

Scandals and Tragedies:  
Beecher, Tuskegee,  
Willowbrook and the Rest

NIH

Ethical and Regulatory Aspects of  
Clinical Research

26 September 2007

Or,  
A (Scandalously) Short History  
of Human Experimentation

James Lind  
(1716-1794)



# Lind's therapeutic experiment

Seamen divided into 6 groups

Each group received different treatment

elixir vitriol

sea water

cider

vinegar

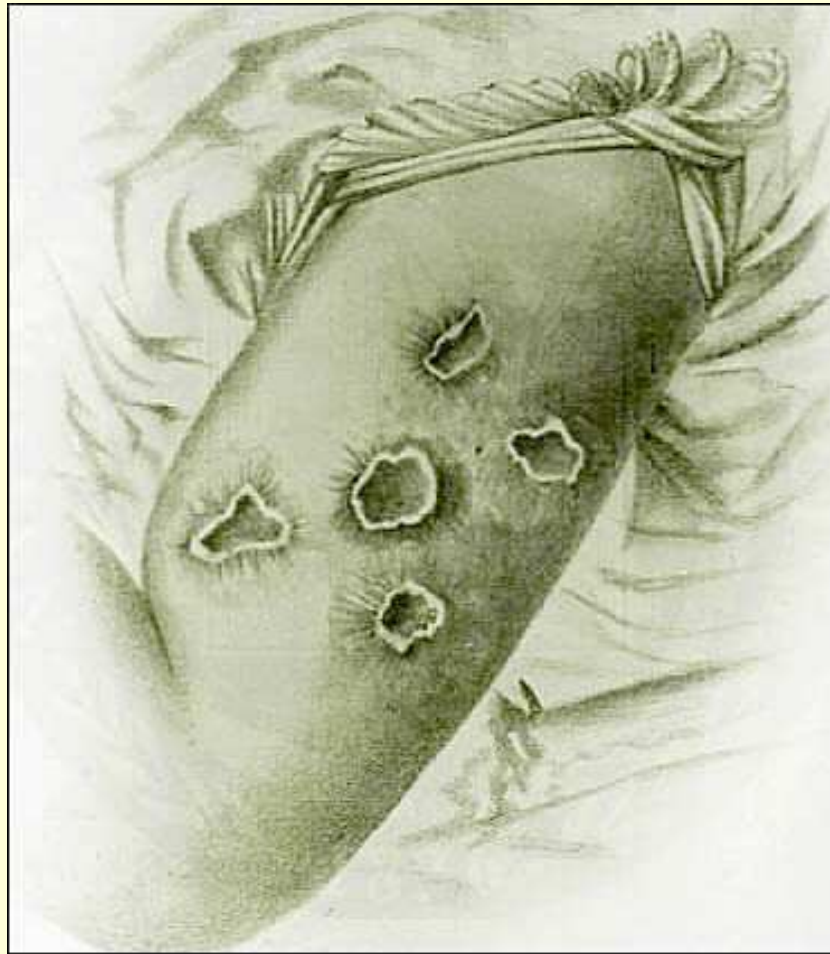
two oranges/one lemon

bigness of a nutmeg

# Smallpox variolation c. 1721



# Vaccination (cowpox from the arm of Sarah Nelme)



# English physician Edward Jenner



- Introduces "vaccination"
- First recipient of the vaccine is James Phipps, an 8-year-old boy, the son of his gardener



Jenner "never forgot the service this child rendered to science." He provided a home for Phipps, complete with a rose garden; this became the site of the Jenner Museum.



# To determine the efficacy of the vaccine

Benjamin Waterhouse, the "Jenner of America," injects smallpox pus into 19 vaccinated children and 2 unvaccinated children at the Noddles Island Asylum

This decisive experiment," in which only the unvaccinated develop smallpox, Waterhouse claims, "has fixed forever the practice of the new inoculation in Massachusetts."

