

UT Southwestern Summer Lecture Series

June 26, 2009

*ETHICS AND RESEARCH II*

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UT Southwestern Medical Center

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U.S. Department of Health & Human Services  
National Institutes of Health  
The Nation's Medical Research Agency

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NIH is the nation's medical research agency - making important medical discoveries that improve health and save lives.

The National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services, is the primary Federal agency for conducting and supporting medical research.

Helping to lead the way toward important medical discoveries that improve people's health and save lives, NIH scientists investigate ways to prevent disease as well as the causes, treatments, and even cures for common and rare diseases.

Medical discoveries require research on humans

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The problem of informed consent.

HOW MEDICAL TESTING HAS TURNED MILLIONS OF US INTO... HUMAN GUINEA PIGS

The problem of conflict of interest.

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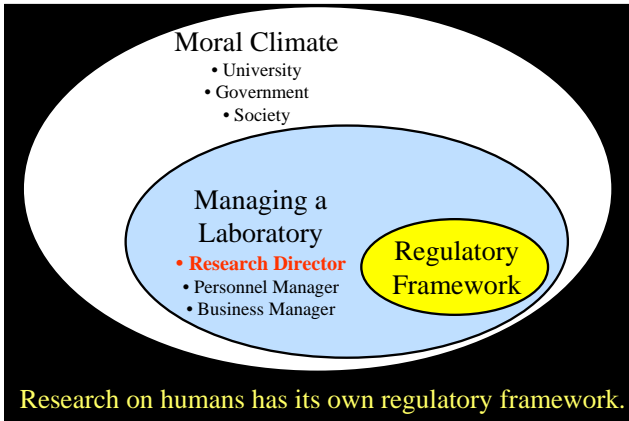
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Nuremberg Code, 1949

1. The voluntary consent of the human subject is absolutely essential...
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

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...because of vast physiological variations between species, human reactions to illnesses and drugs are completely different from those of other animals...

Animal experimentation not only is preventing us from learning more relevant information, it continues to harm and kill animals and people every year.

People for the Ethical Treatment of Animals

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Even the most sophisticated technology cannot mimic the complicated interactions among cells, tissues and organs that occur in humans and animals.

- **Reduce** the number of animals used in each and every study
- **Replace** lab animals with non-animal models whenever possible
- **Refine** the tests to ensure the most comfortable and humane conditions possible

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### TUSKEGEE

For forty years between 1932 and 1972, the U.S. Public Health Service conducted an experiment on 399 black men in the late stages of syphilis. These men, for the most part illiterate sharecroppers from one of the poorest counties in Alabama ...

their doctors had no intention of curing them of syphilis at all. The data for the experiment was to be collected from autopsies of the men, and they were thus deliberately left to degenerate under the ravages of tertiary syphilis

Even when penicillin —the first real cure for syphilis— was discovered in the 1940s, the Tuskegee men were deliberately denied the medication.

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### U.S. - Belmont Report - 1978

**Respect for persons:** Informed consent

**Beneficence:** Minimize risks - maximize benefits

**Justice:** Recruit and select subjects fairly (distribution of burdens vs. benefits)

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The screenshot shows the Southwestern Medical Center website. At the top, there is a navigation menu with categories like Home, Education, Research, Patient Care, Faculty & Administration, and Career. Below this, there is a search bar and a list of services including Centers & Departments, Case Facilities, Post Doctoral Fellowships, Research Services, Clinical Trials, Technology Development, and Research Administration. A contact information for Sheria Orsatt, Program Coordinator, is provided. The main heading is 'Institutional Review Board (IRB)'. Below the heading, a flowchart shows the process: 'Investigator Protocol' leads to 'IRB Review', which leads to 'Research'.

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Challenges to Ethical Practice of Human Research

- The underlying paradox of research
- The problem of informed consent
- The problem of conflict of interest

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Human Research: An Ethical Paradox?

*World Medical Association Declaration of Helsinki, A5: ...the well-being of the human subject should take precedence over the interests of science and society.*

Research by its very nature tends to be in the best interests of science and society and future patients.

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Double-Blind, Placebo-Controlled Studies

Subject as a “typical example.”

Patient’s uniqueness and researcher’s expectations potentially problematic.

Use of a placebo and random, blinded assignment to placebo or drug makes for good experimental design.

(human guinea pigs?)

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Is there really informed consent?

What is the difference between research and therapy?

What is the difference between subject and patient?

