7: Genetics and Stem Cell Research

A.Genetics

1. Introduction

The principal special feature of genetics research is that the result of the study applies not only to the proband but also influences her lineage both in the past and in the future. For example genetic studies demonstrated Thomas Jefferson's sexual relationship with his slave Sally Hemings and defined their descendants to this day. As we all know from television, genetic studies can be done from any tissue fragment that contains DNA so that studies of surgical specimens, biopsy materials, hair, epithelium and blood samples can all be utilized for extensive genetic studies.

2. Sampling

Some DNA is more medically valuable than other. Samples from isolated populations in which a particular disorder is prevalent have a much greater probability of yielding the causal gene(s) because they have fewer genome variations than in the general population. Once isolated, the genetic material associated with the disorder has a good chance of yielding novel diagnostic and/or therapeutic approaches for the disorder.

3. Property rights

A persistent question is whether the providers of the genetic material have any rights to the products created from their genetic material. These days, most consent forms are written explicitly to exclude intellectual property rights from the subjects. As might be imagined, this smacks of exploitation in the developing world. Negotiation of a monetary return to the community has sometimes been concluded. Important and lucrative products have been derived from individuals' genomes without their receiving royalties or other compensation. However, the knowledge, technical expertise, and capital needed to make a useful product from a blood or tissue sample come from the company not the donor.

4. Informed consent

Truly informed consent remains a problem with research subjects from both developed and developing countries. The sample providers may not understand the implications of genetic research for their families and their community. They surely don't understand the many uses to which their genetic material may be applied. They may not be aware that their genes may be used for pharmacogenetics. They are not likely to be fully cognizant of the forensic uses to which their genetic material might be put as our privacy rights continue to be eroded. They are putting their trust in the research establishment and the regulatory controls effected by the

IRB managing grant or contract. Contributors to repositories may not be fully aware of the fact that they are trusting scientifically-oriented review boards to determine how their genetic material will be used long into the future. While anonymization is of great help, in the future, the genome itself may serve to identify the person, especially if they are in more than one repository.

Informed consents for genetic studies using CLIA-approved tests are usually designed to give the subjects the option of finding out their susceptibilities or not. Subjects are told they will not get any feedback from tests that are in the developmental stages because the reliability of such tests is not known.

2. Insurance and stigmatization

In developed countries they might not perceive possible implications for stigmatization and for health and life insurability. Lack of health insurability affects Americans the most because every other developed country has a national health program. In those countries genetic information about disease risks motivates the system to preventive measures. In the U.S., revealing genetic information may exclude individuals from health insurance or make them join undesirable assigned risk pools. Thus knowing her susceptibilities may put a burden on the patient/subject to reveal what could be considered to be a preexisting condition. In fact, the rapidly increasing availability and declining costs of genetic information represent among the strongest arguments for a comprehensive health insurance program in the U.S.

3. Commoditization of genetic material

Patenting genetic material for development as medical tools raises the question of commoditization. Individuals from many countries but especially developing countries feel that their genome is an important component of their selves or souls. Just as some groups feel that they lose something if a photograph is taken of them, many feel that they may be compromised by genetic studies and the patenting of their individuality. In some environments, communities express the belief that there is no such thing as informed consent for genetic studies because the individual is speaking for his ancestors and descendants.

B. Human Embryonic Stem Cell Research

1. Introduction

Human embryonic stem cell (hESC) research is thought to have great potential in disorders in which cellular loss is known to occur. These include Type 1 diabetes mellitus, Parkinson's disease, and the post-myocardial infarction heart. Nevertheless, some believe that pre-implantation embryos are potential human beings with a soul making hESC research immoral. Human embryonic stem cell research raises other important ethical dilemmas as well. As a result of these ethical

and moral dilemmas the government has limited federally funding for hESC research to what has turned out to be 19 pre-existing "registered" cell lines (Sept. 2005. Private sources and states have been left to determine the extent to which they are prepared to support additional hESC research. A number of states, most prominently California, have decided to support research in this area.

