HISTORY OF
UNETHICAL HUMAN EXPERIMENTATION:
WHERE DO WE GO FROM HERE?

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Ethics in Research Lunch and Learn Series – November 12, 2019
OBJECTIVES

• Chronicle the history and approaches to human subjects research globally including timelines for regulations

• Focus on the Beecher Expose’ and its significance in framing ethical expectations for human subjects research

• Compare and contrast human subjects research before, during, and after the Beecher Article

• Identify historical lessons learned and how these lessons have shaped human subjects research today
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)

- 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

A QUESTION OF ETHICS

• Were the Nazi concentration camp experiments due to a lack of knowledge or lack of ethics?

• Goodness of Intellect vs. Goodness of Character: Similar in that both are admirable and praiseworthy. Different in that one is the knowledge of rules and the other is obedience to those rules; one comes from studying and the other comes from discipline - Aristotle
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 NUREMBERG 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, 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
THEMES FROM THE BEECHER ARTICLE

• Urgency, Frequency, and Consent
• Subject assignment/recruitment coercive
• Withholding information or treatment
• Exposure of human subjects to risks unnecessarily
• Risks to subjects excessive compared to potential benefits
• Lack of adequate informed consent
INTERESTING FACTS ABOUT BEECHER AND THE BEECHER ARTICLE

• Beecher regretted a 1948 anesthesia study conducted in his laboratory without adequate informed consent.
• The Article was originally a summary of 50 studies and rejected by the Journal of the American Medical Association (JAMA).
• The Article was published in New England Journal of Medicine (NEJM) after the editor overruled the editorial board’s rejection of the submission. The editor was also a co-author of the Beecher article which had been revised to only include 22 of the 50 studies.

BEECHER’S INTENT

• “…there is the more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator.” - Beecher

• Researchers are not malicious or evil but, rather thoughtless or careless.

• Called for rigorous self-scrutiny rather than public review (no unethical studies were even cited in the Beecher article)

• Profession does not need more outside regulation but, better mechanisms for self-regulation.

• Desired to “rock the profession out of moral complacency”

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
- 1979: Belmont Report – Ethical Guidelines
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 ________________ 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

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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/llb/facts.html).
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1930</td>
<td>Spends $50K for syphilis treatment demonstrations in six states (Alabama: Macon County)</td>
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<tr>
<td>1931</td>
<td>Rosenwald funding is cut for treatment programs; physicians decide to follow the men diagnosed untreated</td>
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<tr>
<td>1932-33</td>
<td>Follow up becomes a study of 399 syphilitic and 201 controls.</td>
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<td>1945</td>
<td>Penicillin accepted as the preferred treatment for syphilis</td>
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<td>1947</td>
<td>PHS establishes treatment centers, penicillin widely used in military operations</td>
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<td>1968</td>
<td>Concerns raised about the study</td>
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<td>1969</td>
<td>CDC reaffirms the need for the study</td>
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<tr>
<td>1972</td>
<td>Study condemned in major news outlets; study ends</td>
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“The future of the Negro lies more in the research laboratory than in the schools” – Dr. Thomas Murrell

Gray, F.D. 1998. *The Tuskegee Syphilis Study*
THE COLD WAR AND PROJECT MK-ULTRA

- 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.

Retrieved from https://www.history.com/topics/history-of-mk-ultra on July 24, 2018
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).

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
UNETHICAL DECISION MAKING FOLLOWS

• Information on primate deaths was withheld from the subjects both on the informed consent form and during the informed consent process

• Information on adverse events was withheld from the subjects both on the informed consent form and during the informed consent process

• Benefits were communicated in an exaggerated manner while risks were downplayed on websites and other recruitment material

• Informed consent was not documented on half of the subjects

• Researchers’ conflict of interest was neither disclosed on informed consent forms nor discussed with subjects
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.
WHERE DO WE GO FROM HERE?

- Regulations were written in light of unethical research involving:
  - Coercion
  - Undue influence
  - Deception
  - Harm

- Will revising the common rule and other regulations adequately address the issue of meaningful protection of human subjects
WHAT IS HUMAN PROTECTIONS?
BEECHER’S INTENT

“…there is the more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator.” - Beecher

“Profession does not need more outside regulation but, better mechanisms for self-regulation.”
  • Rely on informed consent and the virtuous researchers

“A study is ethical or not at its inception. It does not become ethical post hoc – ends do not justify means.”

“Consent in any fully informed sense may not be obtainable. Patients will accede, on the basis of trust.”

EXCELLENCE AND INTEGRITY

• With regards to excellence, it is not enough to know it but we must try to have and use it.

• By philosophy, I do without being commanded what others do only from fear of the law.

-Aristotle
LESSONS LEARNED FROM BEECHER AND THE HISTORY OF HUMAN SUBJECTS RESEARCH

• Use the regulations as the floor not the ceiling – there is no substitute for good judgment

• Use ethical decision making to complement institutional policies and procedures and vice versa

• Use team approach to solve ethical dilemmas

• Focus on outcomes which consider all the stakeholders

• Educate, monitor, then educate again
THE BOTTOM LINE

• Anyone could potentially be in harm’s way as a subject of research.
  • Context over category
  • Lack of information, independence, and importance could be anyone’s situation
• 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.
  • An IRB can consider the ethical quality of human subjects research without hindering the research enterprise.
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QUESTIONS?