, no difference in sex is observed in the osteo-articular lesions alone. Further investigation is necessary in order to obtain a better understanding of this type of lesion.

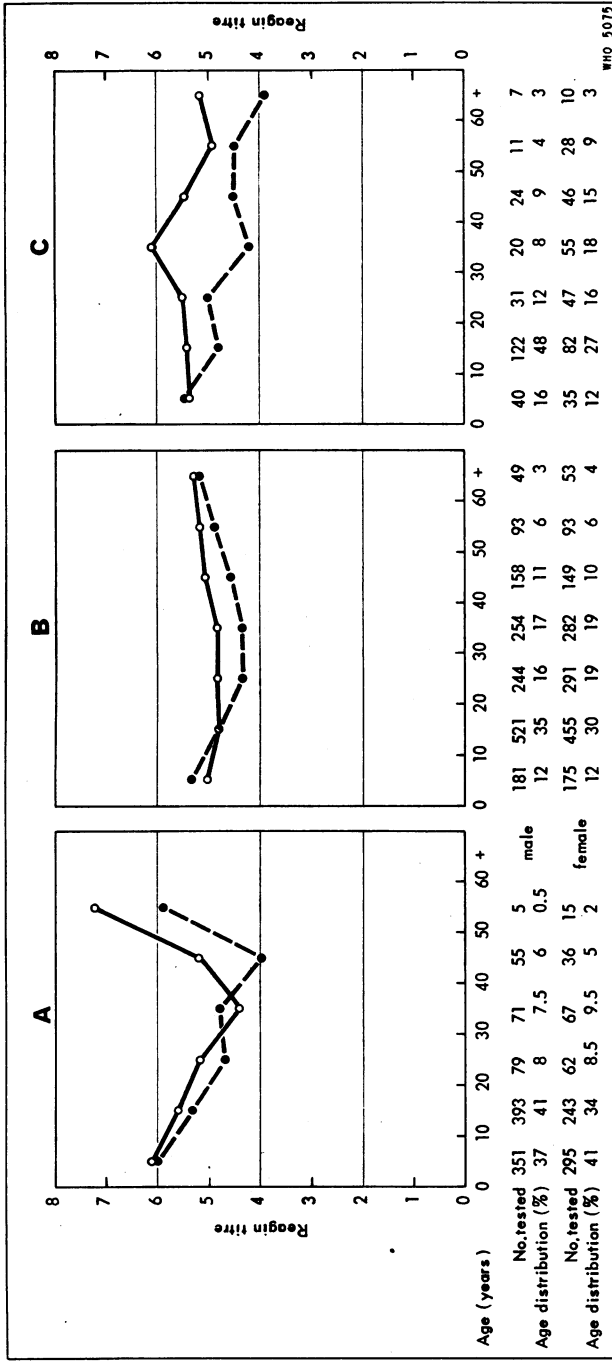
#### **Comparison of Treatment Schedules**

The villages of Tjawas in the Regency of Klaten, which has an estimated population of 33,777 and a yaws prevalence of 15.2%, were selected for this study. The schedules of treatment employed with 300,000 units per ml of PAM are given in table IV.

It will be noted from table V that fewer patients were treated with schedules A and B than with schedule C. Only one village treated with

<sup>5</sup> Moore, J. E. (1949) *The diagnosis of syphilis by the general practitioner*, Washington, D.C. (*J. vener. Dis. Inform. Suppl.* 23)

FIG. 8. DISTRIBUTION OF REAGIN TITRE\* BY AGE AND SEX (SAMPLES FROM BANTUL AND TJAWAS : THE 3,961 CASES IN FIG. 3, PLUS 1,267 ADDITIONAL CASES)



\* The titre is expressed in logarithms to the base two of the dilution.

**TABLE IV. TREATMENT SCHEDULES**

Age-group (years)	A* (ml)	B* (ml)	C (ml)	D (ml)
0-2	2 × 1.0	2 × 0.5	1 × 1.0	1 × 1.5
3-10	2 × 2.0	2 × 1.0	1 × 2.0	1 × 3.0
11 +	2 × 4.0	2 × 2.0	1 × 4.0	1 × 6.0

\* At intervals of one week

schedule A and one village treated with schedule B were re-surveyed. Two villages, in Pundong in the Regency of Bantul, selected in 1951 for this study proved to be inaccessible for further progress by re-survey because of the uncooperative attitude of the village headman. Further, the six months survey in four of the villages treated with schedule D had not been completed when this report was being prepared; these villages could not, therefore, be included in the study.

