Historical Introduction to Research Misconduct

William H. Schneider, Ph.D
wenschnei@iupui.edu
317/274-4740
Outline

• History of Human Subjects Research
• Development of Regulations about Human Subjects Research
• Significance of Tuskegee Syphilis Experiment
Main Points

• Restrictions on research involving humans are not something new.
• Current procedures are direct result of recent misconduct.
• Whatever procedures exist today will change in the future.
Scientific Revolution- 17th cent.

• Developed a method of investigation which included controlled observation and reporting of results for verification
• Expanded number of people doing research
• Method was quickly applied to experiments involving humans
• Subjects were at first often researchers themselves or members of their families
By end of 19th century, a portent of 20th century

- Spectacular success, widely reported in the press, inspired more research
- Used new “germ” theory
- Required a large number of research subjects
- Had large number of research subjects at hand (army troops)
- Used procedure to document proper conduct (consent form)
Twentieth Century Developments

to 1950

• Germ theory
• Increased support: private and government
• More research, more subjects
• Wars (especially WWI, WWII)

Results: more government involvement, examples from U.S.
• Pure Food & Drug Act (1906)
• From US Public Health Service to NIH
• Gov’t funded research
Germ theory: Pasteur and microbe hunters

Joseph Meister in 1885

Homage to Pasteur
Pasteur and microbe hunters

• Pasteur, Walter Reed and others were highly publicized, “heroes” who inspired subsequent generations of researchers to find microbes, causes of diseases.
• Hence, they “motivated” subsequent generations to do research.
# Disease Discoveries, 1876-1910

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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| 1876 | Koch discovers anthrax bacterium  
       | 1879 anthrax vaccine |
| 1879 | Neisser gonorrhea |
| 1880 | Pasteur discovers cholera immuniz.  
       | Laveran discovers malarial parasite |
|      | Hansen leprosy |
| 1882 | Koch tuberculosis |
| 1883 | Koch cholera bacillus  
       | Klebs diphtheria |
| 1884 | Gaffkey typhoid  
       | Frankel pneumonia |
| 1885 | Pasteur cures child w/ rabies |
| 1887 | David Bruce undulent fever |
| 1889 | Nicolaier tetanus |
| 1894 | Yersin & Kitasato discover plague |
| 1895 | Roentgen discovers x-rays |
| 1898 | Loeffler & Frosch foot and mouth |
| 1900 | Walter Reed & Yellow fever virus |
| 1905 | Schaudin & Hoffman syphilis |
| 1909 | Ricketts Rocky Mtn Spotted fever |
| 1910 | Nicolle typhus |
Pasteur and microbe hunters

- Dr Ehrlich’s Magic Bullet
Pasteur and microbe hunters

• Pasteur, Walter Reed and others were highly publicized, “heroes” who inspired subsequent generations of researchers to find microbes, causes of diseases.
• But it also led to many more researchers following their lead, some of whom, overly ambitious, cut corners, and caused scandals in the press.
Failures

In 1891 a French physician reported on the analysis of breast tissue samples from two women. In an effort to test the contagion of cancer, a surgeon had given them cancer grafts while under anesthesia for removal of their other cancerous breasts. Neither patient had given her consent.

• The physician reported that it produced a cancerous nodule which was removed. But when the French Academy of Science heard the report, they immediately called it criminal and refused to hear anything further.
Failures

• In 1892 Albert Neisser, Professor of Dermatology at University of Breslau (had earlier - 1879 - discovered the gonorrhea bacterium) conducted experiments aimed at immunizing healthy subjects against syphilis. He took serum from syphilis patients and used it to inoculate 4 healthy children and 3 adolescent prostitutes.

• In 1895 a New York pediatrician Henry Heiman reported inoculating with gonorrhea a 4-year-old boy “an idiot with chronic epilepsy”, a 16-year-old boy “an idiot”, and a 26-year-old man in the final stages of tuberculosis.
1900-1939

- Growth of government involvement in Food and Drug monitoring
- State and U.S. Public Health Service conducts research on diseases such as typhoid and pellagra
- Private Foundation sources such as Rockefeller establish grant research in medicine by universities and hospitals.
Research Ethics in U.S. after 1945

- Second World War, medical research, atrocities of Nazis and Japanese
- Nuremberg Code-1949
- Thalidomide Tragedy
- Declaration of Helsinki-1964
- Henry Beecher 1966 article in *New England Journal of Medicine*
- USPHS Memo on Review Boards 1966
- Tuskegee Syphilis Study (1932-1972)
- Belmont Report – 1979
- “Common Rule” - 1991
U.S. Army Medical Research during WWII

Oxygen therapy

Army medical lab, Md.

