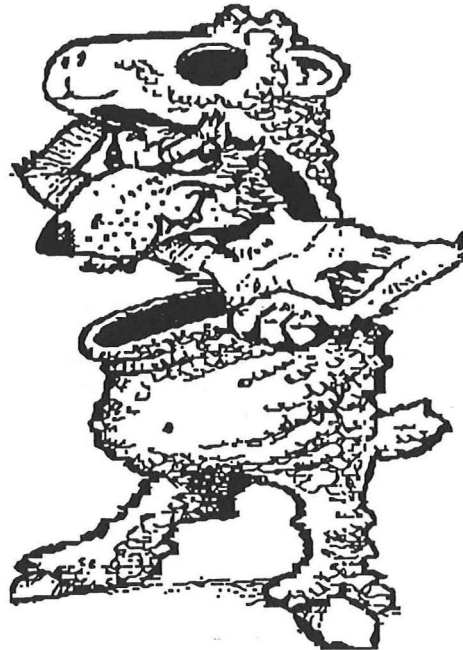


GENETHICS



**John W. Burnside, MD
Professor of Medicine
Division of General Internal Medicine**

"This is to acknowledge that John Burnside, MD has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program."

[Medical Grand Rounds] [May 28, 1998]

A few "what ifs" for your consideration:

1. Your husband and son are in a terrible accident. Your husband has been killed and your son is brain dead on life support. You ask to have a somatic nuclear transfer from your son to one of your ova. Should you be allowed to?
2. You believe you have identified a gene locus for suicide. You have several thousand blood samples in your research freezer and test for the gene prevalence. You find 16 samples with this marker. A quick review of hospital records discloses that indeed 4 of these individuals have taken their life. What is your responsibility to the other 12?
3. Your patient, an eight year old girl, needs a bone marrow transplant. Both parents offer to be donors and submit to testing. Testing shows that neither match and, oh by the way, the father of record could not be the biologic father. What is your response?
4. You stumble onto a selective, very efficient gamete vector. What would you do with it?
5. If cloning in animals results in a shortened life expectancy would this be sufficient for you to support banning human cloning?
6. An employer recognizes that workers with a certain genotype are disposed to toxic effects of the chemicals he manufactures. He argues that he should be allowed to test as a condition of employment to protect workers and himself. He contends it is the same as testing for drug use. Should he be allowed to test?
Suppose the genotype is particularly prevalent in one ethnic group? Should he be allowed to test?

DID YOU KNOW THAT?

- The most common genetic test is to determine parentage
- Impulse control may be on chromosome 16
- The only true clone must come from an individual woman
- > 1,175 gene sequences and 9 animals have been patented

- Science frequently creates moral dilemmas
- Science cannot solve a moral dilemma
- Moral dilemmas are a conflict of values not facts

It is a common mistake for us to search for scientific answers to moral dilemmas. Discovering the fetal age of nerve cell conduction does not satisfy the argument of abortion, for instance. If we prove that cloning is “safe”, do you believe the moral conflict will disappear?

The science creating the dilemma may be new but the conflict of values is very old. The lack of consensus is precisely what makes it difficult to decide - What is the right thing to do?

PRIMA FACIE VALUES

- Non-maleficence
- Beneficence
- Justice
- Autonomy

These four values are at the heart of most major medical ethical dilemmas. Each describes “good actions”. The dilemma occurs when honoring one value subjugates another value. Do you have a rank order or does it depend on the circumstance?

AUTONOMY

- Information
- Understanding
- Competence
- Freedom from coercion

We all want information. We dislike secrets, especially those about us.

Informed consent has been the major stage of autonomy in recent decades. Patients are required to have information and to understand that information. Coercion can take many forms and be very subtle. How do you obtain informed consent from future generations?

SOME PHYSICIAN DILEMMAS

- Autonomy depends on information
- We have a duty not to harm
- We have a duty to keep confidences
- We have a duty to protect the public

To test or not to test. To make decisions requires information. That information may be harmful, be subject to discovery by others, be of value to the health of others, and may be inaccurate.

Consider, too, the problems encountered with unexpected data.

