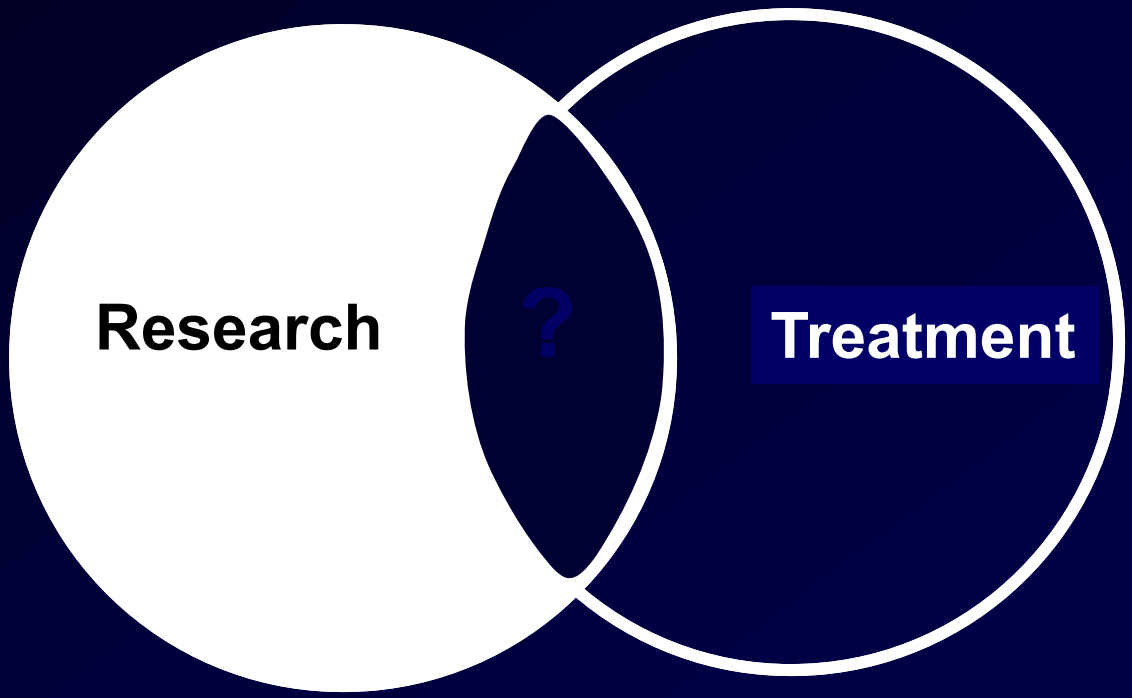
Current Regulations in Clinical Research
"How did we get here?"

