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5. Humorous pieces, because it is important that we not take ourselves too seriously. Relevant verses.

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1. MARTIN G. M.; SPRAGUE, C. A.; and EPSTEIN, C. J. Replicative life-span of cultivated human cells. *Lab. Invest.* 23:86-92, 1970.

Book references should include author or editor, chapter title, edition number, city, publisher, and year.

2. YORKSTON, N. J. Some practical aspects of using propranolol. In *Propranolol and Schizophrenia*, edited by E. Roberts and P. Amacher. New York: Liss, 1978.

3. RACE, R. R., and SANGER, R. *Blood Groups in Man*, 5th ed. Philadelphia: Davis, 1968.

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PERSPECTIVES IN BIOLOGY AND MEDICINE

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THE SCIENTIFIC ENVIRONMENT OF THE TUSKEGEE STUDY OF SYPHILIS, 1920-1960

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The "Tuskegee Study of Untreated Syphilis" has been the source of considerable controversy. Attacks on the study and its organizers became widespread beginning in 1973 and have focused largely on two issues: (1) penicillin should not have been withheld when it became available; (2) the study should not have been initiated because "informed consent" was not obtained from the prospective participants. Furthermore, since the study was conducted by white physicians on black subjects it has been perceived to have been blatantly racist. This negative publicity has been construed to have increased among African Americans a prevalent suspicion of the medical profession, and especially of governmentally subsidized medical research. Difficulties in addressing the current HIV/AIDS crisis among African Americans has been considered a major ramification of this lack of confidence [1, 2].

The present review seeks to place the Tuskegee Study, which was conducted from 1933 to 1972 by the Public Health Service (PHS), into its historical perspective. This requires: (1) appreciation of the perception that developed, beginning in the 1910s into the 1930s, that syphilis was a major public health problem in the United States, including the recognition of

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a race-related difference in its prevalence; (2) comprehension of the risks and potential benefits of the available treatments as perceived by physicians and a small fraction of the general population; and (3) understanding of the concern of medical experts that knowledge of the chronic course of syphilis was inadequate to reliably distinguish therapeutic effect after the initial phases of the disease from the variability of its chronic course. In any long-term investigation unforeseen events may intervene before its contemplated conclusion. The Tuskegee Study encountered two such events: the introduction of penicillin, which might prove to be far more effective than heretofore available medications, and formulation of the legal concept of "informed consent" to receive a particular treatment or to participate in a medical investigation.

The Prevalence of Syphilis and Race-Related Findings of Its Manifestations

In 1930 syphilis remained virtually unmentionable in public discourse, while it was recognized as a major but poorly quantified public health problem by segments of the medical profession. Statistical data were derived from clinic registrations and spot surveys of private physicians, but it was recognized that large numbers of cases were undiagnosed, and even if diagnosed, treated inadequately or not at all. It also was understood that syphilis was more prevalent in urban than in rural communities and, despite the fact that the black population was predominantly rural, its prevalence of syphilis was estimated to exceed that of the white population by 6 to 1 [3, p301]. Surgeon General Thomas Parran estimated in 1937 that more than 1.7 million cases "would be constantly under treatment if each continued until cured" [3, p56].

In 1916 a Texas physician concluded that although 25 to 30 percent of "apparently healthy adult negroes" had syphilis, "the occurrence of syphilis among white people of the same social class . . . would seem to be about the same as that among the negroes" [4]. Parran in 1937 echoed this point, stating: "Wherever education and living conditions among the negro race approximate that of the white race, the syphilis rate approximates that of the white" [3, p177]. However, the victims rather than their poverty were more often blamed for the high prevalence of this disease in the black population. For example, one source declared the difference in rate of disease was "partly a reflection of the greater interest of the white race in its health" [5, p355]. Others implicated a differential lack of understanding of the potential consequences of not completing the arduous treatment and its lesser accessibility:

It is only through education in all of its branches, literary, social and moral that anything will ever be done to lessen or diminish this infection. . . . Persuading

patients to take a sufficient amount of treatment is a most active difficulty at this time (1927). . . . Just as soon as the active symptoms disappear, or the symptoms which caused the patient to seek medical relief begin to subside or disappear, the patient considers himself cured and despite persuasion ceases his visits to the clinic. [6, p349]

A PHS survey conducted in 10 states during 1926 to 1929 included 69,110 cases of late syphilis; 57 percent of the reports of white and 40.3 percent of the black patients were obtained from private physicians. These data substantially underestimated the prevalence of syphilis because they were limited to individuals who were under medical care and because, for socio-economic reasons, this sample was a much smaller proportion of the black than of the white population. Despite these factors, which minimized the recognition of syphilis in the black population, the rate of infection was double that in the white population, the maximum being a 2.35-fold difference in Nashville, Tennessee [7].

Whether there are race-related differences in the manifestations of syphilis was first addressed comprehensively by Zimmermann (1921), who reviewed the international literature and analyzed data from the Johns Hopkins clinic. Comparing 421 white and 466 black patients with tertiary manifestations, he noted some striking differences. Neurosyphilis was more than twice as frequent among the whites (45.3 percent versus 21.0 percent); bone lesions were the most frequent complications among the blacks, being twice as common as among the whites (29.6 percent versus 14.2 percent); while aortitis predominated among the blacks (14.9 percent versus 9.7 percent). He concluded that: "In respect to syphilitic infection there exist inherited biologic differences between white and negro patients" [8, p88]. A survey of 15,000 autopsies that had been performed in Philadelphia during 1927 to 1937 provided another indication of the predilection for cardiovascular complications of syphilis among black patients. While about 40 percent of the total cases were African American, they comprised 68.4 percent of the cases of cardiovascular syphilis, 70.4 percent of cases of aortic valve failure, and 75 percent of aortic aneurysms [9].

The most extensive investigation of gender and race in relation to differences in the manifestations of advanced syphilis was an extension of Zimmermann's study. Ten thousand cases above age 12 from the Johns Hopkins records were reviewed, of whom 6,420 were diagnosed in either the latent (53.2 percent) or the tertiary phase (41.8 percent). Most frequent were lesions of the central nervous (17.8 percent), cardiovascular (10.1 percent), muco-cutaneous (8.8 percent), and skeletal systems (8.8 percent) (see Table 1). Differences in gender and racial prevalence reinforced each other, so that the prevalence of symptoms of neurosyphilis were 5.6 times as frequent in white men as in black women, while cardiovascular syphilis was diagnosed 3.7 times as frequently in black men as in white women. Skeletal lesions were 2.1 times as frequent in black men as in white women,

TABLE 1

GENDER AND RACE RELATION OF MANIFESTATIONS IN 6420 CASES OF LATE SYPHILIS

Cases	White Male	White Female	Black Male	Black Female	Male	Female	White	Black
% Latent	1318	780	1704	2618	3022	3398	2098	4322
% Tertiary	40.3	55.9	41.5	66.4	41.0	64.0	40.1	56.6
Central nervous	59.7	44.1	58.5	33.6	59.0	36.0	59.9	43.4
% of total	39.3	22.3	15.9	7.0	26.1	10.5	33.0	10.5
% of tertiary	66.0	50.6	27.3	20.8	43.6	29.2	61.3	24.3
Cardiovascular								
% of total	8.7	4.8	17.9	7.2	13.9	6.7	7.2	11.4
% of tertiary	14.6	11.0	30.7	21.6	23.2	18.6	13.5	26.4
Muco-cutaneous								
% of total	7.8	11.6	9.0	8.3	8.5	9.0	9.3	8.6
% of tertiary	13.2	26.4	15.5	24.7	14.2	25.2	17.2	19.8
Osteo-articular								
% of total	6.0	5.8	12.7	8.7	9.8	8.0	5.9	10.2
% of tertiary	10.0	13.1	21.7	25.9	16.3	22.3	11.0	23.7
Other								
% of total	7.9	9.0	12.8	11.1	10.6	10.6	8.3	11.8
% of tertiary	13.2	20.3	21.9	17.8	20.0	29.6	15.4	27.2

Turner, T.B., *Bull. Johns Hopkins Hosp.* 46:159-184, 1930. (Ref. 10)
Adapted from Table VI.

while there was no significant difference either by gender or race in lesions of the skin or mucous membranes [10].