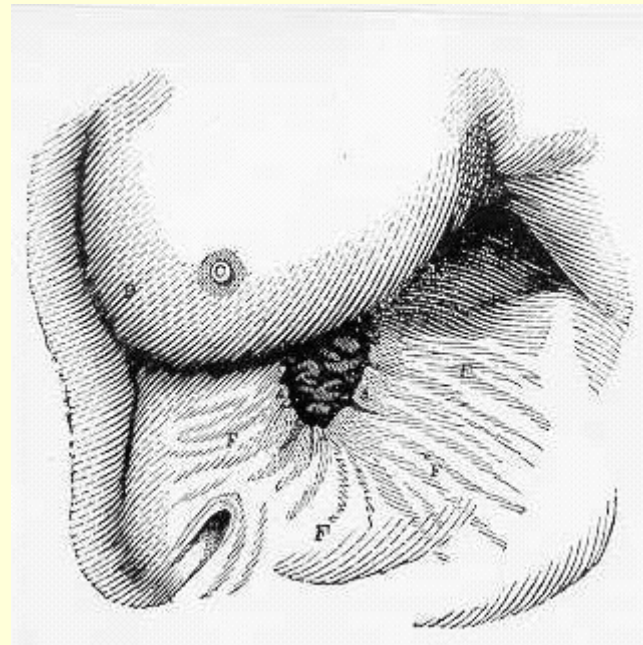


# William Beaumont and Alexis St. Martin

Gastric fistula

Studies of digestion

Paid \$150 for one year



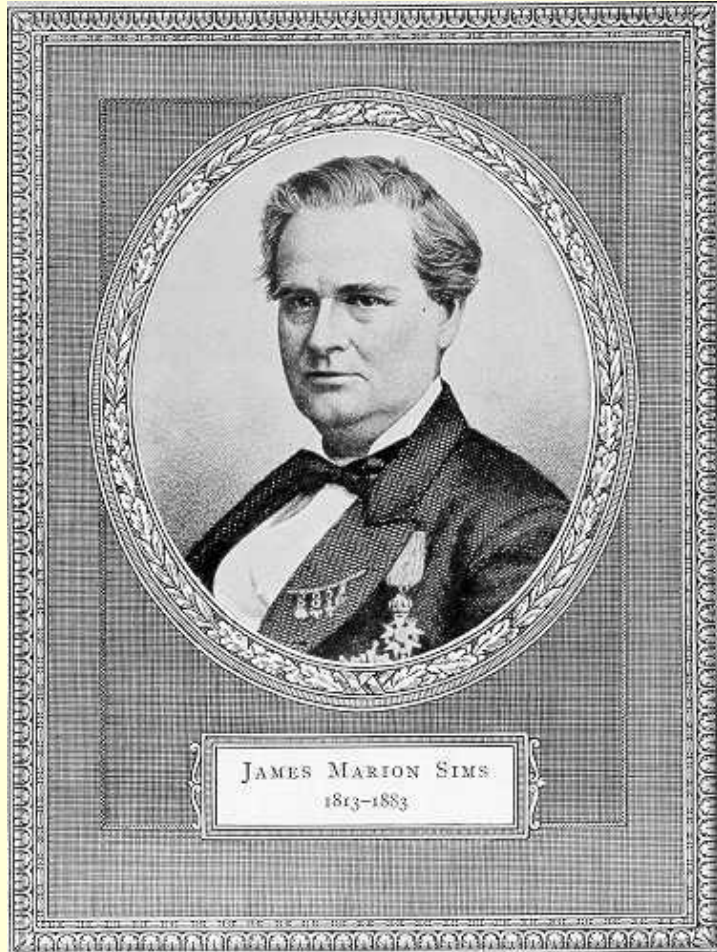
# Contractual arrangements

Submit to, assist and promote by all means in his power, such Physiological and Medical experiments as the said William shall direct or cause to be made on or the stomach of him, the said Alexis, either through or by the means of, the aperture or opening thereto in the side of him,



the said Alexis, or otherwise, and will obey, suffer, and comply with all reasonable and proper orders or experiments of the said William, in relation thereto, and in relation to the exhibiting and showing his said Stomach, and the powers and properties thereof, and of the appurtenances and powers, properties, situation and state of its contents.

# James Marion Sims, M.D.



revered as the  
"father of American  
gynecology"

Developed operation  
for repair of vesico-  
vaginal fistula

# "Great Moments in Medicine" ?



# Louis Pasteur c. 1885

- Development of rabies vaccine
- Successful demonstration of the vaccine on Joseph Meister, aged ten, bitten by rabid dog





# Pasteur's experiments



Laboratory notebooks do not support his public claims about the demonstrated safety of rabies vaccine (on animals)

Fortunate that Joseph Meister survived

Between 1890 and 1920

Criticism and controversy over  
"human vivisection"

# critics

animal protectionists

physicians

citizenry

# Animal protectionists point to

tremendous increase in experiments on children (and others) associated with the germ theory of disease

Including demonstrations that a particular bacterium causes a disease

In 1880s, California physician George Fitch inoculated six leprous girls with "virus of syphilis" in effort to demonstrate that syphilis and leprosy the same disease



# 1895

New York pediatrician Henry Heiman's report of how he infected three people with gonorrhoea:

- a 4-year-old boy ("an idiot with chronic epilepsy")
- a 16-year-old boy (an "idiot")
- a 26-year-old man in the final stages of tuberculosis"

# Tuberculin testing



"Material" comes from orphans and destitute children at St. Vincents Home in Philadelphia

# What is the best way to use tuberculin to test for tb?

compare tuberculin testing in deep muscle, skin, and the conjunctiva.

The conjunctive test required applying tuberculin drops to surface of the eye, but this produced a "decidedly uncomfortable lesion" and in several cases, serious inflammation of the eye. Some children suffer permanent eye damage.