Bill Pickard, RPh, MS

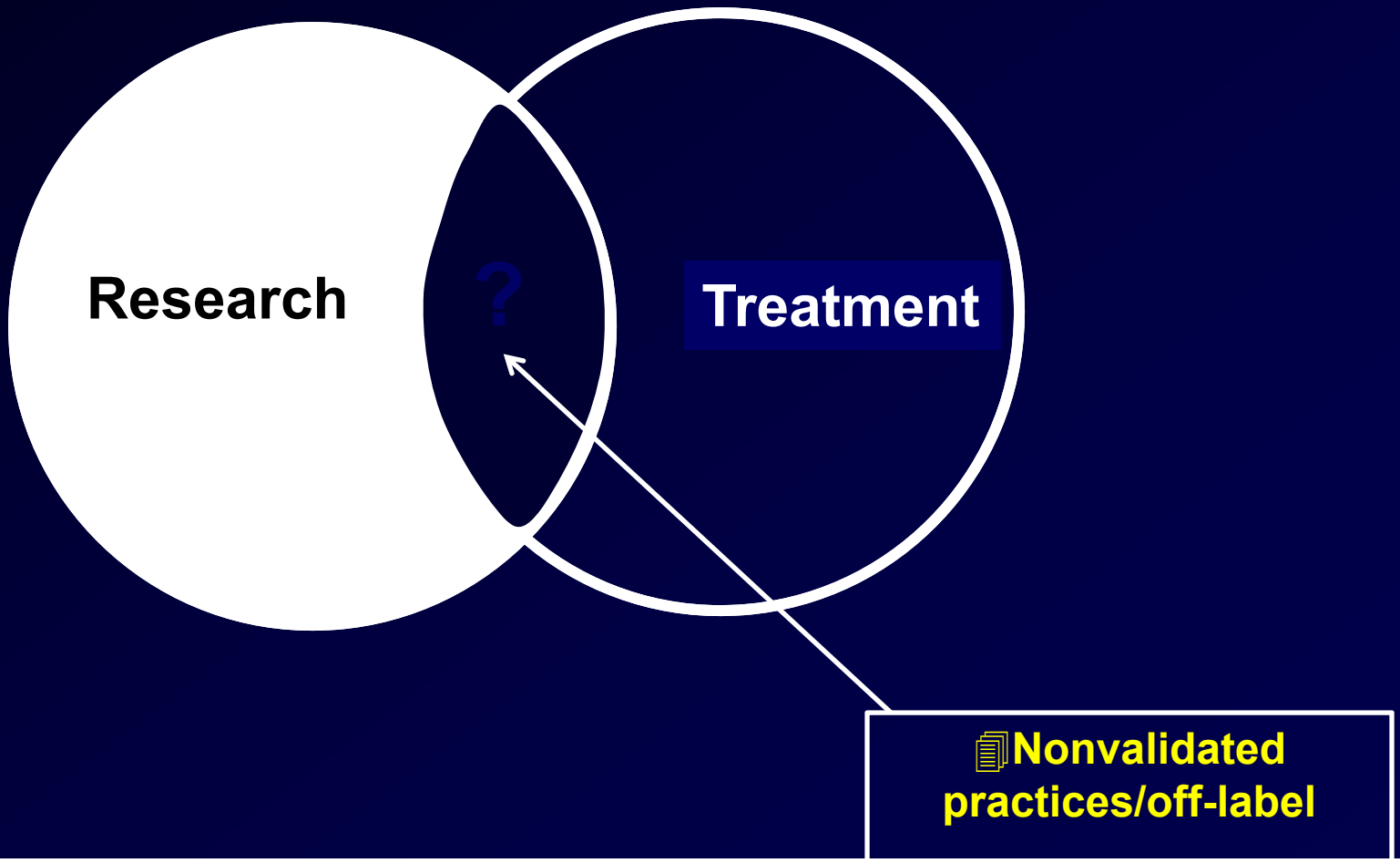
Chair Dept. of Clinical Research

Campbell University College of Pharmacy

Ethical Dilemma



Ethical Dilemma



Practice of Medicine vs. Clinical Research

Practice of Medicine	Clinical Research
• Intervention designed solely to enhance the well-being of an *individual patient* • Treatment guidelines specific to patient • Reasonable expectation of success	• Intervention designed to test a hypothesis and draw conclusions to *contribute to generalizable knowledge* • Formal protocol with objectives and procedures to reach those objectives • Expectation is to benefit society

CLINICAL RESEARCH

"Patient-oriented clinical research conducted with *human subjects*, or research on the causes and consequences of disease in *human populations* involving material of *human* origin (such as tissue specimens and cognitive phenomena) for which an investigator or colleague directly interacts with *human subjects* in an outpatient or inpatient setting to clarify a problem in *human* physiology, pathophysiology or disease, or epidemiologic or behavioral studies, outcomes research or health services research, or developing new technologies, therapeutic interventions, or clinical trials."

National Institutes of Health (NIH)

Regulations vs. Ethics

- Regulations and laws: what MUST be done
  - FDA acts
  - Code of Federal Regulation (CFR)
- Ethics: what SHOULD be done- even if not required.
  - Values
  - Reputation
  - “When no one is looking”

History of Medical Research

- 600 BC Daniel: 10 day open label
  - Daniel 1:8-16
  - N = 4 (Belteshazzar/Shadrach/Meshach/Abenego)
  - Vegetables and H_20 vs royal food (predictor variable)
  - Health outcome (outcome variable)

- 1747: James Lind (British surgeon) - Scurvy
  - 12 sailors afflicted
  - Provided some w/ fruits & vegetables

- 1796 : Edward Jenner – Smallpox
  - Inoculated 8 years of age boy with cowpox exudate
  - 2nd inoculation 2 months later
  - His own son

- 1897: Guiseppe Sanarelli – isolated Yellow Fever organism
  - Five “subjects” injected with organism
  - Three died

History of Medical Research

- 1900: Walter Reed commissioned to identify cause of yellow fever

- "Safeguards" established
  - Self-experimentation
  - Adults only
  - Written contract explaining perils
    - First consent form – need for consent
    - Recognition of "experiments"
    - $100 to be exposed
    - $100 additional compensation if contract disease

Ethics

Latin *ethica* from the Ancient Greek "moral philosophy", from the adjective of *ēthos* "custom, habit"), a major branch of philosophy, is the study of values and customs of a person or group. It covers the analysis and employment of concepts such as right and wrong, good and evil, and responsibility. It is divided into three primary areas: *meta-ethics* (the study of the concept of ethics), *normative ethics* (the study of how to determine ethical values), and *applied ethics* (the study of the use of ethical values).

Organizations Setting Standards of Conduct

- Trustworthy
- Loyal
- Courteous
- Kind
- Obedient
- Cheerful
- Thrifty
- Brave
- Clean
- Reverent

Organizational Standards

- Loyalty
- Duty
- Respect
- Selfless Service
- Honor
- Integrity
- Personal Courage

Personal Standards of Conduct

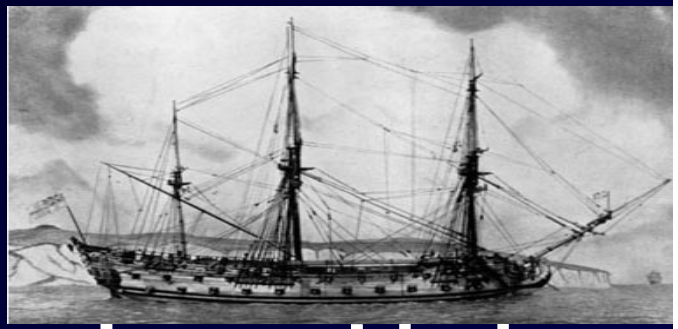
- What are the basis for yours?
- Where did they come from?
- Where should they come from?
- Do you evaluate them regularly?
- Do ethics change over time?

