History of Research with Human Subjects: Ethical Steps Forward and Back

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Outline of Presentation

• Guiding Principles in Bioethics

• History of Human Subjects Research

• Development of Regulations concerning Human Subjects Research
Guiding Principles in Bioethics

- Respect for Autonomy
- Nonmaleficence
- Beneficence
- Justice
Regulation in Ancient Times

• Hammurabi’s Code (18th century B.C.)
  – Gave detailed and explicit penalties for what we would call malpractice

• Hippocratic Oath (5th century B.C.)
  – “To abstain from all intentional wrong-doing and harm, especially from
    abusing the bodies of man or woman, bound or free.”

• Celsus (1st century A.D.)
  – “Nevertheless, it can happen that an illness may require (bleeding), but the
    body seems scarcely able to allow it: but if there appears to be no other
    remedy, and he who is so suffering is about to die unless there is some
    relief even though risky, in this state it is the mark of the good physician
    to demonstrate [to the family] that there is no hope without bleeding, and
    to confess how much risk there is in doing this, and then, if it is
    demanded, to bleed the patient” (De medicina, Book III).
Scientific Revolution (17th cent.)

- Developed a method of investigation which included controlled observation and reporting of results for verification
- Expanded number of people doing research
- Applied to experiments involving humans
- Subjects were often researchers themselves or members of their families
  - In the 18th cent., Edward Jenner demonstrated the value of inoculation against smallpox. After observing milkmaids in rural England who acquired immunity after exposure to an animal form of the disease, Jenner tested the practice first on his own son and then the son of a neighbor.
Historical Changes

• Growth of universities

• Potential commercial applications of discoveries

• Amount of research increased
Codes

• William Beaumont
  – Treated a patient with a unique stomach gunshot wound that permitted him to do experiments to study human digestion. His published account, *Physiology of Digestion* (1833), includes a document of indenture (not exactly consent) signed by the patient wherein he agreed “to assist and promote by all means in his power such philosophical or medical experiments that the said William Beaumont shall direct or cause to be made on or in the stomach of him.” In exchange the patient received lodging and payment of $150 a year.
Claude Bernard
- “It is our duty and our right to perform an experiment on man whenever it can save his life, cure him or gain him some personal benefit. The principle of medical and surgical morality, therefore, consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., to the health of others . . . among the experiments that may be tried on man, those that can only harm are forbidden, those that are innocent are permissible, and those that may do good are obligatory” (Introduction à l’étude de la médecine expérimentale (1865)).
Codes

• William Osler
  – The “final test of every new procedure, medical or surgical, must be made on man, but never before it has been tried on animals.”

  – “Full consent must be obtained from patients, based on full knowledge of the circumstances.”
Failures

– In 1891 a French physician reported on the analysis of breast tissue samples from two women. In an effort to test the contagion of cancer, a surgeon had given them cancer grafts while under anesthesia for removal of their other cancerous breasts. Neither patient had given her consent.
Failures

- In 1892 Albert Neisser, Professor of Dermatology at University of Breslau conducted experiments aimed at immunizing healthy subjects against syphilis. Took serum from syphilis patients and used it to inoculate 4 healthy children and 3 adolescent prostitutes.
Failures

- All of these subjects contracted syphilis, but consent had not been obtained from any of the subjects or their parents or guardians.
- Inflamed by the press, the scandal eventually prompted action by the Prussian minister of Religious and Medical Affairs which promulgated “Instructions to the Directors of Clinics, Outpatient Clinics and Other Medical Facilities.
- This document prohibited “absolutely” medical intervention other than diagnosis, therapy and immunization if,
  - “the person in question is a minor or not fully competent on other grounds.”
  - “the person concerned has not declared unequivocally that he consents to the intervention.”
  - “The declaration has not been made on the basis of a proper explanation of the adverse consequences that may result from the intervention.”
Turn of the Century

• By the beginning of the twentieth century, there was ample experience with ethical problems involving humans in scientific experimentation to produce codes of conduct and government regulations. These included the notions of risk and benefit as well as informed consent, but the codes were not yet widespread or broadly binding.
Research Ethics in the 20th Century

- Nuremberg Code (1949)
- Thalidomide Tragedy
- Declaration of Helsinki (1964)
- USPHS Memo on Review Boards (1966)
- Tuskegee Syphilis Study (1932-1972)
Research Ethics in the 20th Century

- Belmont Report (1979)
- Current Regulations (1981)
- “Common Rule” (1991)
Nuremberg Code (1949)

- On December 9, 1946, the American military tribunal opened criminal proceedings against 23 leading German physicians and administrators for their willing participation in war crimes and crimes against humanity.