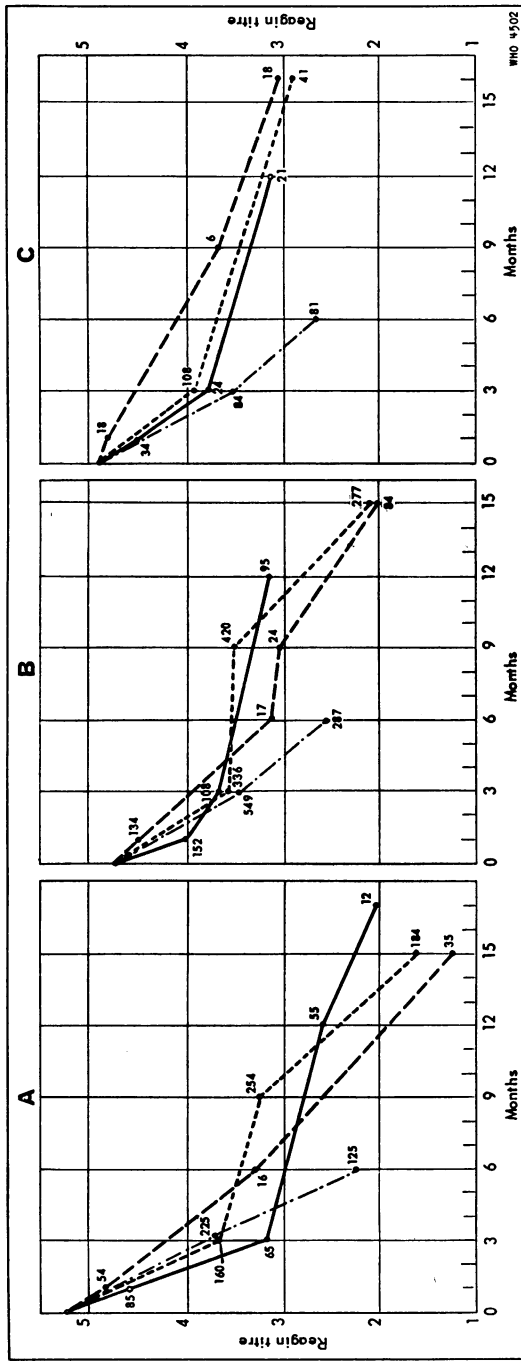
**TABLE V. POPULATION SURVEYED AND RE-SURVEYED AFTER 9-15 MONTHS**

Initial survey		A		B		C	
Total number of persons examined		2,934		2,181		7,361	
No. of uninfected persons	a	2,420		1,749		5,524	
No. of yaws patients	b	514 (17.5)		432 (19.8)		1,837 (25.1)	
Follow-up surveys		9 months	12 months	9 months	15 months	9 months	15 months
No. of uninfected persons re-examined (former patients excluded)	c (c/a)	1,037 (42.8)	1,037 (35.3)	1,324 (75.7)	1,271 (38.3)	2,727 (49.4)	2,471 (44.7)
No. of yaws patients among them	d (d/c)	22 (2.1)	24 (2.3)	76 (5.7)	73 (5.7)	167 (6.1)	172 (6.9)
No. of formerly treated patients re-examined	e (e/b)	235 (45.7)	215 (41.8)	333 (77.1)	317 (73.4)	848 (46.2)	834 (45.4)
No. of yaws cases among them	f (f/e)	15 (6.4)	13 (6.0)	15 (4.5)	16 (5.0)	37 (4.4)	43 (5.2)

Figures in parentheses indicate percentages.

The results from the blood samples obtained immediately before treatment have been presented as part of the analysis of reagin in untreated yaws. It was planned that, following treatment, additional blood samples

FIG. 9. DECREASE IN REAGIN TITRE,\* ACCORDING TO TREATMENT SCHEDULES



Figures shown against the curves indicate the number of patients re-examined.  
 \* The titre is expressed in logarithms to the base two of the dilution.

should be collected after one month, three months, and then at three-monthly intervals. Our re-survey has not been very satisfactory because of difficult circumstances : Rebels occupied Tjawas during the first half of 1952, thus preventing the team from reaching the people. During the dry season many people migrate to other places in search of temporary

**TABLE VI. SEROLOGICAL RESULTS OF FOLLOW-UP SURVEYS 12-15 MONTHS AFTER TREATMENT, ACCORDING TO LESIONS AND TREATMENT SCHEDULES**

Type of lesion	Treatment schedule	No. of persons examined	Serological results *						Sero-negative **	
			increase		stationary		decrease		no.	%
			no.	%	no.	%	no.	%		
Early contagious	A	25	3		1		21	84	1	
	B	15	0		0		15	100	4	
	C	75	1		2		72	96	6	
		115	4	3.5	3	2.6	108	93.9	11	9.6
Early contagious plus hyperkeratosis of palms/soles	A	30	1		2		27	90	1	
	B	20	0		0		20	100	0	
	C	111	0		2		109	98	5	
		161	1	0.6	4	2.5	156	96.9	6	4.7
Hyperkeratosis of palm/soles (3-18 years of age)	A	48	2		3		43	90	0	
	B	33	0		2		31	94	1	
	C	53	2		2		49	92	1	
		134	4	3.0	7	5.2	123	91.8	2	1.5
Hyperkeratosis of palms/soles (19+years of age)	A	55	8		6		41	74	0	
	B	51	2		2		47	92	1	
	C	157	2		15		140	89	6	
		263	12	4.6	23	8.7	228	86.7	7	2.7
Ulcerative ; osteo-articular ; ulcerative plus osteo-articular	A	21	2		4		15	71	0	
	B	20	1		4		15	75	0	
	C	61	1		8		52	85	3	
		102	4	3.9	16	15.7	82	80.4	3	2.9
All lesions	A	179	16		16		147	82	2	1.1
	B	139	3		8		128	96	6	4.6
	C	457	6		29		422	92	21	4.3
Total		775	25	3.2	53	6.8	697	89.9	29	3.6

\* Only cases showing exactly the same titre before and after treatment are classified as "stationary". Cases which were non-reactive before treatment are not included in the table.

\*\* The number of "decrease" cases which gave seronegative reactions

work. Also, during the fasting month, out of consideration for certain members of our team, blood samples were not collected. Sometimes the lure in calling people for re-examination is not very effective; many stay out in the fields, since it is difficult to convince the people of the necessity of a re-check if they feel they are already well.

For the study of decrease in reagin titre following PAM treatment, the mean decrease value from the initial titre was computed for all persons re-examined, regardless of serological and clinical status. Patients with negative initial titres were not included in the analysis. Owing to the small number of patients re-examined in schedules A and B, the patients were combined into three clinical groups, according to the diagnosis made at the time of treatment.

Fig. 9 indicates that there is no marked difference in the mean decrease in reagin titre in all three groups of patients under consideration during the period of 12-15 months' observation, with the exception of schedule D.

It is to be noted that study of the serological results obtained at 12-15 month follow-up surveys (comparing the number of patients showing decreased, unchanged, or increased titre) did not demonstrate that any one schedule employed was more advantageous than another. As expected, the percentage of serological cure and improvement was highest in the cases with early lesions of yaws (table VI).

In general, the serological response of early yaws is comparable with the results obtained by Rein and his co-workers in Haiti,<sup>6</sup> using the same total dosage but a different repository penicillin preparation (crystalline penicillin G in peanut oil with 4.8% beeswax). The number of patients attaining seronegativity is low in our study, but perhaps this difference is due to the type of test employed.