KITTY LOGAN, AN ORPHAN CHILD INTO WHOSE EYE

# Medical criticism

lumbar puncture testing

Arthur H. Wentworth,  
Harvard Medical School, 1895

Describes "control experiments on normal cases" of lumbar puncture.

Withdraws spinal fluid from 29 children, ranging in age from a few months to a few years.

# Wentworth notes



Reports that "the momentary pain of the puncture" caused the children to shrink back and cry out," but concludes that the procedure itself was harmless and would prove to be a useful diagnostic tool.

## Philadelphia physicians label Wentworth's research "human vivisections"

"It must be remembered that there were no therapeutic indications for the operation such as often lead us to justly and properly adopt operative treatment, the positive value of which is still undetermined. These experiments were purely and avowedly experimental. . ."

The diagnostic value of puncture of the subarachnoid space is so evident that I considered myself justified in incurring some risk in order to settle the question of its danger. If it proved harmless, then one need not wait until a patient becomes moribund before resorting to it.

Arthur H. Wentworth, 1896

William Osler

# Animal protectionists and members of the public

Critical of experiments to demonstrate dietary deficiency disease



# Pellagra



(a) Pellagra in a child. Note the 'butterfly wing' on the face, and the rough hands.



# The dietary hypothesis



- Experiments at two Mississippi orphanages demonstrated that those fed a diet of fresh meat, milk and vegetables recovered from pellagra.
- Healthy children who ate the new diet did not contract pellagra.

# Joseph Goldberger, PHS



# Self-experimentation

Goldberger, his assistants and his wife participate in efforts to develop pellagra from ingestion of the excretions of patients with pellagra

# Definitive demonstration



- Permission to conduct experiments at the Rankin Prison Farm
- Healthy men placed on a diet of meat, meal, and molasses

# Animal protectionists

point to inability of prisoners to exercise  
voluntary consent for participation in  
pellagra experiments

# Citizens of Mississippi

Critical that men—convicted rapists, murderers, and embezzlers—were offered parole in exchange for their participation

# Rickets and scurvy

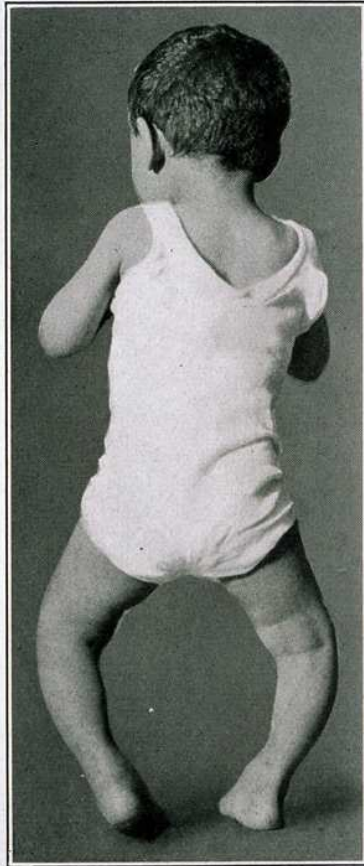


FIG. 24.—Marked bow-legs in an Italian child.

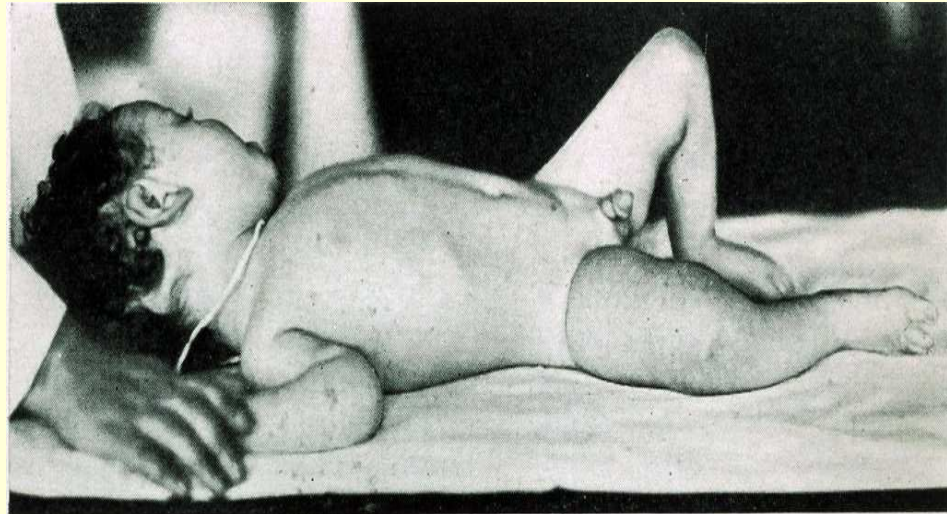


FIG. 18.—Infant with marked scurvy. Characteristic posture and swelling of right thigh.



