WORKING PAPER

Defenses of the Tuskegee Syphilis Study: assessment of empirical claims

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Abstract

Recent defenders of the Tuskegee Study argue that moral condemnation of the study was shaped by identity politics; that it may have been justified to start the study in 1932 and continue it up to 1972; that subjects did not suffer greater morbidity; and that men who developed tertiary syphilis were treated. I have assessed empirical evidence used by the 1973 Tuskegee Syphilis Study Advisory Panel, other contemporaneous material, and cited by the defenders. Challenges to the established narrative cannot be sustained. The Tuskegee Study entailed observation, without treatment, of men with both latent and tertiary syphilis. At the outset the available evidence showed benefit of metal therapy versus harms. Subsequently, clear benefit of metal, and then penicillin, therapy emerged.

An editorial in *The Lancet Infectious Diseases*[1] concluded that to judge the Tuskegee Study of men with untreated syphilis as unethical required an element of 'presentism' (i.e. judging past actions by the standards of today), that it arguably was not racist, and that the whole issue deserved re-examination "free of our contemporary prejudices". This was in relation to a study that has elsewhere been described as demonstrating "the most egregious abuse of authority on the part of medical researchers".[2]

Sometimes moral condemnation of a medical research project is wrong-headed and analysis of the scientific claims can act as a corrective. At other times moral condemnation is appropriate and the appeal to science is a ploy to rationalize the conduct of the research. But the scientific issues are rarely beside the point. If a study involves withholding treatment without consent, or worse if researchers lie to subjects about treatment, this is a serious breech of trust. But if the treatment was not expected

- based on some reasonable evidence - to give potential benefits that outweighed risks; and if subsequent investigation showed that withholding treatment did no harm to subjects (or the study was stopped when evidence of harm emerged), then there should be less room for condemnation. Both the ethical behavior of the researchers and the outcome for subjects matter.

Defense of the Tuskegee Study is not new.[3] But in the 21st Century new people have mounted defences who claim to want us to be attentive to reason and science and to the historical period. They imply that the context of the civil rights movement, in which revelations about the study emerged, led to over-sensitivity to alleged mistreatment of black men. They suggest that identity politics rather than critical reason shaped the Tuskegee story. What is now required, the leading defender asserts, is reason not rhetoric.[4] In particular, the defenders' claim that empirical evidence available at the time may have justified starting the study and continuing it up until 1972.

Historian Susan Reverby, commenting on these 'counter-narratives' in her *Examining Tuskegee* said:

> "There is a truth to what actually happened, and trying to understand it does matter. In this sense the counter-narratives should be read, their facts should be measured, and their arguments should be considered, if for no other reason than to understand why they are being made." [5]

What follows is an attempt to measure these facts and to consider these arguments. A further report (under review) attempts to understand why they have been made and to learn something about the ways in which moral judgements of the past matter in medicine.

EMPIRICAL CHALLENGES TO THE ESTABLISHED TUSKEGEE STUDY NARRATIVE

In 2000, physician Robert White published: *Unraveling the Tuskegee Study of Untreated Syphilis*, a paper defending the study through a "historically correct, empirically based analysis". In a further paper he presented "standard information" and "alternative evidence-based information" about the study.[6] His defense of the study had a worthy motive: to see through the eyes of the medical and public health workers of the time, with the intention of reclaiming the dignity of the African American physicians and institutions involved, and lessening mistrust by African Americans of government and medical services.

The key empirical issue explored by White was the state of scientific evidence and of clinical practice in relation to: (a) treatment of latent syphilis around the time the men were enrolled in the study, and (b) penicillin treatment once it became available. He

also explored a number of other issues where he differed from the established accounts; these are not considered further here.

In 2004, cultural anthropologist, Richard Shweder, also offered what he called a "counter-narrative" of the Tuskegee study.[7] He set out to correct myths about the study: that men were deliberately infected and that the outcome of untreated syphilis was uniformly fatal. About the study itself he proposed it might be reasonable to conclude that: (a) at the time the study started, participation did not involve any substantial increase in risk to the health of the men and might produce some useful knowledge; (b) morbidity and mortality of the men were not significantly influenced for the worse by participation. Shweder offered these propositions for debate: "I am neither endorsing nor dismissing the counter-narrative, but rather spelling it out and suggesting why it is plausible enough to warrant more public attention".

