Research Ethics: Where are we, How did we get here, and Where are we going?

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Bioethics: a Model for Research Ethics

3 main areas of focus:

- Human biomedical ethics
- Animal ethics
- Environmental ethics

Interdisciplinary, fluid approach

Four Principles of Biomedical Ethics

Beauchamp and Childress: principlism in biomedical ethics

(1) Respect for autonomy

(2) Nonmaleficence

(3) Beneficence

(4) Social justice

How did we get here? Why is research ethics important?

Research Ethics – A Bit of History

- 1932-1972: Tuskegee Syphilis Study
- **1932-45: Horrific research performed by German scientists on concentration camp prisoners and by Japanese scientists on Chinese prisoners of war**
- 1944-1980s: US government sponsors secret research on effects of radiation on human beings; subjects not told they were participating in the experiments; subjects included cancer patients, pregnant women, and military personnel
- 1947: The Nuremberg Code for research on human subjects is adopted. The Allies use the document in the Nuremberg Trials to convict Nazi scientists of war crimes.
- Watson and Crick discover the structure of DNA; they secretly obtain key x-ray diffraction data from Rosalind Franklin without her permission. Watson and Crick shared the Nobel Prize in 1962; Franklin was not awarded a Nobel Prize because she died in 1953 from ovarian cancer (at age 37) and the prize is not awarded posthumously.

https://www.niehs.nih.gov/research/resources/bioethics/timeline/index.cfm

The Holocaust: Medical Experiments

- Sterilization
- Treatment of war wounds
- Ways to counteract chemical weapons
- Vaccines and drugs
- Survival of harsh conditions
- Physicians later charged at Nuremberg with crimes against humanity

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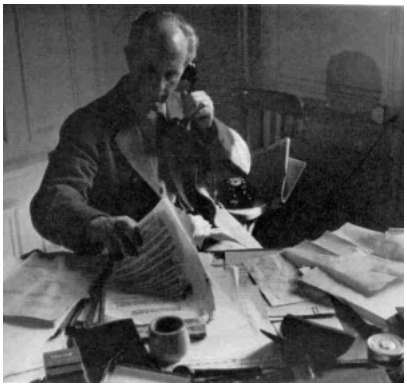
Nuremberg Code: 10 Points

1. Voluntary consent is essential
2. The results of any experiment must be for the greater good of society
3. Human experiments should be based on previous animal experimentation
4. Experiments should be conducted by avoiding physical/mental suffering and injury
5. No experiments should be conducted if it is believed to cause death/disability

See http://www.imarcresearch.com/blog/bid/359393/nuremberg-code-1947

Nuremberg Code: 10 Points



John W. Thompson, father of the Nuremberg Code

6. The risks should never exceed the benefits
7. Adequate facilities should be used to protect subjects
8. Experiments should be conducted by only qualified scientists
9. Subjects should be able to end their participation at any time
10. The scientist in charge must be prepared to terminate the experiment when injury, disability, or death is likely to occur

See http://www.imarcresearch.com/blog/bid/359393/nuremberg-code-1947

Research Ethics – A Bit of History, cont'd

- 1956-1980: Saul Krugman, Joan Giles, and other researchers conduct hepatitis experiments on mentally disabled children at the Willowbrook State School. They intentionally infect subjects with the disease and observe its natural progression. The experiments were approved by NY DOH.
- 1950s-1963: The CIA begins a mind control research program, which includes administering LSD to unwitting subjects.
- 1961: Rachel Carson publishes Silent Spring, which alerts people to the harmful effects on the environment of various toxins and pollutants, including DDT. Her book launches the environmentalist movement.
- **1961-1962: Stanley Milgram conducts his "electric shock" experiments, which proved that many people are willing to do things that they consider morally wrong when following the orders of an authority. He publishes Obedience to Authority in 1974.**

https://www.niehs.nih.gov/research/resources/bioethics/timeline/index.cfm

Milgram Experiments

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- Famous study on obedience to authority
- Participants (all men) believed they were helping a different study, administering electric shocks to a “learner”
- These fake shocks became progressively more dangerous
- Results: a very high proportion of men would fully obey the instructions, despite uneasiness

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Milgram Experiments

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- Participants suffered extreme emotional stress
- But: 84% of participants surveyed later said they were “glad” / “very glad” to have participated, 15% were neutral (92% response)
- Does this experiment correspond well to Nazi Germany?
- Given the survey feedback, was this study ethical?

