

THE OCCURRENCE IN LEPROSY OF POSITIVE  
SERODIAGNOSTIC TESTS FOR SYPHILIS

REPORT OF RESULTS OBTAINED IN AN EVALUATION OF SERO-  
DIAGNOSTIC TESTS FOR SYPHILIS IN THE UNITED STATES

BY DR. H. H. HAZEN

*Washington, D. C.*

DR. H. S. CUMMING

*Surgeon General, U. S. Public Health Service*

DR. ARTHUR H. SANFORD

*Rochester, Minn.*

DR. F. E. SENEAR

*Chicago, Ill.*

DR. WALTER M. SIMPSON

*Dayton, Ohio*

AND

DR. R. A. VONDERLEHR

*Passed Assistant Surgeon, U. S. Public Health Service*

In the early fall of 1934 the Surgeon General of the United States Public Health Service appointed, at the suggestion of the American Society of Clinical Pathologists, a committee of two syphilologists, two clinical pathologists, and one officer of the Public Health Service, to undertake an evaluation of the various tests employed in the serodiagnosis of syphilis. Details and results of this study have already been published (3), but for the convenience of leprosy workers certain points are recapitulated here.<sup>1</sup>

The serologists performing complement-fixation tests were, Walter V. Brem of Los Angeles, John A. Kolmer of Philadelphia, E. Henry Ruediger of San Diego, California and Capt. W. C. Williams of Washington. Those who performed flocculation tests were, Harry Eagle of Philadelphia, William A. Hinton of Boston, F. M. Johns of New Orleans, Reuben L. Kahn (performing the Kahn standard diagnostic test) of Ann Arbor, B. S. Kline (performing the

<sup>1</sup>The full report of the committee giving the work sheets will be published as a special report by the United States Public Health Service.

Kline diagnostic test) of Cleveland, M. B. Kurtz (performing the Kahn presumptive test) of Lansing, Michigan, N. H. Lufkin and F. Rytz of Minneapolis, Charles R. Rein (performing the Kline exclusion test) of New York, and Emil Weiss of Chicago.

The clinical groups from which donors were selected were (a) syphilitic: 43 untreated patients with primary syphilis; 65 untreated patients with eruptive secondary syphilis; 307 variously treated or untreated patients with syphilis of more than two years' duration; and (b) presumably nonsyphilitic: 152 normal persons; 25 normal women, both during menstruation and in the intermenstrual interval; 54 pregnant women; 46 patients with acute febrile diseases (temperature above 38°C. (100°F.), or with physically induced artificial fever above 40.5°C. (105°F.); 51 patients with jaundice due to various causes; 36 patients with malaria; 62 patients with neoplastic disease; 53 patients with tuberculosis; 50 patients with leprosy. The donors were carefully chosen with a view to the possible necessity for clinical and serological re-examination. A careful history of each donor was taken, and a physical examination was likewise recorded.

Blood specimens were collected daily over a period of three months, and a comparable sample was sent by air mail to each participating serologist so that the specimens were received by all serologists on the same day. A total of 1,017 samples were sent to each serologist, or a grand total of 14,238 specimens. The blood was placed in small glass vials fitted with corks, and these were packed in double metal containers conforming to the United States postal regulations. A code letter was used instead of the name of each serologist, so that the members of the evaluation committee did not know the names of the serologists making reports.

The committee found the evaluation of doubtful reports impracticable. Throughout this study specimens giving doubtful reactions were included in the columns headed "specimens examined," but were not counted as positive or partially positive in determining the percentages of positive or negative reports. Although the doubtful reports were thus given a negative rating, the committee recognizes that in clinical practice a doubtful report may often be of value.

The specificity of the various serologic tests was estimated from the group of blood specimens from normal, presumably nonsyphilitic individuals. All of these donors were from a selected group in which the prevalence of syphilis is believed to be lower than the

average for the whole population. The group consisted entirely of medical students and members of the staff of a medical school and hospital. The percentages of positive reports are given in Table 1, first column, together with those obtained in other supposedly nonsyphilitic cases. The donors in the normal, presumably nonsyphilitic group, on whom more than two doubtful results were reported, were re-examined serologically by the participating serologist and were given clinical re-examinations by one or more syphilologists. Only the original serologic report was considered in computing the percentages of negative reports.

#### RESULTS IN LEPROSY

The results of the examinations of sera from cases of leprosy are also shown in Table 1. The donors were presumably nonsyphilitic patients at the national leprosarium at Carville Louisiana. All of the serologists reported very high percentages of positive reactions with these sera. It is to be noted that all of the patients showing more than two doubtful reactions were re-examined clinically by either Dr. Ralph Hopkins or Dr. Oswald E. Denney for the possible existence of syphilis. This inquiry included roentgenological examination of the long bones and of the aorta, but did not include spinal puncture. The possibility of yaws was also investigated. All patients in this series were believed to be free from syphilis or frambesia.