- During WWII, German physicians conducted medical experiments on thousands of concentration camp prisoners without their consent.
  - They shot concentration camp prisoners to test blood clotting.
  - They infected groups of inmates with viruses, then only treated part with the test vaccines, while they observed the course of the disease in untreated inmates.
  - They tested poison bullets to find more effective ways of killing; they tested prisoners to see how long they could remain alive under high altitude conditions of low air pressure and lack of oxygen.
Nuremberg Code (1949)

- Several German doctors had argued in their own defense that their experiments differed little from previous American or German ones.
- In fact, American government experiments during the war had tilted the risk/benefit balance in favor of anticipated benefits to soldiers fighting the war by accepting the increased risk of experiments on subject populations such as children or asylum patients who could hardly be informed or give their consent.
- But these were not widely known, and paled in comparison to the actions of the German doctors which the indictment described as “murder, torture, and other atrocities committed in the name of science.”
- In the verdict issued on August 19, 1947, seven defendants were found guilty and sentenced to death, eight defendants were sentenced to imprisonment from ten years to life, and seven were found not guilty.
Nuremberg Code (1949)

• Voluntary consent is absolutely essential
• Quality of experiments and experimenters
  – Based on animal experimentation
  – For good of society
  – Conducted by scientifically qualified persons
• Safeguards
  No experiment should risk death or disabling injury
  Risk should never exceed importance of problem
  Experiment should be designed to be stopped at any time
Nuremberg Code (1949)

- The requirement that “the voluntary consent of the human subject is absolutely essential” includes “sufficient knowledge and comprehension” by subjects “to make an understanding and enlightened decision.”
- In hindsight, the biggest problem with the code was compliance and enforcement.
  - The Nuremberg Code explicitly left this up to the experimenter.
  - “The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is the personal duty and responsibility which may not be delegated to another with impunity.”
- Although it did not carry the force of law, the Nuremberg Code was a very complete statement about the use of humans in experiments which came at a moment in history which made it internationally visible.
Thalidomide Tragedy

- In 1950s thalidomide was approved for use as a sedative in Europe, not in USA by FDA
- Taken to control sleep and nausea throughout pregnancy
- Caused severe deformities in fetus
- Many woman did not know they were taking an experimental drug nor give informed consent
- 12,000 babies born with severe deformities
Thalidomide Tragedy

- 1962 Dr. Frances Kelsey, FDA medical officer, in keeping the drug off the U.S. market, arouses public support for stronger drug regulation.

- Kefauver-Harris drug amendments passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers are required to prove to FDA the effectiveness of their products before marketing them.
Other Cases: Willowbrook

• Beginning in 1956, the purposeful infection with hepatitis of patients began at the Willowbrook (NJ) State School for Retarded Children.

• Parents gave consent for the injections (after 1964 it was a condition for admitting children), but not clear they were advised of the hazards or merely told they would be given a vaccine against hepatitis (actually a mild form of the virus).
Other Cases: Cornell

• In 1964 a story broke of cancer research begun in 1963 at Cornell Medical School on 22 senile and demented patients at Brooklyn Jewish Chronic Disease Hospital. They were injected with live cancer cells to serve as a control to see if they lived longer than patients with cancer.

• Subjects were “merely told that they would be receiving ‘some cells.’” The word cancer was omitted. Researchers later said they obtained oral consent, but evidence showed attempts at forged written consent to cover up.
Declaration of Helsinki (1964)

• World Medical Association recommendations to guide medical doctors in biomedical research involving human subjects

• Governs international research ethics and defines rules for “research combined with clinical care” and “non-therapeutic research”
Declaration of Helsinki (1964)

- Human research should be based on laboratory and animal experimentation
- Should be reviewed by an independent committee
- Informed consent is necessary
- Should be conducted by qualified individuals
- Risks should not exceed benefits
Henry Beecher Article (1966)

• Beecher detailed 22 published examples of “unethical or questionable ethical studies” done between 1948-1965 in major US medical centers

• Uproar led directly to memorandum establishing Institutional Review Boards
Marginalized Subjects

- The subjects of research in this article were the poor, the developmentally disabled, senile, institutionalized, those who lacked the ability or opportunity to exercise free choice.
USPHS Memo on Review Boards (1966)

- No new, renewal or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates.
• Review should assure and independent determination of:
  – The rights and welfare of the individual or individuals involved
  – The appropriateness of the methods used to obtain informed consent
  – The risks and potential medical benefits of the investigation
Significance

