

Incorporating the Voice and Influence of the Community in Research

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OBJECTIVES

- Chronicle the history and approaches to human subjects research globally including timelines for regulations
- Identify historical lessons learned and how these lessons have shaped human subjects research today
- Discuss current trends in healthcare and research which poises both economic and ethical considerations

HISTORY OF HUMAN SUBJECTS RESEARCH

- 10th century – Roman, Greek, and Arab medical communities
- 13th century- dialogue between physicians and philosophers concluded that human experimentation should not be performed – Maimonides, Bacon, and Bernard
- Resurgence in 18th century
 - Self-experimentation (e.g. surgical anesthesia – Priestly and Davy; oral medication - Jorg)
 - Family members/vaccines/inoculations (e.g. Jenner and Pasteur)
 - Research on prisoners, orphans, and infants (e.g. Princess Caroline 1721-22)
 - Research on slaves (Reference: Medical Apartheid)
- 1916 – Chair of American Medical Association (AMA) Cannon recommended research regulations be adopted but AMA refused stating that misconduct was about rogue researchers not research itself.

NAZI MEDICAL EXPERIMENTS

- 1933 - Nazi regime established the first concentration camps
- Three categories
 - Survival of Axis personnel – altitude for paratroopers; freezing experiments; potability of seawater
 - Drug and treatment trials – exposed to gas to test antidotes
 - ADVANCE RACIAL AND IDEOLOGICAL TENETS OF THE NAZI WORLDVIEW –
Auschwitz twins; serological experiments on “Gypsies”; studies to establish “Jewish racial inferiority”; mass sterilization



THE DOCTORS' TRIAL

- The first trial conducted under the Nuremberg Military Tribunals
- Also known as “Permissible Medical Experiments” and “The United States of America v. Karl Brandt, et al.”
- 23 defendants, 16 were found guilty
- Part of the verdict of the murder trial – Nuremberg Code
- Established requirements for informed consent, absence of coercion, research design, and beneficence
- Brought global attention to the conduct of research involving human subjects and the need for regulation



BUILDING ON THE NUREMBURG CODE

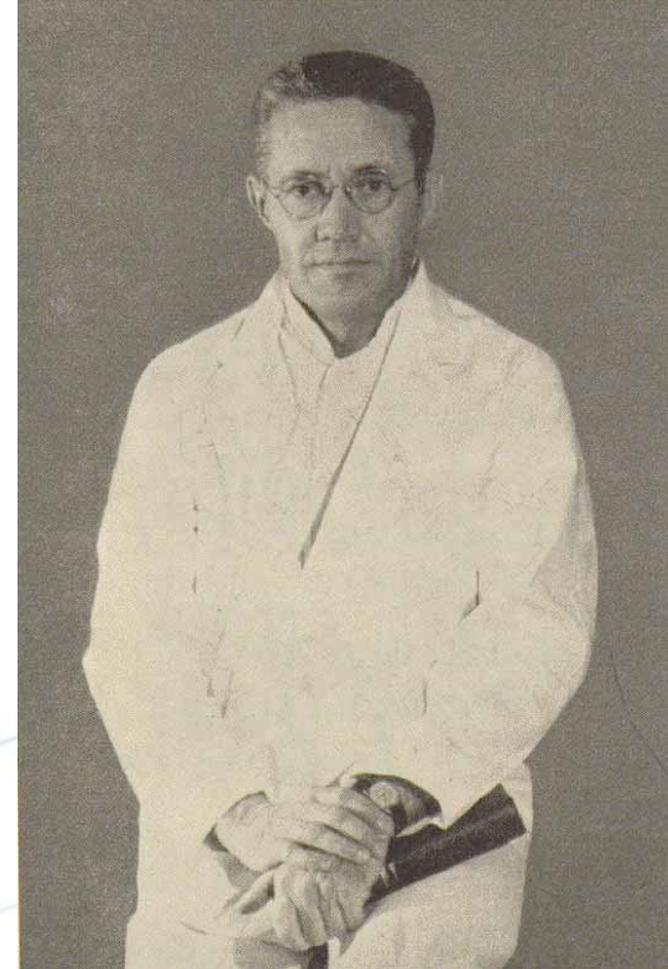
- 1947: Ethical Guidelines for Clinical Investigation (AMA)
- 1953: NIH Clinical Center Policy – Responsibility of the investigator
- 1962: Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act – required informed consent
- 1964: Declaration of Helsinki

MEANWHILE IN THE UNITED STATES...

