NIH OHSRP Education Series
August 3, 2023

MORE ETHICS OR MORE COMPLIANCE: WHAT WAS DR. BEECHER TRYING TO TELL US?

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BALLAD HEALTH

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OBJECTIVES

- Revisit the landmark article "Ethics and Clinical Research" by Dr. Henry K. Beecher
- Address questions surrounding the Beecher Exposé
- Identify historical lessons learned from Beecher and how these lessons impact the clinical research enterprise

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PROTECTING THE HUMAN RESEARCH SUBJECT

- 1931 – German Ministry of the Interior
- Guidelines:
  - Goal must be therapy
  - Informed consent obtained and documented
  - Vulnerable populations should be protected

Grodin M A. Historical origins of the Nuremberg code. In: Annas G J, Grodin MA, eds. *The Nazi doctors and the Nuremberg code. Human rights and human experimentation* . New York: Oxford University Press, 1992:121-44.

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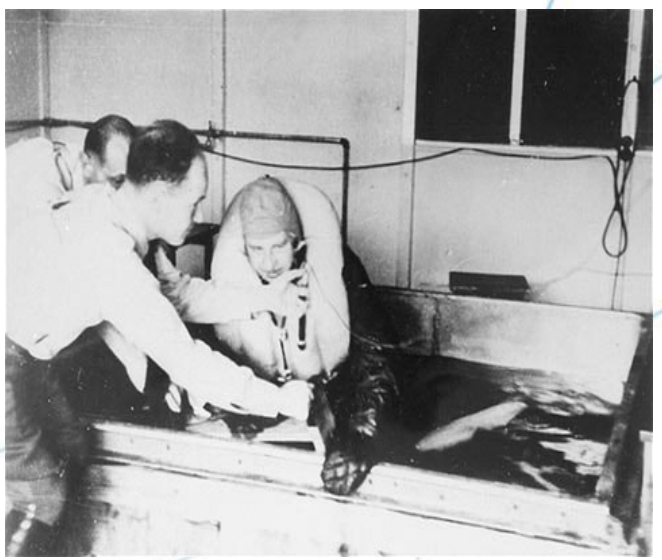
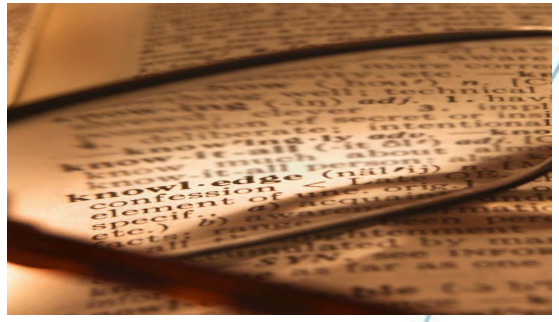
NAZI MEDICAL EXPERIMENTS

- 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



United States Holocaust Memorial Museum. "Introduction to the Holocaust." Holocaust Encyclopedia. www.ushmm.org/wlc/en/article.php?ModuleId=10005143. Accessed on August 3, 2023

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

WHAT IS ETHICS?

- The branch of philosophy dealing with values relating to human conduct, with respect to the rightness and wrongness of certain actions and to the goodness and badness of the motives and ends of such actions
- *It makes no difference whether a good man has defrauded a bad man, or a bad man defrauded a good man: the law can look only to the amount of damage done.* ~ Aristotle

THE DOCTORS' TRIAL: RESPONSE TO ETHICAL VIOLATIONS

- 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
- Dr. Andrew Ivy – represented the American Medical Association at the Doctors' Trial

Jarmusik, N. *Nuremburg Code*. Retrieved July 23, 2018 from http://www.imarcresearch.com/blog/bid/359393/Nuremberg-Code-1947

A QUESTION OF COMPLIANCE

- Was the Nazi concentration camp set of experiments an example of non-compliance since the Nuremburg Code was written after the experiments were conducted?
- *I have gained this from philosophy: that I do without being commanded what others do only from fear of the law* ~ Aristotle

WHAT IS COMPLIANCE?