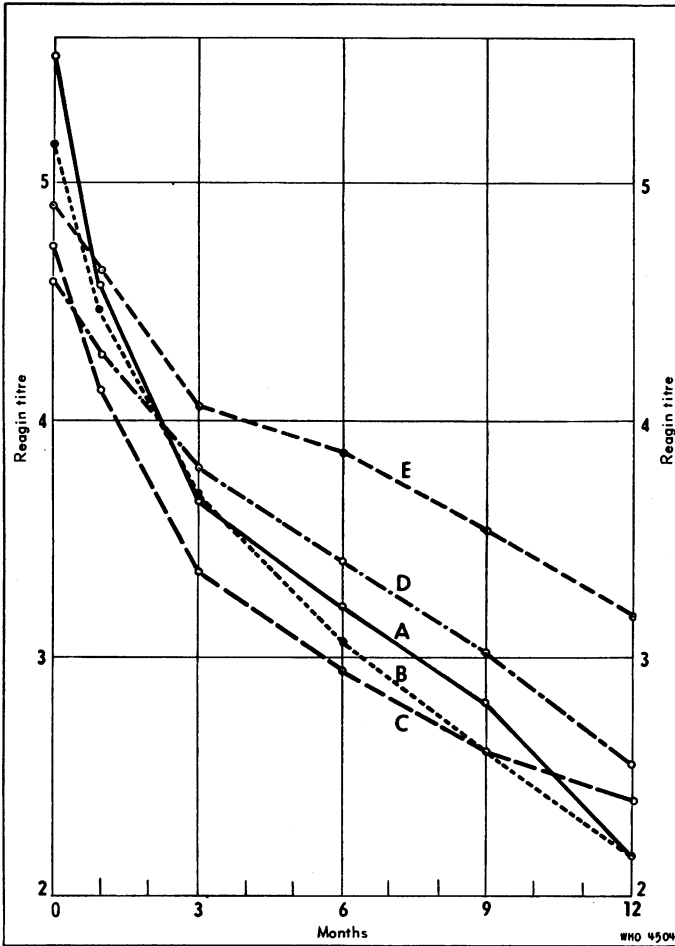
For further comparison, the records of patients requiring re-treatment during the 9-15 months' follow-up were studied (tables VII, VIII, and IX). No important differences were observed with the three treatment schedules under study. One must, however, consider that only about 50% of the original patients were re-examined; nevertheless, the factor which causes people not to return for re-check should be common in villages under similar conditions.

#### Decrease in Reagin Titre according to Lesion and Initial Titre

To study the serological response of each form of yaws following PAM treatment, the patients with the same type of lesion were combined (hyperkeratosis of palms or soles was differentiated between 3-18 and 19+ years of age) for treatment schedule A, B, and C (see fig. 10).

<sup>6</sup> Rein, C. R., Sternberg, T. H., Dwinelle, J. H. & Sheldon, A. J. (1948) *Arch. Derm. Syph. (Chicago)*, 57, 942

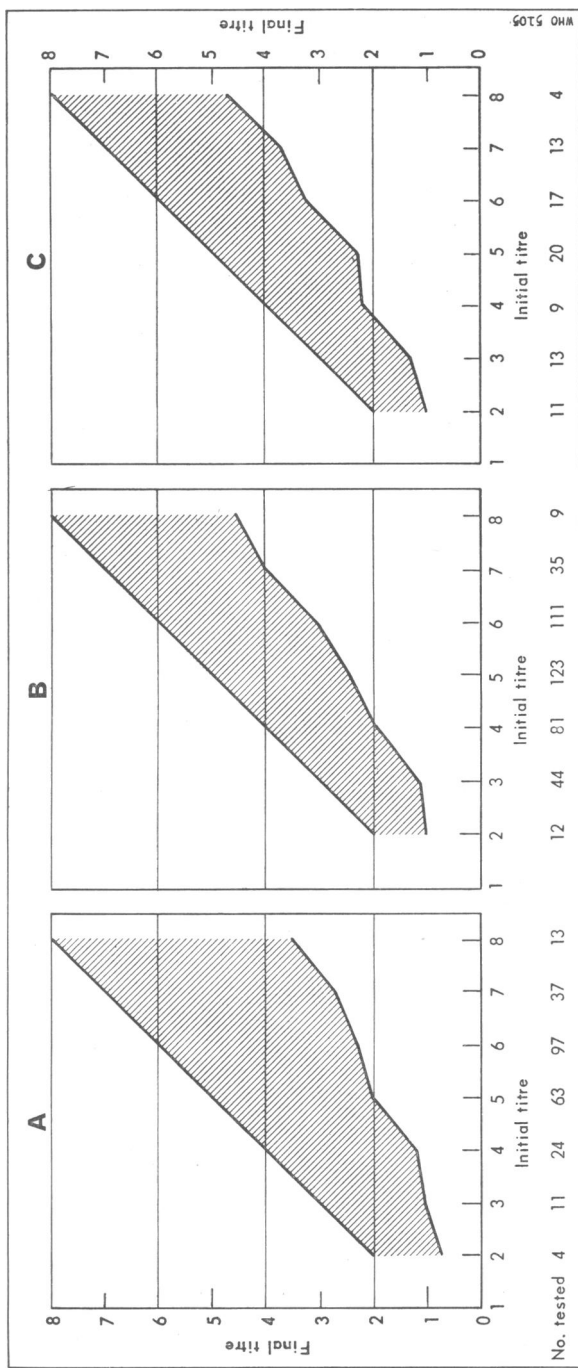
FIG. 10. DECREASE IN REAGIN TITRE,\* ACCORDING TO TYPES OF LESION



- A = early contagious
  - B = early contagious plus hyperkeratosis of palms or soles
  - C = hyperkeratosis of palms or soles (3-18 years of age)
  - D = hyperkeratosis of palms or soles (19+ years of age)
  - E = ulcerative; osteo-articular; and ulcerative plus osteo-articular
- \* The titre is expressed in logarithms to the base two of the dilution.