2. What are embryonic stem cells and how do you make them?

The goal is to have stem cell lines derived from embryonic stem cells. Cells from these lines are "totipotential" because in theory, they can be transformed into any kind of tissue by the appropriate biological and chemical manipulations. Without going into detail and elaborating on all the limitations and caveats, embryonic stem cell lines can be created three ways.

a. Eggs and sperm can be obtained from donors, mixed in a Petri dish and the egg fertilized for the purpose of producing a stem cell line for research. The fertilized egg (zygote) divides into a multicellular embryo. With further incubation a blastocyst, a hollow ball of about 256 cells, is formed. The blastocyst has two kinds of cell groups, a group on the surface that is capable of initiating implantation into the uterus and becoming the placenta, and the inner cell mass with the capacity to become the fetus. The inner cell mass can be removed and encouraged to divide in culture medium. Under carefully defined conditions, these can be induced to become a cell line, dividing indefinitely. With proper chemical treatment the stem cells can, in theory develop into any tissue.

b. Annually, many thousands of infertile couples create embryos for in-vitro fertilization (IVF), by having their eggs and sperm mixed and fertilized in a petri dish. Usually the potential mother is stimulated with hormones and provides a number of eggs. Similarly, the potential father has millions of sperm in his ejaculated semen. Normally all the eggs are exposed to sperm and a number of become fertilized and become embryos. The best looking embryos are incubated long enough to become blastocysts. Usually three are implanted into the potential mother's uterus. The remaining embryos are stored in liquid nitrogen in case of pregnancy failure or for later use if the family wants another child. These embryos are stored in cryobanks. Many of them eventually become available for research. With informed donor consent from both parents, these frozen embryos have the potential for providing most of the necessary raw material for stem cell research.

c. Somatic cell nuclear transfer (SCNT or just NT) was responsible for creating the sheep clone Dolly. In this process, young women donate ova by undergoing the "superovulation" process, as do infertile women. The egg has its nucleus containing the genetic material removed. The nucleus of an adult cell of research interest is

placed into the enucleated egg. By a remarkable process the adult nucleus dedifferentiates in the ovum from, say a skin cell, into a totipotential state and the ovum proceeds to divide and become a blastocyst. Its inner cell mass can be made into a stem cell line. This process has a theoretical advantage in that theoretically stem cells could be produced with any genetic condition of interest by introducing the nucleus from a person with the condition. The major disadvantage of NT is that a supply of human unfertilized eggs is required to do the research. Until a reliable source of human ova can be obtained without either a large payoff or by coercion, this process is unlikely to become the main source of embryonic stem cells. However, it is conceivable that mothers of individuals with a serious disorder such as Type 1 diabetes mellitus would be willing to donate eggs to further research progress.

A major ethical dilemma that has just grounded the highly successful Korean Stem Cell Institute was the provision of ova by laboratory workers who had a dependent relationship to the investigators and were therefore susceptible to coercion.

3. **Ethical Issues**
    a. **The core issue related to hESC research is the status of the early embryo. Is it a human being with a soul that must be protected or is it a collection of cells that will not become part of humanity until a later time. This issue cannot be resolved on a scientific basis but rather plays a central role in religious and political differences within America.**
    b. **Unlike the use of zygotes containing the combined genetic material from a male and a female, as in IVF, NT results in a "clone" of the donor of the adult cell. Implanting such a blastocyst into a woman, termed "reproductive cloning," would result in an individual with the exact genetic makeup of the donor of the nucleus. Agreement has been reached that reproductive cloning of humans is unethical and should not be permitted.**

    c. **NT, which to date is a very inefficient process, requires large numbers of donated ova from volunteers. In other research settings, volunteers may be paid for their trouble but must not be coerced into volunteering either by being dependent on the investigators or by enticing them with compensation. These same criteria are likely to hold for ovum donors although ovum donors for the treament of infertility are being paid large amounts of money for their efforts.**

d. Ovum donation is not a benign procedure. A sample consent form for ovum donation for hESC research purposes is given below.

Bibliography

Genetics Research

Curzer, H. (2004). "The ethics of embryonic stem cell research." J Med Philos **29**(5): 533-62.

This author analyzes the issues surrounding using human embryos to develop stem cell lines for research as a philosopher in a set of philosophical arguments that support the use of embryos and even the creation of embryos for research purposes.

