MEDICAL HISTORY

THE TUSKEGEE SYPHILIS EXPERIMENT: BIOTECHNOLOGY AND THE ADMINISTRATIVE STATE

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The central issue of the Tuskegee Syphilis Experiment was property: property in the body and intellectual property. Once removed from the body, tissue and body fluids were not legally the property of the Tuskegee subjects. Consequently, there was not a direct relationship between a patient and research that used his sera. The Public Health Service (PHS) was free to exercise its property right in Tuskegee sera to develop serologic tests for syphilis with commercial potential. To camouflage the true meaning, the PHS made a distinction between direct clinical studies and indirect studies of tissue and body fluids. This deception caused all reviews to date to limit their examination to documents labeled by the PHS as directly related to the Tuskegee Syphilis Experiment. This excluded other information in the public domain. Despite the absence of a clinical protocol, this subterfuge led each to falsely conclude that the Tuskagee Syphilis Experiment was a clinical study. Based on publications of indirect research using sera and cerebrospinal fluid, this article conceives a very history of the Tuskagee Syphilis Experiment. Syphilis could only cultivate in living beings. As in slavery, the generative ability of the body made the Tuskegee subjects real property and gave untreated syphilis and the sera of the Tuskegee subjects immense commercial value. Published protocols exploited the Tuskegee Syphilis Experiment to invent and commercialize biotechnology for the applied science of syphilis serology. (*J Natl Med Assoc.* 1995;87:56-67.)

Key words • Tuskegee Experiment • syphilis • syphilis serology

Beginning in 1932, the Public Health Service (PHS) conducted a project at the Tuskegee Institute that withheld treatment from a group of black men who had contracted syphilis. Ostensibly, its purpose was to further the understanding of the natural course of the disease. The study continued for 40 years until its exposure in 1972. The US Department of Health, Education, and Welfare convened an ad hoc panel on the Tuskegee Syphilis Study.[1] The panel did not formulate questions, but investigated questions assigned to it by the government using documents indicated to be *directly* related to the Tuskegee Syphilis Study, thereby excluding documents judged to be *indirectly* related to the study. On this basis, all reviews to date have examined narrow aspects of the administration of the study and concluded that the Tuskegee Experiment was a *clinical* study by well-intentioned but scientifically naive investigators whose decisions, against the historical background, were not overtly racist.[1,2] This portrays an effort to benefit the many by unraveling fundamental questions of disease process. This is a primary reason that the government puts forward to engage in human experimentation with its citizens.

This article rejects these conclusions and maintains that the Tuskegee Syphilis Study was instead the economic exploitation of humans as a natural resource of a disease that could not be cultivated in culture or animals in order to establish and sustain US superiority in patented commercial biotechnology. Its use was for

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the applied science of syphilis serology. Initially, the Tuskegee Experiment served to evaluate and standardize the nontreponemal syphilis tests. Later, the Tuskegee Experiment was a resource to develop and commercialize specific treponemal tests. Furthermore, by the 12th year of the study, there was evidence that many subjects did not have syphilis at all. The Tuskegee serological and clinical studies did not address any basic science questions of the pathogenesis or immunology of syphilis other than the practical applied science of serologic testing. The basis of these conclusions are the documents considered to be *indirectly* related to the study.

In the late 1920s, the PHS pursued three avenues of syphilis research. The first was the Clinical Cooperative Study initiated in 1928. The second study was a "serological dragnet" funded by the Julius Rosenwald Fund that began in 1930; it was restricted to African Americans of six southern counties. The third was a 1934 evaluation of serological tests for syphilis developed by US researchers. These lines of investigation conformed to an outline that divided the labor of research across several specialized groups.[3]

UNTREATED SYPHILIS AND DRUG EVALUATION

The principal standard against which to measure the value of therapeutic innovations was untreated disease.[3] This was one purpose of the Tuskegee Syphilis Experiment that, although portrayed as an isolated study, was a member of a constellation with several clinical functions. It provided the general knowledge (ie, untreated disease) against which to check the results of diagnostic, therapeutic, and other research procedures.

The Clinical Cooperative study was a spin-off of a League of Nations study that coordinated observation of syphilis treatment at US and European clinics. Five US sites were under the direction of the PHS Division of Venereal Diseases. These sites included Johns Hopkins University, Baltimore, Maryland; the Mayo Clinic, Rochester, Minnesota; the University of Pennsylvania, Philadelphia, Pennsylvania; Case Western Reserve University, Cleveland, Ohio; and the University of Michigan, Ann Arbor, Michigan.[4-9] This study began in 1928, 4 years before the Tuskegee Study. The presence of Udo J. Wile of the University of Michigan gives some insight to the experimental philosophy of this panel. Wile bored holes in the skulls of mentally ill patients with general paresis at Michigan's Pontiac State Hospital. Then, he aspirated brain tissue to show that this tissue could transmit syphilis to rabbits.[10] This was an important finding for basic science, but it had no therapeutic or diagnostic benefit, and the patients were incompetent to give consent. Wile did not approach the families for consent. In response to public outcry, Wile was unapologetic—"You may quote me as having absolutely no interest in the matter, whatever people may wish to think regarding the experiments."[11]