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Description of a Case

(From *Archives of Dermatology*, 1988): A 69 year old black woman with bilateral leg stasis ulcers and a previous history of vascular insufficiency and vein stripping was enrolled in a randomized, doubleblind study after obtaining informed consent. This patient’s ulcers had been under treatment since February, 1982. The study protocol called for a three week period of experimental treatment with a fibronectin test solution or with a placebo solution containing human serum albumin.

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Endings of clinical research protocols:  
Distinguishing therapy from research.

**Therapy:** For the patient, treatment continues as long as the person continues improving.

**Research:** For the subject, treatment continues as long as the experiment lasts but stops when the experiment is complete even if the person is getting better.

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Therapeutic Misconception

Potential subjects think that *Research = (innovative) Therapy*

- do not understand the relationship between patient and subject.
- turn to research because of need for medical treatment/access.
  - agree/demand to be a subject in order to become a patient.

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Overcoming the “Natural Attitude”

At the end of the experiment we likely will have to stop your treatment even if your health has been improving -- even if your condition might deteriorate as a consequence.

Regardless of how well the therapy appears to work for you, it may never become available to you or anyone else if the manufacturer decides for whatever reason not to continue its development.

In the highly unlikely event that the experimental treatment results in your death, even this tragedy would provide us with valuable data.

**You want me to do what?**

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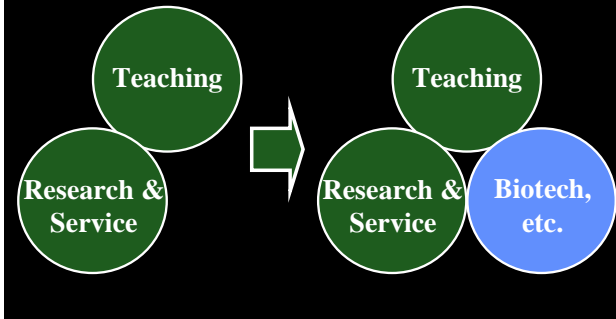
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## Transition of the Research University



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Bayh-Dole Act, 1980: Congress wants federally-funded research patented and developed



Universities now have intellectual property interests  
Patent/license opportunities offer researchers possibility of royalty/equity earnings  
In the UT System 50:50 split

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## The Funding Effect

Positive correlation between industry sponsorship and pro-industry **research findings**.

Positive correlation between industry sponsorship and pro-industry **regulatory decisions**.

Industry restrictions on **publication and data sharing** including withholding of negative data.

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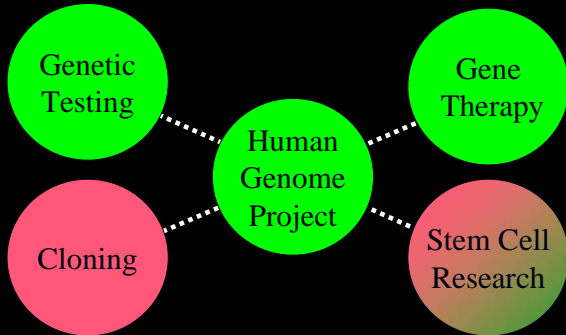
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Human Research and Genetics



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Genetic Medicine

What's a disease?

Who's the patient?

What's a cure?

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The Meaning of Disease

1. How a person feels – disease as dis-ease.
2. Normal physiology – disease as illness.
3. Genetic linkage – disease as prediction – even before the person

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**Genetics as Disease Predictor**

Genetic difference



Abnormal physiology



How a person feels ( Dis-ease)

**Genetics as Disease Explanation**

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**Informed Consent**

UT Southwestern standard language:

If the results of DNA tests show that you or anybody else in your family may develop [insert name of disorder], you and other family members could experience serious stress after receiving such information...

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**Risk of Psychological Dis-ease**

You might learn something about yourself that you wish you did not know -- if not now, then sometime in the future.

**Genetic Future Worth Marrying?**

**Genetic Future Worth Reproducing?**

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## Genetic Uncertainty

Environment, Epigenetics, Epistasis

Predictive tests always probabilistic  
(if, when, how serious)

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## Eugenics (genetic essentialism)

Francis Galton, 1883: social control to improve the racial qualities of future generations, either physically or mentally.

*Using genetics to make better people instead of to make people better.* (Faith Fitzgerald)

Cold Spring Harbor Laboratories -- Eugenic Record Office -- national sterilization policy & immigration policy

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U.S. Supreme Court (commenting on forced sterilization of Carrie Buck Detamore, Virginia, 1927):

*It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind.*

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## Genetic Medicine

What's a disease?

