




History of Research Ethics

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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

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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

MARIANI WINE Quality Business
**HEALTH, STRENGTH,
ENERGY & VITALITY.**

MARIANI WINE
FORTIFIED, FRESHNESS
STIMULATES & REVEIGNS
THE BODY & BRAIN

HASTENS
CONVALESCENCE
especially after
INFLUENZA.

His Holiness
THE POPE

writes that he has
fully appreciated the
beneficial effects of
this Tonic Wine and
has forwarded to Me
Marked as a token of
his gratitude a gold
medal bearing his ap-
proval.

MARIANI WINE

is delivered free to all parts of the United Kingdom by WILCOX & CO.,
83, Mark Lane Street, London, W., price 2/- per Single Bottle, 20/- half-
dozen, 43/- dozen, and is sold by Chemists and Stores.



COCAINE
TOOTHACHE DROPS

Instantaneous Cure!
PRICE 15 CENTS.
Prepared by the
LLOYD MANUFACTURING CO.
219 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 scene

Elixir of Sulfanilamide tragedy 1937



107 deaths

Click the "X" in the upper right hand corner of this window to return

ONE GALLON ELIXIR ONE GALLON

SULFANILAMIDE

Each fluidounce represents:
Sulfanilamide, 40 grs.

SUGGESTED FOR THE TREATMENT OF ALL CONDITIONS
IN WHICH THE HEMOLYTIC STREPTOCOCCI APPEAR

Dose, begin with 2 to 3 teaspoonfuls in water
every four hours. Decrease in twenty-four
to forty-eight hours to 1 or 2 teaspoonfuls
and continue at this dose until recovery.

THE S. E. MASSENGILL COMPANY
Manufacturing Pharmacists
BRISTOL, TENN.-VA.


Please do not copy or reproduce this picture in any way.

Diet and cosmetic dangers c. 1930s




dinitrophenol





Food, Drug and Cosmetic Act of 1938

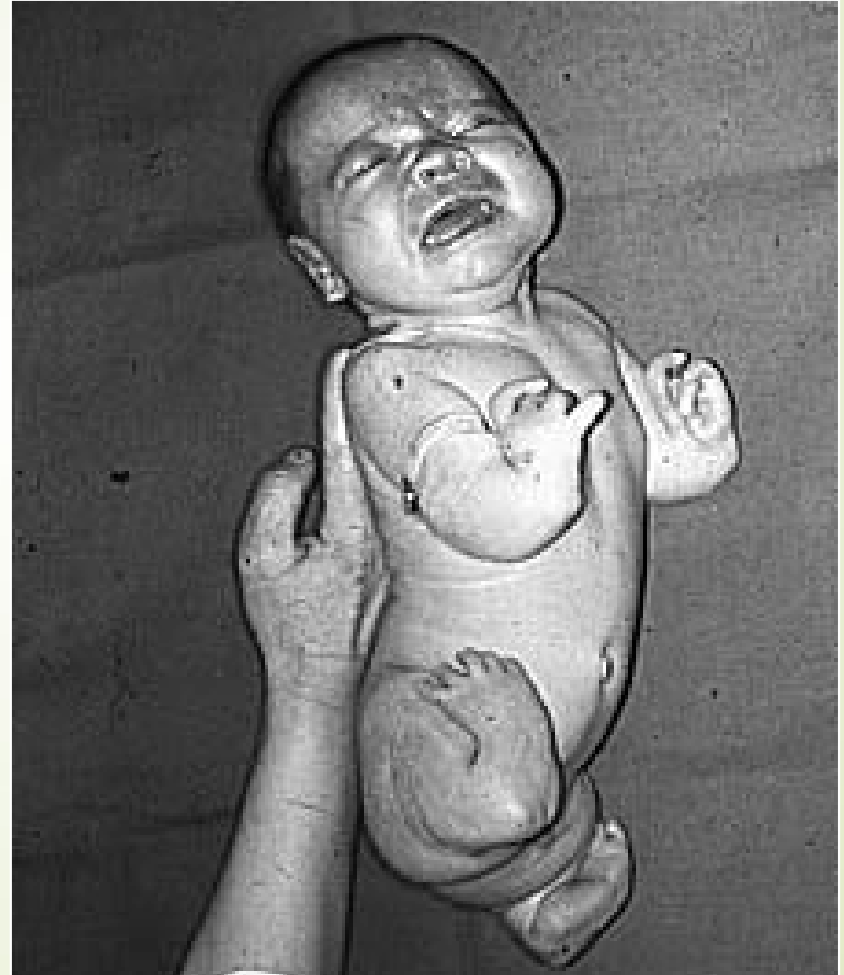
- Drugs and cosmetics must be tested for toxicity before marketing
 - Adequate directions for use need to be on package
 - Some drugs are designated “by prescription only”
- 

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.