Subsequent to the beginning of the Tuskegee Study, evidence of race-related differences in the prevalence of syphilis continued to accumulate. Although limited to young men, the most systematic data were generated from military induction examinations during 1940 to 1941 of 1.9 million men, ages 21 to 35. Since, as with any chronic disease, the prevalence increases with age, and the examinees were skewed to the younger age group, these also were minimal findings. The prevalence of syphilis among white men aged 31 to 35 was 1.9 times as high as in the 21- to 25-year age group; among the black examinees the difference was 3.7-fold. In seven southern states more than 30 percent of the black examinees were found to be syphilitic, with 40.6 percent in Florida being the maximum. The racial disparity was found in every state. The prevalence nationally was 23.5 per 1,000 white recruits and 272.8 per 1,000 Black recruits, differing by a factor of 11.6 [11, 12].

For black teenage examinees syphilis was the leading cause for military rejection, followed by "educational deficiency," while neither was among the 10 top reasons for whites [13]. Publication of these data was hoped to bring recognition of the fact that: "There has been a tendency in official health circles to gloss over or to ignore the high prevalence of syphilis in the Negro. . . . The sooner that this truth is recognized and appropriate steps are taken to control the existing situation, the better it will be for the

Negro race and for the public health of the nation as a whole [12]. In essence, the assessment had not changed since that by Paulin, et al., 15 years before [6]. Nevertheless, according to the PHS, the maximum prevalence per 100,000 civilian population, both white and non-white, for early syphilis was reached in 1947: 36.9 and 404.9 respectively, an 11-fold difference [14].

Problems Presented by Metallic Anti-Syphilitic Drugs

At a 1938 symposium on syphilis, the professor of syphilology at the University of Michigan stated:

Minor and major accidents definitely attributable to treatment are still a source of serious embarrassment to those having to do with syphilis treatment even when the greatest care is exercised. So long as protoplasmic poisons are introduced into the body to counteract the effects of a disease, just so long will our methods of attack be open to criticism and to the invidious comparison of specific remedies in other diseases which combat infection and do little or no damage to the host. [15, p185]

Clearly, both the risks of the available therapy and the longing for more effective therapy were great. Mercury in various forms of administration, never rigorously evaluated, had been the treatment since the 16th century [16] (see Table 2). Its first scientific competitor arrived in 1910, with the

TABLE 2

INTRODUCTION OF SYPHILOTHERAPIES

Agent	Route	Year	Notes
Mercury ointment and rubs	Topical	1505	to circa 1940
Mercury pills	Oral	1535	to circa 1920
Potassium iodide	Oral	1834	to circa 1910
Arsphenamine	I-V	1910	to circa 1944
Neosarsphenamine	I-V	1912	to circa 1944
Malarial fever		1917	to circa 1930 for general paresis
Bismuth compounds	I-M	1922	to circa 1960
Tryparsamide	I-V	1923	to circa 1950; pentavalent, for CNS
Physically induced fever		1929	to circa 1950 for CNS
Arsenoxide (Mapharsen)	I-V	1923	to circa 1950
Amorphous penicillin	I-M	1943	to 1946 for primary syphilis
Crystalline penicillin G + Bismuth	I-M	1946	to 1949
Chlortetracycline (Aureomycin)	Oral	1948	to circa 1970 Penicillin allergic
Procaine penicillin G	I-M	1949	to circa 1955
Procaine penicillin G + Probenecid	Oral	1951	to circa 1960
Other depot penicillins	I-M	1951	
Benzathine penicillin alone	I-M	1960	

introduction of arsphenamine (Ehrlich 606, Salvarsan) and its analogue, neoarsphenamine (Ehrlich 914, Neosalvarsan), in 1912 [17]. Both drugs were at first administered by intramuscular injection, but because of the pain this caused the intravenous route soon became standard for both. If either injection was not entirely within the vein severe local pain still resulted, and arsphenamine, even when administered perfectly, often caused a local thrombophlebitis. Because immediate or delayed pain might occur also in the absence of overt phlebitis, Stokes (1945) recommended pre-treatment of the injection site with a local anesthetic [18, p312].

An arsphenamine solution is too acidic to be administered unmodified, so it was converted into its disodium salt by treatment with lye before it was injected [18, pp235-36]. Neoarsphenamine powder had the advantage of greater solubility and did not require neutralization. However, it was considered therapeutically less consistent, probably because of greater instability once it was dissolved [18, pp275-76]. Thus, the arsphenamines were rather cumbersome medications, both because of the preparation they required and the skill needed for their intravenous administration.

Which arsphenamine was the more effective and the less toxic was still disputed in 1935, when both began to lose favor to arsenoxide (Mapharsen). Mapharsen had been introduced in France in 1922, but it only began to be used extensively in the United States 13 years later. Although it also irritated the vein into which it was injected, it was less toxic systemically. Its practical drawback was that, at least during the first weeks of treatment, the best results required two or three rather than one injection per week [18, pp267-76].

Tryparsamide, introduced in 1923, also for intravenous administration, penetrates the central nervous system better than other arsenicals and is excreted more rapidly. However, it was soon found to be effective only against tertiary neurologic manifestations and was particularly toxic to the optic nerve. Tryparsamide differs chemically in being a pentavalent arsenic compound, while the arsphenamines and arsenoxide are trivalent compounds. This became another research question: should the search for a maximally effective drug consider whether the arsenic is in its trivalent or pentavalent form [18, pp280-82]. Several other arsenical compounds were tested, but none achieved extensive use.

The term "heavy metal therapy" referred either to the use of mercury or compounds of bismuth. Although the latter had been tried as early as 1889, its use in the treatment of syphilis was initiated by Constantin Levaditi in France in 1922. The several bismuth compounds that came into use differed mainly in their rates of excretion. All were injected intramuscularly. Pain at the injection site occurred more consistently with poorly soluble compounds. There were chemical combinations of arsenic and bismuth, such as bismuth arsphenamine sulfonate (Bismarsen), but bismuth subsalicylate became the preferred drug.

While numerous types of toxic reactions were described, a four breath, followed by stomatitis, potentially leading to gangrene of the gums, was the most frequent. Bismuth by itself was recognized as less potent than the arsenical drugs. It was used before beginning an arsenical course, in alternating courses with an arsenical, or continued after completion of the arsenical course, often for months [18, pp194, 213-16].

The Work of the Cooperative Clinics Group

"[S]yphilology of 1925 was a chaos of different regimens of treatment, of different dosages, of private preference for different variations of the arsenical compounds. There were many piecemeal case studies but no accurate data upon which the scientist could judge the relative efficacy of these methods" (15, p188). So said the Surgeon General in 1938. To address this problem the PHS in 1929 sponsored the organization of the Cooperative Clinics Group (CCG). This consisted of five leading research-oriented venereal disease clinics: those at Western Reserve University, Johns Hopkins University, the Universities of Michigan and Pennsylvania, and the Mayo Clinic. The concept was that: "It is necessary to follow large numbers of patients for a long period of years, and to compare the outcome in different groups treated with different drugs and by different schemes of treatment" [19, p135]. No one clinic would have enough cases to achieve this goal, but no multi-center coordination of this magnitude had ever been attempted [19].