Example of Personal "Principles"

- Obey God
- Do right
- Be flexible
- Don't quit
- Don't whine

Violations of Research Medical Ethics: Past to Present

History of Ethics in Research



- 18th century British surgeon James Lind
  - Studied scurvy in sailors (HMS Salisbury)
  - Provided some w/ fruits & vegetables others without
- 1897: Guiseppe Sanarelli, bacteriologist isolated organism causing yellow fever
  - Injected 5 people with the isolate to prove his claim, criticized but soon forgotten

History of Ethics in Research

- 1900: US surgeon general commissioned Walter Reed to identify cause of yellow fever
- Reed established "safeguards"
  - Self-experimentation would be used
    - Not without risk, Jesse Lazear died in experiment
  - Only adults enrolled
  - Written contract that explained peril of undertaking and offered $100 to those who were willing to be exposed and $100 to those who contracted --- one of the first known consent forms
- Yellow fever investigators helped legitimize medical research
- By WWII need to obtain permission from participants was widely accepted

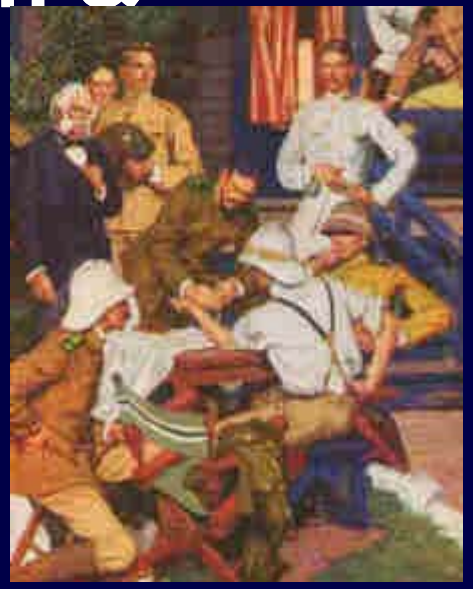
Yellow Fever Experiments
Dr. Walter Reed

- **Conducted in Cuba following the Spanish-American War**
- **Written consent in English & Spanish**
- **Consent was witnessed**