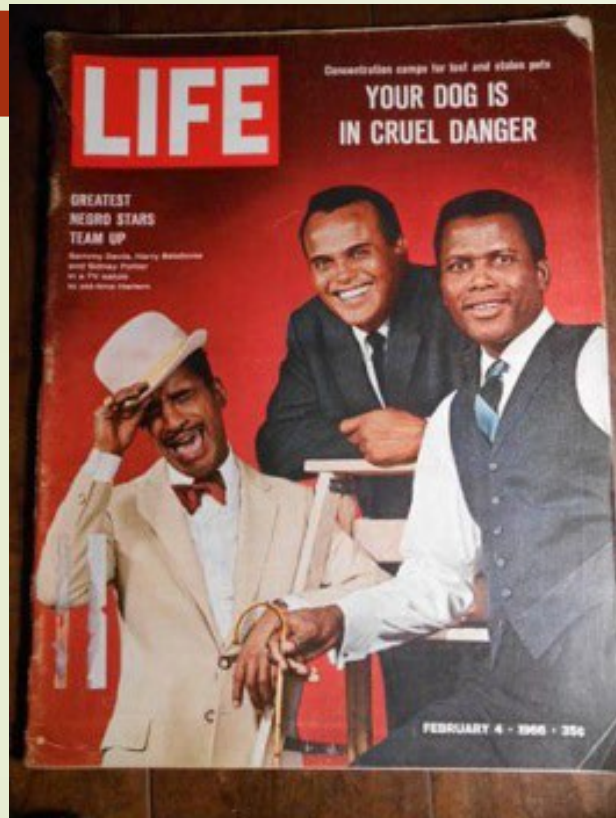
Kefauver-Harris Amendments to FDA

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







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



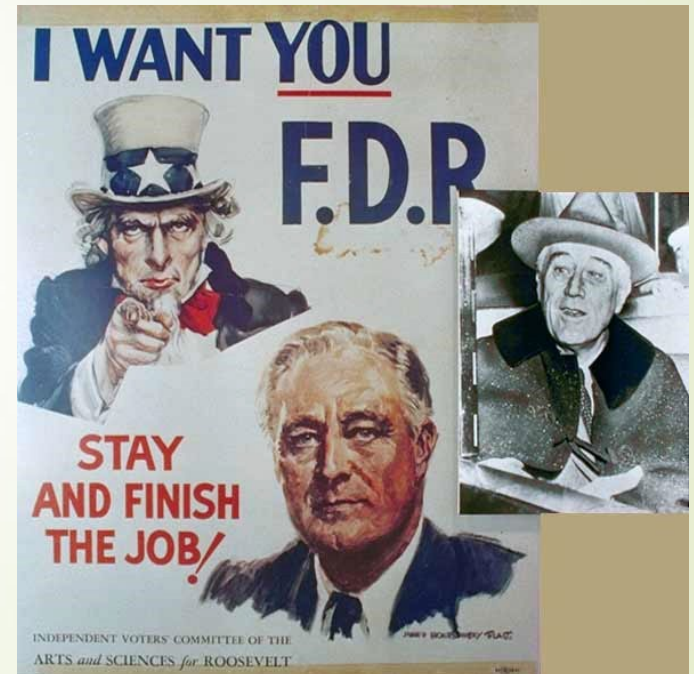


“A written consent was obtained from each one, so that our moral responsibility was to a certain extent lessened. Of course, only the healthiest specimens were experimented upon . . .”

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

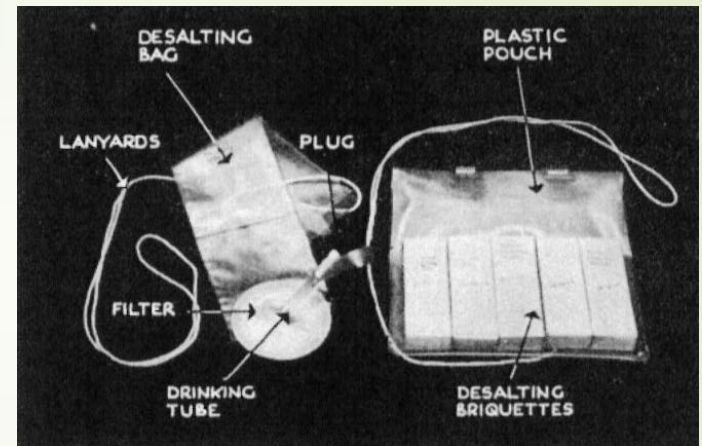
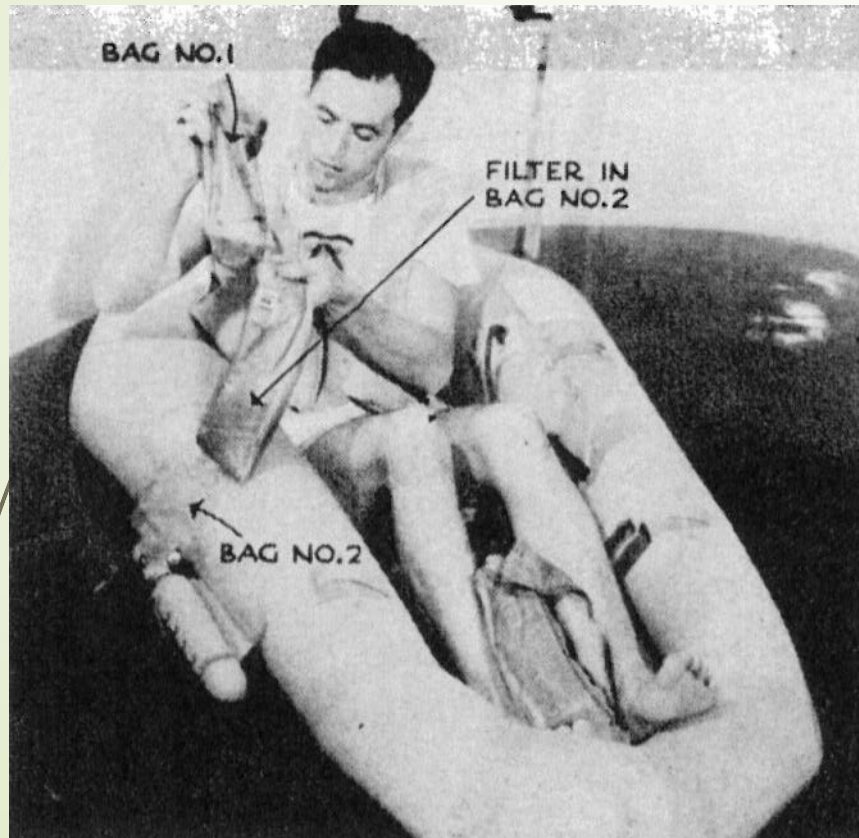
Prevention and treatment of infectious diseases

