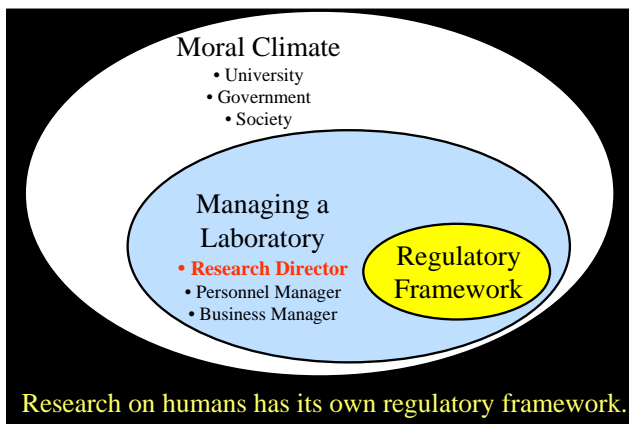


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Human Research Ethics and Genetics

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Medical discoveries require research on humans



Human Research –Translational vs. Basic

Does topical fibronectin treatment promote healing of venous stasis ulcers? (translational)

Agree in advance on what will count for data.
“Good Laboratory Practice”

What is the status of fibronectin in the venous stasis ulcer environment? (basic science)

Problem to distinguish data from noise.
“Good” Laboratory Practice

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.
4. ...

...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



Even the most sophisticated technology cannot mimic the complicated interactions among cells, tissues and organs that occur in humans and animals. Scientists must understand these interactions before introducing a new treatment or substance into humans.

[O]ur scientific and medical research communities are committed to supporting the development of research techniques that:

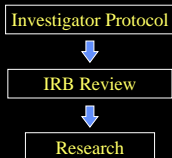
- **Reduce** the number of animals used in each and every study
- **Replace** lab animals with non-animal models whenever possible
- **Refine** the tests to ensure the most comfortable and humane conditions possible

U.S. - Belmont Report - 1979

Respect for persons: Informed consent

Beneficence: Minimize risks - maximize benefits

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



The underlying paradox of research.

The problem of informed consent.

The problem of conflict of interest.

Human Research: An Ethical Paradox?

World Medical Association Declaration of Helsinki, A5:
In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

Rather than the best interests of the subject, research by its very nature – risk/benefit asymmetry -- tends to be in the best interests of science and society and future patients.

Double-Blind, Placebo-Controlled Studies

The subject is studied as a “typical example” of some class or type.

The patient’s personal uniqueness and the researcher’s personal expectations present problems for research.

Random, blinded assignment to different parts of a trial and use of a placebo solves these “problems” and makes for good experimental design. (human guinea pigs?)

Challenges to Ethical Practice of Human Research

The underlying paradox of research.

The problem of informed consent.

The problem of conflict of interest.

Is there really informed consent?

What is the difference between research and therapy?

What is the difference between subject and patient?

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.

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.

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.

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?

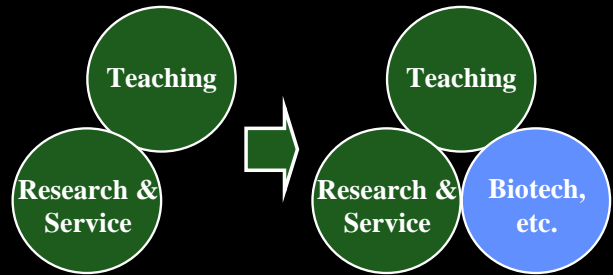
Challenges to Ethical Practice of Human Research

The underlying paradox of research

The problem of informed consent

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Transition of the Research University



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

The Funding Effect

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

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

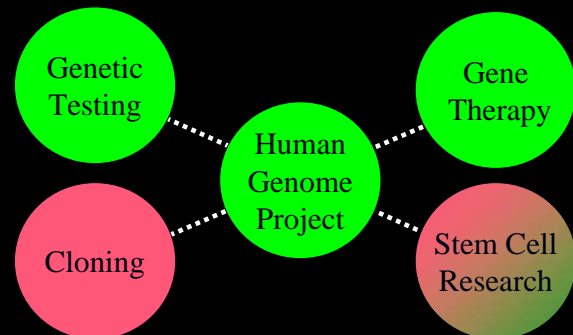
Industry restrictions on **publication and data sharing** including withholding of negative data.