Data suitable for analysis had been recorded from patients who had been seen between 1915 and 1929. There were 3,220 cases of "early syphilis" (primary and secondary stage), and 1,936 cases of latent, meaning asymptomatic, syphilis. The present discussion is limited to the latter category. This was further divided into "early latent," meaning cases that were asymptomatic and seen within four years of the presumed time of infection (571; 29.5 percent), and "late latent," being the more chronic cases (1,365; 70.5 percent). Due to the frequent uncertainty about the time of infection, the "early" and "late" subdivisions usually were guesses. Latency itself is an uncertain diagnosis because it depends on the thoroughness of the examination and the interpretation of non-specific findings [20].

Furthermore, as Warthin showed, at least microscopic findings of syphilis are detectable at autopsy in the majority of cases of latent syphilis. Sites of these lesions ranged from 80 percent of meninges to about 30 percent of livers [21]. Finally, since it was known that as many as 20 percent of patients retain a positive reaction to the Wassermann or a similar test regardless of the amount of treatment, asymptomatic passage of time appeared to be the only reliable criterion of cure.

The Mayo Clinic cohort was entirely white, while 79 percent of all the black CCG cases were seen at the Johns Hopkins Clinic (71.7 percent of its cohort). Comparisons were made between male and female and also

between white and "colored" patients. The principal questions were: what is the optimal course of treatment to achieve a potential cure; when can one confidently state that the asymptomatic patient is not in latency but is cured; and whether symptoms of early syphilis during latency are due to relapse and hence insufficient treatment, or to re-infection [22].

One extreme of practice within the CCG in 1930 was to administer arsphenamine for three consecutive days followed by an unspecified course of mercury rubs or bismuth injections, provide no treatment for three or four months, then repeat this sequence about six times. Others used continuous treatment with various courses of arsphenamine alternating with courses of mercury or bismuth, "until the blood Wassermann had become or had remained negative for one year, or, if the patient was Wassermann fast, for an arbitrary period of two years" [22, p357]. Only the interrupted treatment protocol was unequivocally inferior to the others.

The "best treatment" of early syphilis in 1939 consisted of alternating 8- to 12-week courses of bismuth and neoarsphenamine without interruption for a total of 60 weeks [23, p568]. According to the CCG, if the patient was believed to be in "late latency," the treatment was modified to three 8-week courses of weekly arsenical injections alternating with 10 weekly injections of bismuth (54 weeks), followed by intermittent additional courses of more bismuth for a total of 80 to 100 weeks and ideally an annual course of bismuth for several more years [18, p659]. Similarly, a leading dermatologic textbook stated in 1939: "If no clinical evidence of the disease is to be found after 18 months of treatment, a 6 months' vacation from medication is taken, and . . . [then] a blood test is taken" [24]. Overall, the CCG found that relapses occurred more frequently in men, but that there were no gender or racial differences in tolerance of, or responsiveness to, arsenical therapy [25].

Several intensive treatment protocols, some as brief as five days, were devised, in the hope thereby of improving the proportion of completed treatment. They were recommended only to be used during the first four years after infection. Unfortunately, these trials incurred a higher incidence both of major toxicity and relapse [26]. Nevertheless, the development of brief treatment remained an important research topic until it was made irrelevant by penicillin. Treatment protocols which varied so widely in drugs used, their dosage, frequency, and duration of administration—none of which had a rapidly demonstrable effect—made the evaluation of efficacy extremely difficult.

Toxicity and Completion Rate of Treatment

Stokes, describing problems in the treatment of syphilis in 1939, stated: "[It] is a long, slow painful and expensive grind which can be sold to the victims of the disease only by our utmost in educative and persuasive

power" [23, p567]. Of the CCG's 6,807 initial cases, of those who remained under care for at least 6 months, 20 percent remained for 2 to 5 years, 17 percent for five years, and only 14.4 percent for 5 to 10 years [26]. At the University of Virginia clinic, of 771 cases of early syphilis who were first seen between 1921 and 1933, 60.6 percent were lost to follow-up after less than 5 years, while 12.7 percent were seen after 5 to 15 years [27]. While these figures do not prove that dropouts occurred during treatment, Johns Hopkins clinic data are more specific. Of 873 patients who began arsenical treatment between 1914 and 1934, 43 percent received fewer than 20 arsenical injections, and only 15 percent received at least 40 injections, which then was considered the minimum adequate course [28, p378].

Some degree of reaction occurred after about three-fourths of the first few injections of arsphenamine in cases of early syphilis, but infrequently when treatment was begun during latency. This usually was the transient fever and muco-cutaneous inflammation that had been described by Adolf Jarisch (1895) and Karl Herxheimer (1902) during mercury therapy [29]. These symptoms last from a few hours to two days, and because of their commonness generally were not recorded as complications. This phenomenon was attributed to local inflammation at foci where spirochetes were killed. The greater the burden of spirochetes and/or the spirocheticidal effectiveness of the medications, the more intense the reaction. The goal of killing the pathogen was achieved, but at the expense of focal injury due either to inflammation or to post-inflammatory scarring. If this occurred at sites such as a cerebral artery or the aortic arch, a stroke or heart failure might result. This was called "therapeutic paradox" [18, pp132-33]. Efforts to prevent or minimize these complications consisted of beginning treatment with mercury, or later with bismuth, because they were considered weaker drugs than the arsenicals, or by using smaller arsenical doses than the usual.

By 1931 there were two reports regarding toxicity during large-scale experience with arsenical therapy. Unfortunately they are not closely comparable. The U.S. Navy reported its data, mainly from 1925 to 1928, citing the number of patients who had reactions and the number of injections that had been administered, but not the total number of cases treated. Of 272,354 injections, 87 percent were neoarsphenamine. During these four years 16 deaths were attributed to this drug (1:14,844 injections) and one to arsphenamine (1:22,625). During 1919 to 1924, nine deaths were attributed to the former and seven to the latter drug [31]. Curiously, when the fatality data were extended from 1925 to 1941, there were 50 deaths due to neoarsphenamine (1:362 injections) [18, p367].

A "nitritoid crisis" was a severe vasomotor reaction which was attributed mainly to the too-rapid intravenous injection of the arsenical drug. It was particularly anxiety provoking, being manifested by flushing, facial edema,

sensations of smothering and/or chest pain, tachycardia, and possibly shock. In the 1925 to 1928 experience, this occurred about once per 5,000 injections of neoarsphenamine, and exfoliative dermatitis occurred once per 6,000 injections. Most toxic events, as also shown in other studies, occurred early in the courses of treatment [30].

Civilian experience in Cleveland during the decade beginning in 1921 included both sexes and a wider age range. These findings were based on 78,350 injections, 29 percent of the Navy experience. Contrary to the Navy practice, 76 percent of the injections were arsphenamine. Of the 1,212 cases, 15.3 percent developed one or more reactions, 14.3 percent of those in an early stage and 19 percent of those in a late stage of the disease. The percentage of individuals in whom a reaction occurred increased from the sixth to the 20th injection. Of patients who had one complication, nearly two thirds were able to continue cautiously on arsphenamine treatment, while 28 percent of patients with two complications continued. Mild rashes and/or pruritus were most frequent, constituting 40 percent of all reactions, followed by gastrointestinal disturbances with 33.5 percent. Nitritoid crises were diagnosed in 12.5 percent, severe cutaneous reactions such as exfoliative dermatitis in 7 percent, and hepatitis in 6 percent. There were 12 deaths (1 percent). Six of these were due to hemorrhagic encephalitis, which also was the most frequent cause of death in the naval experience. Five were caused by exfoliative dermatitis, and one by arsenical hepatitis. All occurred during the first six months of treatment [31]. The reason for the more frequent toxicity than was reported from the Navy is uncertain. While it could have been due to the predominant use of arsphenamine rather than neoarsphenamine, a more likely factor is that nearly all naval patients were in an early phase of the disease.