 malaria

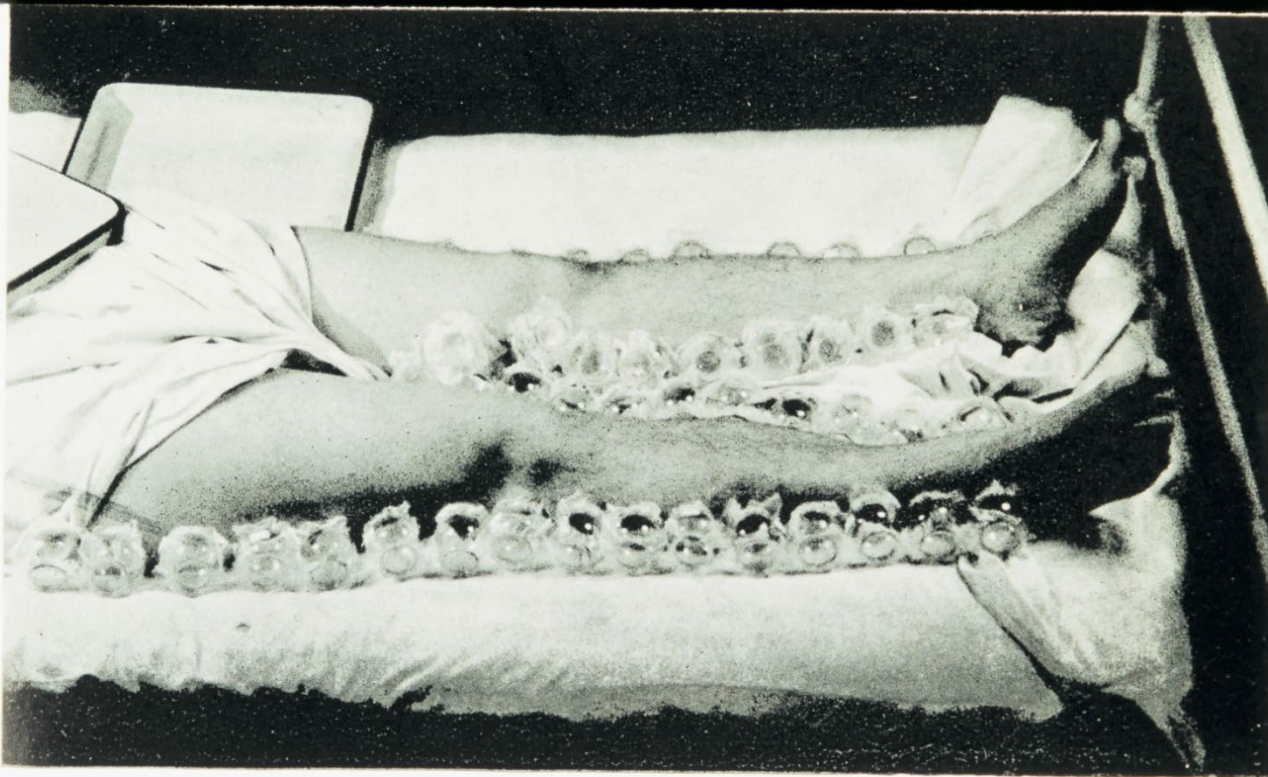
 gonorrhea

 hepatitis

De-salting sea water




Malaria research



U. S. Public Health Service

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

gonorrhoea

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



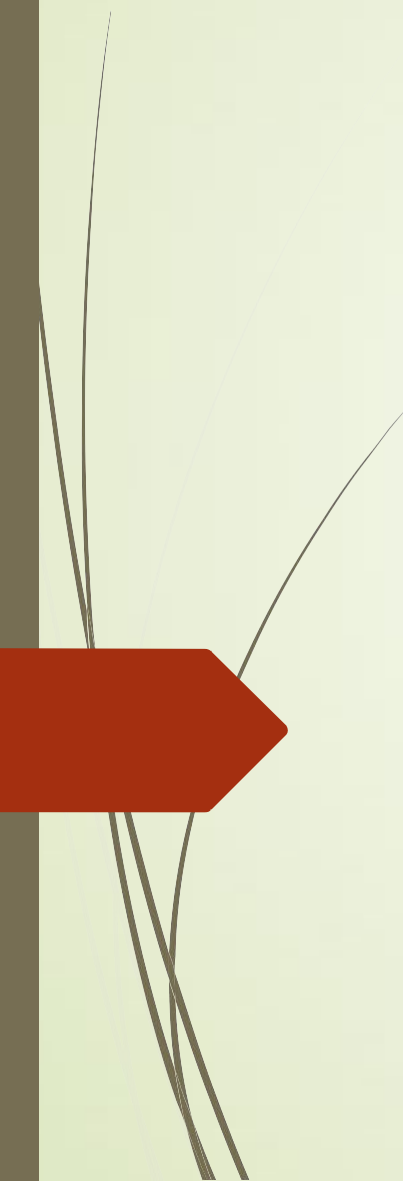
- disfigured leg of a survivor from Ravensbrueck,
- scars resulted from incisions made by medical personnel that were purposely infected with bacteria, dirt, and slivers of glass.

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






Life Photo by Myron Davis

Malarial convicts contribute to knowledge of the disease

LIFE



TO THE AMERICAN PEOPLE:

Your sons, husbands and brothers who are standing today upon the battlefronts are fighting for more than victory in war. They are fighting for a new world of freedom and peace.

We, upon whom has been placed the responsibility of leading the American forces, appeal to you with all possible earnestness to invest in War Bonds to the fullest extent of your capacity.

Give us not only the needed implements of war, but the assurance and backing of a united people so necessary to hasten the victory and speed the return of your fighting men.

William D. Leahy
Joseph P. Kamp
Franklin D. Roosevelt

JUNE 4, 1945 10 CENTS
 BY SUBSCRIPTION, TWO YEARS \$1.00

MEDICINE

PRISON MALARIA

Convicts expose themselves to disease so doctors can study it

THREE DOCTOR-BEING MALARIA-CARRYING NEGROES GET STIMULUS OF BLOOD UNDERGOING, SERVING 10 TO 14 YEARS AT ILLINOIS STATE PRISON

John C. K. malarial convicts who have been imprisoned in various of world are now being used in a new field, medical research. At the U. S. Penitentiary in Joliet, Ill. (Lower Photo) Penitentiary and New Jersey State Penitentiary, convicts are voluntarily being subjected to laboratory tests, which are used to study the disease. The convicts, who are divided by the Office of the Surgeon, Research and the respective, have been given the blood for controlled laboratory work with human.

These convicts all say the same thing about the matter and the same thing. "The prison medical staff are prepared for submitting to laboratory tests, which are necessary to study the disease. They are not interested in the disease, but in the money they can get." The medical staff, however, are not interested in the money, but in the knowledge of the disease. The staff has been a long time to get the disease, but it is now being used to study the disease.

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

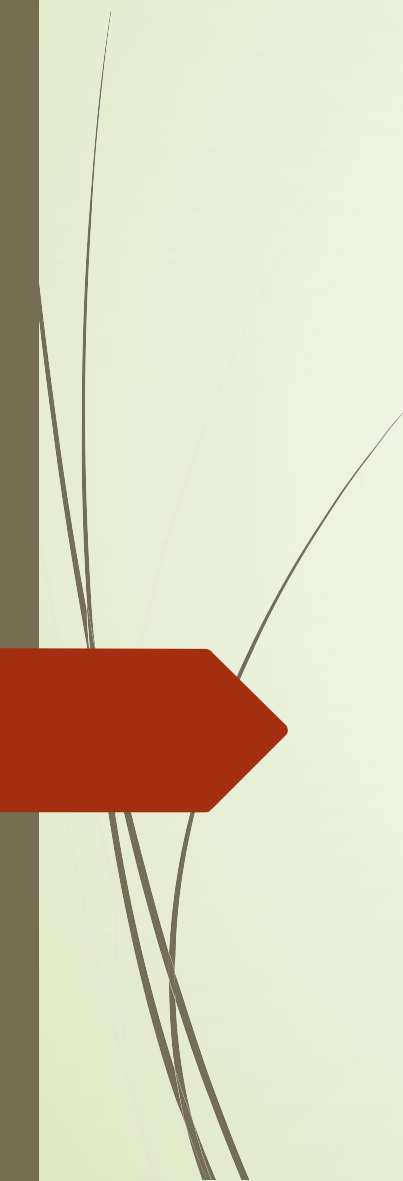
Part of a
symposium about
the limits and
dilemmas posed by
experimentation
on human beings

- ▶ 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

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

3/25/52

NYT

TI

Death of a Volunteer

➔ March, 1952

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."

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



Associated Press Wirephoto

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
(first name) (middle name) (last name)
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



1966

The New England Journal of Medicine

Copyright, 1966 by the Massachusetts Medical Society

Volume 274

JUNE 16, 1966

Number 24

Reprinted from pages 1354-1360.