SCREENING WHO AND FOR WHAT

- Screen only for treatable illness
- Information alone has value
- Screening will lead to discrimination
- Screening is inaccurate
- Screening shows risk not certainty
- Patients have a right not to know
- Patients have a duty to know

This is the language of the arguments about screening.

RISKS OF SCREENING

- Economic disadvantage
- Anxiety, depression
- False reassurance
- Unwarranted prophylaxis
- Breach of confidentiality
- Survival guilt

None of these can be measured. Importantly, most of these are individually perceived by patients. Not screening can be interpreted as paternalistic on one hand or a breach of autonomy on the other.

DISCRIMINATION

- All insurance is risk based
- It's unjust to penalize for a risk not of your own doing
- Low risk should not pay for high risk
- Employer has a duty to protect workers

- Equal employment means no discrimination
- Screening puts groups at risk
- Insurance/employment is voluntary
- Widespread screening will invoke a single payer system

I may choose to live on a flood plain, drive recklessly, or live in the city, but I did not choose my code.

**NATIONAL ADVISORY COUNCIL
FOR HUMAN GENOME
RESEARCH:**

**“...until more information is available ...
it is premature to offer DNA testing or
screening for cancer predisposition outside
... a research environment”**

**AMERICAN SOCIETY OF
CLINICAL ONCOLOGY:**

**“ ... genetic testing should be made
available to selected patients as part of the
preventive oncologic care of families.”**

**NATIONAL BREAST
CANCER COALITION:**

**“ ... genetic testing should only be
available within peer reviewed research
protocols.”**

- There seems to be a consensus of caution. If the test is available, however, it will be impossible to ban its use.

PATENTS:

- Provide an economic incentive for research
- Human body should not be commercialized
- Should be for process, not product
- Man belongs to nature, not vice versa
- Secrecy inhibits exploration

Patents are strongly tied to the concept of property and the right to own property as a mark of a free society.

SAMUEL MORSE:

Granted patent on telegraphic instrument
but not on electromagnetic waves

Samuel Morse obtained wealth from his “invention”. Shasta could not patent his “daisy”.

SUPREME COURT, 1948

"A product must be more than new or useful to be patented: It must also satisfy the requirements of invention."

What is the invention in a description of a sequence of base pairs?

**1980 DIAMOND V. CHAKRA
BARTY - SUPREME COURT ON
HYBRIDIZED BACTERIUM**

"His discovery is not nature's handiwork but his own." "...the result of human ingenuity and research"

The recognition of an altered life form.

1987 - PATENT OFFICE

"... now considers non-naturally occurring non-human multicellular living organisms, including animals, to be patentable subject matter."

Confirmation of that recognition by the patent office. Still the emphasis on non-naturally occurring life.

1992 - PATENT OFFICE

"All cotton seeds and plants which contain a recombinant gene construction"

This decision has been very controversial and is subject to current review. The implication of this decision which is astonishing is the inclusion of seeds --- future generations of a life form.

RELIGIOUS OBJECTIONS:

"Humans and animals are pre-owned beings. We belong to the creator God."

**Richard Land
Southern Baptist Convention**

"Most religious leaders object to the hubris of claims that organisms are intellectual property not to legal regimes per se intended to reward and encourage effort and investment in biotechnology."

Articulated most forcibly by organized religion, this discomfort is widely acknowledged by the lay public.

We abhor commercialization
of human organs or genes

but

If knowledge or use of genes attains significant commercial
value, should not some of that reward be returned to the
original source?

There is precedent for this. The commercial value of cells derived from a patient with hairy cell leukemia was the subject of recent court action. The patient had a splenectomy, and cells were derived from that spleen without his knowledge and commercialized. How far should this be extended? There are research freezers everywhere with material from patients which is being studied and which might be commercialized.

GENE THERAPY

- Somatic and germ cell
- Treatment/Prevention and enhancement

These are four dimensions of gene therapy. Current vector problems give us time for conversation but it won't be long.

The division between treatment and enhancement, I believe, is artificial. We might not wish to enhance physical appearance but suppose we could enhance immune surveillance or DNA repair mechanisms?

