A Review of Ethical Principles Applied in Reviewing Biomedical Research

Robert D. Orr, MD,CM
University of Vermont, USA

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Outline

- History of research ethics
- Principles of modern research ethics
- Important concepts
  - consent
    - research without consent
  - “therapeutic misconception”
  - placebos
  - vulnerable subjects

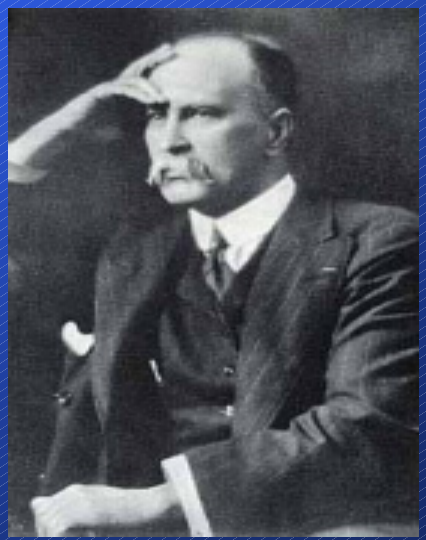
History of Research Ethics

1900 - Germany

- Royal Prussian Minister of Religious, Educational and Medical Affairs
- Directive to hospitals on research
  - subjects must be competent adults
  - subjects must give "unambiguous consent"
  - subjects must be given adequate information

Sir William Osler

Questioning before the Royal Commission on Vivisection, 1908



C: “I understand that in the case of yellow fever the recent experiments have been on man.”

O: “Yes, definitely with the specific consent of these individuals who went into this camp voluntarily…”

C: “We were told by a witness yesterday that, in his opinion, to experiment upon man with possible ill result was immoral. Would that be your view?”

O: “It is always immoral, except with a definite, specific statement from the individual himself, with a full knowledge of the circumstances. Under these circumstances, any man, I think, is at liberty to submit himself to experiments.”

C: “Given voluntary consent, you think that entirely changes the question of morality or otherwise?”

O: “Entirely.”

History of Research Ethics

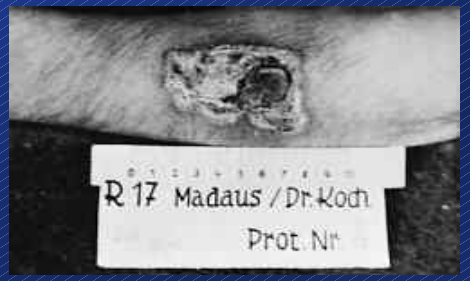
Japanese Research (1932-45)
Chemical & Biological Warfare

- Unit 731 (Imperial Japanese Army) in Manchuria
- directed by Lt. Gen. Ishii Shiro (MD)
- thousands of experiments on Chinese *marutas* re: how to spread & prevent disease
- >100 scientific publications
- war crimes trials in China; >500 punished
- Factories of Death by Sheldon H. Harris, 1994

21. Aerial view of Unit 731's Ping Fan complex

History of Research Ethics
World War II - Germany

- atrocities of Nazi researchers
  - Auschwitz, Dachau
  - high altitude, cold immersion, wound infections, sterilization, poisons
  - twin experiments
  - focused on “the good of the state” instead of the good of the individual
- Nuremberg War Crimes Trials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History of Research Ethics

Nuremberg Code (1947) – important concepts

- voluntary informed consent
  - no provision for children, incompetent adults
- only if results unprocurable by other means
- careful design
- conduct to avoid suffering and injury
- no research if death or disability might result
- only by qualified researchers
- subjects may drop out
- stop if looks like bad outcome

History of Research Ethics

WMA's Declaration of Helsinki (1964 ….. 2000)

- Goes beyond Nuremburg Code
  - Proposals should be evaluated by an independent committee
  - Unethical research should not be published
  - Discusses informed consent for incompetent subjects
    - "…consent should be obtained from the legal guardian in accordance with national legislation."
  - Distinguishes therapeutic from non-therapeutic research
    - Therapeutic - some benefit to the patient
    - Non-therapeutic research only on healthy persons or those whose illness is unrelated to the research