Blood transfusion therapy
Nuremberg
1946-1947
Nuremberg Doctors Trial:

Examples of victims

A prisoner in a compression chamber loses consciousness (and later dies) during an experiment to determine altitudes at which aircraft crews could survive without oxygen. Dachau, Germany, 1942.

A Romani (Gypsy) victim of Nazi medical experiments to make seawater potable. Dachau concentration camp, Germany, 1944.

NARA
Nuremberg Code - 1949

NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
Nuremberg Code - 1949

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an \textit{a priori} reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.
Nuremberg Code - 1949

• Voluntary consent is absolutely essential
• Quality of experiments and experimenters
  – Based on animal experimentation
  – For good of society
  – Conducted by scientifically qualified persons
• Safeguards
  – No experiment should risk death or disabling injury
  – Risk should never exceed importance of problem
  – Experiment should be designed to be stopped at any time
Declaration of Helsinki-1964

- Human research should be based on laboratory and animal experimentation
- Should be reviewed by an independent committee
- Informed consent is necessary
- Should be conducted by qualified individuals
- Risks should not exceed benefits

Note:
- passed by World Medical Association
Scandals continued

• In 1950s-60s thalidomide tragedy
• Willowbrook (NJ) State School for the Retarded children
• 1964 Brooklyn Jewish Chronic Disease Hospital
Thalidomide Tragedy

• In 1950s thalidomide tragedy
• Taken to control sleep and nausea throughout pregnancy
• Caused severe deformities in fetus
• Many women did not know they were taking an experimental drug nor give informed consent
• 12,000 babies born with severe deformities
Other examples

Willowbrook

• Beginning in 1956, the purposeful infection of patients with hepatitis began at the Willowbrook (NJ) State School for the Retarded children.

• Parents gave consent for the injections (after 1964 it was a condition for admitting children), but not clear they were advised of the hazards or merely told they would be given a vaccine against hepatitis (actually a mild form of virus).
Other examples

• In 1964 a story broke of cancer research begun in 1963 at Cornell Medical School on 22 senile and demented patients at Brooklyn Jewish Chronic Disease Hospital. They were injected with live cancer cells to serve as a control to see if they lived longer than patients with cancer.

• Subjects were "merely told that they would be receiving 'some cells.'" The word cancer was omitted. Researchers later said they obtained oral consent, but evidence showed attempts at forged written consent to cover up.
Henry Beecher (1904-76)

- Harvard professor of anesthesiology

- Author of “Ethics and Clinical Research” (1966)

- Member of Harvard ad hoc committee to examine definition of brain death (1968)
Henry Beecher Article - 1966

• Beecher detailed 22 published examples of “unethical or questionable ethical studies” done between 1948-1965 in major US medical centers

• Uproar led directly to memorandum establishing Institutional Review Boards
USPHS Memo on Review Boards - 1966

• “No new, renewal or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates.”
USPHS Memo on Review Boards – 1966

• Review should assure and independent determination of:
  – The rights and welfare of the individual or individuals involved
  – The appropriateness of the methods used to obtain informed consent
  – The risks and potential medical benefits of the investigation
Significance

• Research was no longer entirely at the discretion of individual investigators; for the first time, researchers had to answer to federal regulations and compulsory peer review.

• Revisions
  – 1969- Committees expanded to include non-scientific members
  – 1971 – The use of community standards was added to judge proposals
Tuskegee Syphilis Study – (1932-1972)
Tuskegee Syphilis Study – (1932-1972)

July 25, 1972: story broke in Washington Star

- 600 low income African-American males from rural Alabama with a high incidence of syphilis infection were monitored for 40 years to observe course of disease.
  - Given free medical exams but they were not told that they had syphilis
  - Cure (penicillin) became available in 1950s
  - Participants and families denied treatment
Tuskegee Syphilis Study – (1932-1972)

Newspaper headlines

- “A Violation of Human Dignity” (Houston Chronicle, Aug. 5, 1972)
- ”An Immoral Study” (St. Louis Post-Dispatch, July 30, 1972)
- “Inhuman Experiment” (Oregonian, July 31, 1972)
- “Blot on Humanity” (Chatanooga Times, July 28, 1972)
- “Cruel Experiment” (South Bend Tribune, July 29, 1972)
- “A Shocking Medical Experiment” (New Haven Register, July 29, 1972)
- “Humans as Guinea Pigs” (Richmond Times Dispatch, Aug. 6, 1972)
- “Official Inhumanity” (LA Times, July 27, 1972)
- “Horror Story” (Providence Sunday Journal, July 30, 1972)
- “Nightmare Experiment” (Raleigh News and Observer, July 28, 1972)
- “They Helped Men Die” (Milwaukee Journal, July 27, 1972)
‘NOW can we give him penicillin?’