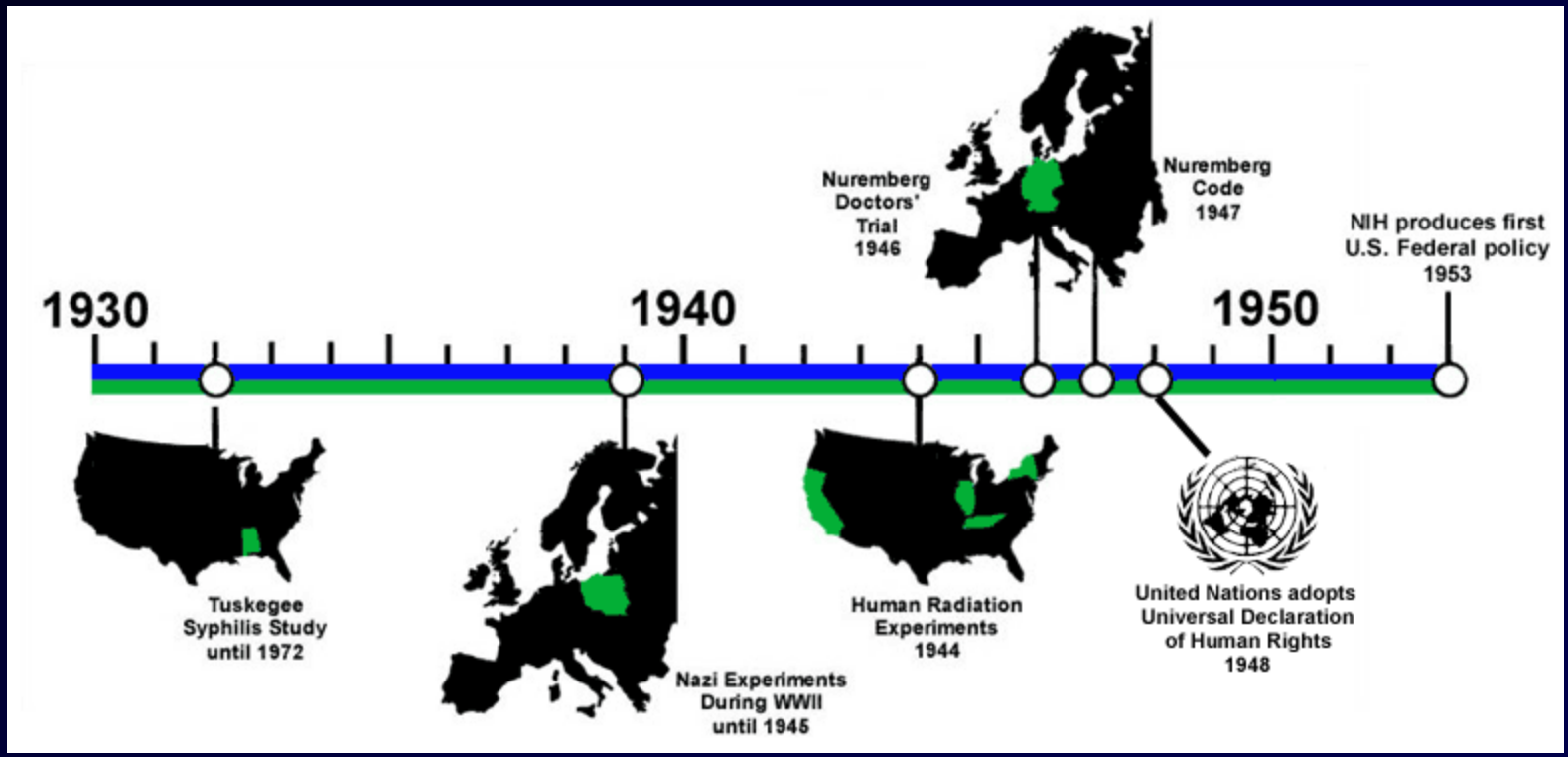
Ethical Dilemma-

-Excessive compensation

-No ability to withdraw

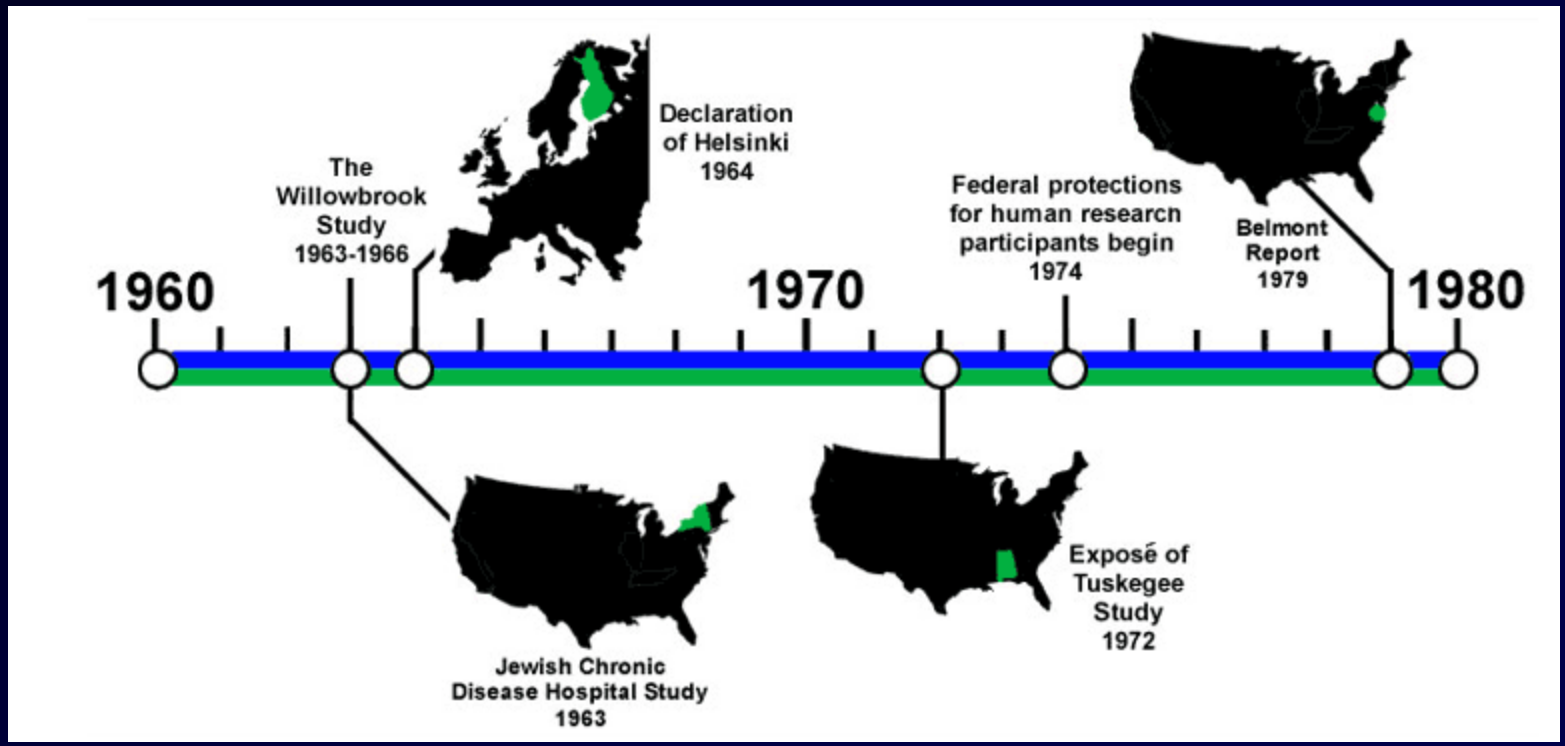


Historical Events That Shaped Research Ethics



http://cme.cancer.gov/c01/a01_10a.htm

Historical Events That Shaped Research Ethics



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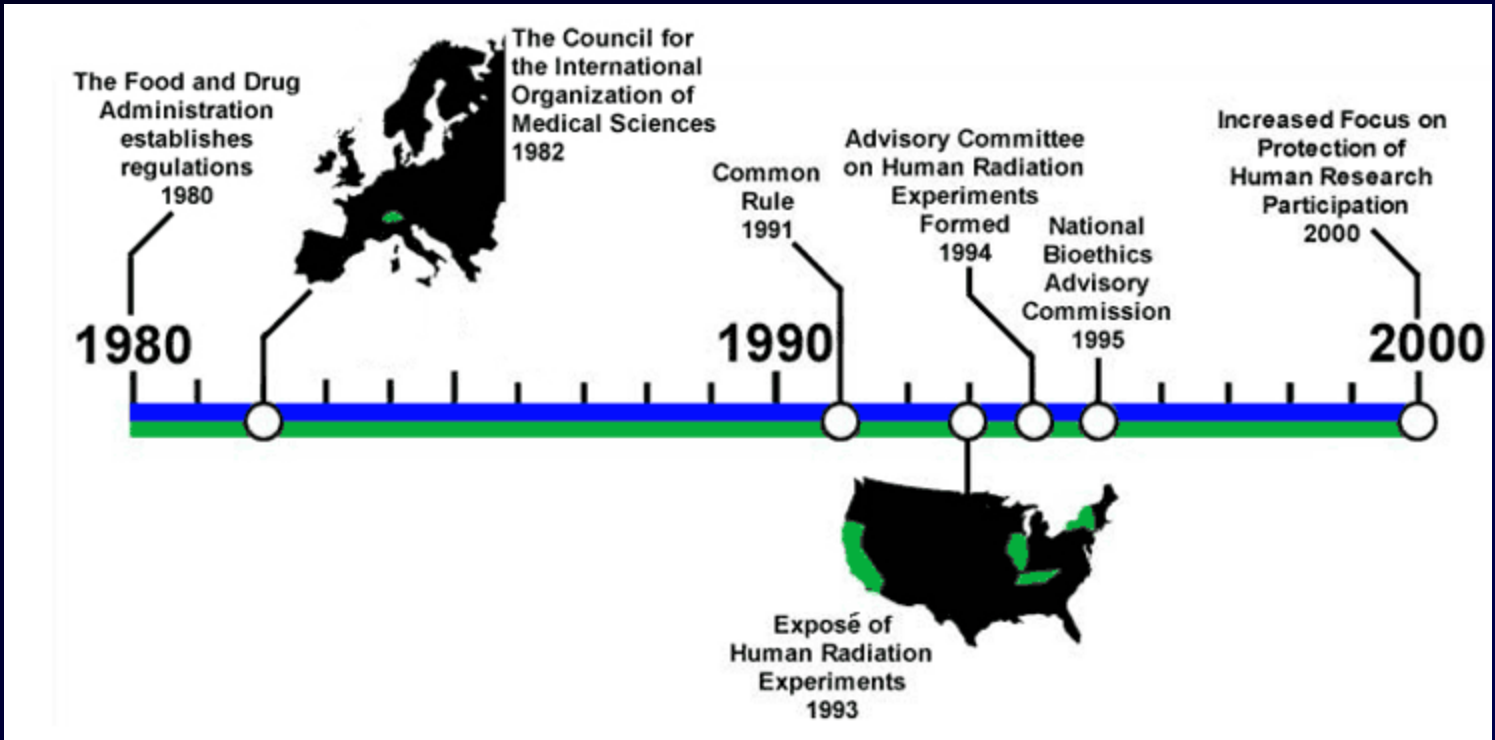
Historical Events That Shaped Research Ethics



http://cme.cancer.gov/c01/a01_10a.htm

History and Evolution of Ethical Principles of CR

- **Beginnings in World War II**

  -Nazi MD's conducted experiments on prisoners in concentration camps to advance the political and social agendas of the Third Reich

  -"Social Hygiene" to produce an Aryan race

Nuremberg Doctors' Trial

Nazi Experiments: WWII

- Freezing
  - Forced to remain outdoors unclothed 9-14 hrs or in baths of freezing water for 3 hrs; rewarming attempted but usually not successful
- Altitude
  - Low pressure tanks to see how long could survive w/o O2
- Seawater
- Sulfanilamide
  - Wounds inflicted and bacterial culture, gangrene producing culture introduced; sulfa given to some, others not
- Tuberculosis
- Poison
  - Fed various poisons, if didn't die were killed for autopsy
- Artificial insemination
- Sterilization
  - Chemical and x-ray
- Twin experiments
- Malaria
  - Infected with malaria and given experimental drugs
- Mustard Gas
  - Deliberately wounded, then wounds infected w/ mustard gas or forced to inhale mustard gas
- Typhus
  - Injected with antityphus vaccine then infected with typhus – control group received no tx
- Incendiary bomb
  - Intentionally burned w/ phosphorous material taken from English bonds so doctors could learn what kind of wounds were produced
- Anthropological investigation
  - Killed to assemble skeletons representing what Nazis called repulsive but characteristic subhuman