# Pediatrician Alfred Fabian Hess



- Medical director of Hebrew Orphans Asylum
- Interested in the etiology of rickets and scurvy

Withholding orange juice until children develop lesions of infantile scurvy

Once lesions heal, orange juice again withheld.

Efforts to develop a diet to induce rickets

c. 1921

"No devotion to science, no thought of the greater good to the greater number, can for an instant justify the experimenting on helpless infants, children pathetically abandoned by fate and intrusted to the community for their safeguarding. Voluntary consent by adults should of course be the sine qua non of scientific experimentation."

# Medical Response c. 1921



well-conducted experiments on orphans provide an opportunity for these children, housed at the expense of others, "to make a large return to the community for the care devoted to them."

# External regulation of human experimentation 1900

US Congress considers Senate bill 3424

would require investigators to disclose in advance the purpose and procedures of any non-therapeutic experiment involving human beings.

# Senate bill 3424

Explicitly ban experiments on those deemed unable to consent, including infants, children under the age of twenty-one, and pregnant women.

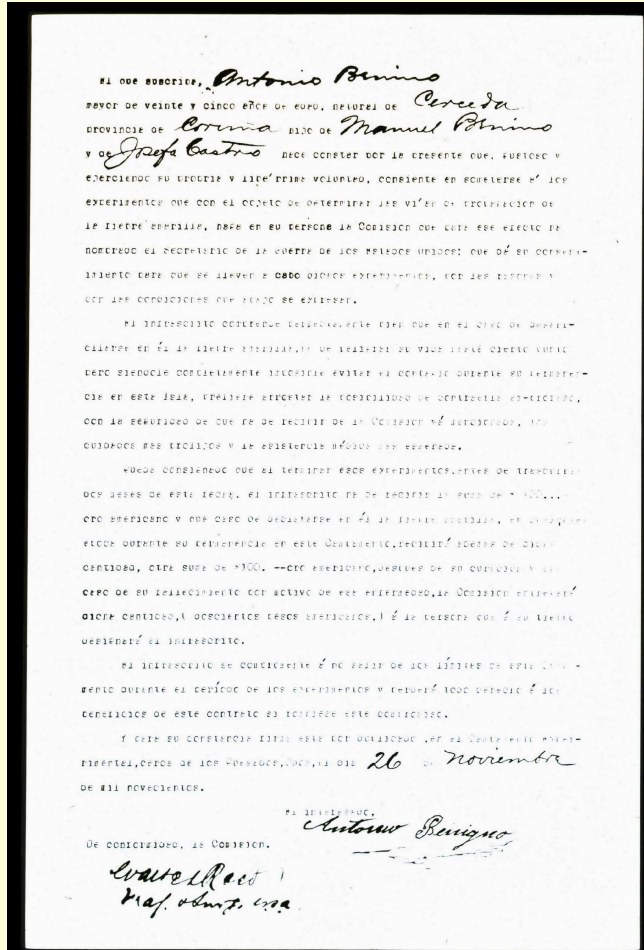
# Internal constraints

Walter Reed and the yellow  
fever experiments





# Introduction of written consent



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.

# Agramonte on the experiment

Naturally they all felt more or less that they were running the risk of getting yellow fever when they came to Cuba and so were not at all averse to allow themselves to be bitten by mosquitoes; they were paid one hundred dollars for this, and another equal sum if, as a result of the biting experiment they developed yellow fever.

Needless to say, no reference was made to any possible funeral expenses. 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 . . .

# Internal attention

1941

Francis Peyton Rous, editor of the *Journal of Experimental Medicine*, receives manuscript from San Diego physician William Black that describes how he had injected a 12-month-old white female "volunteer" with herpes virus.

# Rous rejects ms and writes

"I cannot let this occasion pass without saying that in my personal view the inoculation of a twelve month old infant with herpes virus obtained from an adult was an abuse of power, an infringement on the rights of the individual, and not excusable because the illness that followed had implications for science. The statement that the child was "offered as a volunteer"--whatever that may mean,--does not palliate the action."

- Black's paper appears in the *Journal of Pediatrics* in 1942.

includes reference to the infection with herpes virus of a 12-month-old volunteer.

# World War II

Massive increase in  
funding/personnel for research  
related to war effort



# Types of experimentation

hypothermia

effects of high altitude

de-salinization studies

burns/wounds

blood substitutes

vaccines and treatment

    malaria

    gonorrhoea

    hepatitis

# Dachau hypothermia studies



# Dachau effects of high altitude



- Efforts to make sea water potable



# United States v. Karl Brandt et al



# Prosecution of 23 Nazi medical personnel



# issues

what standard to use to judge these experiments?

what to do with the German medical profession?

how to deal with the Nazi data?