Twelve months after treatment, the mean titre of patients with early contagious lesions and the mean titre of patients with early contagious lesions plus hyperkeratosis were approximately of the same value. The former had still the sharpest drop from the initial titre. In the hyperkeratosis cases, the younger age-group had higher initial titres and showed a greater decrease. Sufferers from ulcerative and osteo-articular lesions showed the least serological response.

**FIG. 11. DECREASE IN REAGIN TITRE 12-15 MONTHS AFTER PAM TREATMENT, CALCULATED FOR THE THREE CLINICAL GROUPS AND THE SEVEN INITIAL TITRES.**



**A** = Early contagious plus hyperkeratosis of palms or soles

**B** = Hyperkeratosis of palms or soles

**C** = Ulcerative; osteo-articular; ulcerative plus osteo-articular



The average decrease in titre (after 12-15 months) was calculated for each of the three clinical groups, and for each group of initial titres (see fig. 11); the method followed is shown in the following example:

titre before treatment — 32 dils (see Harris <sup>7</sup>) = titre 5  
 titre after treatment — (a) 2 dils = titre 1, decrease 4  
                                   (b) 1 dil = titre 0, decrease 5  
                                   (c) non-reactive = titre —1, decrease 6  
 (The titre value for (c) was chosen arbitrarily.)

It is to be noted that the over-all decline is greatest in early contagious lesions and early contagious lesions plus hyperkeratosis (except in cases with 4 dils or less), and that there is very little difference between the other two clinical groups. As expected, the decrease in titre is greatest in the higher dilutions and gradually reaches approximately the same value in the lower dilutions.

#### Patients Requiring Re-treatment at Follow-up

During the re-survey, about one year after the initial treatment, it was generally found that about 5%-10% of the originally treated patients presented lesions that needed additional penicillin treatment. They were re-treated according to the following categories: old lesion improved but not healed; old lesion not improved; new lesions at other sites of the body (relapse); or re-infection.

Among 41 patients examined serologically both before treatment and at the time of follow-up only five had increased and nine unchanged reagin titre (tables VII and VIII).

The diagnosis and the results of serological tests before treatment and at follow-up surveys are given in detail in table IX. The titre obtained during the intermediate follow-up surveys usually falls within the range of the initial and 9-15 months follow-up titres. It is also shown that the majority of the "relapse" cases had lesions of the more advanced stage of yaws.

#### *Sentolo and Lendah*

The villages of the subdistricts Sentolo and Lendah, in the Regency of Kulon Progo, were among the first to be chosen for the campaign. The attendance was good; 93% of the population (estimated at 58,165) were examined, and 11,648 cases of yaws (20%) were diagnosed and treated. Blood samples were collected for the first time at the 15 months follow-up survey. The percentage of former patients needing re-treatment was 10.6. Comparison of the mean titre of seropositives and the percentage of sero-

<sup>7</sup> Harris, A. (1947) *J. vener. Dis. Inform.* 28, 249

**TABLE VII. INITIAL AND FOLLOW-UP TITRES OF 41 PATIENTS REQUIRING RE-TREATMENT**

Initial titre	Follow-up titre									Total
	0	1	2	4	8	16	32	64	128	
512									1	1
256						1		1		2
128				1				1	1	3
64					2			2	1*	5
32		1	1	1	2	2	1	1*		9
16	1		1	2	2					6
8				3	2					5
4			3							3
2		1	2							3
1		1	1**							2
0		1**					1**			2
Total	1	4	8	7	8	3	2	5	3	41

\* Early contagious, clinically improved (see table IX)

\*\* Hyperkeratosis, clinically improved (see table IX)

**TABLE VIII. CLASSIFICATION OF THE 41 RE-TREATED CASES**

Serological status	Clinical status		
	improvement	relapse	reinfection
increase	5		
stationary	4	5	
decrease	16	10	1

negatives from clinically cured and uncured patients with the same type of lesion may be made from the results given in table X.

No important differences are observed between clinically cured and uncured patients at the time of the 15 months follow-up survey in the case of palmar or plantar hyperkeratosis, and ulcerative or osteo-articular lesions. The difference in early contagious lesions is more apparent. The pattern of evolution of lesions shown in table XI was obtained in 1,581 patients from the same area requiring re-treatment at the 15 months follow-up survey.

**TABLE IX. 41 PATIENTS REQUIRING RE-TREATMENT AT 9-15 MONTHS FOLLOW-UP SURVEYS**

Age	Sex	Serological results †				Clinical classification	
		tests	initial survey	follow-up survey		initial survey	follow-up survey
				9 months	15 months		
Treatment schedule A							
5	M	VDRL Kline Kahn	256 32		16 16	early contagious	relapse early contagious hyperkeratosis
6*	M	VDRL Kline Kahn	32	64 32 32		early contagious	improved
17	M	VDRL Kline Kahn	32 32		32 32 4	ulcer	relapse ulcer
38	F	VDRL Kline Kahn	16 4			hyperkeratosis	improved hyperkeratosis
50	F	VDRL Kline Kahn	4 1		2 4	hyperkeratosis ulcer	improved ulcer
56	F	VDRL Kline Kahn	64 128	64 64 16		ulcer	relapse ulcer
70	M	VDRL Kline Kahn	2 2		2 4	hyperkeratosis	improved
Treatment schedule B							
15	F	VDRL Kline Kahn	16 16 8	8 8 2		hyperkeratosis	improved hyperkeratosis
27	M	VDRL Kline Kahn	8 4		4 4	early contagious hyperkeratosis	reinfected early contagious osteo-articular
30	F	VDRL Kline Kahn	32 4	2 8		hyperkeratosis	improved hyperkeratosis

\* See table VII

† All results are given in dilts.