- 1943-1946: The Office of Scientific Research Development used conscientious objectors from Civilian Public Service as subjects for altitude, gas exposure, water potability, and temperature extremes.
- 1945-1947; 1953-1957: The Manhattan Project researchers injected eighteen human subjects with plutonium, five human subjects with polonium, and at least six human subjects with uranium.
- 1946-1953: The Fernald Center, institution for children with developmental disabilities, conducted experiments in which male residents were injected with radioactive iron and calcium.
- All experiments involved coercion, inadequate research design, and lacked beneficence or informed consent.

THE BEECHER ARTICLE

- A World War II U.S. Army physician serving in North Africa and Italy, Dr. Henry Beecher studied Nazi medical experiments
- In the 1950's and 1960's, Beecher pioneered the discussion on research ethics and suspected the U.S. was also guilty of violating research subjects' rights
- "Ethics and Clinical Research" (*NEJM* 1966)



THE BEECHER ARTICLE

- Placebo-controlled studies of strep throat
- Relapse rate of typhoid fever
- Acne study including mentally-retarded and juvenile delinquent children
- Cyclopropane anesthesia and cardiac arrhythmias
- Study of untreated hepatitis



RESPONSE TO THE BEECHER ARTICLE

- 1966: U.S. Surgeon General Policy Statement – all human subjects review requires independent prospective review (Origin of the Institutional Review Board); also FDA defined specific requirements for informed consent
- 1974: National Research Act - Public Law 93-348; first set of overarching U.S. regulations for the protections of human subjects
- 1979: Belmont Report – Ethical Guidelines
- 1981-1991: Regulations revised to establish “Common Rule”

INFORMED CONSENT GONE WRONG

Macon County Health Department

ALABAMA STATE BOARD OF HEALTH AND U.S. PUBLIC HEALTH
SERVICE COOPERATING WITH TUSKEGEE INSTITUTE

Dear Sir:

Some time ago you were given a thorough examination and since that time we hope you have gotten a great deal of treatment for bad blood. You will now be given your last chance to get a second examination. This examination is a very special one and after it is finished you will be given a special treatment if it is believed you are in a condition to stand it.

If you want this special examination and treatment you must meet the nurse at _____ on _____ at _____ M. She will bring you to the Tuskegee Institute Hospital for this free treatment. We will be very busy when these examinations and treatments are being given, and will have lots of people to wait on. You will remember that you had to wait for some time when you had your last good examination, and we wish to let you know that because we expect to be so busy it may be necessary for you to remain in the hospital over one night. If this is necessary you will be furnished your meals and a bed, as well the examination and treatment without cost.

REMEMBER THIS IS YOUR LAST CHANCE FOR SPECIAL FREE TREATMENT. BE SURE TO MEET THE NURSE.

Macon County Health Department

This letter is reproduced from an educational website at the University of Illinois's Poynter Center for the Study of Ethics and American Institutions (<http://poynter.indiana.edu/sas/lb/facts.html>.)



TIMELINE OF EVENTS—UNTREATED SYPHILIS IN THE NEGRO MALE

“The future of the Negro lies more in the research laboratory than in the schools” – Dr. Thomas Murrell

- 1930 – Spends \$50K for syphilis treatment demonstrations in six states (Alabama: Macon County)
- 1931 – Rosenwald funding is cut for treatment programs; physicians decide to follow the men diagnosed untreated
- 1932-33 – Follow up becomes a study of 399 syphilitic and 201 controls.
- 1945 – Penicillin accepted as the preferred treatment for syphilis
- 1947 – PHS establishes treatment centers, penicillin widely used in military operations
- 1968 – Concerns raised about the study
- 1969 – CDC reaffirms the need for the study
- 1972 – Study condemned in major news outlets; study ends

GUATEMALA SEXUALLY TRANSMITTED DISEASE EXPERIMENTS

- In 1946, Public Health Service investigators in a study funded by the National Institutes of Health, with the cooperation of Guatemalan authorities on sexually transmitted diseases
- The study involved at least 5128 vulnerable people, including children, orphans, child and adult prostitutes, Guatemalan Indians, leprosy patients, mental patients, prisoners, and soldiers.
- Between 1946 and 1948, health officials intentionally infected at least 1308 of these people with syphilis, gonorrhea, and chancroid and conducted serology tests on others.
- The public had no knowledge of the experiments for more than half a century, and even today little is known about these violations of medical ethics and human rights.