Establishing the legitimacy of these accounts depends on answers to empirical questions. Two questions are central: (1) was treatment of latent syphilis at the time properly regarded as having benefits that outweighed the hazards (in 1932, and later when penicillin was available), and (2) was morbidity and mortality affected by participation? In addition, White's claims that there was another contemporaneous study of syphilis in which treatment was withheld, and that the Tuskegee men who developed tertiary syphilis were treated, require evaluation.

THE OFFICIAL NARRATIVE OF THE STUDY

In 1972 the Tuskegee Syphilis Study Ad Hoc Advisory Panel, set up by the Department of Health, Education and Welfare (DHEW), was charged with investigating the study, and in particular, with determining whether the study was justified in 1932 and whether it should have been continued once penicillin became generally available.[8] Although this history is well known, most recently through the work of Reverby,[9] the Advisory Panel report provides source documents to assess, and against which to judge, the defenders' claims. Moreover, the Panel reported close to the time the study became public, so if investigation of it was tainted by identity politics, it should have been evident in that report. The findings of the Panel are summarized below.

The study began in 1932 as a six month investigation of 399 African American men with 'historical and laboratory evidence of syphilis which had progressed beyond the infectious stages' [latent and late (or tertiary) syphilis], and who had not been treated. A group of 201 men without syphilis were enrolled as controls. There was evidence that men in the control group who acquired syphilis were transferred to the 'untreated' group. Perhaps 10 men were in this situation, with early infectious syphilis, who appeared not to have been treated, and who would have been infectious to their wives and hence also to future children.

There was no original protocol for the study; the Panel concluded that the intentions of the investigators included: to study the natural history of the disease; to study the course of treated and untreated disease; to study the differences in pathological and clinical course between black versus white subjects; and to provide data for a syphilis control programme for a rural impoverished community. (In fact it is still a puzzle to know exactly why the study was started. Jones[10] suggested that the investigators initially hoped to demonstrate that syphilis was equally damaging to blacks and hence increase pressure to fund treatment. Brandt[11] concluded that, because it was assumed that blacks would not seek or continue treatment, not treating was regarded as 'natural', and studying the natural course was regarded as an experiment in nature.)

There was no evidence of informed consent. Published reports from the study documented individuals voluntarily submitting to examination. Submitting voluntarily is not, said the Panel members, informed consent. Such consent would have included knowledge of the risk to human life, and possible infection of others. In 1932 there was a known risk to life and transmission of the disease in latent and late syphilis was believed to be possible. (Indeed, the Cooperative Clinical Studies report of 1933 noted that: "the latent syphilitic patient must be regarded as a potential carrier of the disease, and should be treated for the sake of the community's health".)[12]

The evidence the Panel used for the risk to human life without treatment was from the Cooperative Clinical Studies reports by Moore et al.[13] The Panel stated that it was "known as early as 1932 that 85 per cent of patients treated in late latent syphilis [with arsenic and bismuth compounds (metal therapy)] would enjoy prolonged maintenance of good health and freedom from disease as opposed to 35 per cent if left untreated". It cited reports from the Tuskegee Study itself showing that the group with untreated syphilis had morbidity far exceeding the non-syphilitic control group. The Panel quoted Wenger's report from a seminar in 1950: "We now know, where we could only surmise before, that we have contributed to their ailments and shortened their lives".

Though the study was described in publications as being of untreated male Negro subjects, in fact by 1968-1970 almost all those still alive had received some therapy, not necessarily for syphilis and not necessarily in doses considered curative. Provision of treatment was by physicians who were not part of the study.

The Panel reported that the therapeutic benefits of penicillin for late and latent syphilis were clinically documented by the early 1950s.The USPHS recommended treatment of syphilitic mothers at all stages of infection in 1953 and demonstrated that penicillin was the most effective treatment known for neurosyphilis in 1960.[14] There was no evidence that participants in the Tuskegee study were given the choice of penicillin therapy once it became widely available.

The Panel received reports that treatment was deliberately withheld, but were also told that individuals were not denied it. Yet there was evidence that treatment had been deliberately withheld outside the study in 1941- 1942 when members of the untreated group were excluded from the lists of army draftees needing treatment on the advice of a study physician.