In the mid-1930s arsenoxide (Mapharsen) began to replace the arsphenamines in practice. A literature review covering 1935 to 1941 found only six deaths attributed to this drug. The Navy reported no deaths related to 288,585 injections [18, p367]. Most patients who had suffered significant reactions to an arsphenamine subsequently tolerated Mapharsen. Only a history of exfoliative dermatitis was considered to contraindicate Mapharsen use [32].

A PHS-sponsored study of the feasibility of shortening the course of treatment by giving Mapharsen thrice weekly by itself or with the addition of bismuth was reported in 1944. Of the cases in latency, 79 percent had received no previous treatment. Most severe toxicity occurred between the second and fourth weeks of treatment, and treatment was stopped due to toxicity in 2.2 percent of the entire population. When weekly bismuth injections were added to the intensive arsenical schedule, an 85 percent cure rate of early syphilis appeared to be achieved—lower than with longer courses. Harry Eagle, the distinguished syphilologist who

led this investigation, believed that: "Because of the generally favorable prognosis of latent syphilis, even with little or no treatment, many years' observation will be necessary . . . to prove that such treatment makes a difference" [33].

Concerns over Resistance to Therapy, Relapse, and Reinfection

At the time the Tuskegee Study was being formulated, the main criterion for "primary resistance" to arsenical therapy was defined as the persistence of spirochetes on microscopic examination of material from as-yet unhealed syphilitic lesions. Some European clinics reported as high as 15 percent resistant cases, while the clinics of the Johns Hopkins and the University of Pennsylvania hospitals reported less than one case per year. This difference was attributed to better quality control of the American medicines. The recurrence of lesions during treatment was considered "secondary resistance or relapse," although reinfection often could not be ruled out. Primary resistance was treated with increased dosage of the same drug(s), a shift to other compounds, or the addition of fever therapy [34].

Hyperthermia was a mainstay in treating involvement of the central nervous system. Originally fever was induced by infecting the patient with malaria, but in 1929 this source had been replaced by electric heating cabinets. The typical course consisted of raising the rectal temperature to 105° to 106°F for five hours once per week for 10 weeks [35].

Reinfection, of course, assumes that the original infection had been cured rather than just suppressed. Halley and Wasserman (1928) reviewed the cases of second syphilitic infection that had been published since 1910. Including their own cases, only 237 met their criteria. The major findings were that 96.7 percent were male, only 1.6 percent occurred when treatment had begun in the latent phase, and none when treatment began in the presence of tertiary lesions. Their interpretation relied on the hypothesis that immunity develops gradually. The scarcity of women with second infections was explained by their diagnosis tending to be made later than in men, permitting more time for spontaneous resistance to develop. Unfortunately, the authors did not discuss the amount of treatment received before the supposed reinfection [36]. Since 70 percent of these cases occurred when treatment was initiated during the primary phase, it seems at least as likely that insufficient arsphenamine had been given to cure the initial infection as that lack of immunity permitted a second infection in a medically cured patient. Stokes (1945) also concluded that most so-called reinfections actually were relapses attributable to inadequate treatment [18, pp645-49].

A decrease in the incidence of autopsy proven cardiovascular syphilis provided inferential evidence for the efficacy of metallothrapy. In the survey of 15,000 autopsies that had been performed in Philadelphia from 1927 to 1937, 1,040 cases (6.93 percent) of cardiovascular syphilis were identi-

fied. Each successive 3,000 cases, this pathologic diagnosis declined: from 92 per 1,000 to 56 per 1,000. Syphilitic cardiovascular lesions contributed to death in only 32.6 percent of the cases in which such lesions could be identified [9]. The uncertainties about what constitutes optimal therapy and the conclusion that only the passage of time could differentiate therapeutic cure from disease suppression or spontaneous resolution led to the belief that: "The only possible method of approach to the question of the natural evolution of untreated syphilis is to follow over a period of many years a large series of patients who have never received treatment" [20, p327].

Such an approach could be entertained for three principal reasons. First, various data (vide infra) indicated that syphilis, although potentially fatal, causes severe debility in a minority of cases and in at least 40 percent causes none. Second, the best available treatment, especially due to its length, had a low completion rate. Third, a majority of syphilitics were remaining untreated. According to the CCG experience, "Of our patients with late syphilis, 50% of white males, 70% of white females, 80% of negro males, and 90% of negro females had never received any treatment prior to admission." Only 5 percent of the white and 0.9 percent of the black patients had received anything approaching adequate treatment: "This in part is attributable to the factor of symptomless infection with syphilis, and in part constitutes a serious reflection on current medical practice in the treatment of early syphilis" [25, p378]. These circumstances led to the attempt to undertake the investigation Moore and his collaborators hypothesized, the Tuskegee Study.

Experience with Untreated Syphilis

Might syphilis be self-limiting? If so, is this usual or occasional? If occasional, are factors that cause spontaneous resolution identifiable? Does available treatment facilitate arrest of the disease, is it actually inert, or may it be detrimental? The more chronic a disease is the more difficult it is to answer these questions. In 1890 Caesar Boeck, the professor of dermatology at the University of Oslo, confronted these questions in regard to his syphilitic patients. He decided to stop treating them with mercury, the universally accepted "specific agent," because he had concluded that it not only was not curative, but also believed that it interfered with natural resistive mechanisms and thereby caused the incidence of tertiary visceral lesions to increase. Thus, between January 1891 and December 1910, 2,181 presumably syphilitic patients were admitted but given no "specific treatment." This policy was stopped shortly after the introduction of arsphenamine [37].

The potential research value of these case files was recognized by Johan Bruusgaard, who had succeeded Boeck as professor. Between 1925 and

1927, 473 patients (21.6 percent) of the untreated cohort were followed. Selection was weighted in favor of the initially more seriously affected cases because they were more likely to have remained under medical care and would therefore be easier to locate. Of the study group, 164 patients (34.7 percent) had died, and in 70 percent of these, including the 40 who had been autopsied, syphilis was not causally implicated in the deaths. The most frequent causes of death were cancer and tuberculosis. Bruusgaard reexamined 309 patients. In view of the selection bias toward the initially sicker patients, it was particularly impressive that 65 percent of the entire cohort of survivors, and 73 percent of those who had been infected more than 20 years ago, were free of syphilitic symptoms. Furthermore, 66 percent of the asymptomatic cases had a negative Wassermann reaction. Thus, at least 43 percent of the 309 cases could be defined as having undergone spontaneous cure [37, 38].

These were the only available data concerning the long-term prognosis of untreated syphilis at the time the Tuskegee Study was being formulated. However, between 1932 and 1946, portions of several other investigations confirmed the conclusions that treatment improves the eventual course of syphilis only in a minority of cases. The insurmountable problem was that there was no objective basis whereby to identify this subgroup, leaving the quandary of subjecting the majority of patients needlessly to the inconveniences and hazards of the treatment. Nevertheless, Moore, et al., for example, stated in 1932 that: "This is not to be construed as an argument for the abandonment of the treatment of syphilis, whether early or latent" [20, p328].

The CCG defined a "satisfactory result" as a normal physical examination and negative blood and spinal fluid Wassermann test one year after completion of treatment. These experienced clinicians estimated in 1932 that spontaneous seronegative "cure" occurs in 25 to 35 percent of cases, and that an equal proportion retain only a positive blood Wassermann reaction. Thus, about one-third of syphilitics were at risk of progressive disease [22]. One half of their 20 patients with latent syphilis who were untreated, and 49.3 percent of 148 who had received fewer than 10 arsenical injections, had a "satisfactory" outcome. This proportion was not improved by courses of 40 or more injections. The authors concluded that 20 weekly injections were sufficient, being associated with the lowest rate of symptomatic relapses (2.7 percent), and that an uninterrupted course of injections was more important than its greater length [22].