Since our original survey was completed a more extensive investigation has been made by Eddy, Black and Ross (<sup>4</sup>), of Carville; the results will be considered here. The complement-fixation test employed by these investigators was a slightly modified Kolmer quantitative test. In the interpretation of this test the weakly positive tests were given the same value as the strongly positive tests. Inasmuch as our committee preferred to consider such reactions as doubtful, and not to be included with the positive reactions, it has been necessary to recast the table of percentages to bring it into harmony with our results. Table 2 represents that revision. It is interesting to note that the authors also tested an antigen made from leprosy bacilli for a complement-fixation test. The results in the two series showed very marked differences. It will be noted that the patients with advanced clinical symptoms and those showing many bacilli are much more apt to show positive reactions than the less

TABLE 1.—Percentages of positive serological reactions in various groups of supposedly nonsyphilitic individuals.

Serologist	Donors									
	152 normal persons	25 women menstruating	25 women intermenstrual	54 pregnant women	46 febrile patients	51 patients with jaundice	36 patients with malaria	62 patients with neoplasms	53 tuberculous patients	50 patients with leprosy
Brem .....	0	0	0	0	2.2	0	14.3	1.7	1.9	44.0
Kolmer .....	0	0	0	0	2.2	0	19.4	1.6	2.0	64.0
Ruediger .....	0.7	0	0	3.8	2.2	2.0	20.6	1.6	7.5	62.0
Williams .....	0	0	0	0	0	0	17.1	1.6	1.9	42.0
Eagle .....	2.0	0	0	0	0	0	12.1	1.7	1.9	72.0
Hinton .....	0.7	0	0	1.9	2.3	0	11.1	3.3	5.7	40.0
Johns .....	3.3	0	0	3.7	4.3	2.0	11.4	0	5.7	58.0
Kahn .....	0	0	0	0	0	0	11.4	0	1.9	60.0
Kline .....	0	0	0	0	0	0	14.3	0	1.9	66.0
Kurta (Kahn) presumptive test .....	3.3	4.4	0	1.9	2.2	3.9	16.7	0	7.7	76.0
Lufkin and Rytz .....	1.3	12.0	0	0	8.9	2.0	11.1	9.7	7.5	70.0
Rein (Kline) exclusion test .....	0.7	0	0	0	0	3.9	19.4	0	1.9	68.0
Weiss .....	0.7	0	4.0	0	0	0	8.6	0	0	52.0

advanced cases or those with few bacilli. Patients with nodular leprosy are much more apt to show positive reactions than are those with the anesthetic type. Likewise, females show a higher percentage of positive reactions than do males.

This study has led to a further investigation of our fifty cases from the same institution. Unfortunately our cases were too few in number to be decisive regarding many points, but the examination

TABLE 2.—*Wassermann reaction in cases of leprosy. (Eddy, Black and Ross, modified.)*

Features of cases	Number examined	Positive		Doubtful
		Number	Per cent	
<i>Type of disease</i>				
Anesthetic .....	22	3	14	1
Nodular .....	47	9	29	5
Mixed .....	162	52	32	5
<i>Stage of disease</i>				
Early .....	26	5	19	0
Moderately advanced .	97	27	28	4
Far advanced .....	108	35	34	8
Arrested .....	28	0	0	1
<i>Number of organisms</i>				
Few .....	53	13	25	0
Moderate numbers ...	66	19	29	3
Many .....	105	39	37	8
Negative .....	35	0	0	1
<i>Sex</i>				
Male .....	171	46	27	10
Female .....	60	22	35	1
<i>Controls</i>				
Normal .....	30	0	0	0
Syphilitic .....	20	20	100	0
Tuberculous .....	54	0	0	0

of each patient by thirteen different serologists yielded much valuable information. Out of 50 patients there were 15 instances (30 per cent) in which all reports were positive or doubtful. Six cases (12 per cent) gave uniformly negative results. In the remaining 29 cases (58 per cent) there was more or less discrepancy. In 8 instances (16 per cent) there were 12 positive or doubtful tests with

but a single negative. In 4 instances (8 per cent) there were 2 negative reports, and in 2 patients 3 negative reports. One patient gave 4 negative reports, and 2 gave 5 negative reports, the remaining tests being positive, with one doubtful reaction each. For the purpose of this study all lepers showing 7 or more strongly positive results were considered as serologically positive.