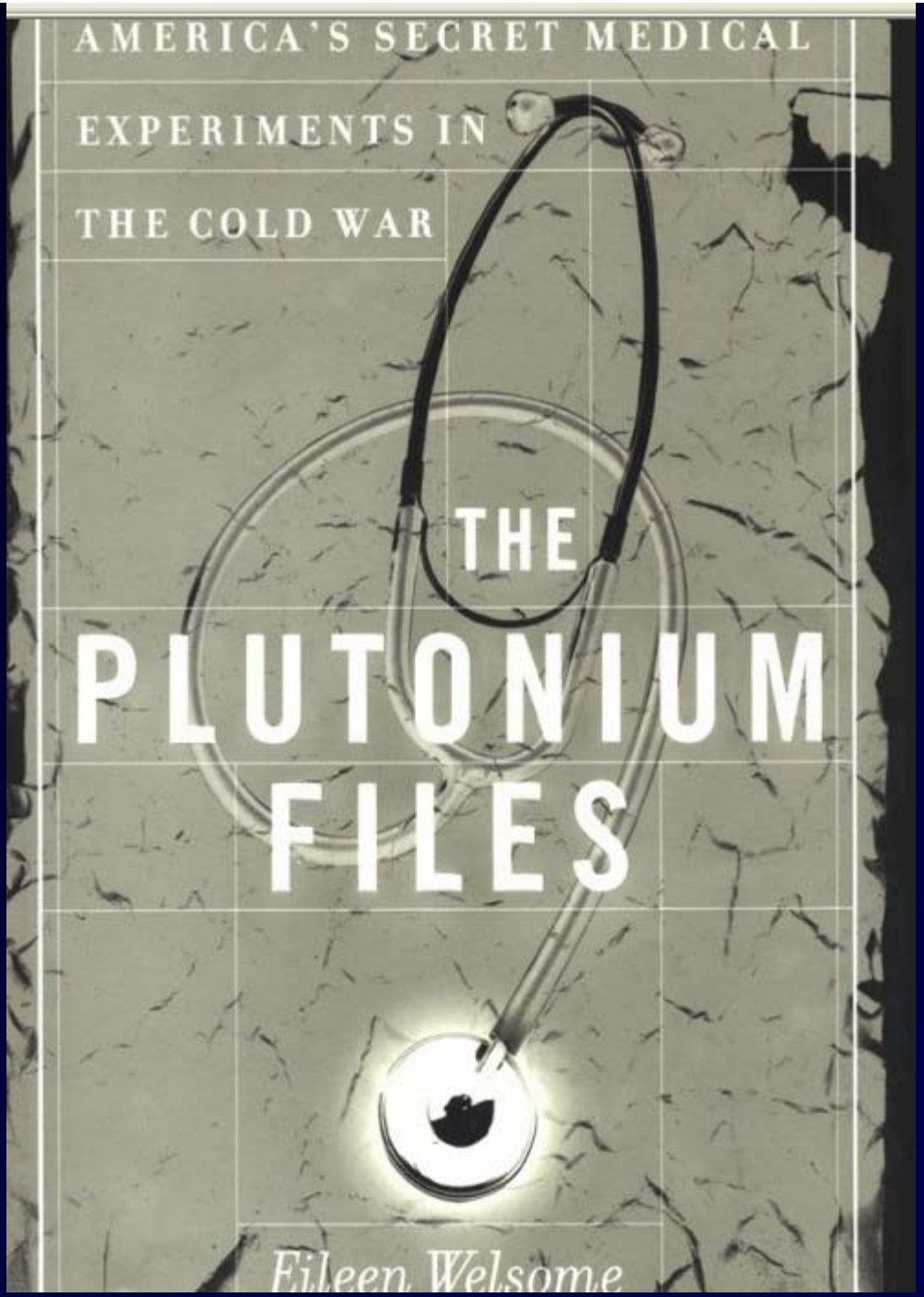
Nazi Doctors' Trial

- U.S. vs. Karl Brandt, one of the many MD's
- Revelation of these experiments horrified the world.
- Nuremberg Military Tribunal declared them to be "crimes against humanity"
- Seven MD's were hung and many others spent the rest of their lives in prison (20)
- Trial results known as the Nuremberg Code

Nuremburg Doctor's Trial/Nuremburg Code

1. Voluntary consent is essential
2. Likely to yield fruitful results for society, not available by other means
3. Based on results of animal experimentation and knowledge of disease; anticipated results should justify study
4. Avoid all unnecessary physical and mental suffering and injury
5. No study should be conducted when there is a priori a reason to believe death or disabling injury will occur
6. Degree of risk should never exceed the humanitarian importance of the problem
7. Preparations should be made and facilities should be available to protect the subject against remote possibilities of injury, disability & death
8. Conducted only by scientifically qualified persons
9. Subject is at liberty to withdraw participation
10. Scientist must be prepared to terminate the experiment at any stage if he/she feels that continuation is likely to result in injury, disability, or death or the subject

http://www.nihtraining.com/ohsrsite/guidelines/nuremberg.html


AMERICA'S SECRET MEDICAL
EXPERIMENTS IN
THE COLD WAR
THE
PLUTONIUM
FILES
Eileen Welsome

Human Radiation Experiments

- Manhattan Project & US Atomic Energy Commission
  - Over 400 listed experiments, 1944-1974; (http://www.eh.doe.gov/ohre/roadmap/experiments/0491terms.html#0491_Listing)
  - Intentional exposure to ionizing radiation
    - Hospitalized pts injected w/ plutonium without their knowledge
  - Intentional environmental releases of ionizing radiation
    - To test effects of ionizing radiation on human health
    - To test the extent of human exposure to ionizing radiation
  - Purpose was to assess and improve safety of radiation workers and to evaluate the potential for plutonium in treatment of bone cancer.

Willowbrook Study

- 1963-1966
- Willowbrook State School for “mentally defective persons”
- Deliberate exposure of children and adolescents to hepatitis to study natural history of disease
- Rationale: nearly every child was likely to contract hepatitis anyway, thus justifying the deliberate exposure
- Coercive recruitment: wards closed to new admissions. Parents of children with severe disabilities received a letter stating that their children could be admitted if they were placed in the research ward

Jewish Chronic Disease Hospital Study

- 1963
- Live cancer cells deliberately injected into debilitated elderly patients without consent
- Goal of research was to determine rate of rejection of human cancer cells
- Rationale: Available evidence suggested that cancer cells would cause immune reaction to expel cells, thus experiment presented no risk to subjects

Declaration of Helsinki

- Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
- Amended by the:
  - -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, South Africa, October 1996
  - -52nd WMA General Assembly, Edinburgh, Scotland, October 2000
  - -53rd WMA General Assembly, Washington, DC, USA, October 2002
  - -55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification on Paragraph 30 added)
  - -59th WMA General Assembly, Seoul, Korea, October 2008
  - -64th WMA General Assembly, Brazil, October 2013

Declaration of Helsinki

- Duty is to protect life, health, privacy, and dignity of human subject
- Must conform to accepted scientific principles, based in knowledge of scientific literature
- Caution in research that may affect environment and welfare of animals must be respected
- Design and performance should be clearly described in a protocol; protocol should be reviewed by ethical board
- Protocol should contain statement of ethical considerations
- Conducted only by qualified personnel
- Study should be preceded by careful assessment of predictable risks & burdens in comparison to benefits to subject or others

Declaration of Helsinki (cont.)