History of U.S. Research Ethics

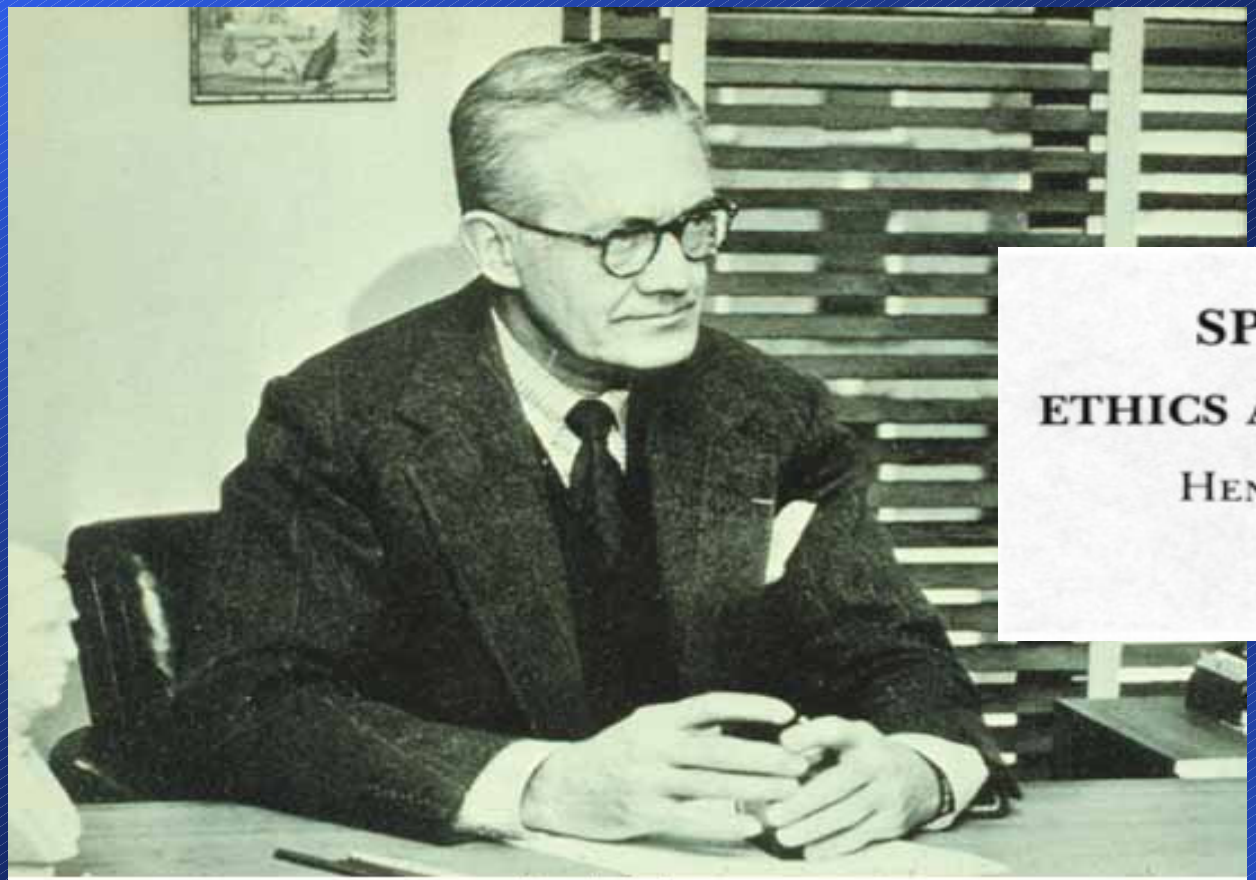
- little government involvement before 1950
- “Nuremberg Code applies to Germans”
- uneven application of ethical standards