PHENOTYPIC PREVENTION:

Forestall clinical manifestations of a genetic disease in an individual

GENOTYPIC PREVENTION

**Avoid transmission of particular
genotypes to subsequent generations**

On behalf of:

Prospective patients

Reproductive risk reduction

Public health

**We tend to be more sympathetic to the plight of an individual than to the “good of society”.
Tinkering with subsequent generations demands a much greater consensus even though it might
hold the promise of “eliminating” disease.**

CLONING

- Molecules/DNA: Insulin, tPA, EPO
- Cells
- Plants
- Animals

The concept and procedures are not new. In addition to the success in medicine, the effects on agribusiness are enormous.

October 1993:

Drs. Hall and Stillman at
George Washington University
reported embryo splitting

Human cloning really started here. It generated less controversy since the model of natural twins was familiar.

FEBRUARY 1997

**Dr. Wilmut and colleagues announce
“Dolly”, the product of somatic nuclear
transfer**

A curious sidelight is that this was first presented in the lay press not the scientific press.

DOLLY:

- **Differentiation and specialization are reversible**
- **Gene expression can be reprogrammed**
- **Egg cytoplasm must be responsible**

For the scientific community, these are of much greater interest than the controversy about human cloning.

DOLLY SCIENCE QUESTIONS

- Was somatic cell mature?
- How “old” is Dolly?
- Why the low success rate?
- What about mitochondrial DNA?

Recall that mitochondrial DNA is a maternal gift. A true clone then would require a somatic cell and an ovum from one woman and would, of course, be a female child. All other combinations offer the possibility of DNA diversity albeit limited.

REASONS TO CLONE

- Produce genetically identical animals for research
- Rapidly propagate desirable animal stock
- Produce transgenic stock for transplantation
- Learn basics of cell differentiation

HUMAN CLONING

- Is there a compelling need to clone humans?
- Banning is justified only if substantial harms are likely
- A nuclear donor has the right to procreate
- Scientists have a right to do research
- A child has a right to individuality

Bans have had little success in the past. At the most, they buy time. Both bans and unfettered tinkering are replete with unintended consequences.

There was no compelling reason to climb Mt. Everest, a potentially harming enterprise.

We have a long history of reproductive rights and freedoms and a long history of the scientific rights and freedoms.

**“children ... replicate neither their father
nor their mother. That is a reminder of the
independence that one must eventually
grant them.”**

**"Ignorance of the effect of one's genome
on one's future is necessary for
spontaneous, free, and authentic
construction of a life and self"**

"We should beget not make children."

**"Human definition turns on a surrender to
the genetic lottery."**

"Is such a child his father's brother?"

**“Repugnance is often the emotional bearer
of deep wisdom beyond reason’s power to
fully articulate it.”**

**“Repugnance is the universal response to
startling new biology.”**

“A supposed affront to human dignity is a flimsy basis on which to erect barriers to research”

Whatever the reason, the flood of public interest and controversy indicated that a very sensitive nerve had been touched.

“ ... will lead to armies of complacent workers, crazed soldiers, brilliant musicians, or beatific saints.”

Again the reminder that these are not scientific questions. The nature of identity, parenting, and destiny are not safety concerns.

Eugenics weakness is that it is a collective program not an individual enterprise. It would require unachievable consensus or vicious dominance.

Whatever consensus might accrue will be part of the body politic, not the scientific community.

PRESIDENT'S COMMISSION

“ It is morally unacceptable for anyone
... to attempt to create a child using
somatic cell nuclear transfer cloning.”

The full report is worth your time to study. The Commission was convened in a hurry and probably came to no other conclusion. It is unfortunate that the major objection was safety of the procedure. Do they mean that if we can prove it safe, there would then be no objection to cloning humans?

ARE THESE DISEASES?

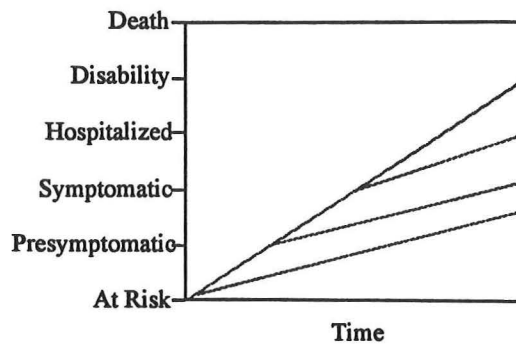
- Obesity
- Ugliness
- Fertility
- Teen pregnancy
- Family violence
- Alcoholism

We “treat” all of these conditions and readily accept challenges to address social concerns. We may play a role; but if we accept total responsibility, we fail.