Padgett, reporting on 551 patients whose treatment began in an early stage of syphilis and who had been followed for at least five years, found no difference between intermittent treatment (38 percent of 26 "cured") and no treatment (35 percent of 17), although even intermittent treatment resulted in less cardiovascular and neurosyphilis. About 20 injections of arsphenamine weekly without interruption during the first year of treat-

TABLE 3

FINAL OUTCOME ACCORDING TO TOTAL NUMBER OF ARSENICAL INJECTIONS OF 926 CASES OF LATENT SYPHILIS FOLLOWED FOR MORE THAN FIVE YEARS

Injections	Patients	Satisfactory	Tertiary Progression		
			CV	CNS	Other
None	53	86.8%	5.5%	3.8%	3.8%
1-9	181	86.7	5.0	2.2	6.1
10-14	81	90.1	2.5	0	3.7
15-19	113	94.7	0.9	1.8	2.6
20-24	108	96.4	0.9	1.8	0.9
25-29	94	97.9	2.1	0	0
30-39	164	97.0	1.2	1.8	0
40+	132	99.2	0	0.8	0
Total, Mean	926	93.8	2.2	1.5	2.2

From Discker et al. (Table VIII) [28]

ment resulted in the cure of about 80 percent, approximately doubling the result without treatment and halving the occurrence of neurosyphilis [39].

A study of 926 cases of syphilis first seen in latency at the Johns Hopkins clinic between 1914 and 1934 gave the strongest indication that most treatment programs were excessively lengthy, but also showed the highest prevalence of spontaneous cure. Of 234 patients who were followed for at least five years and had received from none to nine arsenical injections, 86.7 percent had a "satisfactory" outcome [28]. From those who received 20 to more than 40 injections, the "satisfactory" rate increased only from 96.6 percent to 99.3 percent (see Table 3). These investigators concluded that 20 injections each of an arsenical and of bismuth give optimal results. The proportion of satisfactory outcomes did not change from the fifth to the 14th year of observation, and then it increased slightly. Although this might be explained by a greater death rate of anatomically affected cases, actually none of 43 deaths were attributed to syphilis [28].

Jordon and Dolce (1946) compared the courses of 69 cases of latent syphilis, all of whom had been observed for at least 10 years. The entire cohort finally had been infected for an average of 23 years. Sixty-nine individuals had received about six arsenical and five "heavy metal" injections at irregular intervals; 100 had received 20 to 29 arsenical injections alternating with 40 to 60 injections of bismuth. The interpretation was that "adequate antisyphilitic treatment of persons with latent syphilis results in only a 17 per cent increase in long term serologic reversals over those that occur spontaneously with little or no treatment" [40, p14].

The most important pathologic confirmation of such clinical impressions came from Yale University in 1946, based on 380 syphilitic patients who underwent autopsy examinations between 1917 and 1941. Of these, 198

had been untreated. The duration of the disease was known in only a few cases, and the potential prevalence of late syphilitic findings was minimized by death from other causes when syphilitic lesions might otherwise still have developed. In conflict with Warthin's findings 15 years before, 61 percent showed no anatomical evidence of syphilis. Of the rest, 39 percent (77 cases) revealed lesions compatible with syphilis, but only 23 percent (46 cases) had lesions to which death was attributable. The vast majority of these lesions were aortic [41]. Fatal lesions were even fewer than the Philadelphia review had found [9]. These results substantiated Bruusgaard's findings, wherein death of only 30 percent of 164 cases was attributed to syphilis [37, 38].

Replacement of Metallotherapy with Penicillin

When arsphenamine became available, Boeck decided to initiate therapy. When penicillin became available, the directors of the Tuskegee Study did not respond the same way. This has never been explained, but we will propose that there were two reasons, one that was valid until at least 1960 and has been widely misunderstood, and the other, by inference, that since about 30 years had already been invested and there was by then ample evidence that the disease is benign in the majority of the diseased, it was possible to make the case that the study should not be stopped until the maximum of information had been obtained.

Amorphous penicillin by intramuscular injection was first used to treat primary syphilis in the latter part of 1943 [42, 43]. Resolution of chancres and cure occurred with unimagined rapidity. The substitution of penicillin for arsenicals initially was impeded by inadequate supplies and high cost [18, p1256]. However, by 1945, as penicillin became more available, at least four other factors retarded its consistent use. First, dosage, route of administration, and duration of treatment remained to be determined. Second, new preparations were introduced in rather rapid succession, so that no single treatment plan was focused on for evaluation. Third, inconsistent potency of different lots of the drug became evident. Finally, problems with arsenical therapy were analogized to penicillin, introducing apprehension about potential dangers from using this new drug.

In March 1946, a conference on the penicillin treatment of syphilis was held by representatives of the PHS, the Food and Drug Administration, and the National Research Council. According to an editorial based on this meeting:

It cannot be repeated too often nor too emphatically that penicillin therapy of syphilis is still an experimental procedure. This is true because of the prolonged course of latency and its tendency to recur after periods of latency, and applies with equal force to any new treatment, drug or procedure. . . . [It] cannot yet be said that penicillin is more effective than arsenical-bismuth therapy from the standpoint

of penicillin "cures." Several years of observation on several thousand patients treated under various schedules will be necessary before a dependable evaluation can be made. [44, pp113, 145]

The introduction in 1946 of crystalline penicillin G, a pure, active preparation, increased therapeutic reliability. However, there were two problems. Because of deterioration once it was dissolved in water, like arsphenamine, the medication had to be prepared just before use. More importantly, it was excreted so rapidly that injections had to be given every three to four hours. A recommended course of treatment for cardiovascular syphilis in 1948 required 30,000 units of penicillin G intramuscularly every three hours for three weeks [45]. Therefore, the pharmaceutical research focus became directed at ways to retard the excretion. Several unsuccessful compounds were marketed before procaine penicillin G became available in 1949, and compounds in which penicillin was bound to a fat rather than to procaine soon became competitors. With the addition in 1951 of probenecid, an oral drug that was synthesized specifically to impede the excretion of penicillin, injections could be reduced to twice or even once per day [43].

It had been concluded from metalotherapy that there were two principal categories of untoward reactions: those due either to intolerance of the drug itself or to hypersensitivity to the spirochetes killed by the drug. Since penicillin obviously killed spirochetes more efficiently than any of the metallic drugs, a greater mass of decomposing spirochetes was feared to cause especially violent reactions. In the largest study of Herxheimer reactions, they occurred in 48 percent of the cases of primary syphilis and were unrelated to gender or race. Severe reactions were relatively infrequent and occurred late [46]. In another study of 127 cases of penicillin-induced Herxheimer reactions, 47 percent of the primary and 18 percent of the secondary stage cases generated a temperature above 39°C (102.2°F), while the temperature in no latent cases exceeded 38°C (100.4°F) [47]. The reaction appeared to occur independently of dosage, being induced by as little as 1,000 units [46, 48]. It was shown to be specifically related to spirochetes, since it also occurred in penicillin-treated yaws, another spirochetal disease, but not with gonorrhea [46].