Protecting Subjects, Preserving Trust, Promoting Progress-- Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research

Task Force on Financial Conflicts of Interest in Clinical Research
December 2001

A) ... an institution should regard all significant financial interests in human subjects research as potentially problematic and ... should establish the **rebuttable presumption** that an individual who holds a significant financial interest in research involving human subjects may not conduct such research.

Human Research and Genetics



Genetic Medicine Changes the Meaning of Common Language

What's a disease?
Who's the patient?
What's a cure?

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

Genetics as Disease Predictor

Genetic difference



Abnormal physiology



How a person feels (Dis-ease)

Genetics as Disease Explanation

Informed Consent Risks and Benefits

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...

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?

Genetic Uncertainty

Environment, Epigenetics, Epistasis

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

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

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

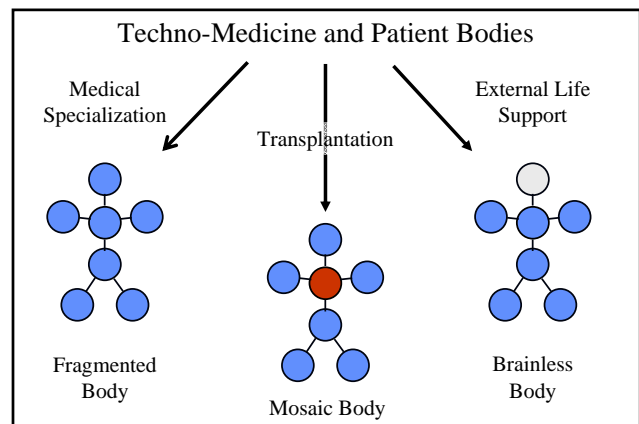
It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind.

Genetic Medicine Changes the Meaning of Common Language

What's a disease?

Who's the patient?

What's a cure?



Genetic Medicine and Patient Bodies

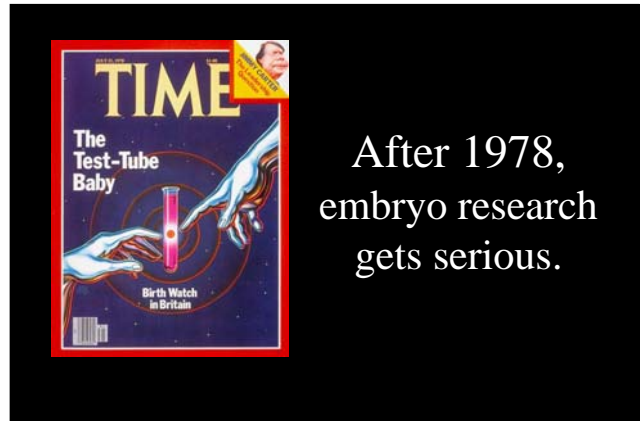
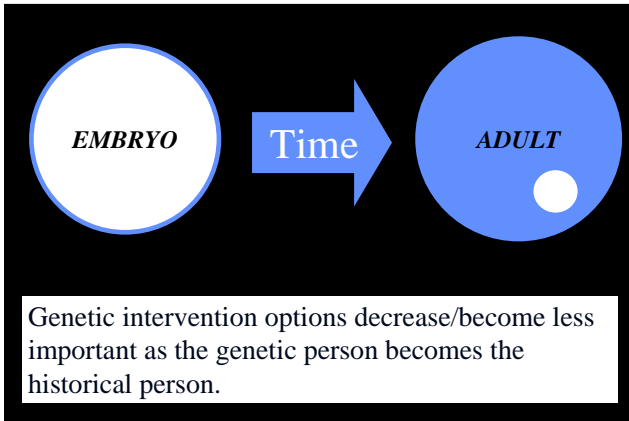
Embryo Cell "Body"