- The action or fact of complying with or obeying an order, rule, or request.
- *Even the best of men in authority are liable to be corrupted by passion. We may conclude then that the law is reason without passion, and it is therefore preferable to any individual.* ~ Aristotle

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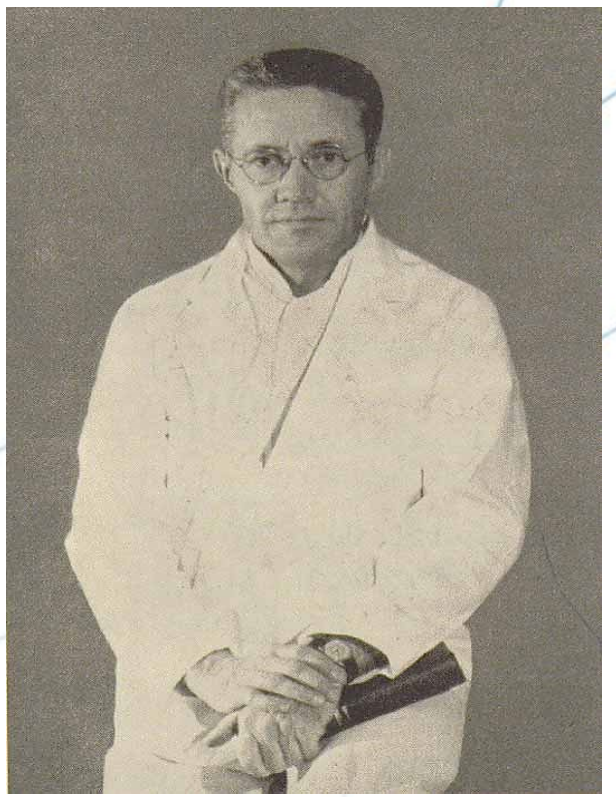
"ETHICS AND CLINICAL RESEARCH" DR. HENRY K. BEECHER

- 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* June 16,1966)
- Summarized 22 examples of unethical human subjects research



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QUESTION #1:

- Did Dr. Beecher only find 22 examples in his review of the literature?
- Answer: Beecher's initial review was based on 17 unethical studies which referenced 50 unethical studies which referenced 186 potentially unethical studies

QUESTION #2:

- Which investigators were mentioned in Beecher's article?
- Answer: No investigators were mentioned in the article. The article only had five references; four were from Europe and one was a reference to one of his previous articles.

QUESTION #3:

- Was Beecher motivated by his stellar record as an ethical researcher?
- Answer: No. A study conducted in Beecher's laboratory in 1948 did not have adequate informed consent. Beecher realized how easy it was for ethics to be compromised in the interest of science.

Jones, D. et al. 2016. *Ethics and Clinical Research – The 50th Anniversary of Beecher's Bombshell*. NEJM:374(24)

CATEGORIES OF THE BEECHER ARTICLE

- Treatment studies
  - Known treatment withheld
  - Study of treatment side effects
- Disease studies
  - Injecting the disease
  - Injecting something to trigger the disease
- Physiologic studies and Technical studies of disease
  - Needles, catheters, and deliberate stimulation of organs with medical instruments

THE BEECHER ARTICLE

- Placebo-controlled studies of strep throat
- Relapse rate of typhoid fever
- Cyclopropane anesthesia and cardiac arrhythmias
- Study of untreated hepatitis

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

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BUT WHAT ABOUT COMPLIANCE?

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"

QUESTION #4:

- Did Beecher write the "Ethics and Clinical Research" article to encourage the clinical research industry to increase regulation and oversight?