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

Experimentation in man takes place in several areas: in self-experimentation; in patient volunteers and normal subjects; in therapy; and in the different

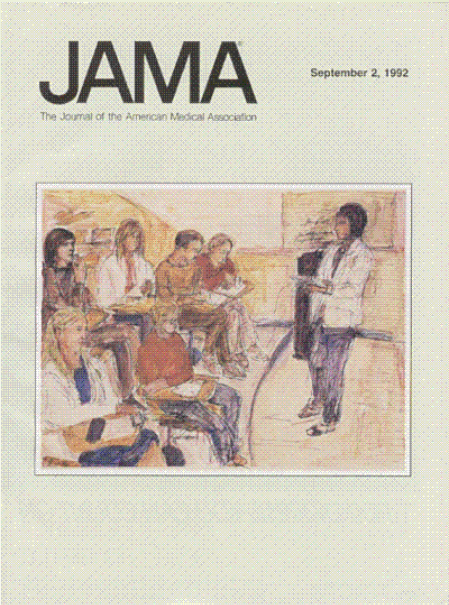


22 examples of “questionable” research practices

Not from fringe BUT from mainstream
researchers and institutions



5



2



5



2

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

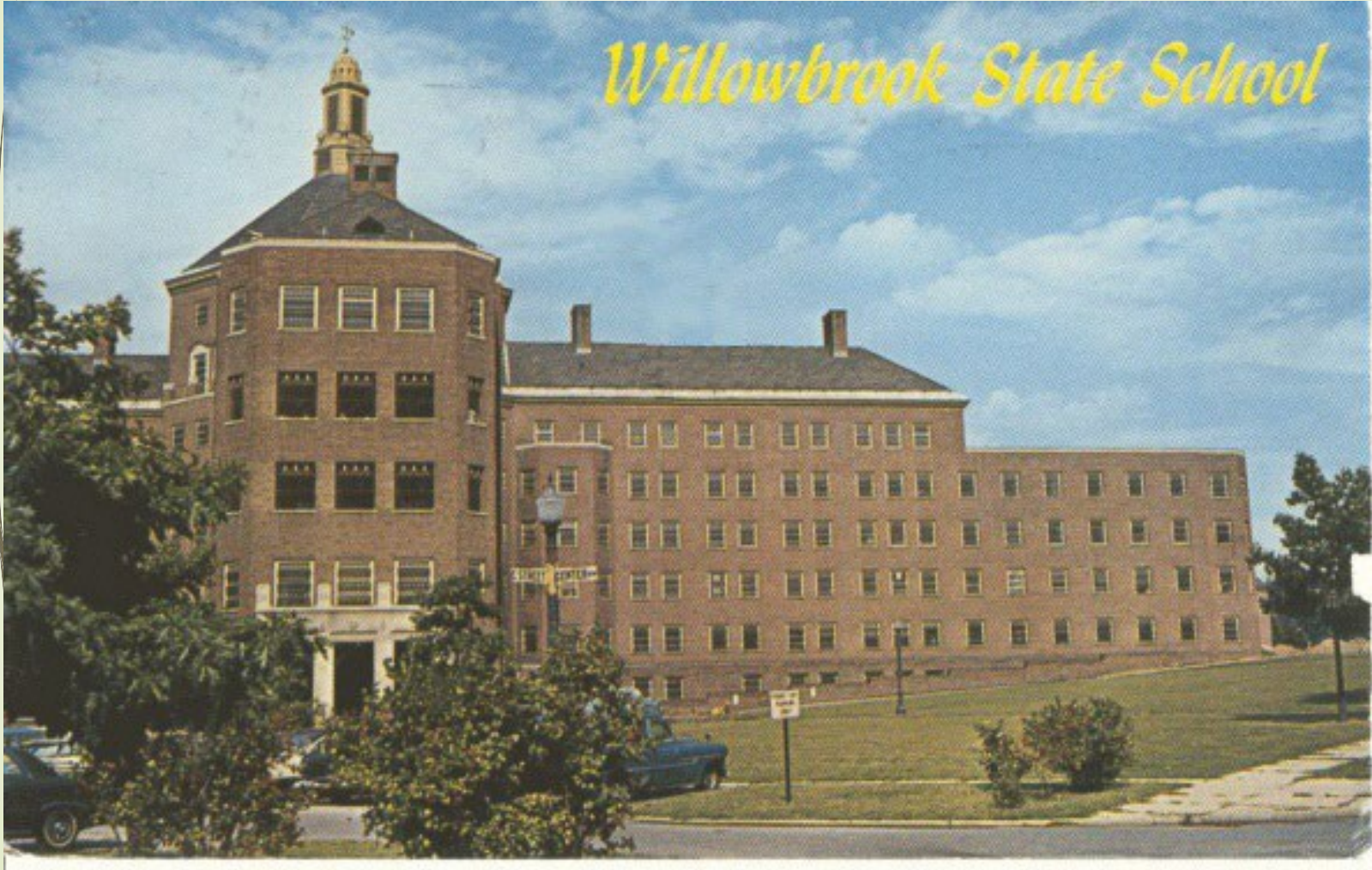
alcoholics

children and newborns

patients at the NIH Clinical Center

Example 16

Willowbrook State School



Willowbrook studies

Newly admitted children (whose parents give consent) are given intramuscular injections of hepatitis or “milkshakes” with hepatitis

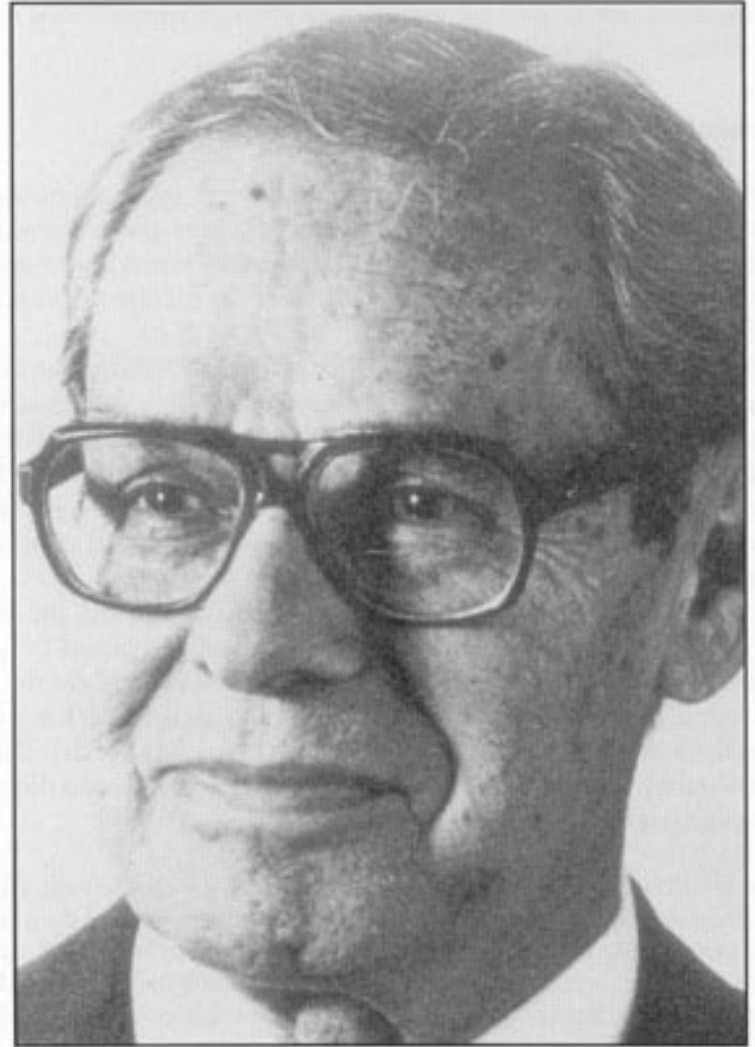


- ▶ Dr. Saul Krugman et al begin studies to acquire information about the natural history of hepatitis and work toward vaccine



Krugman continued to defend the studies but

issues persist about informed consent, coercion, and study design (withholding gamma globulin)



SAUL KRUGMAN, M.D.