The Panel concluded that the study had not been ethically justified in 1932. It noted that hindsight had sharpened its vision, but emphasized "one fundamental ethical rule, that a person should not be subjected to avoidable risks of death or physical harm unless he freely and intelligently consents". Further, the Panel concluded that penicillin should have been made available to the participants, "especially as of 1953 when penicillin became generally available".

ASSESSMENT OF THE STUDY DEFENDERS' CLAIMS

Treatment with metal therapy, effect of non-treatment, other similar studies

The first set of claims are: treatment of latent syphilis around 1932 was viewed as of uncertain value and potentially hazardous; morbidity and mortality was unaffected by participation; and there was a similar contemporaneous study of withholding treatment.

White asserted that "the state of knowledge and practice regarding treatment and non-treatment of latent syphilis seemed to permit doing the Tuskegee study".[15] The editorial in *The Lancet Infectious Diseases* claimed that when the study began the only treatment for syphilis involved "the poorly efficacious arsphenamine compounds, and there was no medical consensus on the usefulness of these drugs in latent syphilis".[16] No specific evidence for those claims was cited. Similarly, White argued there was mixed evidence for the effectiveness of these treatments; that treatment at the time (and subsequently) was often less than standard, and it was standard practice to permit non-treatment of patients with latent syphilis, at least for those older than 50 years.[17] White cited authorities in the 1930s recommending against treatment for syphilis among men over age 50 with no symptoms (30 per cent of the Tuskegee syphilis study men were over 50 years at the outset, but some had symptoms).[18] He described a study of withholding treatment from patients over 50 years who had no symptoms or signs of tertiary syphilis. In addition, Shweder wrote that therapies at that time were "weak, hazardous, lengthy, costly and difficult to administer" and few people completed the full treatment.[19] He cited Benedek and Erlen's[20] review of adverse effects and noted that severe reactions were not uncommon.

The only references White cited as empirical evidence for the effects of treatment versus non-treatment of latent syphilis came from a comparison of the Tuskegee study results – which were reported as showing a reduced life expectancy (8 years) in men with syphilis who had not been treated compared to similar men without syphilis[21] –

with those of another study showing a reduced life expectancy in *treated* men with syphilis (4 years) compared to the general population of that area of Virginia.[22] The latter result could suggest that treatment of syphilis itself reduces life expectancy, while the former that lack of treatment is responsible for the reduction of life expectancy. The differences in reduction in life expectancy might suggest treatment prolongs life, but it is impossible to disentangle the characteristics of the men with syphilis from the effects of treatment (or no treatment). Hence no firm conclusion can be drawn from comparing these studies in non-comparable populations.

White claimed that Stanford University ran a study where patients over age 50, both whites and blacks, were "willfully and intentionally denied treatment".[23] On the face of it, this looks worse than the Tuskegee Study because in this clinic there was a treatment program, unlike the initial situation in rural Macon County for men outside the study. In the paper cited,[24] Blum and Barnett argued that latent syphilis was ordinarily over-treated. "Because of this belief and as a possible means of assessing the value of treatment, we have made it a policy in the Stanford Clinic to permit patients of more than 50 years of age to remain untreated provided the infection was entirely latent and that the spinal fluid was normal." Yet the authors went on to demonstrate that the outcome for untreated patients was considerably worse. The long-term risk of progression to tertiary syphilis was estimated to be 25 per cent, with a risk in the treated group of five per cent. They concluded treatment should be given for latent disease, at least for men under age 60 in good health, rather than waiting to treat tertiary syphilis if it occurred - because the cardiovascular manifestations of syphilis responded uncertainly to treatment, unlike other manifestations of tertiary syphilis.

From the studies referenced by White it would be wrong to infer anything about the effectiveness of treatment; from Shweder's reference it is clear that there were harms of treatment. Surprisingly, White and Shweder both ignored the studies that led the 1973 Panel to conclude that leaving latent syphilis untreated had definite harms compared with treatment.

The Panel relied mainly on the Cooperative Clinical Studies in the Treatment of Syphilis report.[25] This work was undertaken at a set of University clinics (Western Reserve, Johns Hopkins, Pennsylvania, Michigan) and at the Mayo Clinic. These studies received financial support from the USPHS, and so would have been known by USPHS workers, and the reports were published in the year the Tuskegee Study began and the following year.

