The Tuskegee Study of Untreated Syphilis

The 30th Year of Observation

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The year 1963 marks the 30th year of the long-term evaluation of the effect of untreated syphilis in the male Negro conducted by the Venereal Disease Branch, Communicable Disease Center, United States Public Health Service. This paper summarizes the information obtained in this study—well known as the "Tuskegee Study"—from earlier publications,[1-11] reviews the status of the original study group, and reports the clinical and laboratory findings on those remaining participants who were examined in the 1963 evaluation.

In the late 1920's and early 1930's, surveys [7,12] in rural areas of the South revealed a high incidence of syphilis among the Negro population, and it was determined that many of those infected remained untreated. Because of the lack of knowledge of the pathogenesis of syphilis, a long-term study of untreated syphilis was desirable in establishing a more knowledgeable syphilis control program.

A prospective study was begun late in 1932 in Macon County, Alabama, a rural area with a static population and a high rate of untreated syphilis. An untreated population such as this offered an unusual opportunity to follow and study the disease over a long period of time. In 1932, a total of 26% of the male population tested, who were 25 years of age or older, were serologically reactive for syphilis by at least two tests, usually on two occasions (Table 1). The original study group was composed of 412 of these men who had received no therapy and who gave historical and laboratory evidence of syphilis which had progressed beyond the infectious stages. A total of 204 men comparable in age and environment and judged by serology, history, and physical examination to be free of syphilis were selected to be the control group.

The first published findings in 1936 by Vonderlehr et al [1] showed that after infection of 15 years' duration only one fourth of the untreated syphilitics were normal and that most of the abnormal findings were in the cardiovascular system. Morbidity was noted to be approximately fourfold greater in the cardiovascular, central nervous and bone and joint systems of untreated syphilitics under age 40 than in the controls of the same age.

In the first complete reevaluation of these patients in 1938-1939, it was found that many had received some therapy, usually only several injections of arsenic or mercury; however, a few, especially in the younger age group, had received more. Fourteen young, untreated syphilitics were added to the study to compensate for this. At this time it was also discovered that 12 of the controls either had had syphilis or had acquired it during

Read before the 14th Annual Symposium on Recent Advances in the Study of Venereal Diseases, Houston, Jan 24-25, 1964.

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TABLE 1.—*Result of Serologic Surveys of Negroes in Macon County, Alabama*

Year	Group Surveyed	Number Tested	Per Cent Reactive
1930	All ages, males and females	3,684	40
1932	Males and females over 18	4,400	22
	Males 25 and over	1,782	26

the interim; these have been followed as syphilitics since that time.

Where possible, these patients have been followed with periodic history, physical and laboratory examinations, including serology, electrocardiogram, chest x-rays, and urinalysis—and autopsy.

Mortality records during the first 12 years of observation, as reported by Heller and Bruyere,[2] revealed that 25% of the syphilitics and 14% of the controls of comparable ages had died. They calculated that at age 25 untreated male syphilitics would have a reduction in life expectancy of approximately 20%.

By 1952, after 20 years of follow-up, 40% of the syphilitics and 27% of the controls had died; at this time the life expectancy of individuals from ages 25 to 50 with syphilis was determined to be reduced by 17%. Fourteen per cent of the 159 syphilitics examined in 1952 showed evidence of late syphilis, approximately half being of the cardiovascular system. From autopsy information available through 1952, it was calculated by Peters and associates [8] that a Negro male with untreated syphilis of more than ten years' duration and a sustained reactive serology would have approximately a 50-50 chance of having demonstrable cardiovascular involvement. Also, the primary cause of death in 30% of the infected group was attributed to syphilitic involvement of the cardiovascular or central nervous system.