Example 17

Jewish Chronic Disease Hospital case

Funded by USPHS and American
Cancer Society

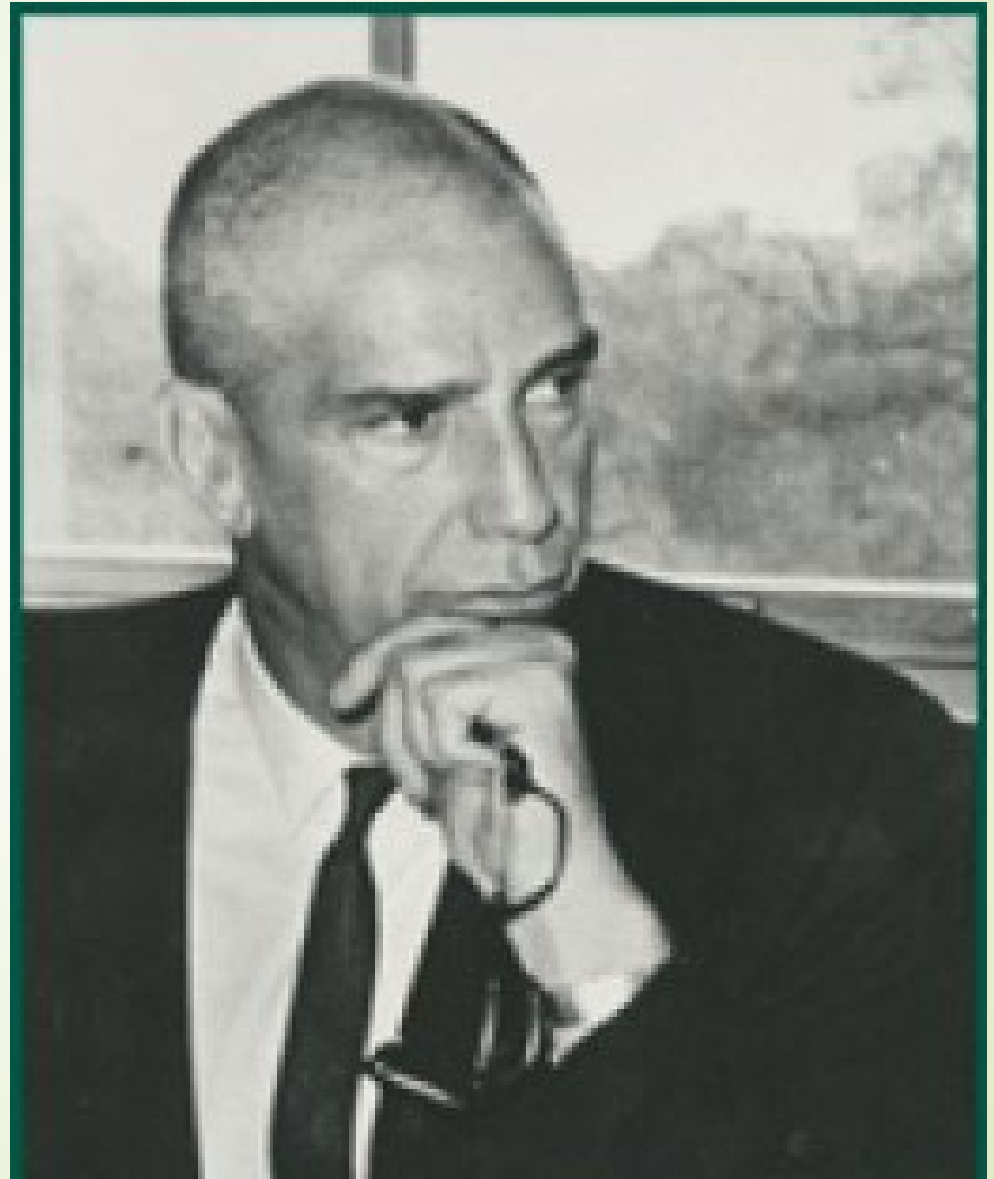
Injections of live cancer cells into
elderly patients without
consent


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

Chester Southam, M.D.

risks and nonetheless eager to take part in it. "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.

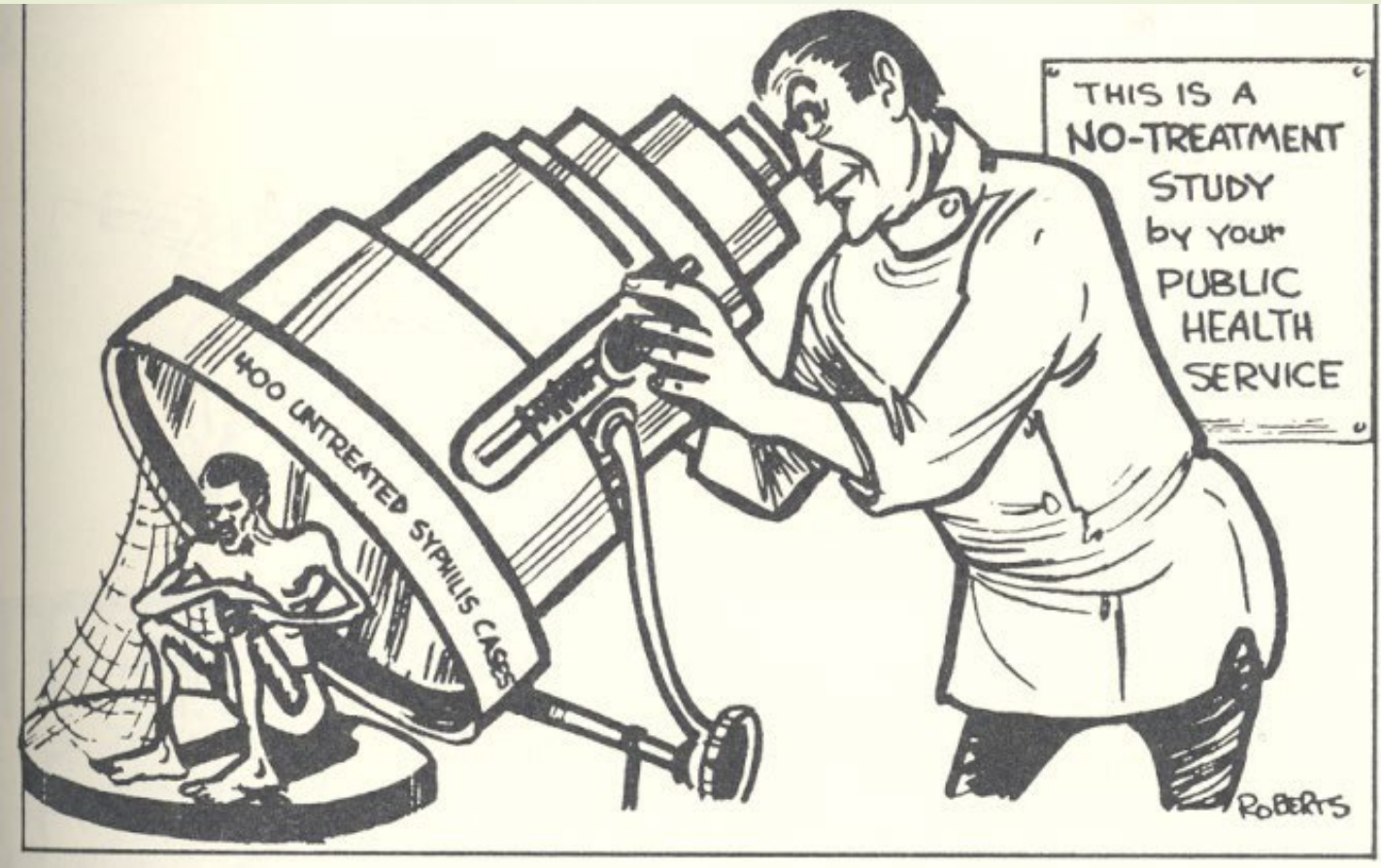
Officials of the health service who initiated the experiment have long since retired. Current officials, who say they