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Research Ethics – A Bit of History, cont'd

- 1964: World Medical Association, Helsinki Declaration, Ethical principles for research on human subjects. Revised several times, most recently in 2001.
- 1964: US Surgeon General's office issues its first of several reports on health problems related to smoking.
- 1966: Henry Beecher publishes an article in N. Engl. J. Med. exposing 22 unethical studies in biomedicine, including Tuskegee and Willowbrook.
- 1960s/1970s: Animal rights movement. Congress adopts Animal Welfare Act (1966, 1970, 1976, 1985), which excludes rodents and birds. States adopt animal welfare laws. US Public Health Service, Policy on the Humane Care and use of Laboratory Animals. American Association for the Accreditation of Laboratory Animal Care (AAALAC).
- 1974: Congress passes National Research Act, which authorizes federal agencies to develop human research regulations, e.g., 45 CFR 46, 21 CFR 50, 54, 56.

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Research Ethics – A Bit of History, cont'd

- 1975: Scientists gather at Asimolar, CA to discuss the benefits and risks of recombinant DNA research; NIH forms Recombinant DNA Advisory Committee
- 1975: Peter Singer publishes Animal Liberation
- 1975: E.O. Wilson publishes Sociobiology, which reignites "nature vs. nurture" debate
- 1978: Louise Brown, the world's first test-tube baby, is born
- 1979: National Commission releases The Belmont Report, principles of ethical research on human subjects
- 1982: William Broad and Nicholas Wade publish Betrayers of Truth, claiming that there is more misconduct in science than researchers want to admit. Their book helps launch an era of "fraud busting" in science.
- 1989: PHS forms two agencies, the Office of Scientific Integrity and the Office of Scientific Integrity Review, to investigate scientific misconduct and provide information and support for universities. The two agencies are reorganized in 1992 as the Office of Research Integrity (ORI).

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Research Ethics – A Bit of History, cont'd

- 1989: The NIH requires that all graduate students on training grants receive education in the responsible conduct of research
- 1990: US launches the Human Genome Project, a $20 billion effort to map and sequence the human genome
- 1991: Revision/unification of human research regulations. All US government agencies, except the EPA, now accept "the common rule" (45 CFR 46).
- 1993: Fertility researchers successfully clone human embryos
- 1997: The ICMJE revises its authorship guidelines
- 1998: Scientists perfect methods for growing human embryonic stem cells
- **1999: Jesse Gelsinger dies in a human gene therapy experiment at UPenn**
- 2002: President's Council on Bioethics recommends that US ban reproductive cloning and enact a moratorium on research cloning

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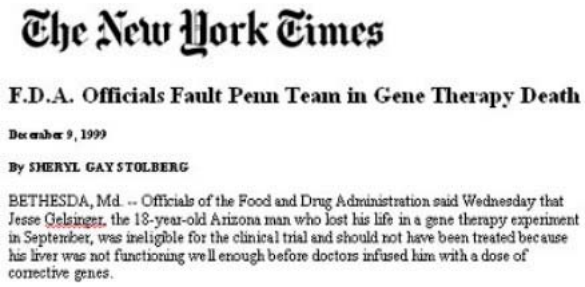
Jesse Gelsinger's Death

- 17-year-old Jesse Gelsinger suffered from genetic disease ornithine transcarbamylase (OTC) deficiency, which prevents the break-down of ammonia
- Jesse volunteered for a gene therapy experiment in which a vector carrying a normal OTC gene was injected into his liver
- He had been informed that previous subjects had had generally no serious complications
- However, a fatal reaction was triggered and Jesse died on September 17, 1999

Jesse Gelsinger's Death



The New York Times

F.D.A. Officials Fault Penn Team in Gene Therapy Death

December 9, 1999

By SHERYL GAY STOLBERG

BETHESDA, Md. -- Officials of the Food and Drug Administration said Wednesday that Jesse Gelsinger, the 18-year-old Arizona man who lost his life in a gene therapy experiment in September, was ineligible for the clinical trial and should not have been treated because his liver was not functioning well enough before doctors infused him with a dose of corrective genes.