The first series of papers examined 3244 cases of early syphilis. Most of the patients received arsphenamine, while 350 received neoarsphenamine. In August 1930, the study group presented the initial results at the International Congress of Dermatology and Syphilology at Copenhagen.[12] The study addressed the comparative effects of different chemotherapies and the response to treatment of clinical manifestations and syphilis serology (Wassermann reaction). From this framework, the group planned to formulate a standard treatment for syphilis.[13]

The study had a major shortcoming, however. There was no control group of untreated syphilitic patients against which to measure the worthiness of the treatments, nor could one assess the usefulness of reversions in serologic testing. The only existing body of data on untreated syphilis was the 1929 report by Bruusgaard of the clinical status of syphilitic Norwegians who remained untreated for more than 30 years.[14,15] In 1890, Caesar P.M. Boeck, Chief of the Syphilis Clinic at University Hospital, Oslo, deliberately withheld mercurials from 1404 people with syphilis. When arsphenamine became available in 1910, all patients at the Oslo clinic received arshphenamine. The Bruusgaard material was the collection of patients who did not return for follow-up and therefore did not receive arsphenamine.

The Cooperative Clinical Study reformulated its data to exploit the Bruusgaard data as an untreated control group.[13] The contrast was dramatic: neurosyphilis was four times more frequent, and bone and skin lesions were up to 26 times greater in untreated patients, while 77% of treated patients had negative serology and remission of symptoms. The Cooperative Group concluded that the clinical efficacy of arsphenamine was incontrovertible. Yet in 1972, to defend the decision to withhold treatment from the Tuskegee subjects, the PHS claimed that arsphenamine was ineffective and would have been of little value to the men of the Tuskegee Experiment.

The use of the Bruusgaard material points to the usefulness of the Tuskegee Syphilis Study as a reliable control group. The Clinical Cooperative Group com-

plained that small numbers, lack of spinal fluid studies, and uncertainty regarding previous treatments made the Bruusgaard material inadequate. The PHS boasted that the existence of controls, serologic examinations, and spinal fluid examinations made the Tuskegee Syphilis Experiment superior to the methodological weaknesses of the Bruusgaard material. Additionally, whereas the Bruusgaard patients were untreated, early syphilis patients lost for a considerable period to follow-up, the Tuskegee Study included untreated late and latent syphilis subjects followed continuously over time.[15] Norwegian scientists later disputed this claim.[16]

THE DEVELOPMENT OF NONTREPONEMAL TESTS

The major utility of the Tuskegee Syphilis Experiment was its provision of sera to develop and standardize serological tests for syphilis. Diagnostic tests and therapeutics had considerable commercial value. Intense international competition for the production and marketing of diagnostics and therapeutics shaped the research policies of several nations.

A series of studies conducted by the PHS had two components: the first concerned the comparison and standardization of existing US serologic tests; the second was the development of new tests. At the request of the American Society of Clinical Pathologists, the PHS organized the Committee on Evaluation and Serodiagnostic Tests for Syphilis to assess the value of existing serological tests for syphilis. Because of the expressly economic intent to support improvement of US tests, competitive British and German tests were excluded from analysis. The protocol for the serological survey was made known in 1934.[17] The sensitivity and specificity of a range of tests were compared using known syphilitic sera (positive controls) and known nonsyphilitic sera (negative controls). Absolute positive sera establish the sensitivity of a test, ie, the ability to detect disease in people who have the disease. Negative sera establish the specificity of the test, ie, the absence of reactivity in people who do not have the disease. There could be no question of prior treatment in positive controls nor any question of syphilis in negative controls to accomplish these ends. During the Tuskegee study, presumed positives who turned out to be negative either by incidental treatment or by seroconversion were deleted from the study, and presumed negatives who tested positive were moved to the syphilitic group. Alterations of diagnostic groups in this way could never be tolerated in a clinical study. However, in retrospect, these maneuvers maintained the credibility of the Tuskegee positive and negative control groups for the purposes of the applied science of serological testing.

The first survey was published in 1935.[18] The numbers of late syphilis, syphilitic spinal fluids, and nonsyphilitic controls corresponded to the numbers in the Tuskegee Syphilis Experiment. This study did not explicitly state that it used Tuskegee sera. The first clinical report on the Tuskegee Syphilis Study in 1936 confirmed that Tuskegee sera comprised the testing sera for the serodiagnostic test evaluation of 1935.[19] The sequence of publication and authorship establish the priority of studies and the utility of the Tuskegee patients. The author for the serological study was Hugh S. Cumming, Surgeon General of the United States. In contrast, Raymond Vonderlehr, author of the clinical paper, was an assistant surgeon. The usefulness of the Tuskegee group was their sera. Their clinical status was only important to establish them as credible positive controls. Treponema could not be grown in culture and it could not be produced artificially. *Treponema pallidum* only grew in living humans or animals (rabbits and monkeys). The PHS repeatedly complained that it was not possible to extrapolate the findings with animals to humans. This was the driving argument for human experimentation. The Tuskegee subjects were a renewable culture source of *T pallidum* and antitreponemal antibodies. Tuskegee sera defined the use of existing serological tests and new ones for the next 40 years.