Pennings, G. and A. Van Steirteghem (2004). "The subsidiarity principle in the context of embryonic stem cell research." Hum. Reprod. **19**(5): 1060-1064.
http://humrep.oxfordjournals.org/cgi/content/full/19/5/1060

The authors deal with the "subsidiarity principal" that indicates human embryonic stem cell research should be a last resort to be utilized only if other research tools cannot do the job. After careful argument, they conclude that the burden should be on those who claim other research achieve the same scientific and humanitarian goals, considering the stakes for human life and well-being.

Scully, J. L. and C. Rehmann-Sutter (2001). "When Norms Normalize: The Case of Genetic "Enhancement"." Human Gene Therapy **12**(1): 87-95.
http://www.liebertonline.com/doi/abs/10.1089/104303401451004

This philosophical paper addresses the question of treating to enhance versus treating to improve to normal. They claim that with the differences of opinion and difficulty characterizing normal, it would be better defining unethical enhancement by a better standard more related to the motivations for and consequences of the "enhancement."

Steinbrook, R. (2006). "Egg Donation and Human Embryonic Stem-Cell Research." N Engl J Med **354**(4): 324-326.
http://content.nejm.org/cgi/content/extract/354/4/324

This paper describes the current status of egg donation for SCNT in stem cell research. The author focuses on the donor risks and the limited benefits that might accrue to the donor. The questions surrounding payment of donors are addressed in detail.

Snyder, E. Y. and J. F. Loring (2006). "Beyond Fraud -- Stem-Cell Research Continues." N Engl J Med **354**(4): 321-324.
http://content.nejm.org/cgi/content/extract/354/4/321

This article published immediately after the Hwang debacle reiterates the self-corrupting characteristics of science and indicates that stem cell research has more challenges than it thought it had. The paper also attempted to assure the public that science and scientists were not all corrupt.

DeCamp, M. and J. Sugarman (2004). "Ethics in Behavioral Genetics Research." Accountability in Research **11**(2): 27-47.

This excellent paper systematically reviews the special issues surrounding behavioral genetics research involving phenotypic designation, involvement of the community, and vulnerability. He also discusses the social obligations of the scientists to deal in advance with the potential of stigmatizing individuals and populations. He indicates some of the adverse consequences of poorly thought out earlier work.

Stem Cell research

Okie, S. (2005). "Stem-Cell Research -- Signposts and Roadblocks." N Engl J Med 353(1): 1-5.

(2000). Ethical Issues in Human Stem Cell Research. National Bioethics Advisory Commission. Volume III, Religious Perspectives.

This booklet contains ten brief thoughtful analyses of the stem cell issues from various religious perspectives. The articles contain in addition to the conclusions the religious rationale for them. This is an extremely worthwhile set of readings for those who, willingly or unwillingly, are entering the discussion of the research use of embryos.

(2000). "Statement on Gene Therapy, April 2000." Am J Hum Genet. 67(2): 272-3.

Abbott, A. (1999). "Sweden sets ethical standards for use of genetic 'biobanks'." Nature 400(6739): 3.

This report details Sweden's laws dealing with gene banks. There are rules for consent, reconsenting, privacy, ethical review of use of materials, and rules for non-exclusivity of materials.

Annas, G. J. (2001). "The limits of state laws to protect genetic information." N Engl J Med 345(5): 385-8.

In this report, the newly passed Massachusetts statute regulating the use of genetic information is discussed as an example of what states were doing. It covered consent, discrimination, privacy, etc. It revolved to a degree on the definition of genetic information and that's what makes it a very interesting paper.

Begley, S. (2004). Is Alzheimer's Field Blocking Research Into Other Causes? Wall Street Journal. April 9, 2004.

She discusses the role of favored theories in getting the bulk of research funding.

Streiffer, R. (2005). "At the edge of humanity: Human stem cells, chimera, and moral status." Kennedy Inst Ethics J **15**(4): 347-70.