- Abstain from research unless they are confident risks have been adequately assessed and can be managed; should cease any study if risks are found to outweigh benefits
- Research should only be conducted if objective outweights inherent risks and burdens to the subjects
- Only justified if reasonable likelihood that population in which research is carried out stand to benefit from results
- Respect for integrity of persons and privacy, confidentiality
- Subjects must be informed of aims, methods, sources of funding, conflicts of interest, institutional affiliations, anticipated risks and potential benefits, right to withdraw, right to abstain, without effecting access to care; consent obtained
- Informed consent should be obtained so as not to coerce patient
- For minors or those incapable of consent assent must also be obtained
- Ethical obligations of authors and publishers; negative results should be made publicly available

Declaration of Helsinki (cont.)

- Combining medical research with medical care is justified to the extent that research is justified by its potential prophylactic, diagnostic, or therapeutic value
- Investigational agent should be tested against the best current methods; does not preclude the use of placebo where no proven method exists
- Patients should be assured of access to best proven treatments
- Fully inform patient which aspects of care are related to research
- Unproven methods used by physicians to save life, re-establish health, or alleviate suffering should be made the object of research when possible

Other Examples….

- Henry Beecher, NEJM 1966;274:1854-60
  - 22 examples of unethical research, published in reputable, peer reviewed, medical journals

Beecher paper

- Withholding of antibiotics to patients with streptococcal infection to study rheumatic fever
- Withholding of chloramphenical for typhoid fever
- Triacetyloleandomycin given to children with mental illness or juvenile behavioral problems with acne, because there was evidence of hepatic dysfunction and further study was desired
- Dose ranging study of chloramphenicol to tests its effects on aplastic anemia – a known side effect
- Thymectomy on survival of skin grafts
- Cyclopropane anesthesia and cardiac arrhythmias
- Ureteral reflux in the normal bladder – 26 normal babies < 48 hours old, exposed to multiple x-rays

Beecher, H NEJM 1966;274:1354-60

- 1932-1972
- US Public Health Service
- Determine natural course of untreated, latent syphilis in black men
- 400 men w/ syphilis and 200 uninfected controls
- Penicillin available in early 1950s
- Intentionally withheld from study participants
- Led to believe they were receiving treatments

Bad Blood: The Tuskegee Syphilis Study

http://www.healthsystem.virginia.edu/internet/library/historical/medical_history/bad_blood/

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,

New York Times, July 26, 1972

EFFECTS OF UNTREATED SYPHILIS IN THE NEGRO MALE, 1932 TO 1972: A CLOSURE COMES TO THE TUSKEGEE STUDY, 2004

SHAMIM M. BAKER, OTIS W. BRAWLEY, AND LEONARD S. MARKS

They said it was a study that would do you good.

(Ernest Hendon, 1908 to 2004,[1] last survivor of Tuskegee Study of Untreated Syphilis)

I am sorry.

(President Clinton, May 16, 1997,[2] apologizing for United States' role in study)

Urology 2005;65:1259-1262

http://clinton4.nara.gov/textonly/New/Remarks/Fri/19970516-898.html

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Belmont Report

- Basic Ethical Principles
  - Respect for Persons
  - Beneficence
  - Justice
- Applications
  - Informed Consent
  - Assessment of Risks and Benefits
  - Selection of Subjects

Belmont Report

- Respect for persons
  - Individuals should be treated as autonomous agents
  - Persons with diminished autonomy are entitled to protection
    - Illness, mental disability, circumstances that restrict liberty, immature, age
- Autonomy
  - An individual capable of deliberation about personal goals and of acting under the direction of such deliberation
- In some cases, respect for persons is a matter of balancing competing risks

Belmont Report

- **Beneficence**
  - Do no harm
  - Maximize possible benefits and minimize possible harms
  - One should not injure one person regardless of the benefits that might come to others
  - However, all (most) research is associated with the potential for harm
  - Does this mean research can't be conducted?
  - Must decide when/if it is justifiable to seek benefits despite the risks and when the risks outweigh the potential benefits
  - Whose right is it to decide this?

Belmont Report

- **Justice**
  - Who ought to receive the benefits of research and bear its burdens?
  - Injustice: when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly
  - How should people be treated equally?
  - Tuskegee – disease not confined to the African American population, but that is who was studied
  - Socioeconomics, race, gender, age
  - Are some selected because of easy availability, compromised position, or manipulability rather than for reasons directly related to the problem being studied

Other Regulatory Guidance

- Common Rule
  - Code of Federal Regulations (CFR Part 46, Subparts A-D)
  - Subpart A: Basic policy for the protection of human subjects (government funded or for registration)
  - Subpart B: Additional protections for pregnant women, fetuses, and neonates
  - Subpart C: Prisoners as subjects
  - Subpart D: Protections for Children
- Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO)
  - International Ethical Guidelines for Biomedical Research Involving Human Subjects
- ICH Harmonised Tripartite Guideline – Guideline for Good Clinical Practice

U.S. Halts Human Research at Duke

By Rick Weiss
Washington Post Staff Writer
Wednesday, May 12, 1999; Page A1

The U.S. government has temporarily shut down federally funded research on humans at Duke University Medical Center, one of the nation's largest and most prestigious medical research facilities, after federal investigators determined that the university could not ensure the safety of participants.