Joseph E. Moore, MD, chief syphilologist at Johns Hopkins University, was the clinical consultant to the Tuskegee Syphilis Study and a principal architect of the Clinical Cooperative Study.[20] Moore criticized the methodology of the 1935 evaluation of serodiagnostic tests for syphilis. He complained that the evaluation assessed serological tests under ideal conditions in the laboratories of the inventors. In his opinion, it was best to evaluate the usefulness or performance of these tests under general laboratory conditions. The need to evaluate serological tests in general laboratory circumstances meant a need to return to the Tuskegee well.

Serological testing was a cornerstone of syphilis control. The second survey, published in 1937, assessed serological tests in the hands of 30 state and private laboratories.[21-23] It recommended annual surveys for state laboratories using positive and negative controls provided by the PHS. The need for serodiagnostic evaluation was clearly put as a need for the PHS to regulate and license laboratories that performed syphilis tests.[24] Therefore, the Tuskegee sera also enabled the PHS to exercise its lawmaking power to regulate the

industry of syphilis serodiagnosis. The PHS used its police power to create the Tuskegee Syphilis Study, which in turn was used as an instrument to further expand the borders of its administrative lawmaking domain. Once a year, the Tuskegee subjects were sampled daily over several weeks for the sole purpose of providing sera for regulatory and standardization purposes unrelated to research.

Useful tests demonstrated specificity equal to 99%; sensitivity was problematic and varied from 65% to 88%. A major drawback for all tests was the false-positive rates in leprosy and malaria of 59% and 15%, respectively. In other words, the nontreponemal tests could not distinguish syphilis from leprosy. Similar conclusions were drawn for the use of these tests on cerebrospinal fluid.[25,26] These observations directed research to develop tests with greater specificity for syphilis diagnosis after 1936.

The market for syphilis serodiagnosis was considerable. The PHS wanted free tests, but was aware of the opposition that would ensue. The committee recommended that state laboratories perform the cheaper flocculation tests, and that Social Security be used to pay private laboratories to perform the more expensive complement fixation tests.[26]

The National Venereal Disease Act of 1938 further extended and centralized the administrative law and police power of the PHS. It also granted greater latitude to pursue human research. If there had been any question of the study's lawfulness, apart from its ethics, the legislation of 1938 provided legal shelter for its continuance. The Tuskegee Syphilis Study was legal. No one was ever indicted or charged with violating the law. The first studies following this act exploited human experimentation to investigate the problem of false-positive reactions in malaria. The PHS inoculated psychiatric patients with *Plasmodium vivax*-infected blood from other psychotic patients, while others were exposed to bites of malaria-infected mosquitoes (similar to the Walter Reed yellow fever experiments).[27,28]

Research continued for improved antigens and better techniques of detecting antibodies. The introduction of cardiolipin improved the sensitivity of the nontreponemal antigen tests.[29] A cocktail of cardiolipin combined with lecithin and cholesterol created a nontreponemal antigen that enhanced reactivity. The NY State Department of Health patented and licensed the use of cardiolipin to companies that marketed syphilis tests.

Movement toward tests that measured specific reaction for treponemal antigens accelerated with the demonstration of high reactivity for Palligen, a commercial suspension of killed noninfectious Reiter strain spirochete manufactured by Sachsische Serumwerk of Dresden, Germany. To ascertain its purity, investigators inoculated animals with the preparation expecting it to induce syphilis. However, Palligen did not induce infection. This raised concern that the preparation did not contain true *T pallidum* but some other treponemal organism. Despite this shortcoming, the Germans clearly made an advance. Scientists in the United States predicted that improved treponemal tests would become the method of choice by reducing the false-positive reactions associated with beef heart lipoidal antigens.[30,31]

The third survey was the Washington Serology Conference of October 1941.[32] From 1936 to 1946, there were no further clinical reports on the Tuskegee patients. The Venereal Disease Research Laboratory (VDRL) implied that the study was abandoned and then resumed in 1939.[33] However, internal memos show that the study was delayed further until a new field physician was properly trained at Johns Hopkins (Vonderlehr R. October 1937. Unpublished data). The critical role of positive sera to the serodiagnostic study more clearly explains the anxiety that some patients had received treatment (Diebert AV. November 1938. Unpublished data). Moore suggested that new untreated syphilitics be added to the group to correct this problem (Diebert AV. March 1939. Unpublished data).

This maneuver remedied the needs of the serodiagnostic study, but it was a violation if it was a clinical study. Patients cannot be added and deleted as desired from clinical studies without undermining the assumptions of the statistical analyses—randomness and equal variance. However, the Tuskegee Experiment was not a clinical study. Movement of subjects between groups enhanced the applied science of the Tuskegee Syphilis Experiment by the deliberate cultivation of positive and negative serum standards. The treated Tuskegee syphilitics were dispensable because it was not a clinical study; a separate clinical serodiagnostic study had more than sufficient numbers of partially treated syphilitics (Vonderlehr R. December 1938. Unpublished data).

