The Continuing Legacy of the Tuskegee Syphilis Study: Considerations for Clinical Investigation

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ABSTRACT: The Tuskegee Study, an observational study of over 400 sharecroppers with untreated syphilis, was conducted by the U.S. Public Health Service to document the course of the disease in blacks, and racial differences in the clinical manifestations of syphilis. The men were not told they had syphilis, not given counseling on avoiding spread of the disease, and not given treatment throughout the course of the study. The study became the longest (1932–1972) nontherapeutic experiment on humans in the history of medicine, and has come to represent not only the exploitation of blacks in medical history, but the potential for exploitation of any population that may be vulnerable because of race, ethnicity, gender, disability, age or social class. It is important for physicians who will be caring for an increasingly diverse nation to understand the lasting implications of this study for their patients, but the effects of the Tuskegee Syphilis Study are demonstrated most strikingly by unsuccessful attempts at improving representation of minority patients in clinical trials. KEY INDEXING TERMS: Tuskegee Study; Bioethics; Clinical investigation. [Am J Med Sci 1999;317(1):5–8.]

Jones states, in *Bad Blood*, that "no scientific experiment inflicted more damage to the collective psyche of black Americans than the Tuskegee Study."[1] This observational study of over 400 sharecroppers with untreated syphilis began in 1932 in Macon County, Alabama. The study, conducted by the United States Public Health Service, was to document the course of the disease in blacks and racial differences in the clinical manifestations of syphilis. Despite the availability of treatment (initially arsenic and bismuth, then penicillin in the 1940s), the men were not told they had syphilis, not given counseling on avoiding spread of the disease, and not given treatment throughout the 40-year course of the study. At the conclusion of the trial, more than 100 men had succumbed to syphilis or related complications.[1] The Tuskegee Study of Untreated Syphilis in the Negro Male, the longest nontherapeutic experiment on humans in the history of medicine, ended in 1972 when a front-page newspaper article detailed ethical concerns about the study.[1]

A quarter of a century after the disclosure, we are still feeling the reverberations. Persistent references to Tuskegee in the lay press and media have kept this landmark study a humbling reminder of the powerful influence of society on medicine. Most recently, in February 1997, a television adaptation of *Miss Evers' Boys*, written by David Feldshuh, aired on the cable network Home Box Office and was watched in over 3 million African-American households.[2] Television, radio, and print media are full of discussion about this troubling mark in medical history. On May 16, 1997, the unrest about this study precipitated a formal apology from the President of the United States on behalf of the U.S. government.

Although the Tuskegee Syphilis Study involved African-American men, analogies can be extended across cultural lines. As physicians who will be caring for an increasingly diverse nation, it is important that we understand the lasting implications of this study for our patients. The study has come to represent not only the exploitation of blacks in medical history, but the potential for the exploitation of any population that may be vulnerable because of race, ethnicity, gender, disability, age, or social class. However, the effects of the Tuskegee Syphilis Study are demonstrated most strikingly by unsuc-

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Considerations for Clinical Investigation

The disclosure of the Tuskegee Syphilis Study in the lay press prompted numerous investigations to review existing federal regulations aimed at the protection of research subjects. Probably the most important sequelae of the study was the 1974 creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and the National Research Act. This act requires the establishment of Institutional Review Boards (IRBs) at institutions receiving federal grants. All federally funded grants are to be reviewed by IRBs to determine if the proposed selection of patients is equitable and to protect the rights and welfare of human subjects. These guidelines established specific criteria for the protection of human research subjects and the expanded the role of laypersons on IRBs.

Initially, these regulations led some investigators to exclude minority patients, contributing to the underrepresentation of certain populations in clinical trials. In the wake of the Nazi experiments, the Tuskegee Syphilis Study, and other research on vul-

-able populations that exposed uninformed per-

s to probable harm,[3] the emphasis in biomedical research had been on the protection of the individual patients. Federal regulations stressed the importance for IRBs to be "particularly cognizant of the special problems of research involving vulnerable populations."[4]

The need for protection of vulnerable populations is clear. However, this emphasis has led to the problem of "too much protection," wherein investigators may have excluded certain populations from clinical research to safeguard against any possibility of exploitation. Svennson has reported that in the majority of studies, the proportion of black patients is less than their proportion in the general population.[5] In his review of clinical trials involving treatment for diseases such as hypertension, only 50% of studies reported data on race.

Underrepresentation of minority patients poses several problems. The bioethical principle of social justice requires that a fair share of the burdens and benefits associated with participating in research be distributed within a society. While there may be personal risk, the potential benefits of cutting-edge medical care, monetary remuneration, and a sense of hope and reassurance that comes with participation in clinical research should not be underestimated.

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also raises the problem of generalizability. The generalization and application of research findings from a homogenous study sample to racially and ethnically diverse populations may not be appropriate. For most classes of medications, for example, there is no knowledge of potential ethnic and/or racial variability in drug efficacy or metabolism. The realization that these gaps in medical knowledge exist has led to new policies to address this issue. The NIH Revitalization Act of 1993 recommends that women and members of minority groups be included in each research project and that a "clear and compelling" reason be given for inadequate representation of these populations.[6]

In response to the NIH recommendations, researchers have begun actively recruiting minority populations, but recruitment efforts are often unsuccessful.[7] Public knowledge of the historical relationship between federally funded research and minority patients has contributed to a sense of distrust of the medical profession in general, and medical research in particular. Jones describes an assertion during the 1990 testimony before the National Commission on AIDS by Mark Smith, MD, from the Henry J. Kaiser Family Foundation: that the Tuskegee Syphilis Study "provides validation for common suspicions about the ethical even-handedness in medical research. . . when it comes to black people."[8]

The retelling of this and other historic events is at the heart of suspicion in the African-American community.[9,10] Thomas and Quinn eloquently illustrated the effect of the Tuskegee Syphilis Study on HIV/AIDS education and prevention programs in the African-American community.[10] As they discuss, the Tuskegee Study's failure to educate its participants and treat them adequately helped to lay the foundation for African Americans' distrust of medical authorities. The persistent lack of open and comprehensive discussion of the Tuskegee Study has also contributed to its use as a source of misinformation. Efforts at controlling the spread of HIV, such as needle exchange programs, the promotion of condom use, and counseling of HIV-infected women to avoid pregnancy, have been interpreted by African Americans as part of a plan for genocide. The emphasis on HIV testing and counseling without appropriate referral to primary care and clinical trials seems to parallel the withholding of treatment by the researchers in the Tuskegee Study.