**TABLE IX. 41 PATIENTS REQUIRING RE-TREATMENT AT 9-15 MONTHS FOLLOW-UP SURVEYS** (continued)

Age	Sex	Serological results †				Clinical classification	
		tests	initial survey	follow-up survey		initial survey	follow-up survey
				9 months	15 months		
Treatment schedule B (continued)							
30	M	VDRL Kline Kahn	8 2	4 4 1		hyperkeratosis	improved hyperkeratosis
35	M	VDRL Kline Kahn	16 8		4 4	hyperkeratosis	relapse ulcer
40	M	VDRL Kline Kahn	64 16	8 8 2		early contagious	improved ulcer
40	M	VDRL Kline Kahn	8 2		4 4	ulcer osteo-articular	improved
45	M	VDRL Kline Kahn	32 8	16 16 8		early contagious hyperkeratosis	relapse ulcer
Treatment schedule C							
4	M	VDRL Kline Kahn	64 64	64 64 16		ulcer osteo-articular	improved
5	F	VDRL Kline Kahn	128 32	64 64 16		early contagious hyperkeratosis	relapse early contagious
5*	M	VDRL Kline Kahn	64 64		128 128	early contagious osteo-articular ulcer	improved
6	F	VDRL Kline Kahn	256 64	64 64 16		early contagious	improved
6	M	VDRL Kline Kahn	32 16	4 8 2		hyperkeratosis	relapse

\* See table VII

† All results are given in dils.

**TABLE IX. 41 PATIENTS REQUIRING RE-TREATMENT AT 9-15 MONTHS FOLLOW-UP SURVEYS** (continued)

Age	Sex	Serological results †				Clinical classification	
		tests	initial survey	follow-up survey		initial survey	follow-up survey
				9 months	15 months		
Treatment schedule C (continued)							
12	M	VDRL Kline Kahn	64 4	8 8 2		early contagious hyperkeratosis	relapse early contagious
13	M	VDRL Kline Kahn	8 4	8 16 2		osteo-articular	improved
14	M	VDRL Kline Kahn	32 8		1 1 1	ulcer osteo-articular	improved
14	M	VDRL Kline Kahn	8 4	8 8 4		osteo-articular	improved
16	F	VDRL Kline Kahn	512 256	128 128		ulcer osteo-articular	improved
16	M	VDRL Kline Kahn	32 16	8 16		ulcer osteo-articular	relapse hyperkeratosis
25	M	VDRL Kline Kahn	32 4	8 8 2		early contagious hyperkeratosis	improved early contagious
30	F	VDRL Kline Kahn	16 2	4 4 1		hyperkeratosis	relapse early contagious
30	F	VDRL Kline Kahn	32 64		32 32	hyperkeratosis ulcer osteo-articular	relapse osteo-articular
30*	M	VDRL Kline Kahn	0 1	32 16 8		hyperkeratosis	improved
32	F	VDRL Kline Kahn	128 32	128 128 64		hyperkeratosis	relapse hyperkeratosis

\*See table VII

† All results are given in dils.

**TABLE IX. 41 PATIENTS REQUIRING RE-TREATMENT AT 9-15 MONTHS FOLLOW-UP SURVEYS** (continued)

Age	Sex	Serological results †				Clinical classification	
		tests	initial survey	follow-up survey		initial survey	follow-up survey
				9 months	15 months		
Treatment schedule C (continued)							
35*	F	VDRL Kline Kahn	1 2	2 4		hyperkeratosis	improved
35	F	VDRL Kline Kahn	1 1	1 1		osteo-articular	improved
36	M	VDRL Kline Kahn	4 1		2 2	hyperkeratosis	relapse early contagious
40	F	VDRL Kline Kahn	16 16		2 2	ulcer	improved
40	M	VDRL Kline Kahn	2	2 4		hyperkeratosis	relapse early contagious
45	M	VDRL Kline Kahn	2		1 1	hyperkeratosis	improved
45	M	VDRL Kline Kahn	128		4 4	hyperkeratosis osteo-articular	improved
50	F	VDRL Kline Kahn	4 4		2 4	osteo-articular	improved
50*	M	VDRL Kline Kahn	0 0	1 1		hyperkeratosis	improved
50	M	VDRL Kline Kahn	16 2		8 16	hyperkeratosis ulcer	relapse ulcer

\* See table VII

† All results are given in dilts.

**TABLE X. PERCENTAGE OF SERONEGATIVES AND MEAN TITRE AT 15 MONTHS FOLLOW-UP SURVEY OF 990 CURED CASES AND 646 CASES NEEDING RE-TREATMENT (FROM THE SENTOLO LENDAH AREA)**

Sex	Clinically cured patients			Total	Patients requiring re-treatment for persistent clinical conditions			Total
	sero-negative		mean titre of seropositives		sero-negative		mean titre of seropositives	
	no.	%			no.	%		
	<b>Early contagious</b>				<b>Early contagious</b>			
M	13	26.5	1.78 ± 0.20	49	4	12.5	3.29 ± 0.33	32
F	13	23.2	1.79 ± 0.23	56	3	21.4	5.00 ± 0.23	14
	<b>Hyperkeratosis of palms/soles</b>				<b>Hyperkeratosis of palms/soles</b>			
M	62	14.7	2.68 ± 0.08	421	84	27.3	2.77 ± 0.12	308
F	21	7.9	3.22 ± 0.07	266	12	14.1	2.56 ± 0.18	85
	<b>Ulcerative and osteo-articular</b>				<b>Ulcerative and osteo-articular</b>			
M	25	28.1	2.78 ± 0.26	89	20	18.5	3.00 ± 0.20	108
F	23	21.1	3.37 ± 0.34	109	25	25.3	3.26 ± 0.26	99

**TABLE XI. EVOLUTION OF LESIONS OF 1,581 PATIENTS REQUIRING RE-TREATMENT AT 15 MONTHS FOLLOW-UP SURVEY (THE 646 CASES SHOWN IN TABLE X PLUS 935 CASES NOT EXAMINED SEROLOGICALLY, ALL FROM THE SENTOLO LENDAH AREA)**

15 months follow-up survey	Initial survey							
	early contagious		early contagious plus hyperkeratosis		hyperkeratosis of palms/soles		ulcerative plus osteo-articular	
	no.	%	no.	%	no.	%	no.	%
Early contagious	49	35.2	18	9.8	21	2.8	4	0.8
Early contagious plus hyperkeratosis	17	12.2	5	2.7	2	0.3	5	1.0
Hyperkeratosis of palms/soles	44	31.7	144	78.7	664	88.3	65	12.8
Ulcerative plus osteo-articular	29	20.9	16	8.8	65	8.6	433	85.4
Total	139	100.0	183	100.0	752	100.0	507	100.0

It is evident that the lesion tends to remain within the same form at the time of follow-up, and that the chance of evolution from one form of yaws to another is much greater with early contagious than with the other lesions. At the follow-up survey, the later forms of yaws—namely, hyperkeratosis and the osteo-articular and ulcerative lesions—constituted the major portion of cases for re-treatment, as is revealed in table XII.