The absolute need for the Tuskegee sera has no greater example than the PHS response to an unforeseen complication. One year before publication of the second serodiagnostic study, a change in the Tuskegee administration threatened access to Tuskegee sera. John Kenney, MD, former medical director of the Tuskegee Institute and adversary of certain PHS policies, returned to his position at Tuskegee (Smith M. November 1941. Unpublished data). The PHS moved its autopsies from

Tuskegee to funeral homes, and curtailed burial payments directly to Tuskegee to escape detection by Kenney. These extraordinary maneuvers must have been political subterfuge intended to keep the study covert. This suggests fear that Kenney (who was at odds with the American Medical Association by his espousal of national health care and criticism of its exclusion of blacks) would oppose the Tuskegee Syphilis Experiment.

This period also corresponds to a pressing development in the competition for diagnosis and treatment of infectious diseases. German pharmacologists developed sulfonamides in 1908 and within a few years had synthesized a number of antibacterial compounds.[34] The most important of these was Prontosil, patented in 1932 in Germany, 1934 in France, and 1935 in England. The first reports of its activity against both experimental and clinical infections with streptococcus, staphylococcus, and pneumococcus appeared in the German literature in 1935.[35-37] These organisms were important causes of skin and wound infections during war. Animal experiments by French investigators in 1935[38] and English clinical trials in 1936[39] confirmed the activity of Prontosil.

The use of sulfonamides for syphilis was unknown. Because they proved to be beneficial treatment for gonorrhea, the sulfonamides cast a specter like arsphenamine before they were even tried in the treatment of syphilis. Until the sulfonamides, there had been no drug to treat gonorrhea. Like arsphenamine, Prontosil was metabolized to an active intermediate, leaving the door open for the patenting and marketing of the intermediate. A 1939 US publication summarized knowledge of the sulfonamides and presciently commented: "The welfare of the patient must not be sacrificed in the race for new and marketable chemotherapeutic compounds."[34]

Thus, before World War II, the PHS acquired financial muscle using the Social Security Act of 1936, added to its regulatory powers using the Venereal Disease Research Act of 1938, and responded to the economic pressures of German science, which introduced treponemal antigens and a new class of therapeutic medications. The United States entered World War II 5 weeks following the Washington Serology Conference. Hopeful to contain the spread of syphilis and gonorrhea, and to make US medicine independent of German advances, the military and the PHS put pressure on domestic researchers.

After 1942, the combination of cardiolipin, lecithin, and cholesterol displaced lipid antigens in the flocculation tests. The prime test of this period that is still used today is the VDRL test.[40] All Tuskegee sera were stored and used by the VDRL in Staten Island, New York before its move to Chamblee, Georgia in the mid-1950s. The PHS used Tuskegee sera to develop the VDRL test.

THE CREDIBILITY OF SYPHILIS DIAGNOSES

One of the driving forces for improved serologic diagnosis may have been the Tuskegee Syphilis Experiment itself. There are indications that the serological surveys of 1935 and 1942 may have relied on dubious samples that were positive reactors in the Wassermann test, but that did not evidence clinical correlates of syphilis. The first clinical report appeared in 1936; it emphasized the incidence of cardiovascular disease.[19] It was an a priori conclusion that cardiovascular disease in blacks with positive Wassermann tests or a clinical diagnosis of syphilis was caused by syphilis. The second report appeared in February 1946 and focused on mortality and reduction in life expectancy.[41] It mentioned that of 129 subjects who had died, 93 came to autopsy. In December 1946, the third paper gave clinical cardiovascular measurements to present contentions of increased disease among the Tuskegee subjects, yet avoided claiming that the etiology was syphilis.[42] This paper followed, in order, in the same journal, an autopsy examination of untreated syphilis from Yale Medical School.[43] In 1950, the fourth paper stated that by 1948, investigators completed a total of 98 autopsies.[44] Finally, in 1955, the pathological study presented 124 autopsies performed from 1933 to 1952.[45]

Table 1 shows a contrast between these reports. The annual rate of deaths for the period 1948 to 1952 was twice that for the period 1933 to 1944. Yet, the rate of autopsies remained constant. Therefore, as the number of deaths rose, the ratio of autopsies to death declined to 47% of that from 1933 to 1944. The periods 1933 to 1944 and 1933 to 1952 showed a similar percentage of deaths that came to autopsy: 72% and 75%, respectively. Yet, the percentage of deaths autopsied for the period 1948 to 1952 was only 34%; this is a 45% reduction.

If the percentage of deaths resulting in autopsies had remained constant, then the PHS would have had to perform at least 55 autopsies to match the doubled death rate. However, the PHS conducted only 26 autopsies. World War II did not interfere in these statistics because an arrangement with the Selective Service Commission excluded both syphilitic and nonsyphilitic control subjects from military service. By conservative and generous estimates, these numbers suggest that between