Many Bodies

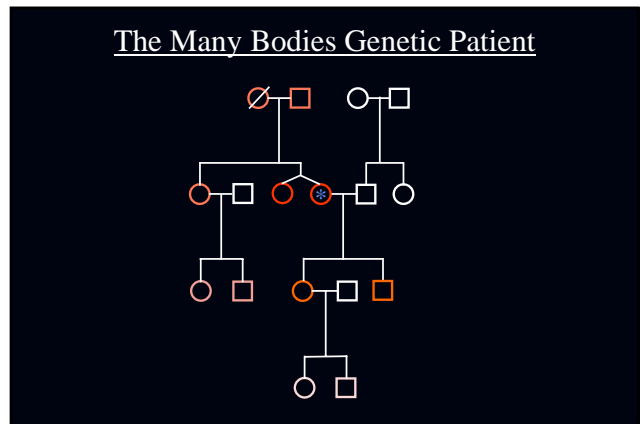
The Embryo is the Purest Genetic "Person"

EMBRYO

Genetic Potential >> Life Experience



- ### 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



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...

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.

Genetic Medicine Changes the Meaning of Common Language

What's a disease?

Who's the patient?

What's a cure?

Curing Genetic Disease
Therapeutic Intervention (PKU)
Disease "Prevention"
Gene "Therapy"

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.

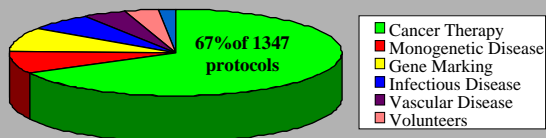
Abort the fetus.

What about gene therapy?

Repair the Defective Gene

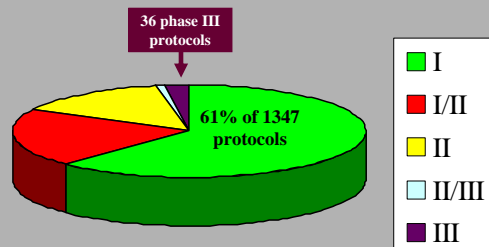
Excise and Replace the Defective Gene

Add a Functional Gene



Gene Therapy Protocols by Disease

Wiley JGM, March 2008



Gene Therapy Protocols by Phase

Wiley JGM, March 2008

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.)

Conventional vs. Biological Engineering

Building vs. Intervention
 Design vs. Design Alteration
 Sole Agency vs. Co-agent (with evolution)
 Direct Causality vs. Indirect (Genetic) Causality

Han Jonas

June, 2002: These results indicate the safety and efficacy of HSC gene therapy. . .

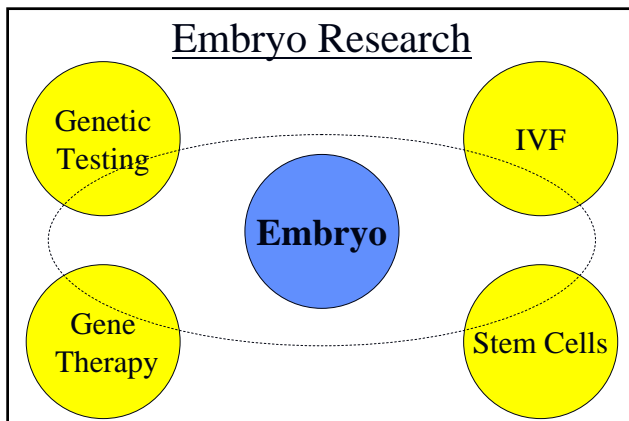
January, 2003: These risks seem surprisingly high. . .

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.



President George W. Bush's 1st Prime-time Speech August 9, 2001

Should Federal funds be used for stem cell research?
 Extracting the stem cell destroys the embryo. Are frozen embryos human life?
 If they're going to be destroyed anyway, shouldn't the embryos be used for a greater good.

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.

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.

Helsinki A5: In medical research on human subjects, considerations related to **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.

Genetics and the Uncertainties of Human Research

Risks vs. benefits

Appropriate subjects (e.g., embryos)

Eugenic implications

(Conflict of Interest)

Vulnerable Subject

-- anyone in circumstances in which the possibility of obtaining informed consent is compromised (from insufficient cognitive capacity to insufficient infrastructural capacity)

Because of increased uncertainties, every prospective subject of human genetics research might be considered vulnerable.

Then what?