Editorial cartoon by Clifford H. Baldowski, *Atlanta Constitution*. (Courtesy Atlanta Constitution)
## Tuskegee Syphilis Study

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<td>July 25, 1972</td>
<td>Story breaks in <em>Washington Star</em></td>
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<td>Aug. 24, 1972</td>
<td>Ad hoc panel created at PHS to review experiment</td>
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<tr>
<td>Oct. 1972</td>
<td>Panel recommends ending the study</td>
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<tr>
<td>Feb-Mar 1973</td>
<td>Edward Kennedy begins Senate hearings</td>
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<tr>
<td>Mar. 3, 1973</td>
<td>HEW Secretary (Weinberger) orders treatment for subjects in study</td>
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### Tuskegee Syphilis Study

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<tr>
<td>July 1973</td>
<td>$1.8 billion lawsuit filed by patients and families</td>
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<tr>
<td>1974</td>
<td>new guidelines for human subject experiments</td>
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<tr>
<td>Dec. 1974</td>
<td>government settles lawsuit ($37,500 to each living survivor and $15,000 to heirs)</td>
</tr>
<tr>
<td>1975</td>
<td>government extended treatment to wives and children who had contracted syphilis</td>
</tr>
<tr>
<td>1997</td>
<td>Clinton apologizes in person to 4 of the 8 survivors</td>
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Tuskegee Syphilis Study

overall question:
-How could it have happened?

Q. How did it get started?
Q. When did study actually begin?
Q. Who proposed it?
Q. Why?
Q. What was goal of study?
Q. Were there precedents?
Q. Did anyone else approve the study?
Q. Any difficulty securing subjects?
Q. When was “one-time” study extended?
Q. How was time extension possible?
Q. How could treatment of subjects be prevented?
Q. How did study continue after 1945 and discovery of penicillin?
Q. How was the project finally ended?
Tuskegee Syphilis Study: FAQ

Overall question: How could it have happened?

• That as late as 1972 four hundred blacks were part of a government-run experiment, part of which was to withhold known treatment of syphilis?
Tuskegee Syphilis Study: FAQ

How did it get started?

- Like most research, for noble reasons. It followed studies in late 1920s to test & treat those least able to get diagnosis and treatment for syphilis: rural blacks.
  - Pilot program in Miss. run by federal Public Health Service and Rosenwald Fund (foundation created explicitly to help blacks, later changed its focus to concentrate on health)
  - Expanded in 1930 to other locations, including Macon Cty. Ala. (30 mi. east of Montgomery, 80% black). Tuskegee Inst. there, plus a veterans hospital. All black with 22 doctors.
    - 1st stage: 7,000-10,000 people tested; 36% tested positive (very high)
    - 2nd stage was treatment with Salvarsan and mercury; 1200 treated by fall of 1930. After another year, high cost and limited effect made Rosenwald announce end of program. State of Ala. could not pick up cost; nor could PHS (until 1934).
Tuskegee Syphilis Study: FAQ

When did study actually begin?

“Tuskegee Study of Untreated Syphilis in Negro Male” began between 1931 and 1934.

Who proposed it?

Taliferro Clark, a PHS worker who came to Ala. during Rosenwald study

Why?

Preferred to treat but no funding for it. Clark noted that of initial 1400 admitted for treatment, only 33 had undergone any previous treatment.

Goal of study?

To learn about effects of syphilis on blacks; to see if it was different than on whites [racist assumption?]
Tuskegee Syphilis Study: FAQ

Were there precedents?

Only anecdotal observations of blacks. Nothing systematic or large scale. But in 1928 an article in a German journal was published with results of a Norwegian study of several hundred untreated patients between 1891-1910. Of note were great frequency in cardiovascular damage, and only rare neurological damage. Common assumptions was that in blacks there was higher frequency of neurological damage. (NOTE: Norwegian study was done before even salvarsan, let alone penicillin was available.)