# Permissible Medical Experiments

Comes to be known as the  
Nuremberg Code



# First principle

- . The voluntary consent of the human subject is absolutely essential.

Would American investigators  
have met the Nuremberg Code?

No.

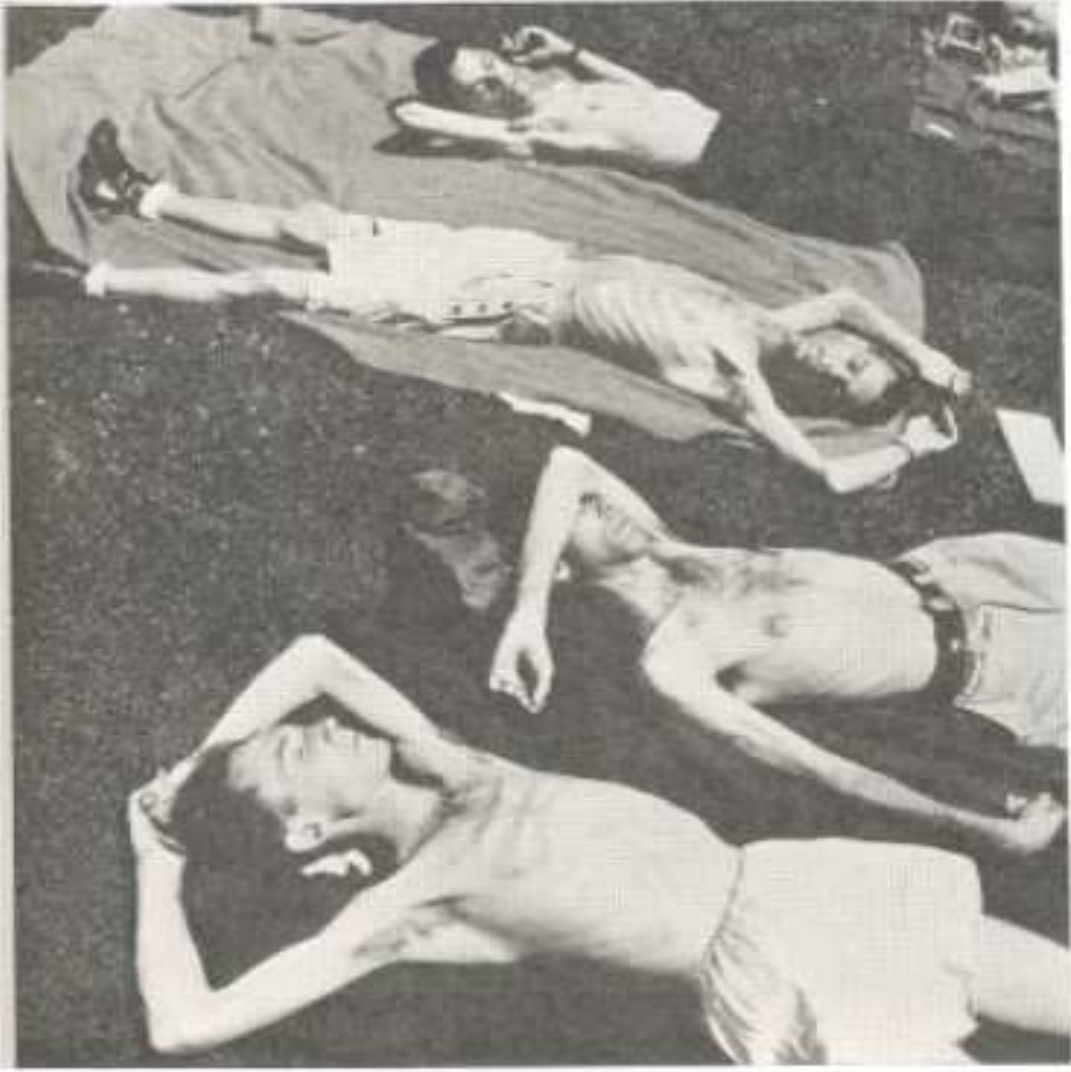
# Postwar research

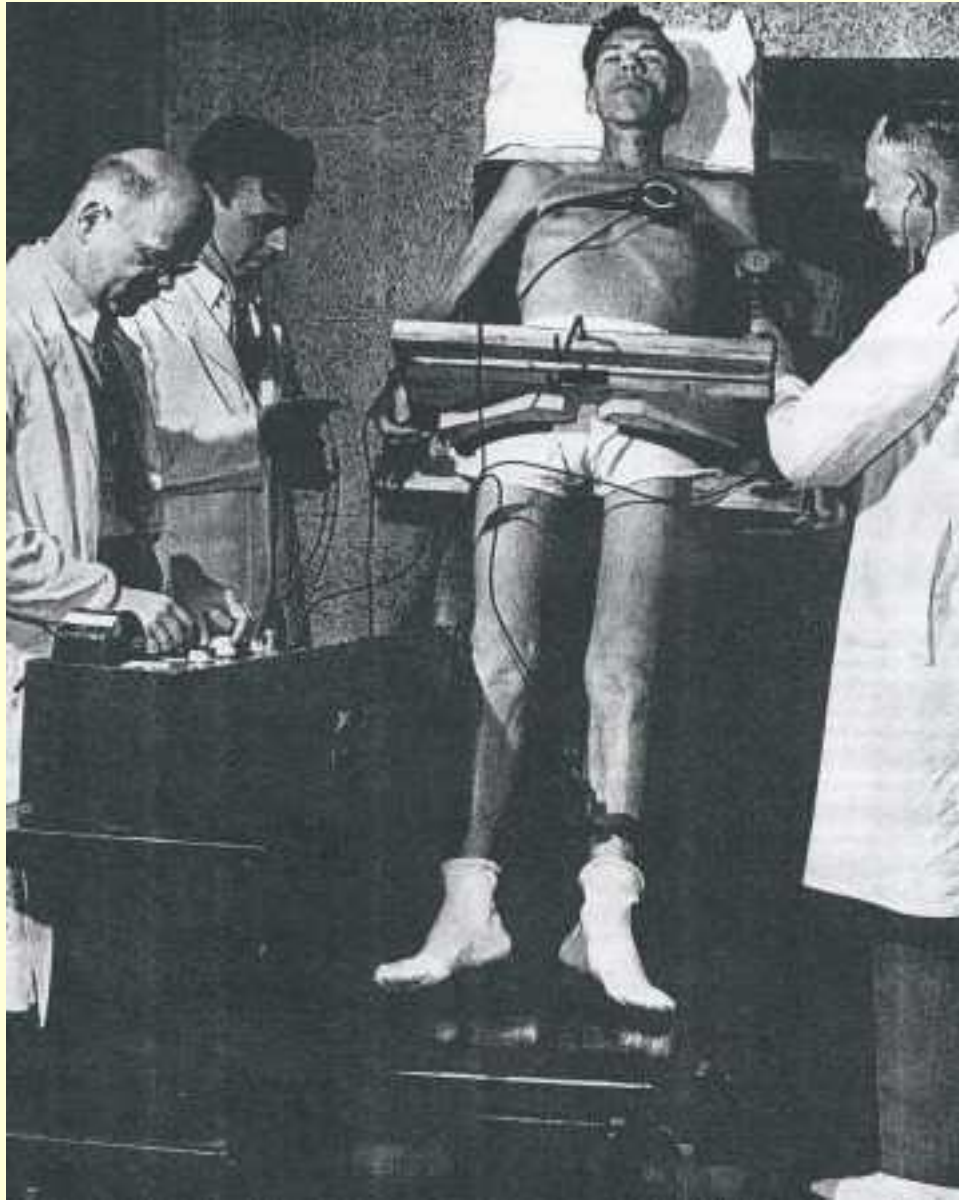
social support for American researchers

valorization of research heroes

Walter Reed Society

volunteers are celebrated





3/25/52

NYT

TI

## Contaminated Blood Injection Kills Youth In Seattle Preservation Research Project

SEATTLE, March 24 (AP)—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."



Associated Press Wirephoto

James Stanley Leedom

# Henry K. Beecher



Professor of  
Anesthesiology at  
Harvard Medical  
School

Also convener of  
Harvard Ad Hoc  
Brain Death  
Committee

# Henry Beecher's Bombshell 1966

- NEJM article Ethics and Clinical research
- 22 examples of "questionable" research practices
- Not from fringe BUT from mainstream researchers and institutions



- Thymectomy as part of a study on skin homografts
- Studying ureteral reflux in newborns (who were catheterized and xrayed)
- Study of effects of new antibiotic on liver function using juvenile delinquents (some of whom developed liver abnormalities and underwent liver biopsies)

# Willowbrook

Saul Krugman et al

Willowbrook State School, Staten Island, NY -institution for severely, mentally retarded

To acquire information about the natural history of hepatitis and work toward vaccine

- Newly admitted children (whose parents consent to their child's participation) are given intramuscular injections of hepatitis or "milkshakes" with hepatitis

- Krugman defended the study but issues persisted about informed consent, coercion, and study design (withholding gamma globulin)



- Jewish Chronic Disease Hospital
  - 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.
  - Southam loses privileges for one year

# Study Revealed July 25, 1972





THIS IS A  
NO-TREATMENT  
STUDY  
by your  
PUBLIC  
HEALTH  
SERVICE

ROBERTS

forty-year study of untreated syphilis  
in some 400 African American men and  
200 controls

deception, including "special free  
treatments"