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,



Study begins in 1932



(Courtesy National Archives)

Public Health Service Surgeon General Thomas Parran,



*Shadow on the
Land*

Head of PHS, 1936-
1948

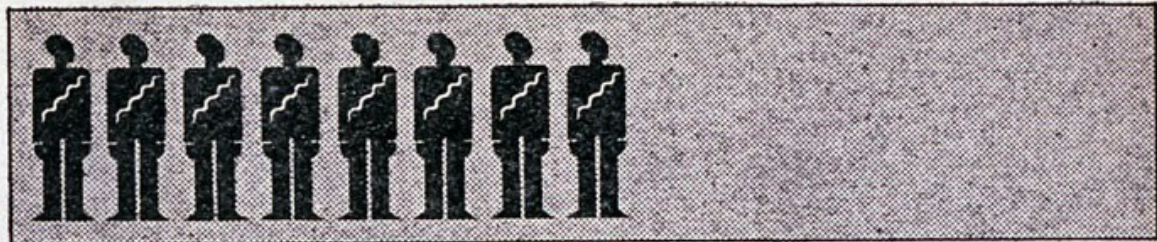
INCIDENCE OF SYPHILIS AMONG NEGROES



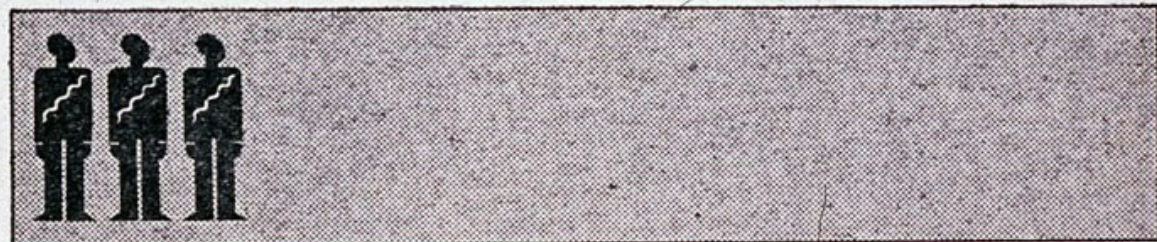
MACON COUNTY, ALA.



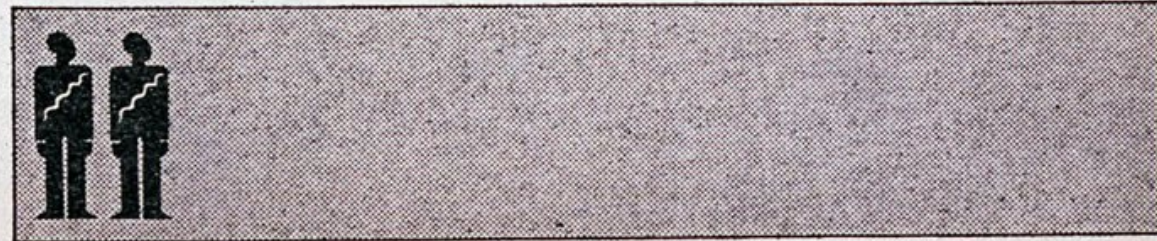
BOLIVAR COUNTY, MISS.




ALBEMARLE COUNTY, VA.



MEHARRY UNIVERSITY, TENN.