- Ethical issues:
  - Subjects' health status: Was Jesse's liver too weak to sustain this experimental treatment?
  - Informed consent: Jesse had not been informed that research animals and some previous human subjects had become sick from the vector
  - Conflict of interest: lead scientist had a financial interest in the vector

Research Ethics – A Bit of History, cont'd

- 2004: Ronald Reagan, Jr. makes presentation in support of federal funding for embryonic stem cell research to Democratic Convention. Stem cell research (and therapeutic cloning) become hot issues in 2004 Presidential election.
- 2005: University of Vermont researcher Eric Poehlman admits to fabricating or falsifying data in 15 federal grants and 17 publications
- 2009: Obama Administration announces it will significantly expand NIH funding of human embryonic stem cell research
- **2010: Lancet retracts a fraudulent paper, published in 1998 by Andrew Wakefield and colleagues, linking autism to the measles vaccine**
- 2016: NIH places temporary moratorium on funding for experiments involving human-animal chimeras while it revises existing rules that govern this research

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Andrew Wakefield

- Now-former doctor who published a 12-person "study" on the measles, mumps, and rubella (MMR) vaccine in *The Lancet* in 1998
  - Suggested a link between this vaccine and the onset of autism
  - This article was later retracted (2010)
- Directly thereafter, epidemiological studies refuted the link between MMR vaccine and autism
- The Wakefield paper continues to precipitate dangerous results, including today's outbreak of measles, despite:
  - Small sample size
  - Uncontrolled design
  - Unsubstantiated conclusions

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Research Ethics Case Study:

Three Identical Strangers

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The Basic Facts

- Three identical triplets (really quadruplets, though one died at birth) were separated as infants and adopted out to three different families, each of which had already adopted a baby girl two years prior. One family was wealthy, one middle-class, and one blue-collar. The brothers' names are Edward (Eddy) Galland, David Kellman, and Robert (Bobby) Shafran.
- By happenstance, the three brothers discover one another at age 19.
- They become extremely close to one another and famous while making talk-show rounds.
- Ultimately, they each get married and later open up a restaurant in NYC together.
- They start discovering strange commonalities among their childhoods, including their having been studied by psychiatrists, who did not explain the purpose of their work to their respective parents.
- All three brothers suffered from mental illness. Sadly, mental illness led to Eddy's suicide at age 33.

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The Controversial Twin Study

- Austrian-born psychiatrist Peter Neubauer conducted a long-term study of Jewish twins (five sets) and triplets (one set—the brothers) separated and adopted during infancy.
- Neubauer and his research team never told their subjects or their subjects' parents the purpose of their study or that any of the children had identical siblings.
- Eventually, the triplet brothers and some of the other twins studied learned about the research and that it involved their deliberate separation in order to conduct a nature-versus-nurture experiment.
- The experiment's results were never published because Neubauer feared public opinion.
- It is believed that at least three of Neubauer's twin-study subjects have committed suicide.

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Research Ethics Issues and Implications

What do you think?

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Research Ethics Issues and Implications

- Temporal context—does this matter? Why or why not?
- What do researchers "owe" their subjects?
- Issue of informed consent—or lack thereof.
- Does it matter that the research was never published?
- What "harm," if any, was inflicted on the subjects?
- Is it problematic that we are now voyeurs as we view the documentary? Are the brothers still research subjects and, if so, do any of the same research-ethics problems still exist?

- "When you play with humans, you do something very wrong" – aunt of one of the triplets
  - Do you agree? If so, in what situations/contexts?

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Where do we go from here?

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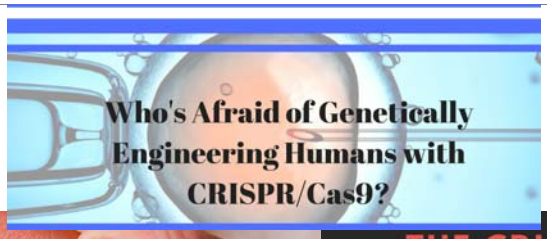
CRISPR Gene-Editing Technology



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