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

GISELLE CORBIE-SMITH, MD

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." 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. 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.

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. 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-
Tuskegee Legacy

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 vulnerable populations that exposed uninformed persons to probable harm, 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."

The need for protection of vulnerable populations is clear. However, this emphasis has led to the problem of "too much protection," wherein investigators have excluded certain populations from clinical research to safeguard against any possibility of exploitation. Swenson has reported that in the majority of studies, the proportion of black patients is less than their proportion in the general population. 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.

Exclusion of certain populations from clinical trials 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.

In response to the NIH recommendations, researchers have begun actively recruiting minority populations, but recruitment efforts are often unsuccessful. 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 ever-handness in medical research... when it comes to black people."

The retelling of this and other historic events is at the heart of suspicion in the African-American community. Thomas and Quinn eloquently illustrated the effect of the Tuskegee Syphilis Study on HIV/AIDS education and prevention programs in the African-American community. 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 so far the withholding of treatment by the researchers in the Tuskegee Study.

Ironically, despite fatal ethical and methodological 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, Emma Rivers, who served the project for its entire 40-year span. She provided transportation for the men in the study, organized, served as a physician, and relationships for a college well community in a local medical community leaders, local media the investigatory effort. During officials also were transportation and for "life-takes."

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study, organized and tracked men for physical ex-
ams, served as a cultural interpreter for the PHS phys-
cians, and provided intimate and trusting rela-
tionships for the men in the study. The investiga-
tors aligned themselves with the Tuskegee Institute, a
college well known for its service to the black com-

munity in Macon County. The public health offi-
cials chose clinical sites that were readily accessi-
ble; physical exams and blood work were conducted
in black schools and churches within the partici-
pants' community. By enlisting the support of com-

unity 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 sti-
pend for "life assurance" intended to cover burial
fees. This example of successful recruitment and
retention highlights the dangers of social marketing,
where social cues 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 polit-
ical ideals and societal values and biases on the

generation of clinical hypotheses. Given the social
and political history of the United States, investi-
gators 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 explana-
tion for differences in health outcomes. In light of
this society's past experience with biologically based
explanations, caution should be exercised in at-
tempting to validate biologic differences in suscep-
tibility 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. The Tuskegee study and other instances of
exploitation of vulnerable populations may be stum-
bling 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 ad-
dition, standard consent forms, which are often be-
yond the full comprehension of fellow clinicians, are
almost always outside the realm of understanding of
the average educated layperson. 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.

We must also address the legacy of the Tuske-
gee Study, where investigators made a conscious de-
cision to withhold information from participants and
actively interfered with their attempts to receive
treatment. We know both patients and physi-
cians 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 pro-
cess as "signing away" their rights to self-deter-
inination.

Another layer in the process of informed consent is
the duality of trust within the doctor-patient rela-
tionship. Without a sense of trust in their doctor,
some patients may be reluctant to consider partici-
pation in a clinical trial. For these patients, an
established clinical relationship, and the open com-
munication it fosters, may be a necessary prelude to
the discussion of risk and benefits in research. Un-
fortunately, as political and economic constraints
increasingly limit the clinical interaction, a trusting
relationship may take longer to develop, if it devel-
ops at all.

In the extreme, as witnessed by Eunice Rivers, a
trustful 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 auton-
omy 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 elucidated before we can reach the goal of increasing autonomy in decision-making. Al-
ternatives to written informed consent that more
effectively transmit information and take into ac-
count different decision making styles can then be
developed.

In order to address the lasting legacy of the Tuske-
gee Syphilis Study in minority communities, inves-
tigators must first arm themselves with an appreci-
ation of the significance of this event. The
implications of this study are far-reaching. On sev-
eral levels, the Tuskegee Study is a barrier in mini-
ority 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.

References

From the Department of Pediatrics and Reproductive Science. Received October 1998.
Correspondence: Dr. Sergio R. Hemo Inhbit.

ABSTRACT:
In end-stage renal disease, inhibition of nitric oxide synthase (NOS) is impaired, and nitric oxide levels are increased. The relationship between inhibition of NOS and cardiovascular disease in patients on chronic dialysis is unknown. The present study investigated the effect of inhibition of NOS in patients on chronic dialysis. Inhibition of NOS was achieved with the use of a competitive inhibitor, N-nitro-l-arginine (l-NAME). The study was conducted in 50 patients on chronic dialysis. The patients were divided into two groups: group A (n=25) and group B (n=25). Group A was treated with l-NAME, while group B was treated with a placebo. The patients were followed for 12 months. The results showed that inhibition of NOS was associated with a decrease in blood pressure and an increase in cardiac output. The study concluded that inhibition of NOS may be a potential therapy for cardiovascular disease in patients on chronic dialysis.