Each symbol represents 3% of all Negroes studied

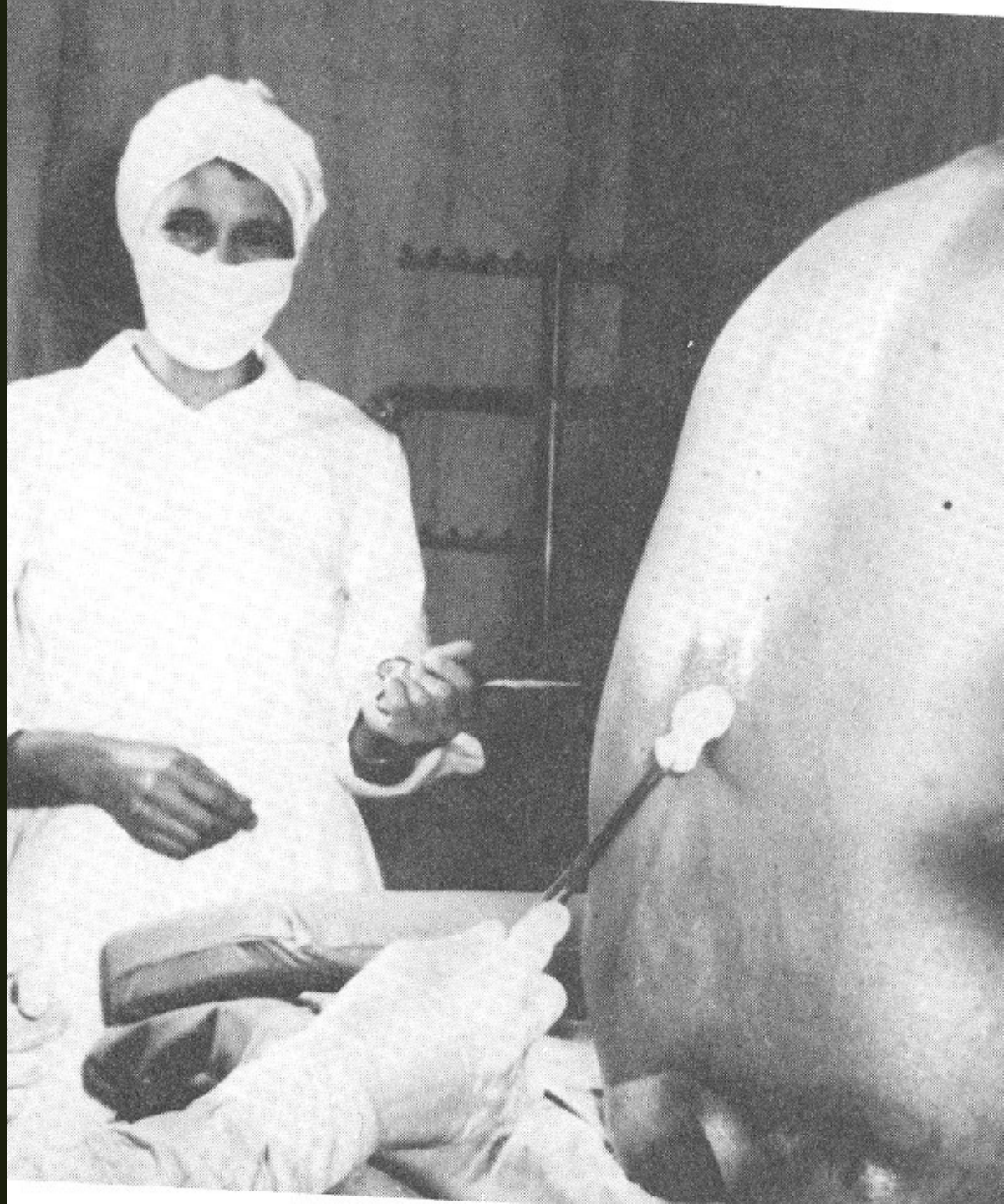
PICTORIAL STATISTICS, INC 

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



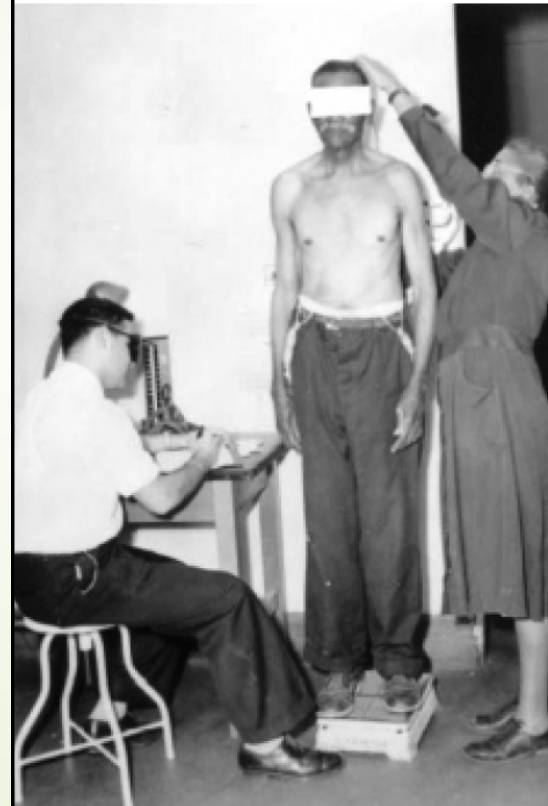
Nurse Rivers

obtains permission
for autopsy

easier when a
burial stipend of
\$50 is provided

only one refusal in
140 requests

Figure 3. An unaltered view. Nurse Eunice Rivers measures a participant in the TSUS. Dr. Stanley Schuman records the data. The photograph was taken in the TVAH in February 1952. (National Archives, CDC, East Point, GA)





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

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.



Leroy C. Burney

Awarded 1958

Surgeon General



1969

--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

Television

FEBRUARY 16-22



Sacrificed to Science

A Docudrama Reopens
A Cruel Chapter
In the Annals of Race

BY MICHEL MARRIOTT





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

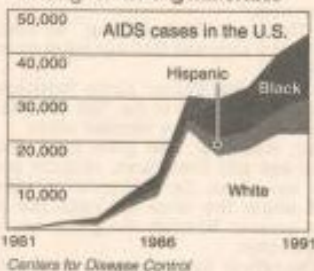
how AIDS got started, there are ways to stop it. Campaign officials reasoned that few blacks would believe government denials anyway. But surely black leaders and public figures with high credibility, such as Magic Johnson, the basketball star, could do much to discredit the pernicious and dispiriting 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.

The Plague Spreads

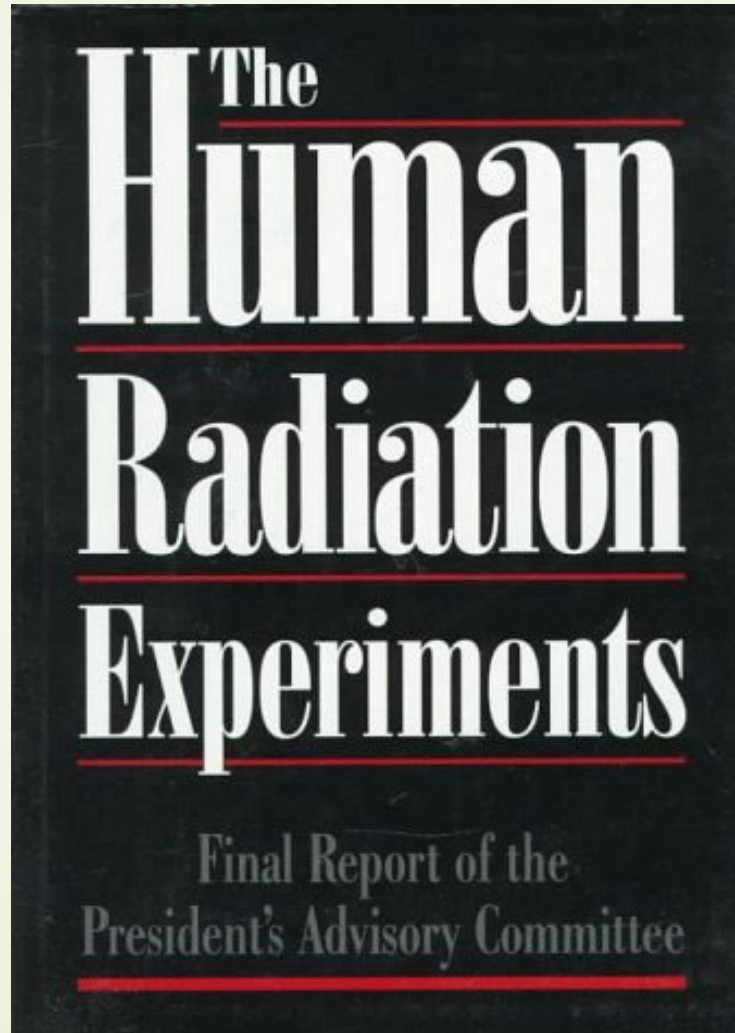
A rising toll among minorities



Centers for Disease Control



Presidential apology 1995



White House Apology for the Syphilis Study,





White House apology ceremony, 16 May 1997. Participants and survivors of the study (first row): Herman Shaw, Fred Simmons, Charles Pollard, Frederick Moss, Carter Howard. White House officials (back row): U.S. Surgeon General David Satcher, President William J. Clinton, Vice-President Albert Gore.