TABLE 1. COMPARISON OF PUBLISHED AND INTERPOLATED DATA FOR TUSKEGEE DEATHS AND AUTOPSIES*

Variable	Time Period				
	1933 to 1944[41]	1933 to 1948[44]	1944 to 1952	1948 to 1952	1933 to 1952[45]
Years	12	16	8	4	20
Total deaths	129	140	87	76	216
Syphilitic	101	(109)†	64	(56)	165
Controls	28	(31)	23	(20)	51
Death rate	10.75	8.75	10.87	19	10.8
Syphilitic	8.4	(6.81)	8	(14)	8.25
Controls	2.33	(1.94)	2.87	(5)	2.55
Total autopsy	93	98	31	26	124
Syphilitic	(69)	(73)	(23)	(19)	92
Controls	(24)	(25)	(8)	(7)	32
Autopsy rate	7.75	6.13	3.88‡	6.5	6.2
Syphilitic	(5.75)	(4.56)	(2.87)	(4.75)	4.6
Controls	(2.0)	(1.56)	(1.0)	(1.75)	1.6
Autopsy/death	0.72	0.7	0.36	0.34	0.57
Syphilitic	(0.68)	(0.67)	(0.36)	(0.33)	0.56
Controls	(0.86)	(0.81)	(0.35)	(0.35)	0.63

*These data are compiled from two clinical reports, Heller[41] and Pesare[44], that made mention of autopsies up to 1944 and 1948, respectively, and the pathological report of Peters.[45] Peters presents data for all autopsies performed from 1933 to 1952. The difference between information from Peters and Heller was taken as the number autopsied between 1944 and 1952, whereas, the difference between data from Peters 1955 and Pesare 1950 represents the number autopsied between 1948 and 1952. The Heller and Pesare reports did not state the specific numbers of syphilitics and controls autopsied. These data are inferred by using the fraction of the total number of autopsies to the total number of deaths for the period 1933 to 1952 as a conservative estimate of the missing data for syphilitics and controls that were autopsied from 1944 to 1952 and 1948 to 1952. This is fair considering that the Public Health Service used this method to make assumptions about the incidence of clinical disease in subjects it was unable to examine.
†The interpolated figures appear in parentheses.
‡Comparing Heller with Pesare, there were just 11 deaths and 5 autopsies between 1944 and 1948. These numbers were too low to analyze separately, but they may contribute to an artifactual reduction of the autopsy rate for the period 1944 to 1952.

1948 and 1952, the Tuskegee investigators deliberately reduced the number of autopsies. Because the clinical reports did not state the specific numbers of syphilitics and controls autopsied, an accurate distribution of the autopsies between groups is not possible. However, the inference is that from 1948 to 1952, autopsies of syphilitic subjects dropped 49%, while that of controls decreased by 60%. Alternatively, the PHS might not have been able to keep pace with the accelerated rate of death. This is an unlikely explanation; the PHS was too efficient. Examiner bias is offered unwittingly in the pathological report by a preamble of excuses that the subjects were black and autopsies were performed "under inconceivably adverse circumstances."[45] These considerations do not alter the conclusion that the PHS manipulated the autopsies of syphilitics to diminish findings that contradicted laboratory and clinical diagnoses of syphilis.

Despite insistence by the PHS that the Tuskegee group displayed clinical evidence of syphilis, there were discrepancies in the clinical reports. Although there was significantly greater cardiovascular disease, there was no evidence that this was syphilitic in nature. The papers avoided stating that syphilis accounted for cardiovascular disease. This conclusion was inferred from the assumption that blacks were syphilitic; therefore, any findings presumably were due to syphilis. Despite clinical evidence of neurologic impairment in some patients, no subject developed tabes dorsalis, general paresis, or other pathognomonic complications or neurosyphilis. The rate for neurosyphilis was inferior to the Cooperative Clinical Study. The Tuskegee patients did not develop neurosyphilis. Furthermore, the clinical reports found reasons not to make comparisons with the Bruusgaard data or earlier Tuskegee reports. These discrepancies did not go unnoticed and met with criticism by Norwegian researchers before publication of the pathological reports.[16] The PHS continued to stand behind the claim that the disease complications noted in the Tuskegee patients were syphilitic. Only one paper that reported titers for 65 syphilitic subjects gives any insight into the criteria for positive syphilis serology: in 1939, 31% were negative, 42% were positive on *undiluted* serum or had titers ≤ 1:4 and 14% were doubtful.[44] Only pathologic diagnosis would resolve the issue of the presence or absence of syphilis.

The pathologic report that appeared 10 years later, in

TABLE 2. COMPARISON OF TUSKEGEE, YALE, AND BRUUSGAARD PATHOLOGICAL REPORTS*

	Study			
	Tuskegee[45]			
	Untreated	Control	Yale[43]	Bruusgaard[14]
Number	89	32	198	473
CNS examined	46	13	116	
Positive STS	60 (67%)		137 (69%)	
Negative STS	29 (33%)		61 (31%)	
Normal autopsy			121 (61%)	307 (65%)
Positive STS	23 (25%)		80 (40%)	68 (14%)
Negative STS	14 (16%)		35 (18%)	132 (28%)
Doubtful			6 (3%)	107 (23%)
Anatomic lesions	18 (20%)		77 (39%)	166 (35%)
Cardiovascular				
Aortitis	19 (21%)	2 (6%)	55 (28%)	
Aneurysm arch	7 (8%)	0	9 (5%)	
Coronary disease			4 (2%)	
Ruptured aneurysm			9 (5%)	
CNS (total)	2 (4%)		7 (6%)	36 (8%)
Tabes dorsalis	0		3 (3%)	
Neurosyphilis	1 (2%)		2 (2%)	
Meningitis	1 (2%)		2 (2%)	
Other organs				
Liver cirrhosis	14 (16%)	6 (3%)	1 (0.5%)	
Bronchopneumonia	43 (48%)	11 (34%)		
Pleural effusion	48 (54%)	20 (63%)		