Reports on this study by Pesare,[4] and Olansky and co-workers,[11] have emphasized that an untreated syphilitic population has considerably greater morbidity and mortality than a similar uninfected group until the age of 55. An analysis in one the most recent papers on the study [10] showed that a small amount of treatment, 3 to 20 arsenical injections, given to patients with syphilis of less than 15 years' duration, influenced the serologic outcome. This report also revealed that 27% of patients with spontaneous serologic reversal had some clinical manifestations of late syphilis, and it was estimated that after 30 years of untreated syphilis less than 50% of those still living would have a reactive Kahn test. Further, it was demonstrated after 22 years' follow-up that the *Treponema pallidum* immobilization (TPI) test showed no evidence of becoming nonreactive in untreated syphilis.

Two other well-known studies dealing with the pathogenesis of syphilis should be mentioned. In 1929, Bruusgaard [13] published an analysis of the outcome of untreated syphilitic patients seen from 1889 to 1910 at Boeck's Clinic at the University of Oslo. He was able to trace 309 living patients and 164 dead of known causes, 40 of whom had been autopsied. Twenty-three per cent had clinical or autopsy evidence of syphilitic pathology of a serious nature. An additional 12% had less serious evidence of syphilis. Fourteen per cent were serologically reactive and clinically negative, while 28% had a nonreactive serologic test and no clinical evidence of syphilis. Twenty-three per cent had cancer, tuberculosis, or other disease. It should be mentioned that Bruusgaard's report has been criticized because the study group was too heavily weighted in favor of serious complications and because it was too liberal in attributing a physical or pathological abnormality to syphilis.[14,15] A detailed review and reevaluation of this study was published in 1955 by Gjestland.[16] He reported that 28% of the syphilitics had developed some type of late lesion, either alone or in combination; 10.4% had mani-

TABLE 2.—*Current Status of Tuskegee Study Group of Original 412 Syphilitics and 192 Controls*

	Dead		Alive		Unknown	
	No.	%	No.	%	No.	%
Syphilitics	242	58.7	85	20 6	85	20.6
Controls	87	45.3	66	34.4	39	20.3

TABLE 3.—*Abnormal Findings in 90 Syphilitics* and 65 Controls Examined 1963*

Abnormality	Syphilitics No.	Syphilitics %	Controls No.	Controls %
Electrocardiographic	41	46	21	32
Cardiomegaly by x-ray	37	42 †	22	34 ‡
Neurologic:				
CVA residuals, peripheral neuropathy	12	13	5	8
Optic atrophy, tabes dorsalis	3	3	0	0
Hypertension (diastolic blood pressure over 90)	38	43 †	29	45 ‡
Cardiac murmurs:				
Aortic systolic	24	27	20	31
Aortic systolic and diastolic	4	4	3 §	5
Aortic diastolic	3	3	0	0
Urine	28	36 ‖	21	33 ‡

* No urine reported on 12 syphilitics and 1 control; no x-rays, no blood pressure reported on 1 syphilitic, 1 control.
† Calculated on 89 reported.
‡ Calculated on 64 reported.
§ One of these had a loud, harsh, mitral systolic murmur, also.
‖ Calculated on 78 reported.

festations of cardiovascular syphilis, 6.5% had neurosyphilis, and 15.8% had benign tertiary syphilis. He found, as did Rosahn,[15] that males developed serious late manifestations almost twice as often as females.

The other well-known study concerning the outcome of syphilitic infection was done by Rosahn [15] at Yale, published in monograph form in 1947. He extensively analyzed autopsy records from 1917 to 1941, consisting of 3,907 cases over the age of 20. Of the approximately 10% (380) who had clinical, laboratory, or autopsy evidence of syphilis, 41% (156) had morphologic lesions of the disease, and 58% (90) of those had died primarily as a result of syphilis. Three out of ten clinically diagnosed patients developed significant tissue lesions, and one out of five of these died as a direct result of the infection. Rosahn found that a reactive serology was more frequently associated with anatomic lesions, since only one fourth of the syphilitics who had lesions of the disease at autopsy were serologically nonreactive. Roughly 80% of the anatomic lesions were of the cardiovascular system, and 15% were of the central nervous system. Of the 380 total syphilitics, there were 313 with serologic tests reported on their last hospital admission; 197 were reactive and 116 nonreactive.