- major oversight did not start until 1978

History of U.S. Research Ethics

- 1950's: radiation experiments
  - exposed unsuspecting people to irradiation without consent
  - "many were wronged, few were harmed" (1990's)
- 1955-1970: Willowbrook hepatitis study
  - hepatitis A intentionally given to institutionalized retarded children
- 1966: Beecher's article in NEJM
  - 22 studies by respected investigators, published in respected journals, that violated 1 or more ethical precepts
- 1932-1972: Tuskegee syphilis study

New Engl J Med 1966;274:1354-60



Henry K. Beecher

SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

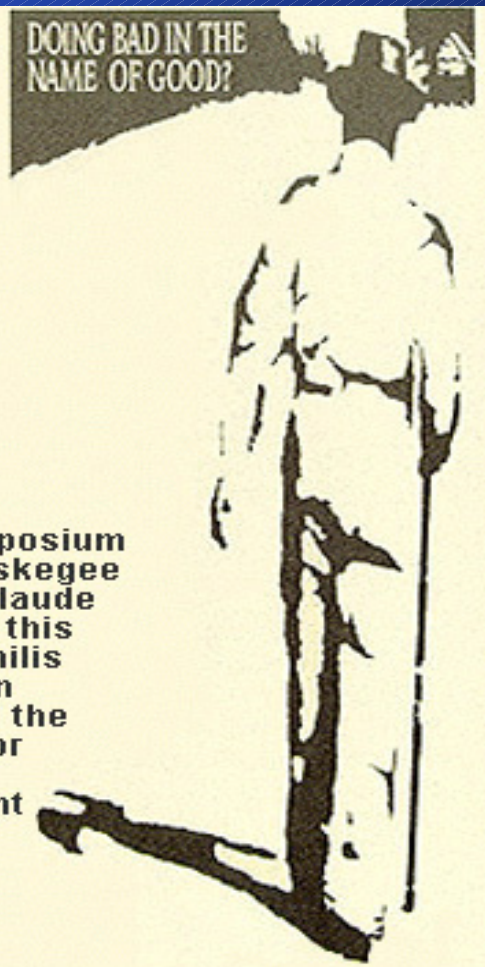
HENRY K. BEECHER, M.D.†

BOSTON

History of U.S. Research Ethics

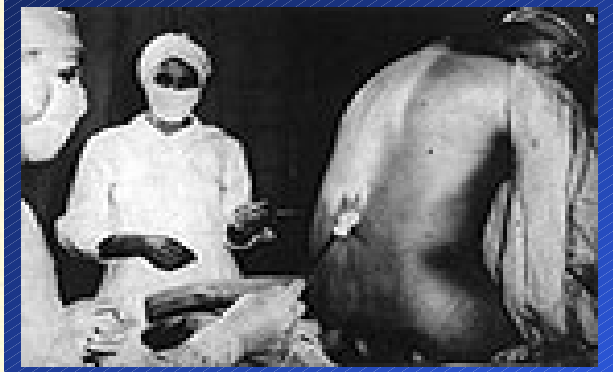
- 1932-1972: Tuskegee syphilis study
  - U.S. Public Health Service research
  - enrolled 400 poor black men with syphilis to study natural progression (no effective treatment)
  - continued for 30 years after introduction of penicillin
  - led to government commission (1974)
    - the Belmont Report (1978)
    - the “Common Rule” (1981)

For forty years, from 1932 to 1972, 399 African-American males were denied treatment for syphilis and deceived by officials of the United States Public Health Service. As part of a study conducted in Macon County, Alabama, poor sharecroppers were told that they were being treated for "bad blood." In fact, the physicians in charge of the study ensured that these men went untreated. In the 25 years since its details first were revealed, the study has become a powerful symbol of racism in medicine, ethical misconduct in human research, and government abuse of the vulnerable.



The 1990s has been a time of reflection upon the Tuskegee Study and its troubling implications. In February 1994, the issue was addressed in a symposium entitled "Doing Bad in the Name of Good?: The Tuskegee Syphilis Study and its Legacy" convened at The Claude Moore Health Sciences Library. The discussion at this gathering led to the creation of the Tuskegee Syphilis Study Legacy Committee which met in Tuskegee in January 1996. In its final report the following May, the Committee urged President Clinton to apologize for wrongs of the Tuskegee Study. The Committee's work bore fruit on May 16, 1997 when the President apologized on behalf of the United States government to the surviving participants of the study. These men and members of the Legacy Committee were invited to the White House to witness the apology.