The Cooperative Clinical Studies reports addressed the question of whether latent syphilis should be treated. Treatment at the time was with arsenic, bismuth, and mercury compounds. The 1933 report compared 1013 people who received treatment for latent syphilis (here defined as clinically non-recognizable disease, and excluding people with abnormal spinal fluid) in the five U.S. clinics, with untreated cases in an

Oslo study. The Oslo Study of Untreated Syphilis, originally conducted by Boeck, with outcomes first recorded by his successor Bruusgaard in 1929, recorded outcomes for primary and secondary untreated syphilis in that city.[26] Satisfactory clinical outcome, defined as freedom from manifestations of syphilis together with reversal of serological tests, was evident in 85 per cent of the treated compared with 35 per cent of the untreated. The other result given was for 'clinical progression or relapse', that is progression to symptomatic (tertiary/ late) syphilis. This occurred in 2 to 5 per cent of those treated compared to 20 to 30 per cent of the untreated group. Harms of treatment were not counted, though were taken into account in determining whether to treat at all: in those with only 10-15 years life expectancy "the risks and discomforts of treatment may well be greater than the risks of syphilis".[27]

Pertinent evidence of the effect of treatment versus non-treatment also comes from an early report of the Tuskegee study itself. Vonderlehr and colleagues[28] compared findings for the 399 men with untreated syphilis with 275 men who had received treatment during the first two years of disease. They concluded: "adequate antisyphilitic treatment prevented all forms of clinical relapse during the first fifteen years of infection, whereas only one fourth of the Negroes with untreated syphilis were normal". Though there is an argument about the comparability of the effectiveness of treatment given in the first two years versus treatment given at a later time, this issue was not raised by Vonderlehr and the conclusions were drawn as if the groups were comparable. According to Vonderlehr's account, by 1936 it was clear *to the study investigators* that the men were being knowingly exposed to harm. Later, the investigators showed that, of the untreated men who had died and were autopsied, 30 per cent had died directly from late syphilis.[29]

Adverse effects of metal therapy (and most especially mercury) were clearly serious, and the lengthy and unpleasant treatment acted as a disincentive to complete a course, though over time the use of mercury was abandoned and shorter courses of treatment were introduced.[30] No information was given by the Panel on the magnitude of potential harms of treatment, though it was cognisant of the risks, noting "the highly toxic nature of the therapeutic agents then available". Benedek and Erlen identified two publications on harms of treatment around the time the study started. Mortality from metal therapy was up to 1 per cent, though they note that following the introduction of arsenoxide in the mid-1930s mortality rates were very much lower.[31] Though painful and lengthy treatment was a disincentive, even incomplete 'inadequate' treatment was shown *by the Tuskegee Study investigators* to be superior to no treatment, in a valid comparison:

> Any treatment at all, despite its inadequacy, is reflected when the inadequately treated patients are compared with untreated patients. Among 86 inadequately treated male Negros whose infection was of three years' duration as compared to 26 untreated patients in the same period of time, 1.2 per cent of the former had cardiovascular involvement as compared to 7.7 per cent of the latter.

> Syphilis of the central nervous system was present in 9.3 per cent of the inadequately treated cases compared to 30.8 per cent of the untreated patients.[32]

In summary, the state of scientific evidence around the time the study started supported the treatment of latent syphilis. Moreover, results of the Tuskegee Study after only a few years of operation showed much worse outcomes for the untreated group. Clinical practice was more diverse, especially with regard to the therapeutic agents used and the length of treatment. Harms of treatment were not reported in the early Cooperative Clinical Studies group publications, but calculating simple proportions of deaths from treatment (up to 1 per cent) versus deaths from syphilis in the absence of treatment after 20 years (12 per cent) confirms that harms of treatment were great, but less than the harms of not treating.[33] There was another study of untreated patients with latent disease, over age 50. In this group the investigators believed (wrongly as it transpired) that treatment might do more harm than good.

In terms of the Panel's own conclusions about benefits of treatment, they reflect the results in the paper by Moore et al,[34] but Moore's analyses themselves left room for bias (see Supplementary material; the later results of more valid analyses are similar, though this is partly a coincidence). Thus there is an argument that the quality of evidence in 1932 was poor and hence the effectiveness of treatment (judged by our standards now) was uncertain. Nevertheless it was accepted by the USPHS at the time as valid and, with Blum and Barnett's publication in 1948, the value of pre-penicillin treatment for latent syphilis was established according to the scientific standards of the time.