A clinical diagnosis of late syphilis in the presence of a reactive serology was verified by autopsy in 78%; however, lesions were present in 21% of those clinically thought to be free of the disease. Rosahn's findings also indicated that syphilis reduced longevity in all age groups; even with no tissue changes, only about half as many syphilitics as nonsyphilitics lived beyond the age of 70. The mere fact of infection adversely affected longevity.

Current Findings and Comment

For the 30-year evaluation, a concerted effort to trace and examine as many as possible of the Tuskegee Study survivors was undertaken. As of Dec 1, 1963, of the original 412 syphilitics, 242 were known to be dead, 85 were known to be alive, and 85 could not be located and were considered lost to follow-up. Of the 14 young syphilitics added to the study in 1938, seven were alive, four were dead, and three could not be traced. Five of the control group who became infected have died, five were alive, and two were unaccounted for. One hundred ninety-two names of men listed as controls remain on the books. Three have not been seen since the original examination, and 36 others could not be located. Eighty-seven of the controls were dead, and 66 were alive. Therefore, of the original 412 syphilitics, 59% were dead, 21% alive,

TABLE 4.—*Therapy and Serology of Syphilitics Examined 1963 Who Have Evidence of Late Syphilis*

Case No.	Diagnosis	Therapy, Date	Current VDRL	Current TPI
329	Cardiovascular syphilis	None prior to 1950; adequate 1950	WR	R
453	"	8 As 1934	N	R
560	"	7 As, 2 Hg 1934	N	R
032	"	3 Hg 1934	N	R
194	"	3 Hg 1934	4 dil	R
336	"	None	2 dil	R
A-10	"	None	1 dil	R
611	Central nervous system syphilis	? 1934; adequate 1952	N	R
108	"	1 Hg 1934; adequate ? 1950	32 dil	R
232	"	6 As, 1 Hg 1934	8 dil	R
500	Old gummatous lesion	2 Hg 1934	N	R

TABLE 5.—*Duration of Infection at Time Evidence of Late Syphilis Detected*

Case No.	Year Abnormality Noted	Year Previous Exam	Duration of Infection, Yr
329	1948	1934 *	14
453	1963	1958	43
560	1963	1952	34
032	1939	1933	25
194	1933	None	31
336	1933	None	17
A-10	1948	1939	22
611	1948	1939	36
108	1948	1939	36
232	1938	1933 †	34
500	1933	None	15

* Patient originally a control, acquired syphilis between 1934 and 1945.
† Questionable abnormality.

and 20% lost to follow-up, while 45% of the controls were dead, 34% alive, and 20% not traceable (Table 2).

The average age of the surviving syphilitic group was 65 years in 1963, and of the control group 66 years. In the last ten years, the average age of the syphilitics has risen four years and the controls six years. At the beginning of the study, approximately twice as many syphilitics as controls were selected in each five-year age bracket so that the ages would be comparable through the years. The syphilitic men were, of course, a preselected group composed of those who had survived their disease. Some, particularly in the older age groups, had survived many years after their infection. How much this factor has influenced findings in this study cannot be determined.

Eighty of the original syphilitics and ten of the syphilitics later added to the study group were examined during the summer of 1963, along with 65 of the controls. The syphilitic individuals continued to demonstrate more abnormalities, but these were not marked—a finding expected, since syphilis would be expected to have taken its toll earlier. After the age of 55 the processes of aging emerge and seem to become the significant factors in both groups.

Current findings in the syphilitics and controls, presented in Table 3, show that most of the abnormalities are cardiac.