ARE THESE DISEASES?

- BRCA-1 gene
- Gene for Huntington’s chorea
- XX genotype
- Gene for low impulse control

At what point does a disease exist? If you have polydipsia, polyuria, polyphagia, and a blood sugar of 300, you have diabetes. If you have fasting hyperglycemia but no symptoms, you have diabetes. If you have the gene(s) but no symptoms and no blood sugar elevation, do you have the disease?



Presymptomatic detection told patients that we knew something about them that they did not know. At what point on this line do you have a disease?

MEDICINE - WEBSTER'S

The science and art of diagnosing, treating, curing, and preventing disease, relieving pain and improving and preserving health.

Tom Peters said that the reason railroad companies fell on hard times was because they thought they were in the railroad business and did not recognize they were in the transportation business.

What business are we in?

DISEASE - WEBSTER'S

- **Any departure from health; illness in general**

- **A particular destructive process in the body, with a specific cause and characteristic symptoms; specific illness; ailment; malady**

- An evil or destructive tendency or state of affairs

If disease is our province, Webster gives us wide latitude.

HEALTH - WEBSTER'S

Physical and mental well-being;
soundness, freedom from defect, pain or
disease; normality of mental and physical
functions

Hmm Disease is the absence of health and health is the absence of disease.

The World Health Organization seems to give us an even greater mandate when they declare that health is the absence of physical, mental, or social distress.

In the gene environment interaction,
how much gene effect is required to
engage our profession?

If a gene is not sufficient, but is a
necessary requirement for a malady,
are we engaged?

It will be the distinct rarity to find any gene which is 100% predictive of a phenotypic expression. Chimeric states and the influence of other genes as in testicular feminization for instance will disallow absolute certainty.

SPECIAL CONCERNS IN PSYCHIATRY

- Manic depressive illness
- Schizophrenia
- Alcoholism
- Somatization

More than any other specialty, psychiatry is influenced by societal values. There is incontrovertible evidence that these conditions are inherited or, at least, the proclivity for them is inherited.

PATTERNS OF BEHAVIOR

- Harm avoidance
- Reward dependence
- Novelty seeking
- Persistence
- Impulse control

Recall that there are no laboratory diagnostic tests for the list of diseases. They are all descriptive, and the diagnosis rests on pattern recognition. This list is no different, but it provokes a different response when you read it. Linkage studies are beginning to assign these "diagnoses" to specific chromosomes.

Total _____ Genetic
Free Will _____ Determinism

PREDICTIONS

- We will all have to be geneticists
- Chem 20 will become Gene 20
- Many adult diseases will be the province of pediatricians
- We will have an astonishing pharmacopoeia

- Human cloning will occur
- We will go to a single payer system
- We will understand cell differentiation
- We will understand cell clocks
- We will be scorned in the future

- There will be unintended consequences

What an exciting time we live in!

TESTING

Cole DE; Gallinger S; McCreedy DR; et al. Genetic counselling and testing for susceptibility to breast, ovarian and colon cancer. CMAJ 1996 Jan 15;154(2): 149-55

Authors support testing only in the research environment.

Vineis P. Ethical issues in genetic screening for cancer. Ann Oncol 1997 Oct 8(10):945-9

A very nice review of duties and rights. Written by someone who understands the science involved as well.

Kodish E; Wiesner GL; Mehlman M; Murray T. Genetic testing for cancer risk. JAMA 1998 Jan 21(279):179-81

What are the risks? They explore some of the implications of screening versus testing.

U S Department of Health and Human Services. Understanding gene testing. Available at http://cancernet.nci.nih.gov/p_genetics.html

A nice primer. I commend it for your library.

Pokorski RJ. A test for the insurance industry. Nature 1998 Feb 26(391):835-6

Examples and history of the insurance industry, discrimination and testing.