LSD EXPERIMENT ON PRIVATE JAMES THRONWELL

[HTTPS://YOUTU.BE/GEO SP2G IGVG](https://youtu.be/GEO SP2G IGVG)

- Private James Thronwell, worked for military communication in New Orleans
- Thronwell, the only Black soldier at the station, was accused of stealing and interrogated with torture including physical attacks, multiple finger pricks, and a barrage of racial epithets
- The multiple finger pricks turned out to be injections of LSD
- Once released, he exhibited antisocial behavior and paranoia and ultimately severe psychiatric disorders.
- He won a lawsuit against the government which awarded him \$625,000 but his normal behavior never returned and was found four years later dead in his swimming pool.

THE COLD WAR AND PROJECT MKULTRA



- During the height of the Cold War Era– U.S. Government feared that its enemies were using mind control on U.S. prisoners of war.
- CIA approved a covert operation to develop techniques that could be used against their enemies to control human behavior with drugs.
- From 1950 to 1974, over 150 experiments involving psychedelic drugs, paralytics, and electroshock therapy.
- Some subjects knew they were in studies but, some had no idea, even when drugs started to impair their physical and mental function.

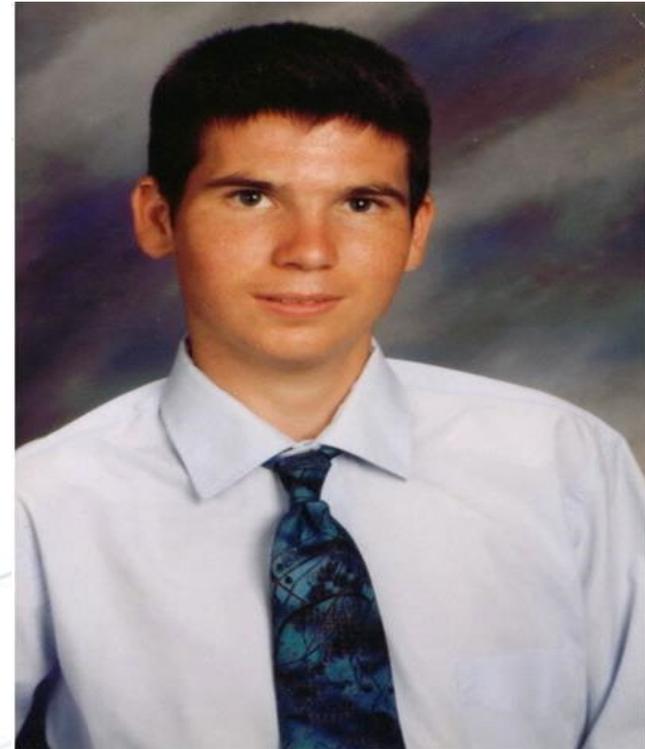
THE LSD ARSENAL OF DEMOCRACY



- Approximately six hundred seven hundred human subjects were used by the government in experiments with psychoactive chemicals such as heroin, MDMA, methamphetamine, and psilocybin
- The most pervasive drug used in the project was LSD
- The CIA conducted the study on military personnel, but also on students, patients, and prisoners
- Operation Midnight Climax – government employed prostitutes lured in unsuspecting men to be research subjects without their knowledge or consent
- Several deaths or permanent emotional injury resulted from the experiments (e.g. Stanley, Thronwell, and Olsen)

THE JESSE GELSINGER STORY

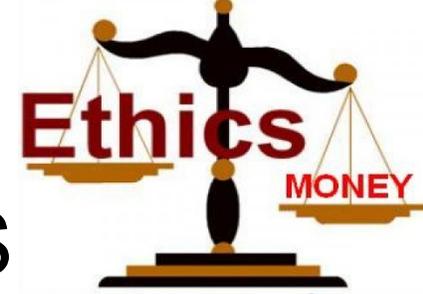
- On September 17, 1999, Jesse Gelsinger, a human subject in a Phase I gene therapy trial died at the age of 18 years old.
- The virus which was used as the vector invaded the liver and surrounding tissue activating the immune system and an inflammatory response.
- The next day, Jesse went into a coma followed by organ failure and ultimately death.



INVESTIGATOR CONFLICT OF INTEREST



- Held patents on multiple gene therapy delivery techniques with the potential for large profits
- Founded the biotech company that would directly benefit from the trial being successful
- With the University, had significant equity in the biotech company
- The Gene Therapy Institute that conducted the research received large sums of money from the biotech company
- The Gene Therapy Institute was headed by the investigator with both sub-investigators and the IRB reporting to him



UNETHICAL DECISION MAKING FOLLOWS

- Jesse did not meet the inclusion criteria; eligibility forms not completed on any of the enrolled subjects
- Two deaths in preclinical studies of primates with the same condition
- Two previous human subjects receiving lower doses of vector had symptoms similar to Jesse; protocol called for suspension of the study to assess adverse events prior to enrolling any more subjects in the study

OTHER NOTABLE UNETHICAL HUMAN EXPERIMENTS

- 2001: A 24-year-old healthy volunteer died one month after inhaling an unapproved drug as part of an asthma study.
- 2005-2009: The SUPPORT study of 1,316 premature infants who were exposed to increased risk of blindness and death due to levels of oxygen.
- 2011: The iCOMPARE and FIRST Trials of medical residents working excessively long hours in the delivery of patient care.
- 2015: The study of therapeutic hypothermia in deceased organ donors which was considered non-human subjects research because donors were deceased and hence did not require informed consent.