1928 Oslo study

Did anyone else approve the study?

Yes.

- Discussed with PHS colleagues, all approved
- Ala State Bd of Health approved, on condition that all were treated. No problem since Clark initially proposed a 6-8 month study; treatment, when funds available, took a year. Ala. also wanted local doctors to participate
- Tuskegee hospital medical director agreed to be local medical participant.
- Protocol submitted to Johns Hopkins Medical School doctors, who suggested study of males, over 25, 2-300 size of sample, insure no previous treatment.
Tuskegee Syphilis Study: FAQ

Any difficulty securing subjects?
• No, because it was deliberately confused with earlier testing and treatment.

When was time of study extended?
• By April 1933 results showed little neurological damage. Idea was first suggested that for little expense, subjects could be observed for 5-10 years to produce more information. Subjects already identified and participating.
• June 1933 Clark retired and was succeeded by new PHS doctor, Raymond Vonderlehr. He proposed to follow subjects to autopsy, because so much more info could be learned.

How was time extension possible?
• Little question about it. Most important was agreement of local doctors, because they would not provide treatment. Most subjects were indigent.
• Nurse Eunice Rivers hired, crucial to keeping men in program. She assured them and suggested “burial stipend” as incentive. (funded by Milbank Memorial Fund).
Tuskegee Syphilis Study: FAQ

How could treatment be prevented?
- In 1937 Rosenwald finally renewed funding of treatment program; in 1939 a mobile PHS treatment program was assigned to Macon Cty.
- Nurse Rivers screened men, saying they were under study; several men prevented from treatment 1939-41. Her justification: doctor’s orders and treatment had side effects. After 1942 draft physicals given (pos. tests required treatment; Vonderlehr got exemptions).

How did study continue after 1945 and penicillin?
- As new officials came across the study and raised questions (1948, 1951, 1952), other PHS officials regarded it as a “never to be repeated opportunity”; 20 years invested in experiment.
Tuskegee Syphilis Study: FAQ

How was the project finally ended?

• All along articles were published on results. As late as June 1965 a doctor in Detroit hospital (Irwin Schatz) read a 1964 article and sent a letter to PHS ("I am utterly astounded by the fact that physicians allow patients with a potentially fatal disease to remain untreated when effective therapy is available.") It was filed in CDC with note it was first such letter. No reply written.

• Peter Buxtun first heard of Tuskegee when hired at SF VD clinic in Dec. 1965. Curiosity and required paper made him research Tuskegee articles (sent by CDC). Based on his reading Buxtun sent a letter in Nov. 1966 questioning the study. No reply, but a CDC official visited him over Christmas to talk to Buxtun, and he was invited to Atlanta for a meeting a few months later. But no change in CDC policy.

1935 article
UNTREATED SYPHILIS IN THE MALE NEGRO
A COMPARATIVE STUDY OF TREATED AND UNTREATED CASES.

1956 article
Untreated Syphilis in the Male Negro
Twenty-Five Years of Serologic Observation in a Selected Syphilis Study Group

1964 article
The Tuskegee Study of Untreated Syphilis
The 30th Year of Observation

Since 1932 there has been carried on a study of the outcome of untreated syphilis in the male Negro. Although the primary indication of this study is the determination of the natural history and course of syphilis in the male Negro conducted and observed over a long period of time. In 1932, a 122
Tuskegee Syphilis Study: FAQ

How was the project finally ended?

- Nov. 1967 Buxtun resigned from VD clinic; fall 1968 he entered law school in SF; Nov. 1968 he wrote another letter to CDC. Now (post MLK assassination riots) it got attention. Feb. 1969 an ad hoc committee met at CDC, serious debate about ending experiment, but in the end it decided to continue. Also, consent to continue was asked from Macon Cty. Medical Society (now mostly black). The men still alive (56 with syphilis and 36 control) would be monitored until their death.

- CDC wrote this back to Buxtun who was still in law school. He talked to a few colleagues (one suggested the ACLU file a suit), but Buxtun left it until he mentioned it to a friend who was a reporter for the AP, who became very interested. It was Feb. 1972. Another reporter, Jean Heller, in Washington got the assignment and the story broke on July 25, 1972.

- An assistant secretary of HEW responded he was “shocked and horrified” at the report. Another ad hoc panel was immediately created (Aug. 24, 1972); Feb. 1973 Sen. Kennedy began hearings.