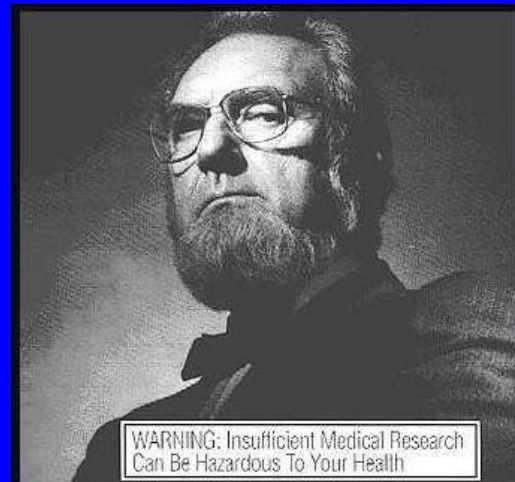


Bioengineering and World Health

Lecture Eleven



Summary of Lecture 10

- Difficulties associated with HIV vaccine:
 - Many forms of the virus
 - Virus mutates rapidly
 - Virus attacks the immune system
 - Need to stimulate cell & Ab mediated immunity
- HIV vaccines in trials:
 - Animal trials → Live, attenuated viral vaccines
 - Human trials → Subunit vaccines, only Ab response
 - Human Trials → Carrier vaccines, good Ab response, some CTL response
 - Early Human Trials → DNA vaccines

Ethics of Clinical Research

- Humans have not always treated each other humanely in the name of science
- Ethics of Clinical Research
 - Famous Case Studies
 - Codes governing ethical conduct of research:
 - Nuremberg Code
 - Belmont Report
 - Case Studies Revisited
 - Functions of the IRB
- Applications to current controversies

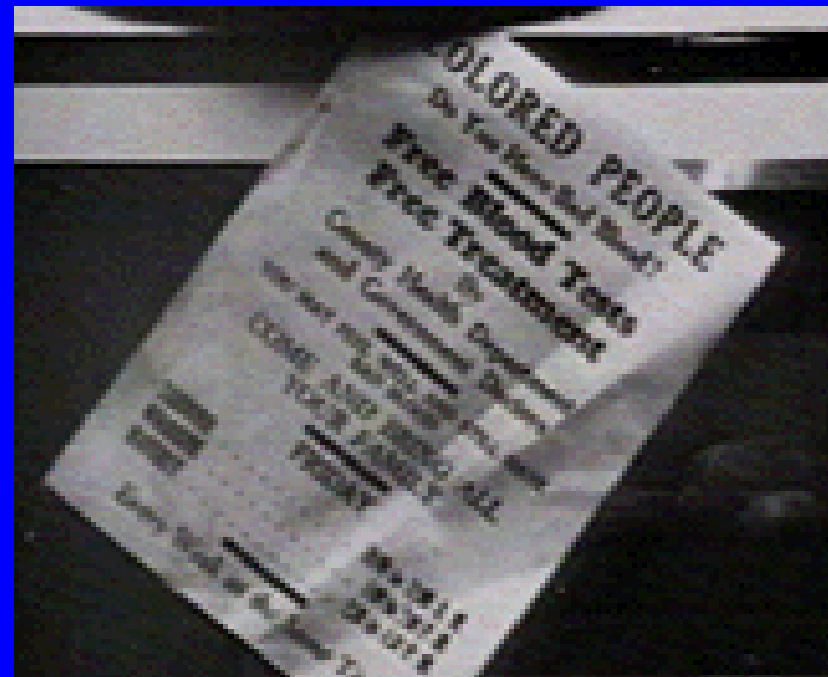
Case I: Tuskegee Syphilis Study

■ Goal:

- Examine natural history of untreated syphilis

■ Subjects:

- 400 black men with syphilis
- 200 normal controls



Case I: Tuskegee Syphilis Study

■ Experiment:

■ 1932:

- Standard Rx: injection of compounds containing heavy metals
- Treatment reduced mortality but heavy metals thought to cause syphilis complications
- Treatment withheld from infected men

■ 1942:

- Death rate 2X as high in treatment group

■ 1940s:

- Penicillin available
- Men not informed of this

■ Study continued until 1972 when first publicized

Case I: Tuskegee Syphilis Study

■ Consent Process:

- No informed consent
- Men misinformed that some study procedures (spinal taps) were free 'extra treatment'

Case II: Willowbrook Studies

■ Goal:

- Understand natural history of infectious hepatitis

■ Subjects:

- Children at Willowbrook State School
- An institution for 'mentally defective persons'

■ Experiment:

- Carried out from 1963-1966
- Subjects deliberately infected with hepatitis
 - Fed extracts of stool from infected persons
 - Injected with purified virus
- Vast majority of children admitted acquired hepatitis

Case II: Willowbrook Studies

■ Consent Process

- Parents gave consent
- Due to crowding, Willowbrook was at times closed to new patients
- Hepatitis project had its own space
- In some cases, only way to gain admission was to participate in the study

Case III: Jewish Chronic Disease Hospital Study

- **Goal: Study rejection of cancer cells**

- Healthy patients reject cancer cell implants quickly
- Cancer patients reject cancer cell implants much more slowly
- Is this due to decreased immunity because of presence of cancer or is it manifestation of debility?