Who's the patient?

What's a cure?

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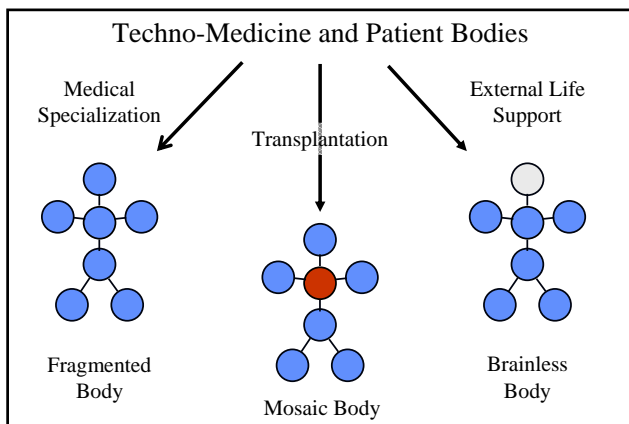
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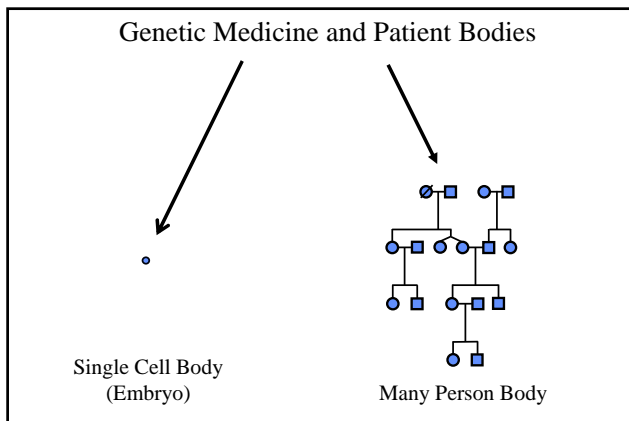
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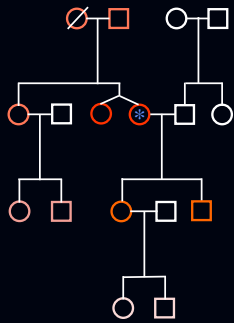
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The Many Bodies Genetic Patient



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Problem of Privacy

Genetic information is both individual and familial.

What if potential harm to a family members is serious and prevention or treatment is available?

Confidentiality vs. the duty to warn...

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Problem of Secondary Subjects

Individual can become a research subject even if that person is not directly interacting with the investigators.

Survey research – you have to ask questions.  
Genetics research – it's automatic.

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Genetic Medicine

What's a disease?

Who's the patient?

What's a cure?

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Curing Genetic Disease

Therapeutic Intervention (PKU)

Disease "Prevention"

Gene "Therapy"

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New Meaning of Disease Prevention

*Public Health Medicine:*

Stop smoking and exercise more

*Genetic Medicine:*

Avoid the marriage.

Don't have children.

Don't implant the embryo.

Abort the fetus.

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## What about gene therapy?

Repair the Defective Gene

Excise and Replace the Defective Gene

Add a Functional Gene

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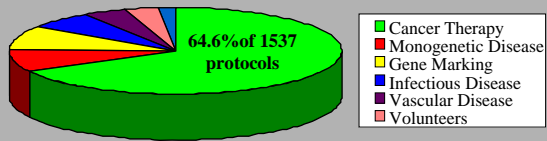
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Gene Therapy Protocols by Disease

Wiley JGM, March 2009

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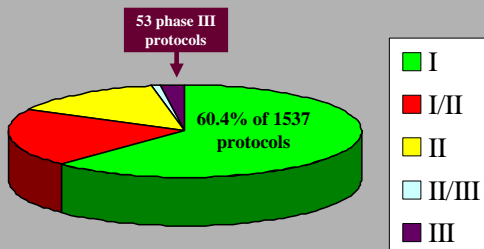
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Gene Therapy Protocols by Phase

Wiley JGM, March 2009

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## Current Status of Gene Therapy

Mostly therapy with genes for multifactorial diseases especially cancer (67%) rather than therapy of genes (responsible for monogenetic disease such as cystic fibrosis, Huntington's disease.)

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## Gene Therapy and Development

Genetic disorders often affect many different cell types.