RECAP: BEFORE REGULATIONS

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ETHICAL CONSIDERATIONS AT NUREMBERG

- Medical necessity/Scientific merit and justification?
  - Benefit Axis personnel and justify the Aryan supremacist stance empirically
- Autonomy?
  - None; "prisoners" with no rights as human beings
- Do no harm?
  - All research subjects were severely injured or murdered
- Do good?
  - None of the experiments held any prospect for subject or greater good benefit
- Justice?
  - Only used the "prisoners"; took on all the risks – received none of the benefits

"The Study of Untreated Syphilis in the Negro Male"

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

Macon County Health Department

ALABAMA STATE BOARD OF HEALTH AND U.S. PUBLICH 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.)

ETHICAL CONSIDERATIONS AT TUSKEGEE

- Medical Necessity/Scientific merit and justification?
  - Research on syphilis untreated with appropriate race comparator (Oslo, Norway)
- Autonomy?
  - Entry to the study was voluntary but deceptive; coerced to stay in the study
- Do no harm?
  - All research subjects entered the study with syphilis
- Do good?
  - The benefits presented to the subjects were both qualitative and quantitative.
- Justice?
  - Subjects were appropriate for the study. Social justice, dignity, and respect was non-existent.

RECAP: AFTER REGULATIONS

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ICOMPARE STUDY

Desai, S *et a*l. 2018. Education outcomes in a duty-hour flexibility trial in internal medicine. *NEJM*. 378: 1494-1508

- 2015-2016 – The Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE)
- One year randomized controlled trial to study the change in work hour standards for first year internal medicine interns
- 63 internal medicine residency programs - Standard duty-hour vs. more flexible hours.
- Observations of the activities of interns, surveys of trainees and intern examination scores.
- IRB reviews ranged from not human subjects research to expedited review

ETHICAL CONSIDERATIONS IN ICOMPARE

- Medical Necessity/Scientific merit and justification?
  - Concern persists that inflexible duty-hour rules in medical residency programs may adversely affect the training of physicians.
- Autonomy?
  - Entry to the study was "voluntary"; leadership volunteered programs with the expectations
- Do no harm?
  - In some cases, subjects in flexible hours arm experienced severe fatigue; patient errors were common
- Do good?
  - The benefits presented to the subjects included the ability to influence change in the ACGME standards
- Justice?
  - Interns were vulnerable due to their entry level position.

MORE ETHICS OR MORE COMPLIANCE?

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

- Can focus on compliance with regulations alone adequately address the meaningful protection of human subjects in clinical research?

LET'S TALK ABOUT 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 (none of the 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"

Stark, L. 2016. *The unintended ethics of Henry K. Beecher*. The Lancet:387

APPLICATIONS OF THE BEECHER ARTICLE

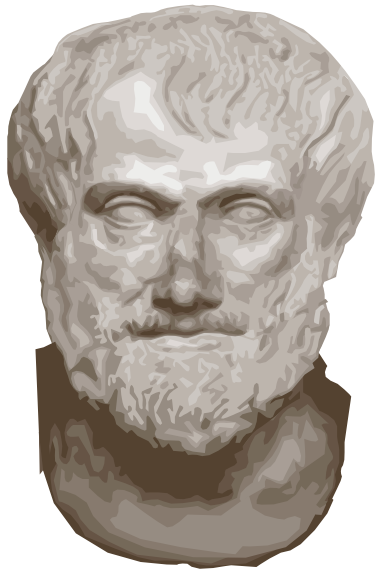
- Use the regulations as the floor not the ceiling – there is no substitute for good judgment
- Use ethical decision making to complement compliance expectations and vice versa
- Apply both ethical considerations and regulatory considerations when reviewing clinical research
- Focus on outcomes which consider all the stakeholders

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 and Compassion
  - Communication

- The good of science can never be considered over the importance of human life.
  - Accountability/ Responsibility
  - Judgment
- Ethics and Compliance are not mutually exclusive.
  - IRBs can consider ethics in concert with compliance

EXCELLENCE AND INTEGRITY



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

QUESTIONS AND DISCUSSION

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