All of our patients were males, so that no comparison of serological response in the male and female sex was possible. Patients with advanced leprosy and those showing many organisms apparently gave a higher percentage of positive reactions than others. Not enough patients were examined to make our figures on the age or race of the patient of any value, although it would seem that the younger patients were more prone to give positive tests than were the older. Table 3 gives the results of our recent study.

A survey of the literature on the serology of leprosy shows many discrepancies, but in general most authors report a high percentage of positive findings. Lloyd, Muir and Mitra (7) reported 286 cases of leprosy with 41.7 per cent positive findings. Nodular cases gave a higher percentage of positives than neural cases. Sixteen patients were given antisyphilitic treatment with the result that the reaction became negative in 9 instances. Simon (13) reported 23 positive reactions in 24 patients. Nicolau and Banciu (11) obtained positive results in 22 out of 27 lepers. Van den Braden (2) found the test positive in 5 out of 24 lepers. Morales Otero (9) reported 25 per cent positive findings in several anesthetic cases, and 85 per cent in nodular cases, and 100 per cent in mixed cases. Salminen (12) recorded 15 positive results in 19 nodular cases of leprosy, and negative reactions in mixed and anesthetic cases. Morales Otero (10) reported 65 per cent of positive reactions in lepers of Puerto Rico, and 14.5 per cent of positive reactions on controls. Yagle and Kolmer (14) reported 28 lepers, examined by the Kahn precipitation test, that showed but 2 positives. Kolmer (5) reported negative results in 125 nonsyphilitic lepers. Lloyd, Muir and Mitra (8) reported 1,027 cases of leprosy, of which 109 gave positive reactions. These were subjected to anti-syphilitic therapy and all became negative. Kolmer and Denney (6) reported 159 cases with evidence of syphilis in 27. In the remaining 132 cases there was uniformity of negative results with an improved antigen. Badger (1) reported a high percentage of positive findings in leprosy. The positive reaction was more frequent in women.

TABLE 3.—Results of examination of 50 sera from cases of leprosy, by the Committee.

Features of cases	Number examined	Positive	
		Number	Per cent *
<i>Type of disease</i>			
Anesthetic .....	2	2	(100.0)
Nodular .....	4	3	( 75.0)
Mixed .....	44	28	63.6
<i>Stage of disease</i>			
Early .....	2	2	(100.0)
Moderately advanced .....	24	15	61.6
Advanced .....	22	16	72.7
Arrested .....	2	1	( 50.0)
<i>Number of organisms</i>			
Few .....	10	6	60.0
Moderate numbers .....	18	10	55.5
Many .....	22	17	77.2
<i>Race</i>			
White .....	28	17	60.7
Negro .....	5	4	(80.0)
Mexican .....	15	12	80.0
Filipino .....	2	0	(0.0)
<i>Age</i>			
17-19 years .....	2	1	(50.0)
20-29 years .....	11	9	81.8
30-39 years .....	13	10	76.9
40-49 years .....	10	7	70.0
50-59 years .....	5	2	(40.0)
60-69 years .....	8	4	(50.0)
70-79 years .....	1	0	(0.0)

\* Percentages on groups of less than 10 are placed in parentheses.

It will be noted that most observers have found that presumably nonsyphilitic lepers frequently show positive serologic reactions for syphilis. A number of observers claim that an "improved" antigen will give a much lower percentage of falsely positive reaction. Kolmer has consistently claimed negative results in nonsyphilitic lepers with both the Kahn and complement-fixation tests, but it is interesting to note that in this study he reported 64 per cent positive results. The patients in our study were from Carville, just as were those in some of his previous studies.

Various reports that antisyphilitic medication promptly causes the reactions to become negative are not to be taken as certain indication that the patients are syphilitic, despite the assertions of some authors. It is a well-recognized fact that cases of late syphilis are not reduced to serologic negativity with any degree of ease.

#### COMMENTS

1. A total of 59.3 per cent of the 50 sera from leprosy patients that were examined in the investigations of this committee showed positive serological reactions. Of these reactions 53 per cent were obtained with the complement-fixation tests, and 62 per cent with flocculation tests.

2. The percentage of positive tests is somewhat higher among patients with advanced leprosy, and in those showing numerous organisms in the lesions.

3. It is still impossible to say whether the anesthetic, nodular, or mixed forms of leprosy yield the highest percentage of positive reactions.

4. It seems apparent that yaws is not the cause of many positive serologic reactions for syphilis among lepers in the United States.

5. There is a marked discrepancy in the results obtained with comparable specimens of blood sent to various serologists.

6. Up to the present time no evidence has accumulated to indicate that a disease caused by an acid-fast bacillus will give positive flocculation or complement-fixation reactions for syphilis. It would seem logical to suggest that the entire question of the etiology of leprosy is in need of re-investigation.

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