History of Research Ethics

Susan E. Lederer, Ph.D.
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Disclosure
I have no relationships to disclose, and I will not discuss off label or investigational use products in my presentation.

Email: susan.Lederer@wisc.edu
Why do we have the rules for research that we have?

U.S. health policy as response to scandal and tragedy
The Patent Medicine Evil in the Early 20th century

MARIANI WINE

COCAINTE TOOTHACHE DROPS

Instantaneous Cure!
PRICE 15 CENTS.
Prepared by the
LLOYD MANUFACTURING CO.
210 HUDSON AVE., ALBANY, N.Y.
For sale by all Druggists.
(Registered March 1885.) See other side.
Upton Sinclair: The Jungle
Food and Drug Act 1906

A nauseating job, but it must be done

Roosevelt takes hold of the investigating muck-rake himself in the packing-house scandal
Elixir of Sulfanilamide tragedy 1937

107 deaths
Diet and cosmetic dangers
c. 1930s
dinitrophenol
Food, Drug and Cosmetic Act of 1938

- Drugs and cosmetics must be tested for toxicity before marketing
- Adequate directions for use need to be on package
- Some drugs are designated “by prescription only”
Thalidomide

1960-1961
83 children were born with unusual birth defects, not linked to thalidomide use.

A German scientist makes connections between thalidomide use and thousands of babies born with birth defects.
Drug makers must establish the effectiveness of drug products before they go on the market, and afterwards report any serious side effects.

Requires clinical studies conducted by qualified experts. Requires informed consent by study subjects.
Animal Welfare Act, 1966
LIFE MAGAZINE
1966
National Research Act, 1974
Both the history of human experimentation and history of controversy over human experimentation much older
United States Congress, 1900

considers Senate bill 3424,

a law that would have required investigators to disclose in advance the purpose and procedures of any non-therapeutic experiment involving human beings.
Senate bill 3424

calls for explicit ban on experiments using those persons deemed unable to consent, including infants, children under the age of 21, and pregnant women.
The U.S. Army Yellow Fever Board in Cuba, 1900
Reed and his colleagues introduce written permission forms available in both English and Spanish.
The undersigned understands... perfectly well that in case of the development of yellow fever in him, that he endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay in this island, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service.
Subjects receive $100 in gold, $200 if death occurs
“A written consent was obtained from each one, so that our moral responsibility was to a certain extent lessened. Of course, only the healthiest specimens were experimented upon . . .”

Aristides Agramonte
World War II experimentation

- President Franklin Delano Roosevelt establishes the Office for Scientific Research and Development
  - Committee on Medical Research
  - Unprecedented federal funding for medical research
Research related to war effort gets greenlight

hypothermia
effects of high altitude
de-salination studies
burns/wounds
blood substitutes
Prevention and treatment of infectious diseases
  malaria
gonorrhea
hepatitis
De-salting sea water
Malaria research

Malarial research: infecting mosquitoes by allowing them to bite an infected patient
Nazi war-time medical research agenda

- hypothermia
- effects of high altitude
- de-salination studies
- burns/wounds
- blood substitutes
- vaccines and treatment
  - malaria
  - gonorrhea
- hepatitis
Nazi researchers use concentration camp inmates as subjects
Dachau Concentration Camp—effects of hypothermia
Dachau Concentration Camp
effects of high altitude
Sea water studies

- A Roma victim of Nazi medical experiments to make seawater potable.
Seawater experiments, Dachau 1944

44 camp inmates (ages 16-49) German, Czech, and Polish Roma.

“recruited” from Buchenwald and Auschwitz for a “clean up work detail”

- Group 1 no water at all
- Group 2 fresh water
- Group 3 ordinary sea water
- Group 4 chemically filtered sea water
- Group 5 sea water with a tomato extract to mask taste (but leaving high salt concentration).
Rudi Taubmann’s testimony at the Nuremberg Doctors’ Trial

- When test subjects refused to drink any more sea water, they were physically held down, and a red tube placed in their mouth in which sea water was added so that it went to the stomach.

- Test subjects undergo:
  - Liver punctures
  - Spinal punctures
Studies of burns and wounds, 1942

- disfigured leg of a survivor from Ravensbrueck,

- scars resulted from incisions made by medical personnel that were purposely infected with bacteria, dirt, and slivers of glass.
United States v. Karl Brandt et al
Nuremberg Doctors Trial
Prosecution of 23 Nazi medical personnel
Issue for the Tribunal: what standards to use to judge these experiments?
Defense attorneys liken Nazi camp experiments to American prisoner research during wartime
American researcher Andrew C. Ivy

- Sent by AMA in 1946 to Nuremberg as medical consultant to the American military tribunal in the Doctors’ Trial.