THE TUSKEGEE SYPHILIS STUDY
AND ITS LEGACY

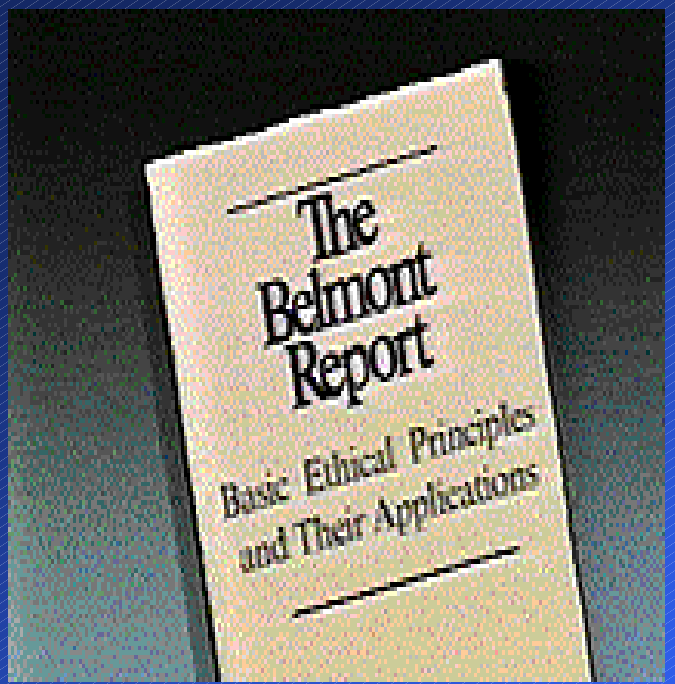


The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

- Created by Congress in 1974
- First public national body to shape bioethics policy in the U.S.
- Reports
  - Research on the Fetus (1975)
  - Research Involving Prisoners (1976)
  - Research Involving Children (1977)
  - Psychosurgery: Report and Recommendations (1977)
  - Research Involving Those Institutionalized as Mentally Infirm (1978)
  - Institutional Review Boards (1978)
  - Implications of Advances in Biomedical and Behavioral Research (1978)
  - The Belmont Report: Ethical Principles and Guidelines for Protection of Human Subjects of Biomedical and Behavioral Research (1979)

Principles of U.S. Research Ethics

- respect for persons
- beneficence
- justice



Ethical Norms

- Good research design
- Competent investigators
- Favorable balance of harm and benefit
- Equitable selection of subjects
- Compensation for research-related injury
- Informed consent

Good Research Design

- Nuremberg 3
  - Knowledge of scientific literature
  - Based on animal studies
- Helsinki I.1
  - Knowledge of scientific literature
  - Based on animal studies
  - Conform to generally accepted scientific principles

Competence of the Investigator

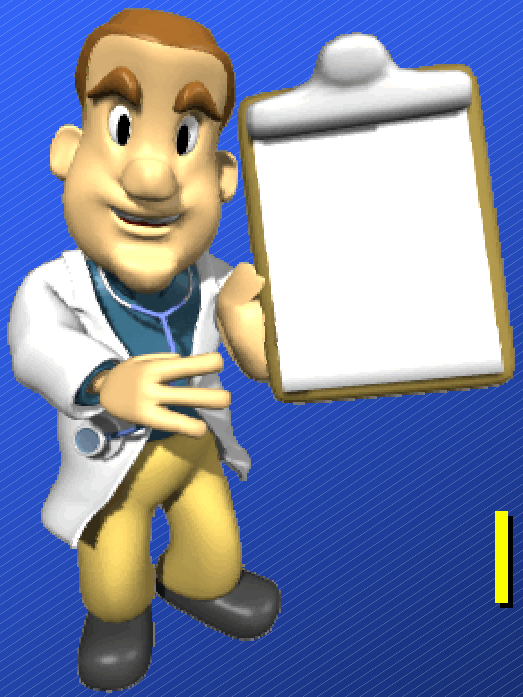
- Nuremberg 8
  - Scientifically qualified
  - Highest degree of skill and care
- Helsinki I.3
  - Scientifically qualified
    - Under supervision of clinically competent medical person
    - Ultimate responsibility lies with the medical person