National Bioethics Advisory Commission. Informed consent and the ethical use of tissue samples. (due very soon) www.nih.gov/nbac/nbac.htm

The commission was challenged to respond to the concerns of special groups of ethnically identified people.

GENE THERAPY

Bacchetta MD; Richter G. Response to □Germ-line therapy to cure mitochondrial disease. Camb Q Healthc Ethics 1996 Summer;5(3):450-7

Author introduces the intriguing problem of mitochondrial DNA alterations.

Fletcher JC; Richter G. Ethical issues of prenatal human gene therapy. J Matern Fetal med 1996 Sep-Oct 5(5):232-44

Benefits, risks, privacy and informed consent.

Fletcher JC; Richter G. Human fetal gene therapy: moral and ethical questions. Hum Gene Ther 1996 Aug 20;7(13):1605-14

A very thoughtful review of the history of thinking about gene therapy and the ethics involved. They conclude that there are more arguments to proceed than to demure.

Juengst ET Prevention and the goals of genetic medicine. Hum Gene Ther 1995 Dec;6(12):1595-605

He urges us to avoid genotypic tinkering.

Peters T. □Playing God□ and germline intervention. J Med Philos 1995 Aug;20(4):365-86.
see also comment 341-6

Author refutes notion that germ line manipulation should be proscribed. His argument is a bit circular and more □clever□ than persuasive.

Macer DR; Akiyama S; Alora AT; et al. International perceptions and approval of gene therapy. Hum Gene Ther 1995 Jun 6(6):791-803

National and cultural differences may not be as marked as one might predict in regard to gene therapy.

PATENTING

Brody B. Public goods and fair prices. Balancing technological innovation with social well being. Hastings Center Rep 1996 Mar-Apr 26(2):5-11

Brody impossibly recommends that the patent office become ethical. He also discounts intellectual and industrial property as of only legal and not ethical concern.

Pompidou A. Research on the human genome and patentability - the ethical consequences. J Med Eth 1995;21:69-71

Argues that the secription of a gene should be protected as intellectual propertybut that the gene as such should not be appropriated or owned. His argument is muddy.

Editorial. Gene donors□ rights at risk. Nature 1996;(381):1

A neat overview of ownership of genetic information. Who should benefit from commercialization?

Thomas SM; Davis ARW; Birtwistle SM; et al. Ownership of the human genome. Nature 1996; Apr 4(380)387-388

Who has the patents and in which countries.

Sagoff M. Animals as inventions: Biotechnology and intellectual property rights. Inst Phil and Pub Pol 1996 Winter (16)No.1

Some fascinating history of the patent office and decisions relevant to biotechnology.

CLONING

Seviani M; Tiranti V; Piantadosi C. Mitochondrial disorders. Med 1998 (77)59-72

If you are as ignorant of the role of mitochondrial DNA as I, then I commend this excellent review. There are some wonderful secrets and implications here.

National Bioethics Advisory Commission. Cloning human beings: Report and Recommendations 1997 9 June

Available on line. Use any search engine. A very comprehensive document with wonderful background, many perspectives and history. Clearly and logically presented. Skip the recommendations - they were ordained.

Thomas L. On cloning a human being NEJM 1974 12 Dec(291):1296-7

Note the date. Should not surprise you that Lewis Thomas anticipated and thought about this topic.

Eisenberg L. The outcome as cause: predestination and human cloning. J Med Phil 1976 Dec(1):318-331

Pompous but entertaining. One fresh perspective presented.

Cohen CB. Future directions for human cloning by embryo splitting: after the hullabaloo. Kennedy Institute of Ethics J. 1994 Sept 4(3) 187-192

This introduces six articles in this issue of the journal. All of the issues are framed. Pick what you like. I recommend the following citation.

Verhey AD. Cloning: Revisiting an old debate. Kennedy Institute of Ethics J. 1994 Sept 4(3):227-234

Freedom, weighing good and evil, personhood, parenting - a broad agenda for discussion. The best of the previously cited six articles.

Editorial. The lamb that roared. Science 1997 Dec 19(278)2038

The best in science reporting. Issues instead of hyperbole.