Abbreviations: CNS = central nervous system and STS = serologic test for syphilis.
*These are methodologically different studies. The Bruusgaard study[14] was a retrospective clinical study, the Yale study (Rosahn[43]) was a retrospective autopsy study, and Tuskegee (Peters[45]) was a prospective autopsy study. Rosahn did not include patients with doubtful or minimal changes as syphilitic, whereas Peters included even doubtful cases, which may have inflated the findings. Peters stated that "some degree of subjective variation is unavoidable." Twenty-five subjects (28%) had anatomical lesions by both gross and microscopic examination, but 7 of these were "minimal"; therefore, 18 subjects are considered to have had definite syphilis. In comparison, Rosahn had 77 patients with definite syphilis. The presence of aortitis was most pathognomonic of syphilis. Rosahn did not report whether the diagnosis of aortitis was based on gross or microscopic examination. Peters reported 29 aortitis based on the presence of linear striations on gross examination. However, microscopic examination showed only 19/89 (21%) syphilitic subjects that met definite histologic criteria for aortitis (12 with gross thickening of the aortic wall and 7 with medial necrosis). Syphilitic gumma were reported for 9/168 (5.4%) Yale subjects, whereas none were reported for Tuskegee subjects.

1955, did not support these assertions.[45] This is important because the pathological examination was the only part of the Tuskegee clinical study that followed a protocol. The pathologist was blind to the history or diagnosis before autopsy and followed strict criteria for gross and microscopic examination to establish a pathologic diagnosis of syphilis. The Yale autopsy study of 1946 compared its findings against the Bruusgaard material. However, the Tuskegee pathologic report avoided any comparisons. Table 2 compares data from the three studies. The Yale study reported summary data not differentiated by race for 150 whites and 48 blacks. The Bruusgaard data was interpolated for comparison.[46] The Tuskegee Experiment had six criteria for gross examination, but only one criteria—linear striations of aortitis—distinguished syphilitics from the controls. A histological diagnosis of syphilis had to meet seven criteria. By microscopic examination, only 24 (27%) had definite syphilis; if the assessment excludes 5 doubtfuls and includes 12 minimal reports, this percentage rises to 40%. Eight cases with arteriosclerosis were attributed incorrectly to syphilis. Microscopic and gross examinations agreed on a diagnosis of syphilis in only 25 (28%) subjects; they excluded syphilis in 37 (42%).

Although the clinical reports of Tuskegee assumed an increase of syphilitic cardiovascular disease in blacks over whites, the pathologic report shows an equivalent incidence compared with the Yale study. Positive syphilis serology did not correlate with a pathologic diagnosis of syphilis. Sixty-nine percent had positive serological tests, but only 38% of these met criteria for syphilitic aortitis. The rate of positive syphilis serology equaled that of the Yale study, which also showed an unreliable relationship between the serologic test for syphilis and pathological diagnosis of syphilis. This relationship was even more tenuous for Tuskegee blacks than for whites.

There also was no correlation between clinical and pathological diagnoses of aortitis. Thirty-six of 62 autopsies had clinical diagnoses of aortitis, but only 16 were confirmed; eight of the negative autopsies had arteriosclerosis with fusiform dilatation—an equally common finding in the controls. The most provocative findings were the equivalent presence of bronchopneumonia and pleural effusions in both syphilitics (48% and 54%, respectively) and controls (34% and 63%, respectively). Coupled with the high incidence of cirrhosis of the liver that was 32 times greater in Tuskegee syphilitics than Yale syphilitics, these conditions raise the consideration that environmental and nutritional factors, shared by both syphilitics and controls, interfered in clinical diagnosis, pathological diagnosis, and serological testing. None of these conditions were reported for the Yale or the Brussgaard studies.

The clinical and pathological papers of the Tuskegee study were worthless but tolerated because shortcomings of this kind were explained on the basis of biological differences between blacks and whites that supposedly led to different biological outcomes in the presence of disease. The a priori principle that explained the presence of disease also explained its absence. Because of biological differences, blacks were more syphilitic than whites; because of biological differences, the absence of findings meant that blacks had syphilis that escaped detection until better means of diagnosis were available.

Unlike the serological reports and the initial clinical report, the pathological report, which was to be the most important, was not published in *JAMA*. The report stopped at 1952. Yet for 3 years, it remained unpublished and did not appear until 1955 in the first issue of the *Journal of Chronic Diseases,* a new journal edited by Joseph E. Moore, clinical consultant to the Tuskegee Syphilis Experiment. Moore was also editor of the *American Journal of Syphilis, Gonorrhea and Venereal Diseases,* the more appropriate venue for a report of this kind. However, it was not published there. This raises the consideration that established journals rejected the paper on scientific merit and that it was published finally through political influence. Its style avoided presenting data directly. Lack of syphilis at autopsy corroborated the lack of syphilis in the clinical study. Negative studies receive low priority for publication. The shortcomings in clinicopathologic correlation also may account for the limitation of the use of Tuskegee samples to 82 of 410 presumed syphilitics after 1946. This is 20% of the total numer of syphilitics, which corresponds to indications that only 20% of those autopsied had true syphilis. It is unlikely that this is a random occurrence. There is no doubt that some of the Tuskegee subjects had syphilis. However, the PHS could not establish syphilis in the majority. It fell prey to its prejudice, to a priori reasoning, and to its own advances in syphilis diagnosis based on those Tuskegee subjects who had syphilis.