WHAT NOW?



Move From Principle to Practice

- Be aware and acknowledge your own biases – confront your own beliefs and values
- Call out anything or anyone that violates your collective values – silence is not an option
- Do not be color-blind
- Understand that comfort level and thresholds of offense vary and are very situational
- Understand the “why” as well as the “what”
- Educate and be clear on expectations

Converge Advocacy with Allyship



Allyship is using one's power, positionality, and privilege to challenge systems, remove barriers, and create space so that those with less power and privilege can flourish.

Track the Destination with Deliverables

- What does success look like for your organization?
- Who is keeping score and how often?
- What stakeholders are involved? What systems exist which keep some stakeholders engaged and informed and others left out of the discussion?
- Who is responsible and who is holding those who are responsible accountable?
- Who is crafting the value proposition and how is the value proposition being socialized?
- Will we every arrive at our destination?

PROTECTING THE COMMUNITY

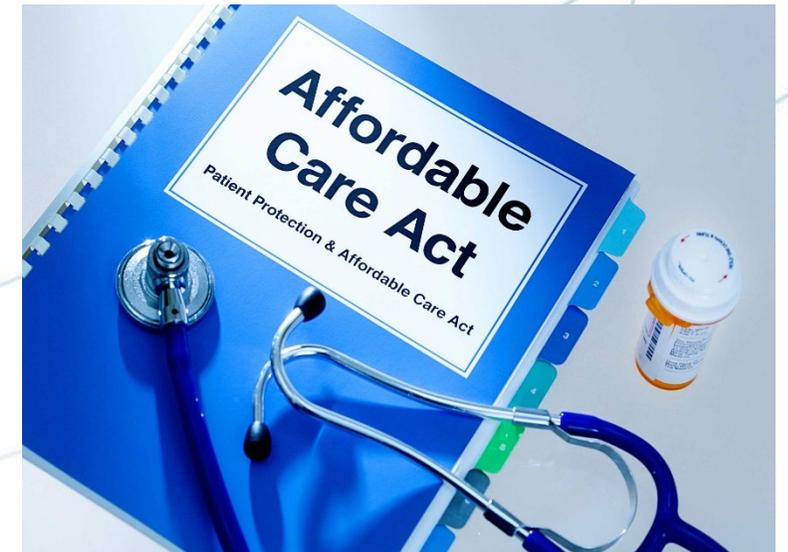


- Anyone could potentially be vulnerable as a subject of research.
 - Location
 - Environment
 - Status
- Respect for persons is much more than obtaining informed consent.
 - Trust
 - Communication
 - Compassion
- The good of science can never be considered over the importance of human life.
 - Accountability
 - Responsibility
 - Judgment
- Ethics and Compliance are not mutually exclusive.
 - Do the right thing because it is the right thing

CURRENTS TRENDS IN HEALTHCARE AND RESEARCH: CONSIDERATIONS FOR COMMUNITIES

HEALTHCARE AND THE WHITE HOUSE

- Repeal vs. Retain the Affordable Care Act (ACA)
 - No subsidies for individuals who do not get insurance from employers
 - No mandate for insurance companies to cover routine costs for individuals on clinical trials
 - No mandate to cover preexisting conditions
 - No prohibition for dollar limits of benefits
 - Medicaid Expansion
- Overturn Roe vs. Wade
 - Refine when life begins
 - Clinical trials on the “morning-after” pill
 - OTC vs. Prescription



THE NEW VULNERABLE POPULATIONS

- Homeless
 - Convenient
 - Easily influenced by very small sums of money
 - Easily influenced by other enticements (e.g. food, warm place to stay)
- Mentally Ill
 - Antipsychotics
 - Very profitable
 - Multiple dangerous and disabling side effects from uncontrollable twitching to arrhythmias



CONSCIENTIOUS OBJECTIONS

- Clinician refuses to perform procedures
 - Delays in treatment
 - Patients will be ignorant of services
 - Patients self-medicate
- Equity
 - Workload
 - All reproductive care and research in jeopardy
 - Cultivates discrimination



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