**TABLE XII. DIAGNOSIS MADE AT INITIAL SURVEY AND AT 15 MONTHS FOLLOW-UP SURVEY OF 1,581 YAWS PATIENTS REQUIRING RE-TREATMENT**

	Early contagious		Early contagious plus hyperkeratosis		Hyperkeratosis		Ulcerative plus osteo-articular	
	no.	%	no.	%	no.	%	no.	%
Diagnosis made at initial survey	139	8.8	183	11.6	752	47.5	507	32.1
Diagnosis made at follow-up survey	92	5.8	29	1.9	917	58.1	543	34.4

### Serological Testing in Persons Clinically Negative for Yaws

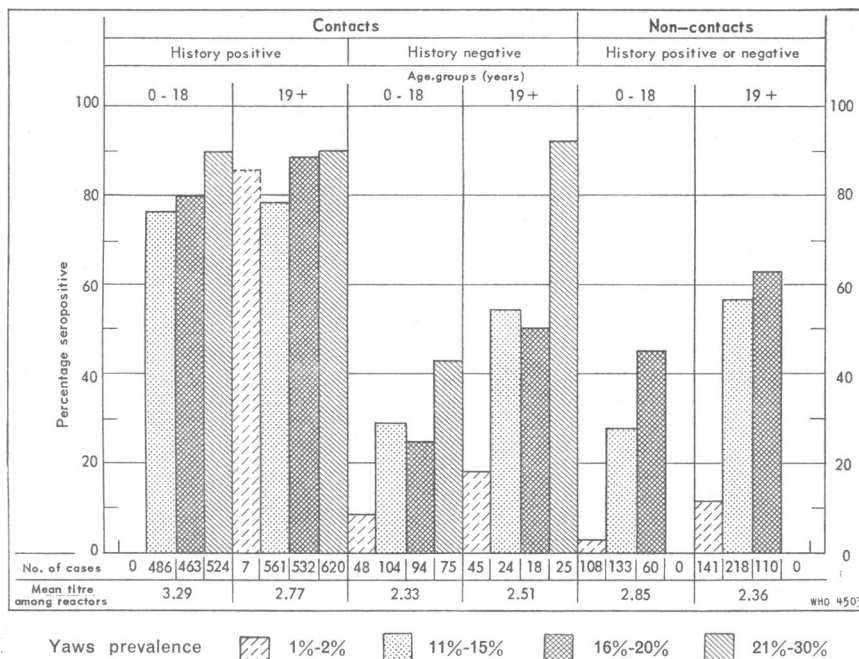
From some of the villages of the Regencies of Klaten and Sleman blood samples were collected from household contacts and non-contacts during the general campaign. (By household contacts is meant the members of a family in which one or more clinically positive cases were found, regardless of whether they were contagious or non-contagious.) History of yaws was obtained, and old yaws scars, which might indicate infection in the past, looked for. Cases giving positive history of yaws and cases giving negative history but having signs indicative of past infection were regarded as history positive. An analysis of the data by age-groups and by prevalence of yaws in the area from which the data were collected is given in fig. 12, from which it may be seen that:

1. There was no difference in the percentage of seropositives in the 0-18 age-group and the 19+ age-group among the household contacts. The rate was high in villages with a yaws prevalence of 11%-15%, 16%-20%, and 21%-30%, and no important difference between them was observed.

2. The number of seropositives in the history-positive groups was significantly higher than in the history-negative groups in the household contacts. In the older age-groups the difference was less, but the number involved was too small to justify comparison.



**FIG. 12. SEROPOSITIVITY-RATE AMONG FAMILY CONTACTS, BY HISTORY AND AGE IN AREAS OF DIFFERENT PREVALENCE**



3. No difference of importance ( $P = 0.10$ ) is observed between, on the one hand, contacts, history negative, and, on the other, non-contacts, in the 0-18 age-group.

4. The prevalence of seropositive reactors in villages of low yaws prevalence was 18% for contacts and 7.3% for non-contacts.

The number of families with yaws patients in the villages of different prevalence are given in table XIII.

**TABLE XIII. FAMILIES WITH YAWS IN AREAS OF DIFFERENT PREVALENCE**

Yaws prevalence (%)	Total number of families	Families with yaws	
		no.	%
21-30 (3)	1,319	622	47.2
16-20 (3)	1,267	615	48.5
11-15 (4)	2,154	592	27.5
1-2 (2)	2,873	134	4.7

Figures in parentheses indicate number of villages examined.

The estimated seropositive prevalence in contacts, non-contacts, and the entire population in the areas of different yaws prevalence are presented in table XIV; these figures are based on the data contained in table XIII and fig. 12.

**TABLE XIV. ESTIMATED SEROPOSITIVITY IN CONTACTS, NON-CONTACTS, AND THE TOTAL POPULATION IN AREAS OF DIFFERENT YAWS PREVALENCE**

Yaws prevalence (%)	Percentage seropositive			
	contacts plus patients	contacts	non-contacts	total population
21-30	95	90	60	77.5
16-20	90	84	53	71.0
11-15	85	75	40	54.0
1-2	40	18	7	8.5

The population of two villages, one with a moderately high prevalence (14%), and the other with low prevalence (1%), were examined clinically and serologically to determine the seropositive incidence among the clinically negative persons. According to history given, and physical evidence of infection in the past, they were divided into history-positive and history-negative groups. The results of the survey are shown in table XV.