The PHS marketed the Tuskegee subjects as the most syphilitic subjects in the United States. Yet the percentage of subjects with definite anatomical lesions of syphilis was 49% and 43% that of the Yale and Bruusgaard studies, respectively. It took scientific fraud to reach this percentage. The PHS did not inoculate the Tuskegee subjects with the syphilis organism, but it did give them the diagnosis of syphilis, and it seems that it did what it could to make it stick. Although one consequence of these actions was to further entrench biologically deterministic conventions regarding African Americans and venereal disease, its prime motivations were the potentially damaging economic consequences for US serological tests; an industry relied on and was regulated by PHS research at Tuskegee. The negative clinical and pathological studies undermined the credibility of serological standards that the PHS used to elevate and enhance the competitive stance and profitability of American tests. Any revelation that the sera were not syphilitic would have caused irreparable damage to the commercialization of US serological tests. The PHS restricted its future studies, particularly the development of treponemal tests, to unequivocally syphilitic Tuskegee sera. Despite having collected sera from 410 syphilitic subjects, the next series of studies employed only 82 sera.

THE DEVELOPMENT OF TREPONEMAL TESTS

In 1948, Robert Nelson of Johns Hopkins University successfully maintained infectious *pallidum* (Nichols strain) isolated from rabbit testicular syphiloma in culture for several days.[47] In 1949, Nelson and Mayer[48] used cultured *T pallidum* to demonstrate several things. First, antibody from syphilitic human serum immobilized virulent *T pallidum* in vitro. Second, the antibody bound complement to kill the organism. The cultures became noninfectious. Antitreponemal antibody was distinct from Wassermann reagin[48]. This became known as the *T pallidum* Immobilization (TPI) test. The TPI was highly specific. It had an exceptionally low incidence of false-positive reactions in leprosy and malaria, while being highly sensitive. Moreover, it

allowed quantitative titration of antitreponemal antibody. It became the standard measure of all newly developed tests. However, because of its technical difficulty and requirement for rabbit colonies, it was an impractical and expensive test for diagnostic purposes (as much as $100 per test in the 1950s).

Despite these shortcomings, the TPI was a pivotal invention in syphilology. The PHS recognized its importance immediately.[49] In 1952, the PHS convened a meeting of all laboratories under the Division of Venereal Disease for the sole purpose of standardizing the TPI within and across laboratories—including laboratories in other countries. The initial studies used antibodies from rabbits with experimental syphilis. Subsequent studies examined the TPI in humans.

Collaborative studies performed with sera from the VDRL in Staten Island, New York, in the early 1950s used Tuskegee sera.[50,51] The VDRL examined the TPI in treated and untreated patients with syphilis.[52,53] The sera for untreated late syphilis included "Macon County Health Department, Tuskegee, Alabama" from the Tuskegee Syphilis Study. The publication of pilot serological studies based on Tuskegee sera preceded a publication confirming the continued credibility of their syphilitic status.[54] There was preparation for yet another serologic evaluation survey. The new serodiagnostic survey was the Serology Evaluation Research Assembly (SERA) Study of 1956-1957.[55] This publication did not state explicitly the use of Tuskegee sera. However, subsequent publications from the PHS mentioned that Tuskegee sera from the VDRL serum bank comprised sera used in the SERA study.[56] Tuskegee sera also were used to assess the worth of additional tests: the Reiter protein complement fixation test[57,58] and the Treponema complement fixation test-50.[59]

Tuskegee sera ushered in the most important diagnostic test since the TPI—the fluorescent treponemal antibody absorption test (FTA-ABS). The FTA-ABS is the present standard for syphilis diagnosis. The introduction of the TPI test in 1949 also provided a method to extract crude treponemal antigen from infected rabbit testicles. The initial fluorescent conjugate to detect antibacterial antibody used fluorescein isocyanate. In 1957, the VDRL used unimpeachable positive human syphilis sera from "laboratory stocks," ie, Tuskegee sera, to develop a fluorescent antibody test that would demonstrate antibodies for *Treponema*.[60]