Favorable Balance of Harm and Benefit

- Must balance risk to subjects with risk of loss of substantial benefits of research
- Systematic assessment of benefits / harms
- Rules
  - Brutal or inhumane treatment never justified
  - Risks should be reduced as far as possible
  - If there is significant risk of serious impairment, IRBs must verify need for the research
  - If vulnerable populations are involved, their involvement must be justified
  - Full informed consent of harms / benefits

Equitable Selection of Subjects

- Social level
  - All classes of people are not the same
  - Vulnerable should come last
  - Powerful should come first
    - "No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects." (Nuremberg 5)
- Individual level
  - Fairness expected; Can't play favorites



Informed Consent

Informed Consent:

What it is:

- ✓ An ongoing process of communication and mutual understanding

What it isn't:

- ✓ A piece of paper
- ✓ A moment in time
- ✓ A legal contract

The Consent Process

An **educational process** between the investigator and the prospective or enrolled subject.

Necessary elements include:

- Full disclosure of the nature of the research and the subject's participation
- Adequate comprehension on the part of the potential subjects, and
- The subject's voluntary choice to participate

Basic Elements

1. Research
   - Purpose
   - Duration
   - Procedures
2. Risks / harms / burdens
3. Benefits
4. Alternatives
5. Confidentiality
6. Compensation for Injury
7. Whom to Contact
8. Right to Refuse or Withdraw

Comprehension

- Informed consent is not valid unless the consenter understands the information that has been provided.
  - fluent in language
  - understandable terms
  - adequate time
  - answer questions

Voluntary Consent

- To be valid, consent must be freely given – free from all forms of coercion.
- In addition to overt coercion, the investigator needs to avoid undue influence
  - social pressure
  - requests from authority figures
  - undue incentives for participation.

Documentation of Consent

Usually involves the use of a written consent form signed by the subject or their legal representative.

- The form is merely the documentation of informed consent and does not, in and of itself, constitute informed consent.
- A consent form signed by the subject does not mean that he understood what was being agreed to or truly gave her voluntary consent.
- Informed consent is a process that is documented by a signed consent form.

Additional Elements of Informed Consent

1. May involve unforeseeable risks
2. Situations in which the investigator may terminate subject's participation
3. Any additional costs to subject
4. Consequences and procedure for subject's early withdrawal
5. Revelations of new finding
6. List the number of subjects involved in the study

Research on Emergency Therapy
(when consent is not possible)

- apply for government “waiver of consent”
- requirements:
  - life-threatening situation; no standard therapy
  - consent is not feasible
  - potential for direct benefit to subjects
  - study could not be done without waiver
  - must get consent as soon as possible
  - community involvement (disclosure, discussion, opt out, independent data-monitoring)

Therapeutic Misconception
(related to “undue influence”)

- Clinical trials referred to as “therapeutic research”
  – chance of benefit from Phase I oncology study, 4-10%
- Investigational chemicals referred to as “medicine”
  – no, these are “investigational drugs”
- Research participants referred to as “patients”
  – no, they are “research subjects”
- Investigators referred to as “physicians”
  – no, they are “investigators” or “researchers”

“Our current research suggests that as many as 70% of subjects in a wide variety of clinical research studies may suffer from a therapeutic misconception.”

– Appelbaum, *AJOB* 2(2):22, 2002

Roles

- Physician
  - Care of individual patient
  - Empathy
  - Always act in patient's best interest, the good of the one,
  - and is thus trustworthy
- Scientist
  - Quest for generalizable knowledge
  - Willing to sacrifice one patient's best interest for the good of many
  - Unable to modify regimens for benefit of individual patients
  - Is he trustworthy?

