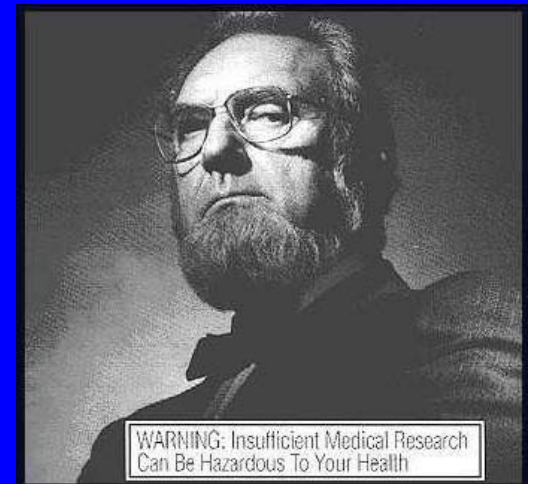


# Biomedical Engineering for Global Health

## Lecture Ten



# 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

## Nurse Takes Plunge in Ebola Test

- <http://www.npr.org/templates/story/story.php?storyId=1513230>

# HIV Vaccine

- Third Largest AIDS vaccine trial in history
  - Cost \$105 M
- Vaccines Tested
  - Sanofi-Aventis Alvac-HIV
    - Carrier vaccine
    - Canarypox virus with 3 AIDS virus genes grafted onto it
    - Stimulate cell mediated immunity
  - Gentech Aidsvac
    - Non-infectious vaccine
    - Contains protein found on surface of HIV
    - Stimulates Ab mediated immunity

# HIV Vaccine

- Each failed when used individually
- 2004 editorial in Science signed by 22 top AIDS researchers:
  - Suggested trial was a waste of money

# HIV Vaccine

## ■ Study Design

- Followed 16,402 Thai volunteers
- Men & women, aged 18-30
- Recruited from general population
- Half got six doses of two different vaccines
- Half got placebo
- Followed for 3 years

# HIV Vaccine

## ■ Ethics:

- All were offered condoms
- Taught how to avoid infection
- Promised lifelong ARVs if infected

# HIV Vaccine

## ■ Results:

- Placebo group: 74 infected
- Vaccinated group: 51 infected

## ■ Vaccine is 31.2% effective

## ■ Those who become infected have as much virus in blood whether they got vaccine or placebo

- Suggests vaccine does not produce neutralizing antibodies

# Dangers of Vaccine Trials

- Most researchers feel first HIV vaccines will not be more than 40-50% effective
  - Will vaccinated individuals engage in higher risk behaviors?
  - Vaccine could cause as much as it prevents
- **AIDS Vaccine Study Results Explained**
  - <http://www.npr.org/templates/story/story.php?storyId=113177004>
- Future vaccines cannot be tested against placebo, would be unethical

# 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
- 19<sup>th</sup> 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