Other untoward reactions to penicillin diminished to about 2 percent when pure products became available. These also were not related to gender or race, and hives were the most frequent [50, 51]. Transient exacerbation of secondary lesions were the next most common reaction [51]. Thus it became apparent within the first five years of its use that penicillin in general was a much safer drug than any of the metallic compounds. However, fatal Herxheimer type reactions, usually considered to be instances of "therapeutic paradox," were reported in patients from 21 to 75. These mainly were acute or delayed cases of cardiovascular failure [52-56]. Four examples of the latter were described in 1952, in whom, 6 to 18 months

after penicillin treatment for neurologic symptoms, aortic insufficiency had developed. This was hypothesized to have been due to scarring from the penicillin-induced healing of critically located, previously asymptomatic syphilitic lesions [56]. So, just as bismuth was used in part in the belief that it would diminish an excessive reaction to the more potent arsenicals, it was also combined with penicillin therapy in cases without neurologic symptoms. In these fever was the preferred adjuvant. The great value, both in regard to compliance and economy, was the brevity of penicillin administration—10 days to three weeks versus a year or longer. In 1948 in Boston, 53 percent of patients who were demented due to neurosyphilis showed improvement from a 15-day course of penicillin combined with malaria fever [57].

A particularly worrisome review of penicillin therapy from the influential Johns Hopkins clinic stated in 1948:

Treatment failures following the use of penicillin in late syphilis have been observed to occur as a result of (a) drug resistance, (b) clinical progression, (c) recurrence of lesions following an initially favorable response and (d) the subsequent development elsewhere in the body. Further observation is required before it safely can be assumed that penicillin is significantly and lastingly efficacious in late syphilis. Until such evidence is available, caution is enjoined in the use of penicillin as the only therapeutic agent in the treatment of patients with late syphilis. [58, p241].

Similarly, according to a major textbook of cardiology in 1950: "The dosage of penicillin has not yet been standardized and its usefulness in cardiovascular syphilis cannot be properly evaluated until many years have elapsed" [59, p830]. Much of this pessimism would soon be attributed to the use of insufficient doses of penicillin.

In 1951, Curtis, et al., stated:

Many physicians still are undecided about which is the better course to follow—the administration of penicillin alone or penicillin combined with heavy metals and, for some cases, with fever therapy. The accumulated experience of many syphilis clinics . . . clearly indicates the superiority of treatment with penicillin alone in the vast majority of cases. It is only in an occasional case that supplemental treatment is necessary. [60, p1223]

These University of Michigan investigators recommended using penicillin-aluminum monostearate (PAM) to treat both latent and tertiary syphilis, with 600,000 units given intramuscularly for 10 injections either on consecutive days or twice per week for five weeks.

Barnett, et al., reiterated in 1954: "Without any treatment most cases of latent syphilis do not progress, and evaluation of a new method must be entirely comparative. The effect of penicillin must therefore be judged against a background of knowledge of the incidence of progression in untreated patients and in those treated by the older methods." According to their findings (in California), "a higher incidence of persistently positive

Wann reactions followed penicillin therapy than metal therapy" [61, pp91,96].

In 1958, Harrison's *Principles of Internal Medicine* stressed the uncertainty of the efficacy of penicillin in late syphilis:

Penicillin has not been evaluated in late latent syphilis. Since the prognosis of this stage of the disease is so good and since the drug is known to be effective in both early and late symptomatic syphilis, it is presumed to be of value in patients with latent infection. . . . The value of antisyphilitic therapy in late cardiovascular syphilis is difficult to determine. Many syphilologists believe that treatment does not delay the ultimate development of myocardial failure or aneurysmal rupture. . . . The results of treatment of neurosyphilis depend largely upon the type and duration of the neuropathologic process. If the predominant lesion of the central nervous system is degenerative, as in tabes and optic atrophy, little response to any form of treatment can be expected. If the tissue reaction is chiefly inflammatory, as in syphilitic meningitis, rapid and almost complete return of function will occur. [62, p1009]

However, Harrison noted that "Gummatous lesions of the skin, mucous membranes, bones, and viscera usually respond promptly to penicillin therapy."

In 1960, the official PHS therapeutic recommendation for latent syphilis was 4.8 million units of benzathine penicillin G alone, in any one of several treatment schedules; for cardiovascular or neurosyphilis a total of 6 to 9 million units. If there was a history of penicillin allergy, erythromycin or tetracycline could be substituted [63].

Wilner and Brody (National Institutes of Health) pointed out in 1968 that it was a misconception "that penicillin can almost universally arrest paretic progression" [64]. Evaluation of 100 patients who had been treated for general paresis more than 10 years earlier showed that the disease had progressed in 39 of the patients who had been treated with penicillin with or without malarial fever, and in 17 of those whose treatment had not included penicillin. The total penicillin dosage ranged from 3 to 30 million units. How many patients had received treatment that had come to be considered inadequate was not provided [65]. However, it was stated by Whiteside as recently as 1989 that "The appropriate dose and duration of penicillin for the treatment of neurosyphilis has not been established" [65, p225].

The Tuskegee Study of Untreated Syphilis: Why Begun, Why Not Stopped Sooner?

Six observations that were relevant to the justification of the Tuskegee Study were deemed important in 1930: (1) syphilis was recognized to be a major public health problem; (2) it was most prevalent in the black population; (3) there was disagreement about its optimal treatment; (4) all treat-

ment programs were lengthy, painful, and potentially toxic, with a very poor completion rate; (5) a large proportion of the syphilitic population obtained no relevant treatment; and (6) according to one retrospective study, the disease resolved spontaneously in a majority of cases.

As strange as it now seems, "when the study was started in the fall of 1932 no plans had been made for its continuation," according to a 1938 letter from Assistant Surgeon General R.A. Vonderlehr [37, p40]. None of the 13 published reports about the study during its existence describe its planning. Whether the impetus originated with members of the CCG or from officers of the PHS who were cooperating with the CCG is unclear. In 1932, the same CCG authors wrote in connecting articles: "It is necessary to follow large numbers of [syphilitic] patients for a long period of years, and to compare the outcome in different groups treated with different drugs and by different schemes of treatment" [19, p135]. The critical concept was stated four months later: "The only possible method of approach to the question of the natural evolution of untreated syphilis is to follow over a period of many years a large series of patients who have never received any treatment" [20, p327].

The CCG had undertaken the former project and found that the intermittent, repeated short-course schedule was inferior to all of the others. Since the Norwegian retrospective study seemed to show that syphilis frequently is a self-limited disease, at least in a Scandinavian population [37, 38], and no abrupt benefit could be expected from the available treatments, the most direct way to evaluate future therapy was against a documented prospectively gathered baseline of the untreated course of the disease. The question whether the Norwegian findings were applicable to the predominant American syphilitic population which had an African ancestry would best be clarified by performing such a study on a black syphilitic population. In 1930, the Julius Rosenwald Fund had selected one rural county in each of six southern states in which to conduct a demonstration venereal disease control project. A preliminary serologic survey of black inhabitants was made in each, and the highest prevalence of positive serologic tests for syphilis was found to be in Macon County, Alabama, of which Tuskegee was the county seat [37, 66]. Before deciding on Macon County as the site for a study of untreated syphilis, the PHS in 1931 conducted another serologic survey there. The prevalence of positive blood tests was lower than in the Rosenwald survey, probably because children were excluded. Nevertheless, 26.5 percent of men who were at least 25 years of age were diagnosed as syphilitic [67, 68].

The prospective subjects of the investigation were medically quite isolated. Macon County in 1932 had only one black and eight white physicians. Furthermore, the potential participants lived farthest from where the physicians were practicing, making access to these care providers very difficult. There were two hospitals. Few if any of the subjects were eligible for care

in the veterans Administration Hospital because they had not had military service; the community hospital was out of their reach economically. Based on these circumstances, Olansky, et al., concluded (1954) that: "medical progress has not been so great nor medical care so widespread among our patients in Macon County as to defeat the project as a study of untreated syphilis" [68, p694].