Use of Placebos in Research

- Consensus about some uses
- Continued debate about other uses

When placebos can be used (consensus)

- No established effective treatment
  - Standard therapy has dubious efficacy
  - Standard therapy has serious side effects
- Low risk of administering placebo and withholding effective intervention
  - Condition is minor & placebo itself not harmful
  - Withholding intervention causes only “temporary discomfort or delay in relief of symptoms”
- Subject must know the chances of getting placebo vs active agent.

When placebos can be used (debated)

- Helsinki 2000 (clarified 2001): “Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a … method.”
- CIOMS: “When use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.”

Should placebo's be used here?

- 120 subjects with known peptic ulcers
- randomized to receive for 6 weeks:
  - new histamine$_2$ blocker
  - placebo
- BUT, two H_2 blockers are already approved

- No. Control subjects exposed to known risks of ulcer disease which could be prevented by treatment

Vulnerable Subjects

- Children
- Prisoners
- Pregnant women (or might become pregnant?)
- Mentally disabled persons
- Economically or educationally disadvantaged
- Staff and students
- Racial minorities
- The very sick and the institutionalized

Two basic requirements for using vulnerable subjects in research

- Equitable selection
  - Purposes and setting
  - Is a vulnerable population necessary?
  - Has the research already been done on non-vulnerable populations?
- "When some or all of the subjects are likely to be vulnerable to coercion or undue influence … additional safeguards have been included in the study to protect the rights and welfare or these subjects." (CFR 46.111[b])

Children as Research Subjects

Philosophical Positions

- Paul Ramsey: no research on children
  - A research subject must give consent
  - Children can't give consent
  - Therefore, children can't be research subjects
- Richard McCormick: only if no discernible risk
  - Children may participate if we believe they would have given consent, if they were able
  - People usually seek out health
  - There is a moral obligation to contribute to generalizable knowledge

Children as Research Subjects

Regulations

- Common Rule (Title 45, §46.4)
  - Minimal risk
    - Definition: “the probability and magnitude of physical or psychological harm that is normally encountered in our daily lives, or in the routine medical or psychological examination, of healthy children”
    - Assent of child
    - Permission of one parent / guardian
  - More than minimal risk and prospect of direct benefit
    - Risk justified by benefit
    - Risk/benefit at least as favorable as with alternatives
    - Permission of one parent / guardian

Children as Research Subjects

Regulations (cont'd)

- Common Rule (Title 45, §46.4)
  - More than minimal risk and no direct benefit
    - Only minor increase over minimal risk ("…reasonably commensurate with those inherent in their actual or expected medical, psychological, or social situations")
    - Likely to yield generalizable knowledge about the child's condition which is of vital importance
    - Permission of both parents
  - Research not otherwise approvable
    - Public comment & approval of Secretary of HHS
    - Conducted under ethical standards
    - Permission of both parents

What if the child refuses?

"If the IRB determines … that the intervention or procedure holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition …"

Prisoners as research subjects

- Pros
- Cons

Prisoners as research subjects

Why not use prisoners?

- risk of coercion (lack of consent)
- unjust (unequal access to benefits)
- prisoners may not be typical of general population
- access is too easy, leading to loose application of ethical principles

Prisoners as research subjects

Why consider using prisoners?

- autonomy
  - restriction of some freedoms, not all
- beneficence
  - should have access to non-validated treatments
- justice
  - should not be excluded as a class

Prisoners as research subjects

Regulations

- Unique IRB composition
  - Racially and culturally diverse
  - At least one prisoner or prisoner representative
  - Majority with no relationship to the prison
- Benefits are not so great as to impair free choice
  - Choice remains rational
- Risks would be accepted by nonprisoner volunteers
- Fair selection from within prison
- No effect on parole

Review

- History of research ethics
- Principles of modern research ethics
- Important concepts
  - consent
  - “therapeutic misconception”
  - placebos
  - vulnerable subjects