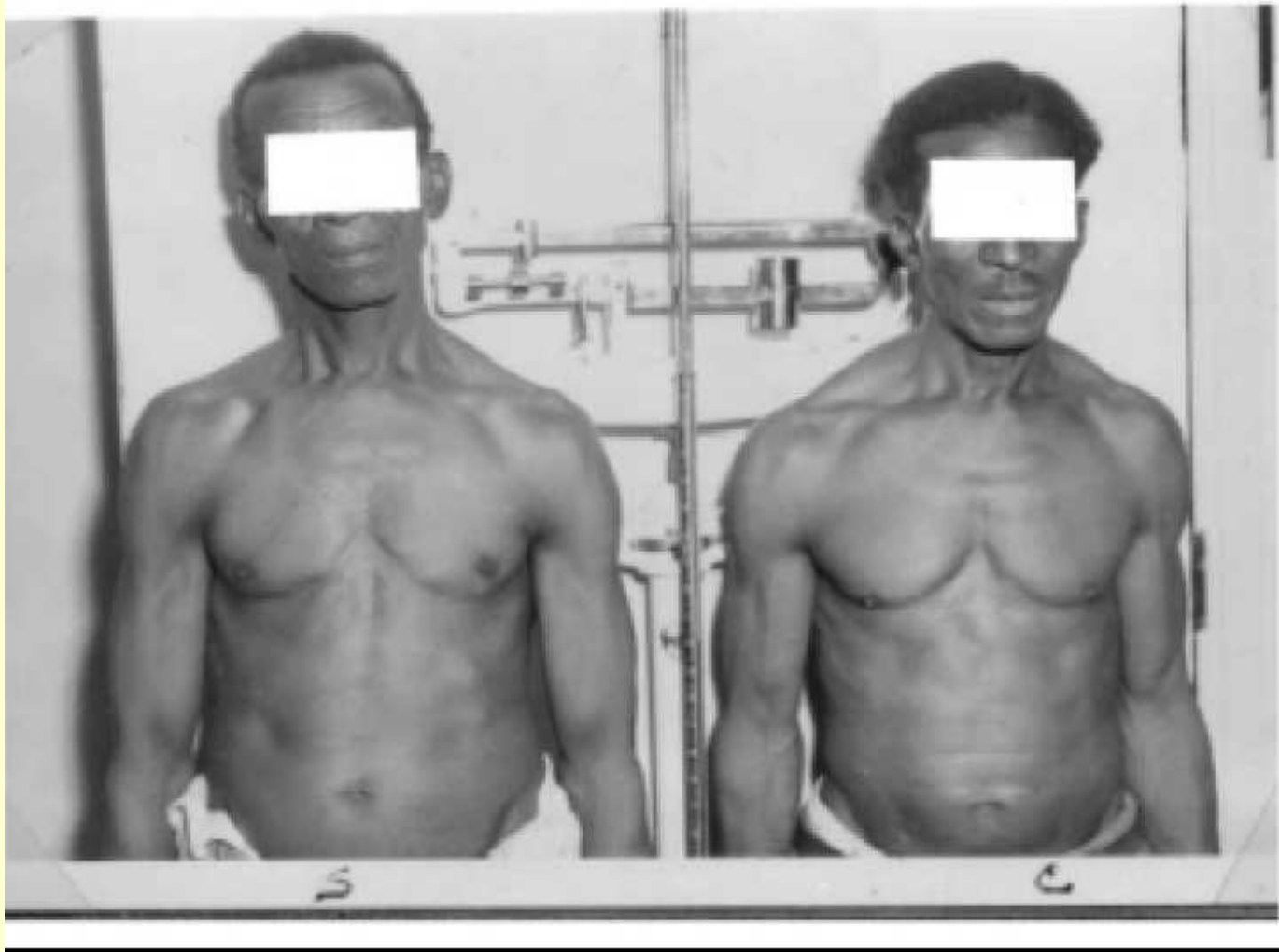
# Lumbar puncture (to obtain spinal fluid for diagnosis)



# Nurse Eunice Rivers



# 13 publications in medical literature 1936-1974



1954

for the first time, men in the study identified as "volunteers with social incentives"

TABLE I. TABULAR LISTING OF DIFFERENCES IN THE UNTREATED SYPHILIS STUDIES IN ALABAMA AND IN NORWAY

	ALABAMA	NORWAY
Study population composition	Rural Negro men	White men and women
Control	Nonsyphilitic controls observed	No controls
Percentage autopsied of those who have died	63.3 per cent	24.3 per cent
Patient motivation for study participation	Volunteers with social incentives	Sickness and disability
Treatment status	Small amounts, especially in younger men	Less treatment available, especially in early years of study
Clinical facilities	Newer x-ray, EKG, and serologic techniques	Best medical facilities of the time (1925-1927)
Spinal fluid examination	Most of the syphilitic patients had spinal fluid examinations at start of study	No routine spinal fluid examination reported
Selection of patient material	Acute syphilis and younger patients treated and omitted at start of study; early and late latent patients studied and followed	Only early, untreated syphilis included

U. S. PUBLIC HEALTH SERVICE

25

This certificate is awarded to

In grateful recognition of 25 years  
of active participation in the  
Tuskegee medical research study.