Penicillin treatment

The second set of claims by White are: that there "was not"… "clear scientific evidence for the use of penicillin" for latent or late syphilis while the study was being conducted,[35] and that there was a prevailing belief that the use of penicillin in these circumstances might be useless and/or harmful, especially for cardiovascular complications. The papers he cited do not support his claims of uselessness. Two of them, one published in 1939 (before penicillin) and the other on outcomes from the Oslo study, do not provide relevant information. The other by Kampmeier[36] mentioned the possibility of paradoxical worsening, as part of the healing process; noted that treatment with penicillin was effective for neurosyphilis; and opined that, for latent disease it "must have a similar effect".

White also cited a Report of the National Commission on Venereal Disease.[37] He suggested that the Report stated: "it was unclear what role currently available penicillin preparations had in the treatment of late-latent syphilis" and noted it called for additional research. In fact, the Report stated that penicillin "continues to be the treatment of choice" although it had been many years since the treatment of late latent and tertiary syphilis had been appraised. For these conditions it called for studies of

newer penicillins and other antibiotics and noted instances of treatment failure and allergies to penicillin. Yes, as White claimed, it did call for additional research; but this was couched as a need to establish the best treatment among a range of new formulations, not as doubt about penicillin treatment altogether. Not one of the papers gives support to White's claim that penicillin treatment might be useless.

Neither White nor the Panel referenced the Handbook for Physicians on the diagnosis and treatment of syphilis published in cooperation with the USPHS in 1948.[38] The handbook recommended penicillin for latent syphilis. Its recommendations were based on a review of evidence published in *JAMA*.[39] In that review, Altshuler and colleagues assumed that, as penicillin was effective in early and late syphilis, it would be effective in latent disease. Nevertheless, they noted that it would take some time to determine whether "penicillin offers the patient the 95 to 98% chance of future clinical health which is offered by six months of arsenic and bismuth therapy". But penicillin already offered the advantage of brevity and safety.

The Handbook also summarized evidence for safety based on data from rapid treatment centers. Severe reactions to intensive arsenotherapy were observed in 41 per 1000 cases treated compared to 4.5 per 1000 with penicillin. One death in 1,873 cases treated with arsenotherapy was compared to no deaths in 39,839 cases treated with penicillin.

The Panel had concluded that the therapeutic benefits of penicillin were clinically documented by the early 1950s, based on USPHS reports. The clinical studies on which recommendations were based were prospective studies of treated patients with no control group.[40] Thus of 469 patients with late latent syphilis followed for 3-12 years, none progressed to tertiary syphilis and there were no 'side reactions'. For cardiovascular syphilis, results for 1168 patients followed from one month to 12 years were mostly reported as 'satisfactory', though there were some deaths from complicated aortitis. Adverse reactions to treatment were recorded among 22 and there were six deaths.

According to modern standards, these studies are limited by lack of a control group randomly assigned to placebo/ no treatment. Yet it was obvious that once penicillin had been shown in such prospective clinical studies to be virtually 100 per cent effective in primary syphilis, as shown by serological and clinical outcomes,[41] it would be unethical to randomise to a no-treatment group because there would not be equipoise. Similarly, initially, there were sound biological reasons to expect penicillin would also be effective in latent disease. For cardiovascular syphilis, it is unclear whether the deaths were due to disease or reactions to treatment, and a controlled trial might have been ethical. In the sense that controlled trials had not been used to evaluate penicillin, there was not 'clear scientific evidence' for this use. But White is himself being 'presentist' to expect that the scientific standards of the 2000s should apply to the 1950s.

In summary, within a few years of penicillin becoming available, the USPHS, which ran the Tuskegee Study, recommended that it should be used in latent syphilis. The effectiveness of metal therapy was already established, penicillin treatment was expected to be as effective, and it was considerably safer and required a shorter course of treatment than arsenic compounds. Prospective studies confirmed effectiveness. White is correct in noting that there were early concerns about therapeutic paradox in cardiovascular syphilis treated with penicillin, but authoritative sources recommended its use.