- Self-experimenter in seawater studies, high altitude studies and experiments on volunteers for US Naval research
Permissible Medical Experiments
Comes to be known as the Nuremberg Code
First principle

The voluntary consent of the human subject is absolutely essential.
9 additional principles

- Based on animal experimentation
- Must avoid all unnecessary suffering, injury
- No reason to think that death will result
- Risk should not exceed benefit
- Only scientifically qualified personnel
Outcome of Doctors Trial

7 acquitted,
7 received death sentences,
9 received prison sentences ranging from 10 years to life imprisonment.
Karl Brandt sentenced to death

- Offers his body for experimentation
- US Army rejects the offer
- Executed at Landsberg Prison June 2, 1948
The Nuremberg Code
Meaning for American medical researchers?
The Nuremberg Code

- Published in Science in 1953
- Part of a symposium about the limits and dilemmas posed by experimentation on human beings
- Adopted by Secretary of Defense Charles Wilson in 1953 for the US armed forces
- Classified as Top Secret
- Implementation failure
Would American investigators have met the Nuremberg Code?
No.
Many American researchers regarded the Code as unworkable. They would not allow experiments on children, those in institutions, the dying, and the mentally ill.
In the 1950s, Medical research in US --associated with volunteers

--traditions of self-experimentation

--anticipated significant advances in medicine
Contaminated Blood Injection Kills Youth
In Seattle Preservation Research Project

SEATTLE, March 24 (UPI)—An 18-year-old college honor student died yesterday of an injection of bacterially contaminated blood given during an experiment connected with war research on blood preservation by the University of Washington.

James Stanley Leedom, a freshman at Seattle University, was one of forty volunteers who participated in the project seeking better ways to preserve whole blood.

He died three days after the injection despite every effort to save his life.

Dr. Robert H. Williams, head of the University of Washington Department of Medicine, said the blood had become contaminated “by some phenomenon” after it had been refrigerated.

“The only way we can explain it,” said Dr. Williams, “is that the bacteria was able to grow in some manner while the blood was at freezing temperature and not at body temperature.”

Both Dr. Williams and Dr. Clement A. Finch, Associate Professor of Medicine in charge of hematology at the university, said they would gladly participate in the project if it would help save lives.

James Stanley Leedom

Thrives when chilled. It produces shock and high fever.

The father, Stanley P. Leedom, said he held no one at fault for his son’s death.
Polio epidemic c. 1952
PARENTAL REQUEST FOR PARTICIPATION OF CHILD IN POLIOMYELITIS VACCINATION FIELD TRIAL

The National Foundation for Infantile Paralysis, Inc., in cooperation with state and local health, medical and educational authorities, is conducting a nation-wide field study of the effectiveness of a vaccine which may be protective against paralysis due to poliomyelitis. The vaccine consists of chemically killed poliomyelitis virus of all three known types. For purposes of this study, several thousand children will be given three injections of this vaccine into the arm over a period of several weeks; at least an equal number of unvaccinated children will be observed so that a comparison can be made between the two groups. The children in each group, those who are vaccinated and those who are not, are equally important to the study. In certain instances it will be necessary to test small samples of blood at intervals during the study to determine the amount of antibodies against poliomyelitis that are present.

I HEREBY REQUEST that my child, ________________________________, be vaccinated if selected, or otherwise be permitted to participate in the procedures described above without cost to me.

Date ____________________________

Signed ____________________________

Relationship to Child ________________________________
(Must be parent or legal guardian)

School ________________________________

(Street Address or Rural Location)

Grade ________________________________

(City, Town or Township) ___________ (State)
Efforts to create a workable code of ethics for human experimentation

- To protect human subjects
- To enable medical research to advance
- Undertaken by the World Medical Association and its committee on ethics
1964

DECLARATION OF HELSINKI

Recommendations Guiding Doctors in Clinical Research
Declaration of Helsinki (1964)

- Distinguished clinical therapeutic research and nontherapeutic biomedical research.

- Clinical therapeutic research is justified if it improves the well being of the patient.

- Non-therapeutic biomedical research is justified as long as the interest of society does not become more important than the concern for the well being of the patient.