- **Subjects:**

- Patients hospitalized with various chronic debilitating diseases

- **Experiment:**

- Took place in 1963
- Patients injected with live liver cancer cells

Case III: Jewish Chronic Disease Hospital Study

■ Consent Process:

- Negotiated orally, but not documented
- Patients not told that cancer cells would be injected because this might scare them unnecessarily
- Investigators justified this because they were reasonably certain the cancer cells would be rejected

Case IV: San Antonio Contraceptive Study

■ Goal:

- Which side effects of OCP are due to drug?
- Which are by-products of every-day life?

■ Subjects:

- 76 Impoverished Mexican-American women with previous multiple pregnancies
- Patients had come to a public clinic seeking contraceptive assistance.

Case IV: San Antonio Contraceptive Study

■ Experiment:

- Took place in the 1970s
- Randomized, double-blind, placebo controlled trial
- Cross-over design
- All women were instructed to use vaginal cream as contraceptive during the study
- 11 women became pregnant during study, 10 while using placebo

■ Consent Process:

- None of the women were told study involved placebo

Nuremberg Code: 1949

- Voluntary consent of the human subject is absolutely essential
- Experiment should yield fruitful results for good of society, obtainable in no other way
- Experiments should avoid all unnecessary mental and physical suffering
- No experiment should be performed if it is believed that death or disabling injury may occur

Belmont Report: 1979

- From Dept. of Health, Education & Welfare
- Statement of:
 - Basic ethical principles and guidelines to resolve ethical problems associated with conduct of research with human subjects
- Three basic ethical principles:
 - Respect for persons
 - Beneficence
 - Justice

Belmont Report: What is research?

■ Clinical Practice:

- Interventions designed solely to enhance well-being of an individual patient that have a reasonable expectation of success

■ Research:

- An activity to test a hypothesis
- Permit conclusions to be drawn
- Contribute to generalizable knowledge
- Usually described in formal protocol that sets forth an objective and procedures to reach that objective

Respect for Persons

- All individuals should be treated as autonomous agents
- Demands that subjects enter into research:
 - Voluntarily
 - With enough information to make a decision
- Persons with diminished autonomy are entitled to special protection
 - Prisoners
 - Children

Beneficence

- Make efforts to secure patients' well-being
 - Do No Harm
 - Maximize possible benefits
 - Minimize possible harms
- One should not injure one person regardless of benefits that may come to others

Justice

- Who should receive benefits of research and who should bear its burdens?
- Some ways to distribute burdens & benefits:
 - To each person an equal share
 - To each person according to individual need
 - To each person according to individual effort
- 19th Century:
 - Poor ward patients were research subjects
 - Wealthy private patients received benefits of research
- Selection of research subjects must be scrutinized:
 - Are some classes are being selected because of easy availability, compromised position or manipulability.

Application of Belmont Report

- Informed Consent
- Assessment of Risks and Benefits
- Selection of Subjects

Informed Consent

■ Information:

- Research procedure, purpose of study, risks and anticipated benefits, alternative procedures, statement offering subject opportunity to withdraw at any time

■ Comprehension:

- Must present information in a way subject can understand
- Must not be disorganized, too rapid, above subject's educational level

■ Voluntariness:

- Consent must be given voluntarily
- Persons in positions of authority cannot urge course of action

Assessment of Risks & Benefits

- Research must be justified based on favorable risk/benefit assessment
 - Risk:
 - Possibility that harm may occur
 - Brutal or inhumane treatment of subjects is never morally justified
 - Risks should be reduced to those necessary to achieve research objective
 - Benefit:
 - Positive value related to health or welfare

Selection of Subjects

■ Individual Justice:

- Researchers must select subjects fairly
- Must not select only potentially beneficial research to some subjects in their favor
- Must not select only “undesirable” persons for risky research.

■ Social Justice:

- Distinctions be drawn between classes that ought and ought not to participate in research based on ability of that class to bear burdens
- Adults before children

Case I: Tuskegee Syphilis Study

- Respect for persons
- Beneficence
- Justice
- 1997:
 - President Clinton formally apologizes to subjects of the study
 - <http://www.npr.org/programs/morning/features/2002/jul/tuskegee/>

Case II: Willowbrook Studies

- Respect for persons
- Beneficence
- Justice

Case III: Jewish Chronic Disease Hospital Study

- Respect for persons
- Beneficence
- Justice

Case IV: San Antonio Contraceptive Study

- Respect for persons
- Beneficence
- Justice

Role of IRB

- Work with investigators to be sure that the rights of subjects are protected
- Educate research community and public about ethical conduct of research
- Resource centers for information about Federal guidelines
- Not a police force

Real Controversies

■ Egg Donation

- <http://www.eggdonor.com>
- <http://www.npr.org/templates/story/story.php?storyId=5035034>

■ Life Threatening Situations

- <http://www.npr.org/templates/story/story.php?storyId=1045001>

■ Nevirapine

- <http://www.npr.org/templates/story/story.php?storyId=4524733>

■ Terminally Ill Patients