The treatment status of the surviving syphilitics is interesting, since 86 of the 90 examined this time have now received some therapy: 45 of these having received an average of five to ten injections of arsenic and bismuth; 11 others only several injections of mercury; 20 have probably received adequate treatment; and 10 more *may* have had adequate therapy. At the time of the second examination in 1939, it was found that approximately 42% of those examined had received some therapy. In 1963, a total of 69, or 77%, of those examined had received some therapy by 1939. The fact that a greater proportion of those who had received some, but inadequate, therapy were still living probably reflects only age differentials. However, an earlier publication [10] concerning this study indicated that these injections influenced serologic outcome by causing more to become nonreactive. Since a reactive serology is more apt to be associated with anatomic abnormalities and therefore a higher mortality,[15] these findings would not be unexpected.

Eleven patients, or 12% of the 90 syphilitics examined in 1963, had abnormalities indicative of late syphilis, seven of the cardiovascular system, three of the central nervous system, and one of the gummatous type (Table 4). Two of these had received no therapy, and three others had received two to three injections of mercury only. Of the 11, three who had received adequate treatment had evidence of late syphilis at the time of therapy. Six had a reactive VDRL slide test, three of which were reactive at four

TABLE 6.—*Current Serologic Findings on Syphilitic Study Subjects Who Have Nonreactive TPI or FTA-ABS Tests*

Case No.	VDRL	KRP	TPI	FTA-ABS
103	N	N	N	N
375	N	N	N	N
053	N	N	N	N
137	N	N	N	N
351	N	N	N	R
574	R	R	N	R
505	R	R	N	R
050	N	R	N	R
130	N	R	N	R
004	R 2 dil	N	N	R
482	N	N	R	N

TABLE 7.—*Current Serologic Findings on Six Control Subjects Who Have Reactive TPI or FTA-ABS Tests*

Case No.	VDRL	KRP	TPI	FTA-ABS
379	N	N	N	R
290	N	N	R	R
383	N	N	R	R
407	N	R	R	R
570	N	R	R	R
404	R	R	R	R

dilutions or more, and all 11 had a reactive TPI test. Most of the 11 had evidence of late syphilis by the 1948-1949 examination (Table 5), and in 1963 only two new cases were detected who had lesions possibly due to syphilis. In ten of these syphilitics the duration of infection was 36 years or less when a significant abnormality was noted. Most of these probably developed their late lesions before thirty years of infection.

The Tuskegee Study has been very useful in evaluating serologic tests through the years. Some analysis of the current results seems indicated since we now have 30 years of serologic tests for study. This year, serologic tests were performed * on 93 of the supposedly syphilitic group and 66 controls.† Sixty men or 65% of the syphilitic study group were reactive by VDRL slide testing, and 83 or 89% were reactive by TPI testing. Only 48 of the 91 tested by the Kolmer Reiter Protein (KRP) test were reactive; this test was reactive 12 times when the VDRL slide test was not, and four times when the TPI was nonreactive. An improved fluorescent treponemal antibody (FTA) test, as modified recently by Deacon and associates [17,18] and labeled the fluorescent treponemal antibody absorption (FTA-ABS) test, was reactive in 88 of the 93 presumed syphilitics tested. It was reactive in all 48 men who were KRP reactive.

Current serologic data for the ten supposedly syphilitic patients who were TPI nonreactive at this examination and the five men who were FTA-ABS nonreactive are shown in Table 6. The first two (No. 103 and 375), although tested many times, have never had a reactive TPI, FTA, or other treponemal test and have been serologically nonreactive since their original examination in 1933. Since evidence of syphilitic infection is questionable, they probably should be excluded from the study group. Five men (No. 053, 137, 351, 574, and 505), previously TPI reactive, have become nonreactive during the past five years. Three of these (No. 351, 574, and 505) remain reactive by the FTA-ABS method. No. 050 and 130 have never been TPI reactive. No. 004 was TPI nonreactive this year when tested for the first time by this test. The latter three men were FTA-ABS reactive, and No. 050 and 130 have previously been FTA reactive. Also, case No. 130 has good clinical evidence of congenital syphilis; No. 004 has a perforation of the nasal septum; and No. 050 has been KRP, RPCF and TPCF reactive in the past. Only one of the group, No. 482, is FTA-ABS nonreactive, while the TPI test continues to indicate past syphilitic infection.