Onset of genetic disease often begins before birth and can cause irreversible damage during development.

In principle, embryos would make the best gene therapy candidates.

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## The Embryo is the Purest Genetic "Person"



Genetic Potential >> Life Experience

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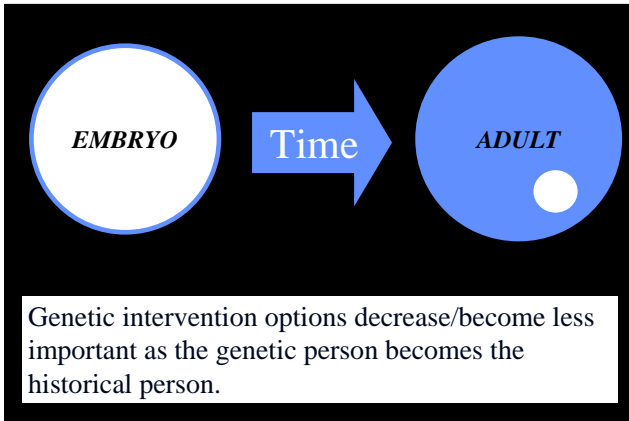
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- ### Embryo Research Time-line
- 1970: In vitro fertilization (IVF) with human eggs.
  - 1975: NIH ethics advisory board never appointment (politicized context of 1973 Roe v. Wade)
  - 1978: Louise Brown born; first IVF baby
  - 1979: NIH ethics advisory board recommends research (safety and efficacy of embryo transfer)
  - 1979-present: No federal research program; 20-30% IVF success rate; multiple embryo transfers (births); 500,000 embryos in US freezers
  - 1998: Embryonic stem cells derived from frozen embryos

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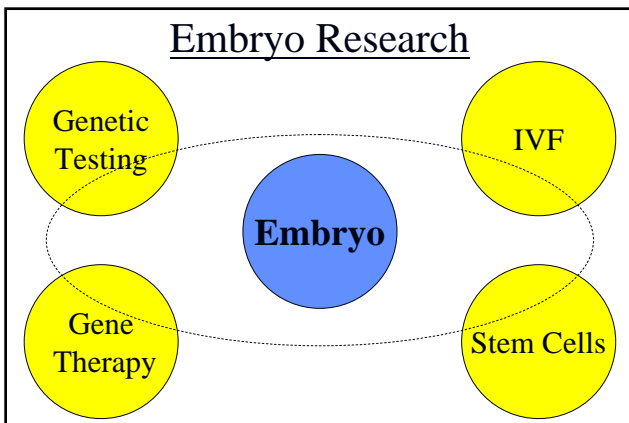
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### Existential Perspective of the Embryo

Personhood is not inherent in the organism but emerges after:

- Embryo implantation -- Full potential for development.
- Day 14 of development – Last day for twinning.
- Birth – Independence from mother.

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### Essentialist Perspective of the Embryo

- The person's meaning is constituted from the moment living human potential is established (i.e., formation of the embryo).
- Each human life reflects a single continuum.
  - The embryo is the person not yet born.

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*Helsinki A5: the well-being of the person should take precedence over the interests of science and society.*

If the embryo is a person, then research that results in the death of the embryo would be unethical regardless of the scientific or medical benefit.

If the embryo is not yet a person, then research resulting in the death of not yet person embryos would be ethical if warranted by the scientific/medical benefit.

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Genetics and the Uncertainties  
of Human Research

Risks vs. benefits

Appropriate subjects (e.g., embryos)

Eugenic implications

Conflict of Interest

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*Human Genetics Research: We Love the Knowledge, How We Fear the Data!*

The Gaylord Opryland Resort & Convention Center • Nashville, TN  
November 13, 2009

*Faculty*

Barbara Handelin, PhD  
*President  
Handelin Associates*

Pearl O'Rourke, MD  
*Director, Human Research Affairs  
Partners Healthcare System, Inc.*

**Program Description**

This full-day program will provide foundational knowledge in human genetics research and tissue banking/repository practicalities. Genetics has been a significant factor of biomedical research involving human subjects since the late 1980s, yet these protocols continue to invoke angst and confusion for IRBs, ethics councils, investigators, and volunteer subjects. Research on the genome produces some of the most important—and disruptive—medical knowledge. This program will address the risks of conducting genetics research with volunteer human subjects, hot topics in genetics research and specimen banking, and more. Attendees will also have the opportunity to ask questions and participate in discussions.

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