- Permits proxy consent
Declaration of Helsinki Amended

- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 59th WMA General Assembly, Seoul, Republic of Korea, October 2008
- 64th WMA General Assembly, Fortaleza, Brazil, October 2013
Return to US and response to scandal and tragedy
By the 1960s no longer faith in medical researchers

Henry Beecher’s bombshell

Revelation of apparent abuses of human subjects, especially the Tuskegee Syphilis Study
HENRY K. BEECHER, M.D.

Professor of Anesthesia Research at Harvard Medical School

Convener of the Harvard Ad Hoc Brain Death Committee
The New England Journal of Medicine

Volume 274   JUNE 16, 1966   Number 24

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SPECIAL ARTICLE
ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†

BOSTON

HUMAN experimentation since World War II has created some difficult problems with the increasing employment of patients as experimental subjects. Experimentation in man takes place in several areas: in self-experimentation; in patient volunteers and normal subjects; in therapy; and in the different
22 examples of “questionable” research practices

Not from fringe BUT from mainstream researchers and institutions
Why HENRY K. BEECHER?

Christian faith?

anesthesia?

experience with human subjects research?
Beecher concerned about young researchers who fail to understand their responsibilities
Who were the research subjects in Beecher’s 22 examples?

“mentally defective” children
mentally retarded and delinquent children
the very elderly
soldiers in the armed forces
charity patients
the terminally ill
alcoholics
children and newborns
patients at the NIH Clinical Center
Example 16
Willowbrook studies

Newly admitted children (whose parents give consent) are given intramuscular injections of hepatitis or “milkshakes” with hepatitis.
Dr. Saul Krugman et al begin studies to acquire information about the natural history of hepatitis and work toward vaccine
Krugman continued to defend the studies but issues persist about informed consent, coercion, and study design (withholding gamma globulin).
Example 17

Jewish Chronic Disease Hospital case

Funded by USPHS and American Cancer Society

Injections of live cancer cells into elderly patients without consent

"did not wish to stir up any unnecessary anxieties in the patients" who had "phobia and ignorance" about cancer.
Chester Southam, M.D.

"I would not have hesitated," Southam said, "if it would have served a useful purpose. But," he continued, "to me it seemed like false heroism, like the old question whether the General should march behind or in front of his troops. I do not regard myself as indispensable—if I were not doing this work someone else would be—and I did not regard the experiment as dangerous. But, let's face it, there are relatively few skilled cancer researchers, and it seemed stupid to take even the little risk."

Science, 1964
Revelation of the Tuskegee Syphilis Study
July 25, 1972

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men,
This is a No-Treatment Study by Your Public Health Service.
Study begins in 1932
Public Health Service Surgeon
General Thomas Parran,

Shadow on the Land

Head of PHS, 1936-1948
INCIDENCE OF SYPHILIS AMONG NEGROES

Macon County, Ala.

Bolivar County, Miss.

Albemarle County, Va.

Meharry University, Tenn.

Each symbol represents 3% of all Negroes studied
From treatment to “a study in nature”

Dr. Raymond Vonderlehr offers Negro men “last chance for special free treatment” for their “bad blood”
Lumbar puncture (to obtain spinal fluid for diagnosis)
World War II

- PHS asks Tuskegee draft board to exempt the men in the study from the draft
- They serve in another war
Nurse Eunice Rivers
Nurse Rivers obtains permission for autopsy easier when a burial stipend of $50 is provided only one refusal in 140 requests.
1954

“for the first time, men in the study identified as “volunteers with social incentives”
One dollar for each year the men are in the Study.
--CDC convenes a blue-ribbon panel to determine whether Tuskegee study should continue

--the only physician not familiar with the Study argues that the experiment should end and the men receive treatment

--the Study continues until 1972
Study Revealed July 25, 1972
Senator Ted Kennedy holds hearings on human experimentation including the TSS

Legislation passed 1974

National Research Act
1974 National Research Act

creation of a National Commission to study the moral issues posed by human experimentation

new federal regulations for IRBs and written informed consent
Sacrificed to Science

A Docudrama Reopens
A Cruel Chapter
In the Annals of Race

By Michel Markiott
Persistent stories about the deliberate infection of the men in Tuskegee with syphilis
The AIDS ‘Plot’ Against Blacks

Bizarre as it may seem to most people, many black Americans believe that AIDS and the health measures used against it are part of a conspiracy to wipe out the black race.