The prevalence of seropositives in the history-positive groups of the two villages is about the same, but the difference in the percentage of sero-

**TABLE XV. SEROPOSITIVE PREVALENCE AMONG CLINICALLY NEGATIVE PERSONS IN AREAS OF DIFFERENT PREVALENCE, BY HISTORY AND AGE-GROUPS**

Village	Age-groups (years)	Total no. examined	History positive				History negative			
			examined		seropositive		examined		seropositive	
			no.	%	no.	%	no.	%	no.	%
Pandjanguredjo (14%)	0-19	194	64	33	42	66	130	67	18	14
	20-49	284	142	50	64	45	142	50	24	17
	50 +	87	28	33	11	41	59	67	13	22
	All ages	565	234	41	117	50	331	59	55	16
Sleman (1%)	0-19	347	7	2	6	86	340	98	7	2
	20-49	210	34	16	16	47	176	84	25	12
	50 +	78	11	14	6	55	67	86	11	16
	All ages	635	52	8	28	54	583	92	43	7

positives in the history-negative groups is significant, and the main difference lies in the 0-19 age-group. It is also in the younger age-groups that the main difference in percentage of history positives is to be found.

There seem to be definite indications that seropositivity is truly associated with yaws and is not a consequence of other non-specific factors.

### Discussion

It is well known that the immunological response varies widely in individuals under the same stimulus, and that the serological titre varies also in the same individual at different stages of the disease. Consequently, the mean reagin titre of various groups of patients under similar conditions was computed and used for this study. Perhaps closer co-operation between clinical and laboratory teams would have given easier access to the clinical data. Previous polyclinic treatment, even though inadequate in dosage, should have been recorded, as a few injections of arsenicals may have changed the course of the disease and, thereby, the reagin titre. In dealing with large groups of patients, especially if the popularity and the expansion of the mass-treatment campaign are of primary importance, some reservation must be made in regard to research and scientific approach to the problem.

The reagin titres in the natural course of yaws appear to decrease with the lapse of time, as indicated by the lower mean value in plantar or palmar hyperkeratosis, as compared to that of early generalized papillomata. It should be further noted that within the same type of lesion the titre is higher in children. The titre for the older age-groups in the latent stage is also lower than for the younger age-groups. Only a small fraction of patients develop ulcerative and osteo-articular lesions, and these are accompanied by a rise in titre.

It is not readily understandable why the mean titre is persistently higher in females than males (except in the case of early contagious lesions), nor why the percentage of seronegative persons is always lower in females. From fig. 8 it is evident that males in the younger age-groups have a higher titre in the three types of lesions considered; the reverse is observed in the older age-groups. Apart from the differences in immunological response, perhaps the higher titre in females is also a reflection of the fact that the disease tends to affect females in somewhat later years of life. Apart from contracting the disease in childhood, she has also a greater chance of being infected by the children she brings up. In the endemic area one encounters fairly often infants with generalized lesions in the arms of mothers with early yaws. Males, by nature, are more subjected to trauma, and are, therefore, more likely to have non-treponemal ulcers diagnosed as yaws ulcers.

Further study is necessary for a better understanding of the nature of ulcerative lesions, which occur much more frequently in females, and the more apparent difference in the height of titre between males and females.

A wider range in the total dosage of PAM applied to the different villages would have given a better picture of the serological response to treatment. There is indication that a single intensive dose of PAM is more effective in achieving serological improvement, but whether this is in fact due to the type of treatment or rather to environmental or other induced factors, deserves further observation.

It is generally believed that there is close relation between the rise of serological titre and the recurrence of clinical lesions. Since the patients diagnosed at re-surveys as "relapse" were, for the most part, not associated with the increase in titre, one doubts whether they were really suffering from specific lesions. General health and nutritional status have a bearing upon tissue repair, especially in extensive ulcerations, which were frequent among "relapse" patients. Though treponemes may be exterminated following specific therapy, the healing process of the ulcer may be so slow as to permit secondary infections to recur, after the tissue penicillin level has fallen below the bacteriostatic level for the secondary invaders. Thickening and desquamatic lesions of the palms and soles are difficult to heal, due to trauma, especially if the patient has to labour daily in the fields.

As in syphilis, serological reversal in yaws is more readily achieved in the early course of disease, and persistently unchanged serological reaction following intense therapy has often been observed, as in late syphilis. Unchanged serological titre and clinical signs in the advanced phase of yaws do not necessarily mean unfavourable response to PAM treatment.

It appears that much effort was lost at the follow-up surveys in attempting to cure unhealed patients suffering from late yaws. We noticed time and again patients who had been treated at each follow-up (1, 3, 9, and 12 months) with one or two shots of PAM, but who showed no beneficial results either clinically or serologically. Some may even have had negative serological titres throughout the course of the follow-up.

Darkfield microscopy should have been more extensively used at re-surveys. However, field testing at re-surveys is of practical value only when serological testing is done at the time of initial treatment.

Cardiolipin antigen is known to be highly specific, especially with regard to reactivity with the blood of malaria patients.<sup>8</sup> The prevalence of leprosy is low in Mid-Java, and a separate study of the prevalence of seroreactors among 200 leprosy cases revealed only 32%. The difference observed in the number of seropositives among clinically negative persons in villages of high and low yaws prevalence suggests that these cases are likely to be in the latent asymptomatic stage, or in the process of spontaneous convalescence.

<sup>8</sup> Rein, C. R. & Kent, J. F. (1947) *J. Amer. Med. Ass.* 133, 1001

It is probably feasible to treat the entire population in an area of high prevalence (16% and over), to treat household contacts plus children and adolescents in an area of medium prevalence (6%-15%), and to treat only the clinically positive cases and household contacts in areas of low prevalence (below 5%).

It is felt that, for the general campaign, the interval between re-surveys (at present one month and 12 months) can be lengthened as more people are included in the treatment. In this way, if contacts and children are treated with the full dose of PAM regardless of clinical signs and serological results (persons in the incubation period would be seronegative), the source of infection will be eliminated, and the recurrence of early contagious lesions (5.8% of persons obtaining re-treatment after one year, see table XII) following the mass treatment will also be reduced. Thus labour expended on re-surveys could be applied to a more rapid expansion of the campaign to the neighbouring districts, which would further reduce the possibility of introducing new cases into the area already treated.