The fluorescent treponemal antibody (FTA) test was tested in the SERA study. It was more sensitive than treponemal pallidum complement fixation. However, the original FTA detected antibodies for both group and specific antigen. This was overcome in two ways. In 1958, an alternative fluorescein conjugate was introduced, fluorescein isothiocyanate (FITC).[61,62] The VDRL immediately tested FITC as an alternative to fluorescein isocyanate "by examining well-documented serum specimens." Fluorescein isothiocyanate was an improvement over the original FTA test that used fluorescein isocyanate.[60] Preabsorption of sera with sonicates of Reiter strain Treponema eliminated the antibodies for group antigen. Subsequent testing for specific antibody to *pallidum* demonstrated increased sensitivity and specificity. "Eighty-two specimens were included from the 1962 Tuskegee study" to develop the FTA-ABS.[61] The FTA-ABS may have benefited in another way. It could distinguish false-positive serology from true syphilis, a fact of no small importance in a group in which some subjects may have been incorrectly considered to have syphilis for 30 years. The FTA-ABS was commercialized. Internal memos from the Venereal Disease Branch of the PHS were explicit:"... the development and our endorsement of the FTA-ABS test rested on Tuskegee sera"(Lucas JB. February 1970. Unpublished data).[68]

The FTA-ABS quickly became and remains the standard diagnostic test for syphilis. It replaced the TPI. A 2-year study of the World Health Organization (WHO) globalized the FTA and FTA-ABS tests.[63] The VDRL distributed control sera to Japan, Italy, Denmark, England, and France for use in serological surveys. The Tuskegee patients were a likely source of control sera distributed to state and private laboratories in the United States and, through the WHO, to laboratories throughout the world.[64] The WHO was a market for syphilis serology. Other nations were dependent on the PHS for standardization and application of a US test. From the myriad national tests of the 1920s, the world came to use two US tests, the VDRL slide test and the FTA-ABS, both rooted in the Tuskegee Syphilis Experiment.

Serological tests for syphilis were commercially lucrative. In the United States, syphilis testing increased from 2 million in 1936 to 28 million in 1943 and remained steady at 12 million annually into the 1960s.[65] The predictability of this market was assured by laws requiring syphilis testing for marriage certificates, newborns, military recruits, industrial physical examinations, and admissions to hospitals.

United States hegemony in syphilis serology lapsed following the demise of the Tuskegee Syphilis Experiment. Whether there is a causative relationship is uncertain. However, it would appear that technological

developments in other countries that usurped US tests preceded the undoing of the Tuskegee Syphilis Experiment. In 1965, a test using smaller volumes of serum detected antitreponemal antibodies by hemagglutination of sheep red blood cells; use of an absorbent eliminated group-specific antibodies.[66] This test became known as microhemagglutination. The test is easier to perform than the FTA-ABS and does not require fluorescent microscopy. Variations of this test slowly replaced the FTA-ABS and are marketed in the United States by Japanese companies. Another test by British manufacturers is the hemagglutination of turkey red blood cells without the use of an absorbent.[67] Microhemagglutination tests dominate syphilis serology outside the United States. It is unclear to what extent the development of these tests exploited positive syphilitic control sera (Tuskegee sera) provided by the VDRL through the WHO program for standardization.

COMMENT

The Tuskegee Syphilis Study became an instrument of PHS international health politics. It must be recalled that the PHS initiated the Clinical Cooperative Study as part of a League of Nations study. In 1920, the Supreme Court distinguished authority of the United States from authority of the Constitution (*Missouri v Holland*, 252 US 416). International agreements fell under authority of the United States, outside of the reach of constitutional questions or interpretation. This granted unlimited power to the government regarding activities falling under international agreements. Therefore, with regard to its use for international health, the Tuskegee Syphilis Experiment may potentially have been at the discretion of the absolute power of the state. From 1932 to the 1970s, the Tuskegee Syphilis Experiment allowed US investigators and biotechnology to wrest control from German researchers to dominate and maintain leadership in syphilis serology. The monopoly of syphilis technology contributed to a superior position in the WHO. The PHS dominated the World Forum on Syphilis and Other Treponematoses in 1962. Its utility to biotechnological competitiveness in diagnosis and treatment of venereal diseases is a hidden but more plausible reason that the Tuskegee experiment was not terminated.

The utilitarian economic advantages of the Tuskegee Experiment prejudiced the science. The Tuskegee Experiment progressed within concepts of science and scientific method that had an analytical philosophical basis in positivism. Positivism ignores data that contradict a convention. Positivism considers that established conventions remain true, but that contradictory data point to different relationships between conventions. Consequently, the scientist reorders the relationship between accepted conventions to fit the data. Syphilology established several conventions, and it became the function of experimentation to verify these conventions. The most important convention was that the positive serological test for syphilis was infallible and was a certain demonstration of syphilis. The next convention was that African Americans had more syphilis and suffered less from it. This evolved from 19th century US ethnological descriptions of Africans as biologically inferior and insentient beings comparable to animals; this justified their use in experimentation and was also the basis of social and educational policy regarding blacks. The potentially fraudulent behavior of PHS scientists not only protected conventions in syphilology, but also more importantly sustained the integrity of biological determinism.

The discrimination between documents *directly* and *indirectly* related to the Tuskegee Syphilis Experiment was a deception that continues to protect biological determinism and contributed to a lopsided ethical examination and legal regulation of the commercialization of human products. This device protected two unexplained issues. First, there was no clinical protocol because the purpose of the study was not clinical; however, there were strict protocols for the serological studies. Second, although never mentioned by historians or the ad hoc panel, the original contract between the PHS and the Alabama Department of Health to initiate the Tuskegee Experiment contained a patent agreement that made any invention sole property of the United States.

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