Ironically, despite fatal ethical and methodical flaws of the Tuskegee Study, the PHS investigators who conducted it effectively employed culturally sensitive approaches to ensure the recruitment and participation of the study participants. The investigators were studying a problem, "bad blood" (a colloquialism of the rural South that represented myriad ailments and diseases), which was perceived as important in the community. They hired a black public health nurse from Macon County, Eunice Rivers, who served the project for its entire 40-year span. She provided transportation for the men in the

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study, organized and tracked men for physical exams, served as a cultural interpreter for the PHS physicians, and provided intimate and trusting relationships for the men in the study. The investigators aligned themselves with the Tuskegee Institute, a college well known for its service to the black community in Macon County. The public health officials chose clinical sites that were readily accessible: physical exams and blood work were conducted in black schools and churches within the participants' community. By enlisting the support of community leaders in black churches, plantation owners, local medical societies and health departments, the investigators ensured a successful recruitment effort. During the course of the study, public health officials also overcame barriers to care by providing transportation, meals, and incentives such as a stipend for "life assurance" intended to cover burial fees.[1] This example of successful recruitment and retention highlights the dangers of social marketing, where social clues and nuances are exploited to advance the agenda of investigators.

For investigators involved in clinical trials, the Tuskegee study raises other important issues. First, this study highlights the impact of prevailing political ideals and societal values and biases on the generation of clinical hypotheses. Given the social and political history of the United States, investigators have the burden to deal fairly and thoughtfully with apparent racial differences in diseases and manifestations of illness. While it is necessary to explore possible genetic differences in, for example, drug efficacy, investigators must be mindful that racial differences are not exclusively interpreted as genetic. Historically great harm has come from our willingness to use supposed genetic and biologic differences as an explanation for susceptibility to disease, in the process stereotyping or stigmatizing a particular group. When examining differences in morbidity and mortality, priority should be given to exploring the possible social, cultural, economic, and environmental determinants of disease before using biologic differences between groups as an explanation for differences in health outcomes. In light of this society's past experience with biologically based explanations, caution should be exercised in attempting to validate biologic differences in susceptibility to disease.

The Tuskegee Syphilis Study also underscores the inadequacy of the consent process. In our current efforts to maintain and bolster patient autonomy, fully informed consent is an ideal that is difficult to realize.[11] The Tuskegee study and other instances of exploitation of vulnerable populations may be stumbling blocks for potential research participants when giving informed consent. The considerations of personal risk may loom too large for patients to see IRB-approved studies as risk-benefit neutral. In addition, standard consent forms, which are often beyond the full comprehension of fellow clinicians, are almost always outside the realm of understanding of the average educated layperson.[11] For patients with inadequate literacy skills, or those for whom English is not their native language, informed consent as currently practiced can fall considerably short of its goals.[11]

We must also address the legacy of the Tuskegee Study, where investigators made a conscious decision to withhold information from participants and actively interfered with their attempts to receive treatment. We know both patients and physicians[12,13] believe the consent document is a legal requirement and not an opportunity for facilitating patient autonomy in medical decision-making. In this context, patients may not believe that they are being fully informed or may view the consent process as "signing away" their rights to self-determination.

Another layer in the process of informed consent is the duality of trust within the doctor-patient relationship.[14] Without a sense of trust in their doctor, some patients may be reluctant to consider participation in a clinical trial. For these patients, an established clinical relationship, and the open communication it fosters, may be a necessary prelude to the discussion of risk and benefits in research. Unfortunately, as political and economic constraints increasingly limit the clinical interaction, a trusting relationship may take longer to develop, if it develops at all.

In the extreme, as witnessed by Eunice Rivers, a trusting clinical relationship may actually impede consent; interpersonal trust may override a truly informed and carefully deliberate decision. In this instance, a patient may relinquish his or her autonomy and follow the unquestioned advice of a trusted clinician. Patients at the extremes of age and those with low literacy skills may be most vulnerable to the negative consequences of trust.

These critical components of the consent process must be further elucidated before we can reach the goal of increasing autonomy in decision-making. Alternatives to written informed consent that more effectively transmit information and take into account different decision making styles can then be developed.

In order to address the lasting legacy of the Tuskegee Syphilis Study in minority communities, investigators must first arm themselves with an appreciation of the significance of this event. The implications of this study are far-reaching. On several levels, the Tuskegee Study is a barrier in minority populations for access to the state-of-the-art therapies available through clinical trials. However, this study also gives us an opportunity to examine closely the relationship between investigators and

vulnerable populations in the context of clinical research. It highlights the powerful subtext of trust in that interaction on an interpersonal and societal level. To demonstrate that their work is ethically sound, investigators should develop culturally sensitive methods of involving minority communities in the process of clinical investigation. Such approaches may promote open discussion about the benefits of participation and, most importantly, emphasize the safeguards in place for protection of the participants. Such well-thought-out approaches will be necessary to improve access for minority patients to this health service.

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