Awarded 1958



*Lesay C. Burney*

Surgeon General

# 1969

CDC convenes a blue-ribbon panel to determine whether study should continue

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

the Study continues until 1972



- Kennedy holds hearings on human experimentation including the TSS
- Legislation passed 1974
- National Research Act



# 1974

## National Research Act

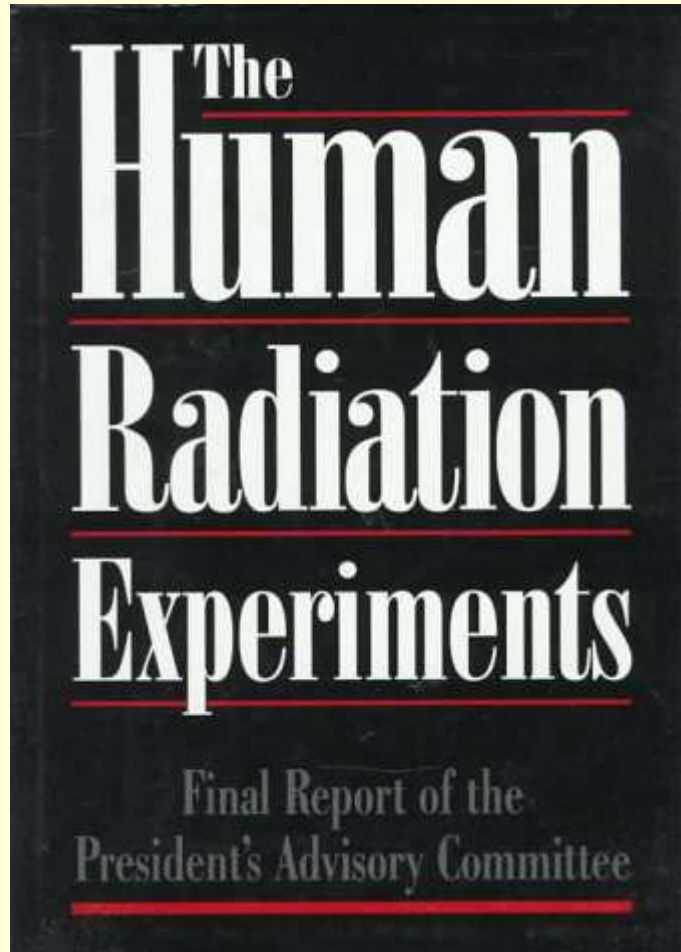
creation of a National Commission to study the moral issues posed by human experimentation

new federal regulations for IRBs and written informed consent

# White House Apology for the Syphilis Study, May, 1997



1995



Coming to terms with the  
past?

# Settlements for Plutonium injectees

Federal government settles out of court  
with families of 16/18 participants

Relatives of 13 patients receive  
approximately \$400,000

Simeon Shaw's family receives  
\$262,500

# Fernald settlement

April 1998

Quaker Oats and MIT agree to pay \$1.85 million to 45 former test subjects

Commonwealth of Massachusetts to pay another \$676,000 to 27 participants

# Cincinnati TBI Settlement

total body irradiation studies

Federal judge approves a \$5.4 million settlement for families of patients at Cincinnati General Hospital

Saenger refuses to provide an apology

# Vanderbilt settlement

Spring, 1998

\$10.3 million to women who received  
"radioactive iron cocktails"

(\$3 million to lawyers)



# Implications for Legal Action

ACADEMIA AND CLINIC

## The Rise of Litigation in Human Subjects Research

Michelle M. Mello, JD, PhD, MPhil; David M. Studdert, LLB, ScD, MPH; and Troyen A. Brennan, MD, JD, MPH

Owing to widespread public concern about the adequacy of protections for human research subjects and recent instances of serious injury to subjects at several major research institutions, lawsuits against investigators, institutional review boards, and academic institutions are becoming increasingly common. Several claim-promoting conditions are ripe to promote the further growth of this litigation and raise the stakes for research institutions. While this litigation may serve a valuable compensation function

for injured subjects, it will also have profound effects on institutional review boards, leading to a more legalistic, mechanistic approach to ethical review that does not further the interests of human subjects or scientific progress.

*Ann Intern Med.* 2003;139:40-45.

[www.annals.org](http://www.annals.org)

For author affiliations, see end of text.

See editorial comment on pp 71-72 and Letter on p 77.

What standards do we use to judge past experimental practices?

How can we protect research subjects and advance medical knowledge?

Is it possible to have a more equitable or just distribution of research benefits and costs?