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



US Infected *Thousands of* Guatemalans With STDs

Earlier reports said
hundreds were victims

Sep 2, 2011 8:48 AM CDT

John Cutler, STD studies



John C. Cutler
From the National Library of Medicine

- ▶ 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



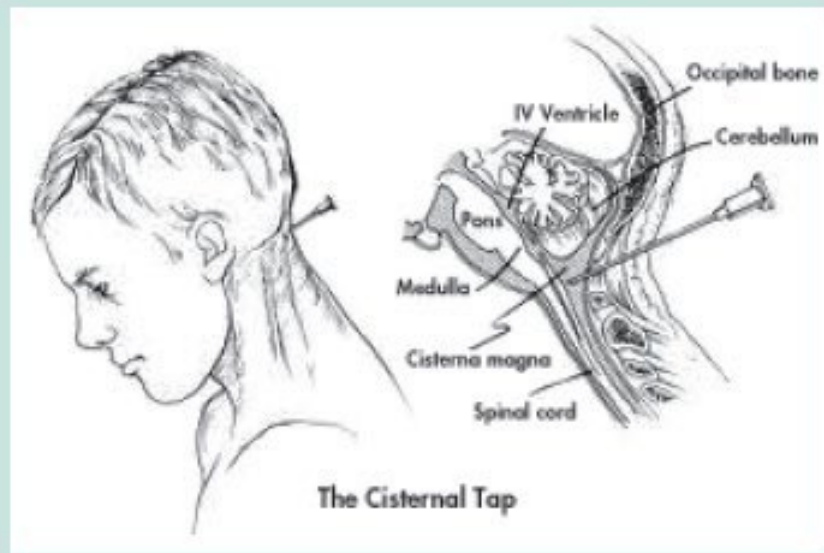
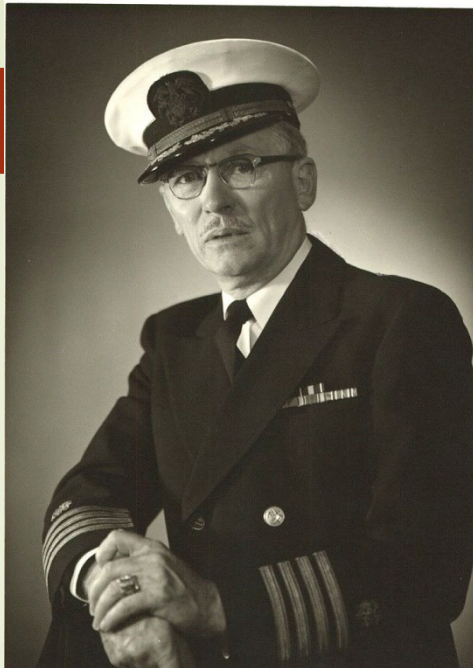


Diagram of a cisternal puncture.
From Alexander G. Reeves, M.D. and Rand S. Swenson,
M.D., Ph.D., "Disorders of the Nervous System"

- ▶ 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.



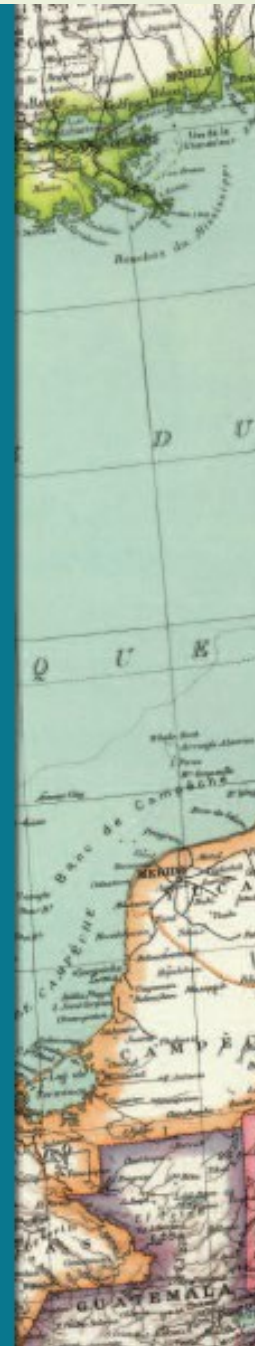
I saw Doctor Parran on Friday and he wanted to know if I had had a chance to visit your project. Since the answer was yes, he asked me to tell him about it and I did so to the best of my ability. He was familiar with all the arrangements and wanted to be brought up to date on what progress had been made. 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."

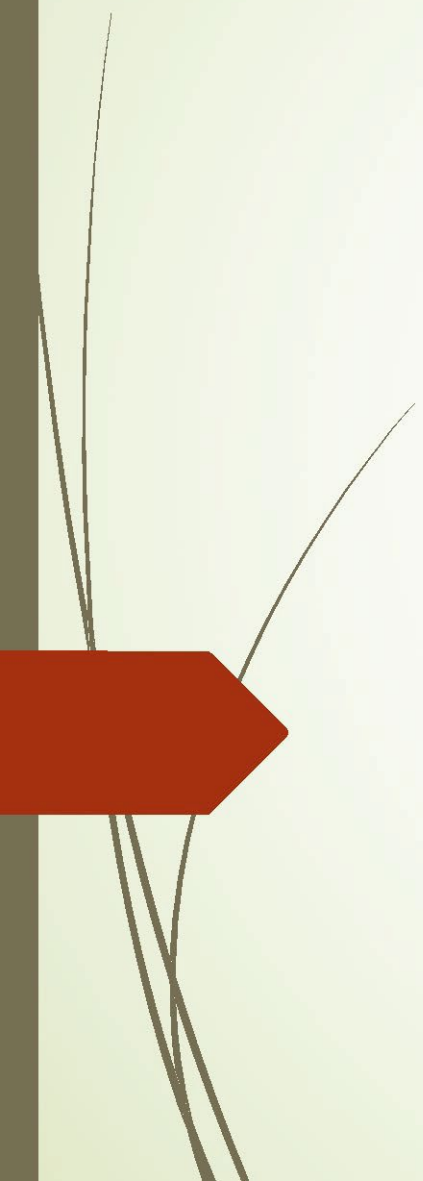


“ETHICALLY IMPOSSIBLE”
STD Research in Guatemala
from 1946 to 1948

Presidential Commission
for the Study of Bioethical Issues

September 2011





Ongoing challenge
to protect human
subjects and
advance medical
knowledge