• Research was no longer at the discretion of individual investigators; for the first time, researchers had to answer to federal regulations and compulsory peer review.
Revisions

- 1969 – Committees expanded to include non-scientific members

- 1971 – The use of community standards was added to judge proposals
Tuskegee Syphilis Study (1932-1972)

- 600 low income African American males from rural Alabama with a high incidence of syphilis infection were monitored for 40 years
- Given free medical exams but they were not told that they had syphilis
- Cure (penicillin) became available in 1950s
- Participants and families denied treatment
Importance

• There remains a distrust both of science and of scientists in minority communities that makes it difficult to recruit minority subjects

• Results of the recent AIDS vaccine trial suggests that some minority populations may react differently to vaccines, therefore their participation is vital
Belmont Report (1979)

- On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles.
Belmont Report (1979)

The Commission was directed to consider:

• the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine,

• the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects

• appropriate guidelines for the selection of human subjects for participation in such research and

• the nature and definition of informed consent in various research settings.
Belmont Report (1979)

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects.
Belmont Report (1979)

- Basic Ethical Principles
  - Respect for Persons
  - Beneficence
  - Justice

- Applications
  - Informed consent
  - Risk/benefit assessment
  - Selection of subjects of research
Current Regulations (1981)

• Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) issued regulations based on the Belmont Report:
  – DHHS issued Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (Protection of human subjects)
  – FDA issued CFR Title 21 (food and drugs) Parts 50 (protection of human subjects) and 56 (Institutional Review Boards)
Common Rule and FDA Regulations

• Protect Human Subjects by:
  – Assuring compliance by research institutions
  – Guidelines for IRB membership, function, operations, review of research and record-keeping
  – Obtaining and documenting informed consent
  – Additional protections for vulnerable subjects (pregnant women, prisoners and children, fetuses, cognitively impaired).
Two Essential Protections

• Independent review of research to assess risks and potential benefits

• An opportunity for people to voluntarily and knowledgeably decide whether to participate in a particular research protocol
Basic Informed Consent Requirements

• Written in a language understandable to the subject population

• Provide sufficient information to fully inform the subject

• Contain NO exculpatory language
Basic Informed Consent Elements

• Explain:
  – Research
  – Purpose
  – Procedures
  – Risks and Benefits
  – Compensation
  – Alternative Procedures
  – Confidentiality
  – Costs
  – Contacts
Additional Informed Consent Elements

- Unforeseeable risks
- Termination and/or withdrawal
- Significant new findings
- Number of subjects
Recent History

- Jesse Gelsinger death
- Death of Ellen Roche at Johns Hopkins
What Happened

- Jesse had agreed to participate in a gene therapy experiment for a rare disorder he had called ornithine transcarbamylase deficiency (OTC). About one infant in 40,000 is diagnosed with this genetic disorder which prevents the liver from metabolizing ammonia. It is fatal for infants with the most severe form of the disorder.
What Happened

• Twenty hours after being injected with a modified adenovirus, the same one that causes the common cold, 18-year-old Jesse Gelsinger developed jaundice and sank into a coma. His organs began to fail at an alarming rate and he was placed on life support. Three days later, he was dead.
Jesse Gelsinger Case
FDA’s Preliminary Findings

• Information withheld from patients, IRB, NIH, and FDA
  – Monkeys had died in previous experiments
  – Human volunteers suffered serious side effects
Jesse Gelsinger Case
Settlement – February 9, 2005

- Institutions involved in case will pay a settlement of over $500K each to the government
- Individual researchers involved in case will have restrictive controls placed on their clinical research activities for the next 3-5 years
- Institutions involved in case will implement new safeguards to ensure compliance in future clinical research activities by all institutional researchers
Death of Ellen Roche

- 24-year-old participating in study exposing human subjects to drug hexamethonium which induces wheezing in people with asthma in order to study physiological response in the lungs

- Complications led to death
Findings

- JHH “failed to ensure that risks to subjects were minimized and reasonable.”
- Researchers failed to obtain published literature about the known associated between hexamethonium and lung toxicity.
- Researchers failed to report previous subjects’ unanticipated coughing and shortness of breath.
Additional Reading

• **Belmont Revisited**
  *Ethical Principles for Research with Human Subjects*
  Edited by James F. Childress, Eric M. Meslin, Harold T. Shapiro
  Georgetown University Press, 2005

• **Principles of Biomedical Ethics, 5th ed.**
  Tom L. Beauchamp and James F. Childress
  Oxford University Press, 2001
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Questions & Answers
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• Question 4
Thank You