Excluding the two men who probably have never had syphilis, the TPI test this follow-up did not detect syphilis antibodies in eight and the FTA-ABS test in three of the study group. Therefore, after 30 years' follow-up and 30 or more years of infection, the TPI test detected a past syphilis infection in 83 of the 91, or 91% of the survivors. The

TABLE 8.—*Syphilitics Who Have Become TPI Nonreactive*

Case No.	Last Year TPI Reactive	1st Year TPI Nonreactive	Duration of Infection (Yr) 1st Year TPI Nonreactive	Year Treated With Penicillin
053	1958	1959	39	1955 (6 inject.)
137	1955	1958	34	1951 (5 million units)
351	1958	1963	49	None
574	1958	1959	40	1956 (6 inject.)
505	1960	1963	38	Questionable 1954 (2-3 inject.)

* Tests performed by the Venereal Disease Research Laboratory according to PHS publication No. 411, 1959 Revision, *Serologic Tests for Syphilis.*

† Includes three syphilitics and one control who did not have physical examinations.

FTA-ABS test demonstrated an even higher degree of sensitivity, detecting 88 or 97% of the surviving syphilitics. Excluding the same two questionable cases, the VDRL slide test was 66% reactive.

Six of the control group of supposedly nonsyphilitics had a reactive FTA-ABS test, and five of the six had reactive TPI tests (Table 7). All five have previously been TPI reactive as well as being reactive by other tests and are now considered syphilitics. In case No. 379, in which there is no other supporting evidence of syphilis, it is not determined if the FTA-ABS is detecting latent syphilis or is falsely reactive. The former possibility is not unreasonable considering the high incidence group and the high level of sensitivity of the new FTA procedure.

From the data in this study, the FTA-ABS test appears to have both a high degree of sensitivity and specificity. Once it is reactive, duration of infection and previous therapy apparently have little or no effect on it. TPI tests remained reactive in approximately 90% of the Tuskegee Study group 30 years and longer after the original syphilis infection, and in only five individuals was there indication that it may become nonreactive after infection of more than 30 years' duration. Data on the duration of infection and therapy in these men who have become TPI nonreactive are presented in Table 8. All five had received five to ten injections of an arsenical in 1933 or 1934.

In the 30 individuals who had possibly received curative therapy, no obvious effect was noted on the VDRL at this time, since 63% of this group also remained seroreactive. However, the disease process was of long duration in all but one at the time significant treatment was given.

Since this study has now been affected by so many variables, we have not attempted to analyze all the findings. Such a report awaits a reevaluation of findings and detailed analysis correlating duration of infection, ages, therapy, physical, laboratory, and autopsy findings; a complete review is now under way. We have attempted only to make a brief summary of the study and to report some of the findings of the 30th year of follow-up.

Summary

The syphilitic group continues to have higher mortality and morbidity than the uninfected controls, with the cardiovascular system most commonly involved.

As of Dec 1, 1963, approximately 59% of the syphilitic group and 45% of the control group were known to be dead, and the average age of the survivors in each group was 65 and 66, respectively.

Approximately 96% of those examined had received some therapy other than an incidental antibiotic injection, and perhaps as many as 33% have had curative therapy.

Twelve per cent of the syphilitics examined have clinical evidence of late syphilis, 64% being cardiovascular involvement; most of these have been known since 1948.

Sixty-six per cent of the syphilitics continued to have detectable reagin by the Venereal Disease Research Laboratory (VDRL) slide test, 91% had reactive *Treponema pallidum* immobilization (TPI) tests, and 97% were reactive by the fluorescent treponemal antibody absorption (FTA-ABS) test. The latter two tests were quite sensitive in detecting past syphilis infection which had passed the early stages, regardless of duration or therapy.

Factors in selection and therapy in this study, which must be evaluated more thoroughly, probably tend to minimize the effects of untreated syphilis.

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