On purely humanitarian grounds, possibly it is not advisable to make clinical, serological, and microscopic observations at intervals without specific treatment of clinically positive cases. However, clinical and serological observations both of seronegative and seropositive clinically negative persons in villages with different yaws prevalence at six- to twelve-month intervals will provide valuable information regarding the natural course of yaws and the intensity of the reservoir of the infection. Study of the behaviour of the reagin titre in seropositive clinically negative cases (early and late latent) following PAM treatment is also of interest. Perhaps it will help to solve the problem of the occurrence of biologically false-positive reactions in the tropics where yaws is prevalent.

Whether or not the serological laboratory should play a role in the mass campaign against yaws remains a question to be debated. However, it is considered essential that the serological laboratory should be set up to work in close association with a medical field team in a well-chosen, well-planned control area before, or at least at the same time as, the mass campaign is in progress. Together they should serve as guide in the determination of policy—whom to treat and re-treat, with what dose, and at what intervals in the general campaign—so that the maximum efficiency and economy, both in manpower and penicillin, can be achieved.

### Conclusion

Experience acquired in 1951-3 indicates that if the serological laboratory is working in close co-operation with medical field teams in selected experimental areas in the early stages of the campaign, it may serve as a check on the accuracy of diagnosis, as the means of detecting asymptomatic latent yaws, and as a guide for adequate treatment. This information may

provide a sound basis for determining the policy for expansion of the programme.

The reagin titre in untreated yaws is highest in the early generalized stage, decreases steadily with the advancement of the disease, and rises again in late ulcerative lesions. With the same type of lesion, females tend to have a higher titre than males, and the titre is lowest in the middle years.

There appears to be no advantage in  $2 \times 4$  ml as compared with  $2 \times 2$  ml or  $1 \times 4$  ml of PAM as revealed by the mean decrease in reagin titre and the number of relapses observed in the villages receiving different schedules of PAM.

The serological response following treatment is best in early contagious lesions and least in ulcerative and osteo-articular lesions. Within the same type of lesion the serological response is better in the younger age-groups.

The decrease in reagin titre is more marked in patients with high titres than patients with low titres, and in patients with early lesions than in patients with the later forms. The amount of decrease is approximately the same in low titres (4-8 dils) in all the forms of yaws considered.

Plantar and palmar hyperkeratosis, ulcerative lesions, and lesions of joints and bones, constitute the major part of patients seemingly not cured by the treatment. Since these cases at the time of re-treatment were not associated with increase in reagin titre, it is doubtful whether they were actually no-benefit patients.

As expected, the percentage of seropositives in household contacts and non-contacts is in direct proportion to the prevalence of yaws in a given area. It is suggested that the incidence of yaws, as determined at the time of survey, may be used as the guide for the intensity of treatment of the population.

## RÉSUMÉ

Les auteurs indiquent dans cette étude les résultats des analyses sérologiques pour le diagnostic du pian à Java, effectuées de 1951-53 dans le laboratoire collaborant au programme de lutte contre les tréponématoses en Indonésie. Jusqu'en avril 1953, 596.485 cas de pian ont été diagnostiqués et traités. Les sérums ont été soumis aux tests quantitatifs sur lame des VDRL et de Kline (avec antigène à base de cardiolipine) au test de Kahn ou à l'ensemble de ces tests. Les expériences faites au cours de ces deux années ont montré que le laboratoire sérologique, travaillant en collaboration étroite avec l'équipe médicale dans une zone convenablement choisie, dès le début de la campagne, est d'une grande utilité en permettant de confirmer le diagnostic et de découvrir les cas asymptomatiques et latents.

Pour cette étude, on a choisi une zone de quelque 33.000 habitants, où la prévalence du pian était de 15,2%. Le titre des réagines dans le pian non traité est maximum au stade d'infection récente généralisée. Il décroît à mesure que la maladie évolue pour s'élever à nouveau, au stade des lésions ulcérales tardives. Le titre est en général plus élevé chez les femmes que chez les hommes, au même stade de la maladie. Il est minimum dans les groupes d'âge moyens.

Douze mois après le traitement — effectué à l'aide de PAM — la baisse du titre était particulièrement accusée chez les sujets atteints de lésions récentes contagieuses avec ou sans hyperkératose. Elle était minimum chez les sujets atteints de lésions ulcérales osseuses et articulaires.

La posologie selon laquelle PAM est administré ( $2 \times 4$  ml,  $2 \times 2$  ml,  $1 \times 4$  ml) ne paraît pas influencer sur le résultat du traitement, à juger d'après le titre des réagines et le nombre de rechutes observées.

L'enquête de contrôle effectuée environ une année après le traitement initial indiqua que 5% - 10% des malades traités la première fois présentaient des lésions nécessitant un nouveau traitement. Il s'agissait d'anciennes lésions anciennes non améliorées, ou améliorées mais non guéries, de rechutes (nouvelles localisations) ou de réinfections. L'état de santé général du sujet ainsi que son état nutritionnel ont une influence sur la cicatrisation des plaies et les reconstructions tissulaires, surtout lorsque les ulcères sont étendus ou profonds. Bien que les tréponèmes aient disparu à la suite du traitement, la cicatrisation de l'ulcère peut être si lente qu'une infection secondaire peut fort bien se produire, après que la pénicillémie s'est abaissée au-dessous du niveau inhibiteur. Le travail aux champs, d'autre part, rend difficile la cicatrisation des lésions palmaires et plantaires. Les hyperkératoses, les lésions articulaires et osseuses constituent la plupart des cas que le traitement n'a apparemment pas pu améliorer.

Le pourcentage général des cas cliniquement positifs mais séronégatifs est de 4,5. Cette proportion est particulièrement faible (1,6%) parmi les malades atteints de lésions contagieuses récentes avec hyperkératose. Les antigènes à base de cardioline ont donné d'excellents résultats dans le diagnostic du pian.

Dans une région donnée, le pourcentage de sujets séropositifs parmi les contacts domestiques et les non contacts est proportionnelle à la prévalence du pian.

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