Tertiary/late syphilis

A third claim is that the men in the Tuskegee Study received treatment if they had tertiary syphilis.[42] White examined the implications of withholding treatment for latent syphilis as if it were the only relevant matter. This would be the case if men in the study were all negative for signs of tertiary syphilis, including a negative spinal fluid examination on enrollment, and if they had been offered treatment when they developed symptomatic disease.

On the first point, in the description of the study men at baseline it is clear that many already had manifestations of tertiary syphilis. Only 16 per cent of the group had no evidence of morbidity compared to 61 per cent of the non-syphilitic control group. Manifestations included evidence of cardiovascular and neurosyphilis.[43] No mention of therapy for these manifestations was made.

On the second point, whether therapy was given for initially asymptomatic individuals when they developed symptoms, there is conflicting evidence. The study papers report death as the endpoint. Vonderlehr et al[44] reported that the investigation offered an opportunity to study the untreated syphilitic to the death of the infected person, and that a number would ultimately be brought to autopsy. And in 1938 Vonderlehr wrote about the beginning of the study: "Such individuals seemed to offer an unusual opportunity to study the untreated syphilitic patient from the beginning of the disease to the death of the patient".[45] Taylor took up this point in *Lancet Infectious Diseases* when he asked: "Did the study at any time contain a clear provision for the currently established therapeutic measures to be instituted if the patient became symptomatic?"[46] White[47] replied and quoted from one of the study reports which said: "It is the practice of the Public Health Service to refer men who develop syphilitic or non-syphilitic conditions requiring therapy to the proper sources for treatment."[48] None of the other reports of the study make reference to referral for treatment in this way even though there are reports of symptomatic disease and of therapy, usually judged to be inadequate, being given outside the study.

In conclusion, it is clear from the first report of the Tuskegee study that many men with symptomatic disease at baseline were included and not offered treatment; during follow up, treatment outside the study may sometimes have been offered, but

symptomatic disease was never a key end point. Hence the study was of untreated latent *and* tertiary syphilis.

Treatments for tertiary syphilis, especially fever treatment for neurosyphilis, were available throughout the duration of the Tuskegee Study and there was evidence for the latter's effectiveness.[49] Treatment for cardiovascular syphilis was less effective[50] and when penicillin became available there was also concern that a Herxheimer reaction (therapeutic shock) was more likely in this condition, and preparatory treatment with bismuth was recommended.[51]

CONCLUSIONS

The recent challenges to the empirical evidence, when assessed alongside other evidence, including that used by the DHEW Panel, are not sustained. The evidence available in 1932, although it was limited by today's standards, suggested that metal therapy for latent disease had a marked effect in reducing the occurrence of tertiary syphilis. Evidence was much more robust by the 1940s. Treatment of tertiary syphilis, especially neurosyphilis with fever therapy, also reduced morbidity and mortality. Treatment was hazardous and the balance of benefit versus harm might have justified initially not offering men over 50 years treatment for latent disease. But a 1948 report on the outcome of not treating such people showed the benefit of treatment even at this age. The harms of treatment with arsenic and bismuth compounds were important, but were generally agreed in the 1930s and 1940s to be less than the harms of not treating; estimates of risk of death with and without treatment support this judgement. None of the studies cited by White supports his contention that there was no clear scientific evidence for the use of penicillin while the Tuskegee Study was being conducted, or that it might be useless or harmful, though initially the evidence was indirect. As early as 1948 penicillin was recommended by the USPHS for the treatment of latent syphilis, on the basis of its effectiveness against other forms of syphilis. The scientific evidence on which such recommendations were based was appropriate for the time.

The Tuskegee Study entailed observation, without treatment, of men with both latent and tertiary syphilis (and in a few cases, early syphilis) at a time when there was already evidence that treatment was likely to be beneficial, and continued for 30 years as evidence accumulated for the clear benefit of heavy metal and then penicillin treatment.

This re-examination supports the established view of an "egregious abuse of authority" by those who knew that effective treatment existed but continued to withhold it. It is not therefore 'presentist' to criticise the study. The USPHS

physicians pursued a study of the natural course of disease because they could, ignoring the increasing evidence of harms to the men involved.

Finally, these defenses have partly arisen because there has never been a detailed examination of the original study data held by the USPHS. I support Benedek and Erlen's contention that it is owed to the men who were subjects to fully document the outcomes of the experiment.[52]

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