A survey of black church members in 1990 found that an astonishing 35 percent believed AIDS was a form of genocide. A New York Times/WCBS-TV News poll in 1990 found that 1 black in 10 believes the AIDS virus was “deliberately created in a laboratory in order to infect black people” and an additional 2 in 10 thought that might be so. A Gallup/Newsweek poll in March produced similar results.

Even some dedicated black health workers engaged in the fight against AIDS decline to disavow these fears. Testifying before the National Commission on AIDS, one said that “until proven otherwise” she considered AIDS a man-made disease.

Worse yet, the treatments and preventives against AIDS have become suspect. Some blacks believe that AZT, the harsh drug used to combat the disease, is a plot to poison them ... that campaigns urging use of condoms, the best way to prevent sexual transmission, are a scheme to reduce the number of black babies ... that distributing clean needles to slow transmission among addicts is a plot to encourage drug abuse.

At its most destructive, the paranoia causes many blacks to avoid medical treatment. Unless black and Hispanic leaders play a more vigorous role in countering the fears and mistrust, it will become ever harder to slow the epidemic.

The task is urgent because the disease is now spreading most rapidly among minorities. Last year, for the first time, the number of AIDS cases reported for minorities exceeded the number for whites. Most worrisome for the future, blacks account for a majority of AIDS cases in women and children. “AIDS in future generations may be primarily a disease of black people,” the New York Department of Health warned last month.

Yet the response to this growing crisis has been sluggish. Financially pressed minority organizations and local governments have little energy for fighting AIDS, especially given the stigma attached to its main victims, homosexuals and drug addicts. But whether financing for minority AIDS programs has lagged behind white programs, as some black leaders charge, is not clear. Federal and state funds to minority AIDS organizations have gone up and the Government’s central programs, like counseling and testing services, have huge minority caseloads.

No programs, even if well financed, will succeed without a change in attitudes. Thus it is welcome news that the New York State Health Department, with the help of black politicians and community leaders, has started a media campaign to encourage blacks to mobilize against AIDS.

The campaign rightly stresses that AZT and condoms are not plots against blacks. But it refuses to counteract the paranoia about AIDS as genocide, saying only that no matter how AIDS got started, there are ways to stop it. Campaign officials reasoned that few blacks would believe government denials anyway. But surely black leaders and public figures with high credibility, such as Magic Johnson, the basketball star, could do much to discredit the pernicious and dispiriting rumors.

Meanwhile, Federal, state and local health officials need a far better assessment of the flow of AIDS money into minority communities and stronger programs to fight the disease there. Costly drug treatment ought to be provided to all who seek it, an investment that would yield dividends far beyond slowing the spread of AIDS. And more vigorous outreach programs might persuade more individuals to avoid risky behavior.

As white Americans, shaken by the riots in Los Angeles, search for ways to help afflicted and distrustful minorities, there’s no wiser way to start than AIDS. A failure to treat and prevent AIDS among minorities: That would be the true genocide.
Presidential apology 1995
White House Apology for the Syphilis Study,
Revelations of scandal and tragedy continue
2010

- President Obama and Secretary of State Hillary Rodham Clinton apologize to people of Guatemala for studies conducted in 1946-1948
John Cutler, STD studies

- Using prostitutes infected with syphilis and gonorrhea to deliberately infect Guatemalan soldiers and prisoners

- Infecting prisoners manually with STDS
Guatemala, 1946-48

- Infecting inmates of mental hospital with STDS
experiments in Guatemala that eventually expose 1,308 prisoners, soldiers and patients at a psychiatric hospital to STDs.

The US team also takes blood from 1,384 orphans and other children to assess STD diagnostic tests.

Diagram of a cisternal puncture.

From Alexander G. Reeves, M.D. and Rand S. Swenson, M.D., Ph.D., “Disorders of the Nervous System”
I saw Doctor Parran on Friday and he wanted to know if I had had a chance to visit your project. Since the answer was yes, he asked me to tell him about it and I did so to the best of my ability. He was familiar with all the arrangements and wanted to be brought up to date on what progress had been made. As you well know, he is very much interested in the project and a merry twinkle came into his eye when he said, "You know, we couldn't do such an experiment in this country."
“ETHICALLY IMPOSSIBLE”
STD Research in Guatemala from 1946 to 1948

Presidential Commission for the Study of Bioethical Issues

September 2011
Ongoing challenge to protect human subjects and advance medical knowledge