Of those who met the required criteria, 84.5 percent were entered into the study. "An hour or more" was spent in obtaining each medical history. Whether the 15.5 percent who did not enter the study were excluded because of their unwillingness to participate or for other reasons was not explained [67]. The interviewing physicians have retrospectively been criticized for talking to the interviewees about having "bad blood" rather than specifics of syphilis [2]. Parran commented in this regard on the Tuskegee interviewing process: "Though most of the audience did not know the word syphilis, many of them were familiar with what they called 'bad blood' disease and the miseries it brought" [3, p165]. Thus it seems highly unlikely that using the local terminology misled these men into participating. This also would have been inconsistent with the assessment of the physicians by J.H. Jones, in his widely cited book *Bad Blood*, in which he states: "The PHS officials behind the Tuskegee Study were racial liberals by the standards of the 1930s. Within the medical profession they were truly progressive. They began the experiment because they were interested in black health, in studying the effects of syphilis on black people" [69, p172].

Allegations have been made that the PHS "infected Black men with syphilis" [2, p1499], a libel that for at least two reasons would be senseless. If that were the intent of the investigators, the elaborate methods to locate an area in which syphilis was particularly prevalent, making the assembling of research cohorts relatively easy, would have been unnecessary. Also, quite apart from ethical considerations, this would have been an approach to study the early phase of the disease, while research interest pertained to its later course. Indeed, "The patients who had syphilis were all in the latent stage; any acute cases requiring treatment were carefully screened out for standard therapy" [70, p391; emphasis added]. Actually, 11.5 percent were not in the latent but the tertiary stage at the study's start.

The syphilitic and the non-syphilitic control populations were weighted toward older men, 56 percent of each were at least 40 years of age. In 1932, 14 and 5 percent, respectively, were at least 70 [71]. Inclusion of subjects who had already exceeded their mean life expectancy is evidence that a chronic investigation was not initially contemplated. For example, the projected life expectancy of a syphilitic black man in his late 30s was 28 years [72] (see Table 4). Chest roentgenograms appear to have been made on everyone, and 68 percent of the syphilitics had a spinal fluid examination. The participants reflected the general poor health of their community, with only one-sixth of the syphilitics and three-fifths of the controls showing "no

TABLE 4

PROJECTED LIFE EXPECTANCY FOR BLACK MEN,
MACON COUNTY, AL, 1933-44

Age	Non-syphilitic	Syphilitic
35-39	34 years	28 years
40-44	30	24
45-49	25	20
50-54	21	17
55-59	16	14
60-64	12	10
65-69	8	7
70-74	4	4

Adapted from Heller and Bruyere [73]

disability." Signs of cardiovascular diseases were found in 46.6 percent of the syphilitics, and the roentgenograms of 23.6 percent were suggestive of aortitis, a finding particularly associated with syphilis. Among the controls these figures were 24 and 5 percent respectively. Osteoarticular abnormalities were found in 12.5 percent of the syphilitics and 4.5 percent of the controls. The greatest difference pertained to "diseases of the central nervous system." Among the 26.1 percent of such syphilitics, there was "definite clinical evidence" that the symptoms were syphilitic in 7.8 percent, while only 2.5 percent of the controls had signs of some form of CNS disease [67] (see Table 5). How advanced the findings of the various diseases were at the inception of the study, which obviously are factors in life expectancy, was not estimated.

The predominance of cardiovascular symptoms of syphilis over neurologic symptoms confirmed the finding of Zimmermann and of Turner [8, 10] (see Table 1). Turner had shown that persistent latency versus the development of tertiary manifestations was influenced more by gender than race, men being more likely to become symptomatic [10].

TABLE 5

CHARACTERISTICS AT INCEPTION OF THE STUDY (1933)

Age	Syphilitic			Control
	25-35	40+	Total	
Number	174	225	399	201
No disability	25.3%	8.4%	15.8%	61.2%
Cardiovascular findings	25.3%	63.1%	46.6%	23.9%
Central nervous findings	23.0%	28.4%	26.1%	2.5%
Osteo-articular findings	12.1%	12.9%	12.5%	4.5%

From Vonderlehr et al. [68]

At the first reevaluation, in 1938, the syphilitic cohort was modified. Twelve subjects were found to have received at least 10 injections of anti-syphilitic medication and were removed. They were replaced by 14 other men with latent syphilis [73]. The long-term value of the control cohort also soon came into doubt. During the reexamination in 1939, "approximately fifteen of the control cases were found to have either clinical or serological evidence of a syphilitic infection" [37, p41]. These men were removed from the study and sent for treatment, but not replaced [37]. There is no information whether additional control subjects later contracted syphilis.

Although it was hoped to eventually obtain autopsies on all subjects, the sole report on this aspect contained data only through 1952. At that time, 40 percent of the syphilitic cohort had died and 92 autopsies (56 percent) were obtained, while only 27 percent of the control cohort had died and 32 autopsies (65 percent) were obtained. Fifty-one percent of these syphilitics and 50 percent of the controls were at least 65 years old. Examination of the aortas of 60 serologically positive subjects revealed gross or microscopic evidence of aortitis in 23 (38 percent); among subjects who had become serologically negative, 2 of 27 (7 percent) had such findings. Only 2 of 46 pathologic examinations of the central nervous system revealed unequivocally syphilitic abnormalities [74].

The death rate of the syphilitics consistently exceeded that of the controls. At 12 years it was 25 versus 14 percent, at 20 years 39 versus 26 percent, and at 30 years 59 versus 45 percent of the traceable cases [72, 75, 76]. Shafer, et al., estimated that the difference cumulatively at 20 years was 17 percent, the same conclusion reached by Jordon and Dolce [40, 76]. How much of this difference is attributable to the greater overall morbidity of the syphilitic cohort and how much to syphilis is uncertain. Remarkably, a similar analysis in which deaths in the CCG patient population, which included a sizeable proportion of treated individuals, was compared to the general U.S. black population in 1929 to 1931, showed survival of the syphilitics to be 30 percent poorer [77]. The most logical explanation of this seeming paradox is that it reflects the situation that the general health of the black Macon County population was worse than that of the black population nationally at that time. The disparity of morbidity between the two cohorts narrowed with aging. According to the last report in 1973, at year 36, there were for the first time no differences in morbidity found between the 71 syphilitic and 51 control subjects who were then examined [78].

Valid and Dubious Criticisms

The more powerful a therapeutic agent is, the easier it is to demonstrate at least its short-term effect. However, all of the anti-syphilitic drugs of the

1930s were rather weak, and no dramatically more potent drugs were anticipated. Therefore, particularly detailed knowledge of the range of variability of the therapeutically unaltered course of the disease would be desirable to determine as early as possible whether a new treatment significantly altered its course. A prospective investigation may with far greater reliability than a retrospective survey assess the sequence and rate of pathologic and serologic changes. In order to optimally perform a non-therapeutic observational study of the course of a disease, a population is required who on entry know approximately when they were infected, and could be rigidly prevented from obtaining relevant treatment. The inadequate histories that most of the participants were able to give and, particularly, the limited prospective controls both on treatment and recognition of new infection diminished the potential value of the Tuskegee investigation from its outset.

The initiation of the Tuskegee Study should have required a waiver of the Alabama venereal control act of 1927, which required infected persons "to report for treatment to a reputable physician and continue treatment until such disease, in the judgement of the attending physician, is no longer communicable" [37, p43]. In the absence of such an exception, the investigation was illegal. The duration of infectiousness was among the most important questions. Although it was stated in 1932 that "It is probably true that in most instances the disease is infectious with diminishing frequency for no more than five years" [20, p328], the authoritative equivocation in 1939 was that "Over 92 per cent of infectious lesions are said to occur in the first two years of the disease . . . [but] the more searched for, the longer found, up to ten or more years" [24, p566]. In 1945, opinion again changed: "infectiousness in late latent and late active syphilis is accepted as extremely rare" [18, p168]. The infectiousness of the cohort, except for the newly infected control cases found in 1939, was unknown.