The suspension of Duke's federal license to conduct human research is only the fourth such move by the government in nearly a decade and appears to be the largest yet in terms of the number of studies and people affected and the amount of money at stake. The Durham, N.C., center receives about $175 million a year from the federal government for medical research, officials said.

Among the problems cited by the government in its May 10 suspension letter to Duke was an oversight committee's failure to keep track of human studies after they began – the only way to make sure people are not being unexpectedly harmed by research – and a failure to document that special, federally mandated protections for children were in place.

Duke officials emphasized yesterday that there is no evidence anyone was harmed by the oversight lapses, which they characterized as largely "administrative" failings, such as poor recordkeeping. They expressed their support for research protections and said they hoped the issues could be

http://www.washingtonpost.com/wp-srv/national/daily/may99/duke12.htm

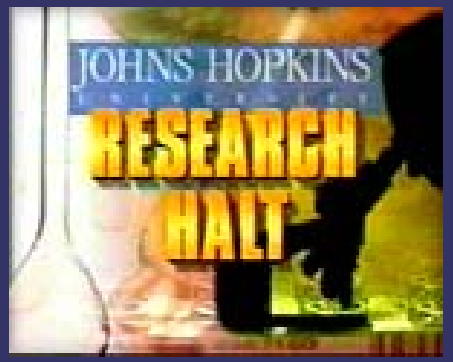
Online NewsHour

a NewsHour with Jim Lehrer Transcript

ONLINE FOCUS

RESEARCH HALT

July 20, 2001



A federal oversight agency suspended almost all of Johns Hopkins federally financed medical research involving human subjects.

The NewsHour Health Unit is funded by a grant from The Henry J. Kaiser Family Foundation.

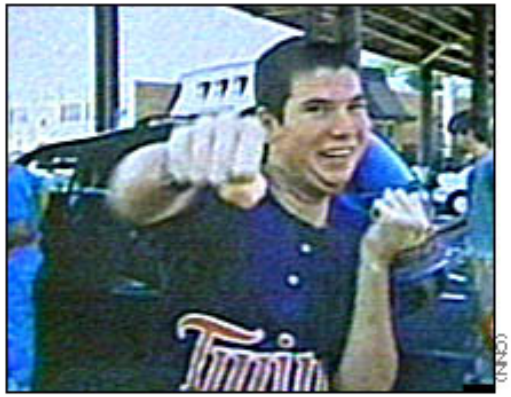
The decision was prompted by the recent death of Ellen Roche, a 24-year-old volunteer enrolled in an asthma study. Roche, a lab technician, died on June 2, one month after inhaling an unapproved drug as part of a study into the causes of asthma.

http://www.pbs.org/newshour/bb/health/july-dec01/hopkins_7-20.html

Father of gene therapy participant says researchers acted 'irresponsibly'

February 2, 2000
Web posted at: 3:42 p.m. EST
(2042 GMT)

From Medical Correspondent
Elizabeth Cohen



Jesse Gelsinger, 18, was receiving an experimental gene therapy for an incurable inherited liver disease prior to his death in September

(CNN) -- The father of a young man who died during a gene therapy trial at the University of Pennsylvania told a Senate hearing on Wednesday that researchers acted "irresponsibly" and they downplayed possible risks to his son.

Paul Gelsinger testified during the Senate Health, Education and Labor Subcommittee hearing on whether the Food and Drug Administration did the right thing in shutting down gene therapy trials at the University of Pennsylvania after 18-year-old Jesse Gelsinger of Tucson, Arizona, died in September.

http://archives.cnn.com/2000/HEALTH/02/02/gene.therapy.02/

http://www.pbs.org/newshour/bb/health/jan-june00/gene_therapy_2-2.html

Ethical Challenges of Randomized Controlled Trials (RCT)

- Physician (practice of medicine) are obligated to always act in the best interest of the patient
- Scientists (researchers) are concerned with answering questions
- Can a physician-scientist randomize a patient in a trial and still be acting in the patient's best interest?

Ethics of Placebo Controls

- Placebo controlled trials might be justified:
  - High placebo-response rate
  - Standard therapy is questionable or low efficacy or has not been shown superior to placebo
  - New therapeutic class
  - Standard therapy has a high frequency of side effects

Ethics of Placebo Controls

- Process to minimize harm:
  - Protocol clearly defines those at risk to exclude (severely ill, severe suffering)
  - Placebo period limited to the minimum required for scientific validity. Open label period
  - Subjects carefully monitored
  - Explicit and specific criteria for withdrawal of subjects who have adverse events
  - Access to free or transitional care PRN

Discussion Topics

- Should data obtained from unethical research be used?
- What effects do the past unethical research practices have on current/future research?
- What effects do regulations have
  - On the safety of human subjects
  - Of the ability to conduct research
  - On unethical researchers who place personal agendas above the protection of human subjects?
- Are the current regulations adequate to cover advances in technology?
- Do you feel that some of these cases represent intentional vs. unintentional (but negligent) harm?
- Can the regulations and guidance documents we current have in place address both?

We see many cases where investigators professional careers were destroyed by their breech of integrity. This should not surprise us. Solomon warned us of this from the book of Proverbs:

Proverbs 11:13: The integrity of the upright guides them, but the unfaithful are destroyed by their duplicity. (NIV)