A waiver was obtained for a second deviation from regulations. It was the policy of the Selective Service, beginning in 1940, to have every recruit who was found to have a positive test for syphilis treated. To avoid losing members of the syphilitic cohort to treatment, the Macon County Selective Service Board was furnished the names of 256 men under age 45, with the request that they be excluded from the treatment requirement. This was acceded to [37].

The Tuskegee Study lacked a master protocol and remained severely underfunded. In 1932 there was virtually no experience with prospective investigations, and the country was in a severe economic depression. The nadir of funding for venereal disease control in the PHS budget was reached in 1935, when it was reduced to only \$58,808 for the entire nation [79]. One may ask whether the study, for financial reasons, should have been undertaken. However, this brings us to consider a particularly insidious pitfall in historical interpretation, namely "presentism," the consideration of past

behavior or events in terms of modern knowledge and concepts. This fallacy has recently been discussed by medical historians Edwin Wallace and Jack D. Pressman [81, 82].

Presentism pervades the criticisms of the Tuskegee Study, particularly in regard to the recruitment of the subjects and the alleged withholding of penicillin. The final PHS report on the Tuskegee Study (1973) stated:

If the requirement of informed consent is to be taken seriously, should impoverished and uneducated Blacks from rural Alabama have been selected as subjects in the first place? Or should a concerted effort have been made to find subjects from among the more educated within the population at large, or at least to select from the given subgroup those most capable of giving "informed consent." [37, p92; 82, p29]

This often-repeated charge against the investigators neglects the crucial fact that the legal concept of informed consent was not formulated until 1957, a quarter century after the inception of the Tuskegee Study [83]. The tradition of paternalistic secrecy in the doctor/patient relationship was enunciated in the Hippocratic Corpus, and there were no generally accepted ideas before World War II about what information physicians were obliged to give their patients [84]. The code of research ethics that was published in 1947 by the U.S. government as a result of the Nuremberg war crimes trials states in the third of its 10 paragraphs that: "The experiment should be based upon . . . a knowledge of the natural history of the disease or other problems under study" [85, p206; 86, p1448]. The ramifications of learning that natural history are not addressed. A federal informed consent policy was not promulgated until 1960 [87].

Another major criticism of the Tuskegee Study resulted from a pervasive misunderstanding of the reception of penicillin as a revolutionary anti-syphilitic drug. For instance, according to Jones:

The only valid distinction that can be made between the two acts [withholding arsenicals and penicillin] is that the denial of penicillin held more dire consequences for the men in the study. . . .

Within a few years of its discovery in the early 1940's penicillin was hailed as a wonder drug by medical authorities around the globe. Relatively inexpensive, safe for most patients, fast acting and incredibly effective, penicillin gave physicians the best treatment for syphilis the world had ever known. [69, pp9, 164]

Similar claims were made by many authors, such as a noted ethicist who wrote in *The Hastings Center Report* that: "they were denied antibiotic therapy when it became clear in the 1940's that penicillin was a safe and effective treatment for the disease" [88, p29].

As it turned out, the Tuskegee Study was *not* an investigation of untreated syphilis, as all but one of the investigators' 13 publications stated. It was a series of comparative studies on syphilitic men who could potentially avail themselves of unorganized and largely undocumented treatment and of

another group who may or may not have contracted syphilis during the course of the investigation. The evaluation of 160 participants in 1952 elicited information that 34.4 percent had received 3 to 11 arsenical injections, and 2.5 percent had received 12 to 22. Twenty percent had received occasional injections of penicillin, and 7.5 percent had received a therapeutic course [69]. Of the 90 syphilitics who were examined in 1963, 96 percent had received some treatment. For 20 this was considered to have probably been "adequate therapy," and for another 20 possibly so [75].

It is impossible to know whether penicillin would have been offered systematically had there been persuasive evidence that such treatment would be effective 20 to 40 years after the disease was contracted. The evidence reviewed in this article indicates that venereologists initially were apprehensive about harming patients with late syphilis, even though the effectiveness of penicillin in the primary and secondary stages was rapidly accepted. By 1960, when the PHS published therapeutic guidelines from which metallothiopy was deleted, the investigators could have attempted to evaluate the utility of penicillin so late in the disease by treating a portion of the remaining subjects [79]. This was not done and, in retrospect, would have been unlikely to demonstrate clear benefits.

Jones stated without documentation that: "Scores of men died from a disease that could have been cured. Some had gone blind, others insane" [69, p212]. The improbability of cure at the stage of disease at which these men were seen has been documented in this paper. The proportion that died of tertiary syphilis is unknown. The life expectancy of men with a history of untreated syphilis was found to be shortened, but pathologic examinations indicated that only about one-third died of syphilitic lesions. Thus the existence of lethal cofactors somehow associated with syphilis was discovered but not—even speculatively—explored.

Conclusions

The numerous manifestations of syphilis were well known in 1930. These included suggestive evidence that under some as-yet-unidentified circumstances the disease was self-limited, at least in a Scandinavian population. In the United States, syphilis was far more prevalent in the African American than in the white population. Race appeared to influence the development of specific late manifestations, but neither therapeutic nor toxic responses to medications. The need for more rapidly acting and safer treatment was deemed urgent. Clearly, syphilis presented important challenges to basic science, clinical medicine, and public health. The medical ethics standards in 1930, particularly the absence of the legal doctrine of informed consent, presented no obstacles to the mounting of a prospective observational, non-therapeutic investigation, and these standards would not be modified until after World War II. The questionable legal aspects

of the Tuskegee Study pertain to the extent of the authority of the PHS to overrule state and local authority, the venereal disease control act, and the Selective Service Board, respectively. As far as we know, these matters have not been explored. The various clinical findings that were reported between 1936 and 1973 were useful in confirming existing information about syphilis, but failed to address problems for which, even within the limitations of the study's resources, new information might have been obtained. The most obvious of these were effects of syphilis on the family: for instance, the occurrence of congenital syphilis in relation to the duration of the father's disease, and the effect of a standard course of penicillin on the serologic findings in late latent syphilis. The lack of both an ongoing research protocol and adequate funding during this 40-year study seriously limited the obtaining of much important knowledge. The irony in the history of this investigation lies in the fact that the investigators have been attacked particularly for having withheld treatment from their subjects, while it was their inability to do so that frustrated achievement of their principal goal, which was to document the uninfluenced outcome of latent syphilis.

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WRITING ABOUT THEIR SCIENCE: AMERICAN INTEREST IN SOVIET PSYCHIATRY DURING THE POST-STALIN COLD WAR

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In May 1953, three months after Stalin's death, the lead article in the *New England Journal of Medicine* was a paper by a graduate student in sociology, Mark Field, entitled: "Some Problems of Soviet Medical Practice: A Sociological Approach." The paper portrayed Soviet physician certification of worker disability and illness as a social mechanism to ease the difficulties of life, "one of the many 'adjustive mechanisms' that keep the social organism going by limiting discontent and hence disaffection" [1, p.925]. That physicians were looking for insights into the social functions of medical practice and saw in Soviet experience an appropriate field upon which to take their investigations begs historical interest. What drew American physicians to the Soviet Union?

In fact, Soviet practices were the object of intense interest by American psychiatrists, which—given disclosure about the use of psychiatry to discredit and institutionalize dissidents—raises questions as to how this interest flourished. While widespread awareness of uses of psychiatry with dissidents did not occur until the 1970s, tracking published work in American clinical psychiatric research journals before, through, and beyond such disclosures is enormously revealing, showing how debates about the shape of psychiatric knowledge can frame and restrict investigation of broader political and ethical questions. Those who wrote and published on Soviet practices did so to address specific problems and concerns about psychiatry at home, even during the height of condemnation and scrutiny of these

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