The author addresses in great detail the ethical issues that arise when considering the production of chimeras by introducing human pluripotential stem cells into other species. The core question is whether the moral standing of the recipient animal is enhanced and, if so, how to handle that. The world of entertainment is rife with creatures exhibiting human characteristics to whom we have assigned moral standing so this is not a trivial question in our society. Purely technical proposals might generate considerate concern.

Aguilar, L. K. and E. Aguilar-Cordova (2003). "Evolution of a Gene Therapy Clinical Trial." Journal of Neuro-Oncology **65**(3): 307.

This is an excellent review of the promise and pitfalls of gene therapy trials. Specific examples are given to illuminate the issues. A very worthwhile paper.
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1023/B:NEON.0000003659.04633.6e

Baylis, F. (2002). "Human embryonic stem cell lines: the ethics of derivation." J Obstet Gynaecol Can **24**(2): 159-63.

The author points out that unusable embryos are relatively rare in Canada and should be utilized for important research. This lack could either impede research or create a demand for the purposeful creation of embryos for research. Interesting.

Christiani, D., R. Sharp, et al. (2001). "Applying genomic technologies in environmental health research: challenges and opportunities." J Occup Environ Med **43**(5): 526-33.

This article describes the promise of molecular genetics in identifying environmental hazards and developing methods for analyzing, preventing, and treating exposures. They describe the ethical, legal, and social challenges in carrying out such studies.

Cohen, C. (2005). "Promises and perils of public deliberation: contrasting two national bioethics commissions on embryonic stem cell research." Kennedy Inst Ethics J **15**(3): 269-88.

The author analyzes philosophically the ethical approaches of the two national bioethics commissions and finds suggestions as to how such commissions may have to operate in considering issues under public debate.

Beskow, L. M., W. Burke, et al. (2001). "Informed Consent for Population-Based Research Involving Genetics." JAMA 286(18): 2315-2321.

What follows is the abstract of a report by a group formed by the CDC to determine some rules for approaching population-based genetic research. Bridging the gap between gene discovery and our ability to use genetic information to benefit health requires population-based knowledge about the contribution of common gene variants and gene-environment interactions to the risk of disease. The risks and benefits associated with population-based research involving genetics, especially lower-penetrance gene variants, can differ in nature from those associated with family-based research. In response to the urgent need for appropriate guidelines, the Centers for Disease Control and Prevention formed a multidisciplinary group to develop an informed consent approach for integrating genetic variation into population-based research. The group used expert opinion and federal regulations, the National Bioethics Advisory Commission's report on research involving human biological materials, existing consent forms, and literature on informed consent to create suggested language for informed consent documents and a supplemental brochure. This language reflects the premise that the probability and magnitude of harm, as well as possible personal benefits, are directly related to the meaning of the results for the health of the participant and that appropriate disclosures and processes for obtaining consent should be based on an assessment at the outset of the likelihood that the results will generate information that could lead directly to an evidence-based intervention. This informed consent approach is proposed to promote discussion about how best to enable potential participants to make informed decisions about population-based research involving genetics and to suggest issues for consideration by research sponsors, institutional review boards, and investigators.

Clayton, E. W. (2003). "Ethical, Legal, and Social Implications of Genomic Medicine." N Engl J Med 349(6): 562-569.

This excellent article describes a number of cases in which genetic information formed the basis of legal action. She described the public's worries about the availability of their genetic information to insurance companies and government agencies, its use in forensic investigations, and its use for discrimination in employment, even for medically sound reasons. She describes state regulations. She presents the dilemmas in the physician-patient relationship. Very worthwhile reading.

Clayton, E. W., K. K. Steinberg, et al. (1995). "Informed consent for genetic research on stored tissue samples." JAMA 274(22): 1786-1792.

This somewhat dated report describes the results of a consensus development process arranged by the CDC. The diverse group involved concluded that consent was important unless samples were anonymized, that IRBs could usefully review proposals to use tissues, and that the matter was not settled.

Dickenson, D. (2004). "CONSENT, COMMODIFICATION AND BENEFIT-SHARING IN GENETIC RESEARCH." Developing World Bioethics 4(2): 109-124.

This is a very thoughtful and interesting paper. It deals with the issues surrounding getting blood or tissue samples for genetic diagnostics and for the development of treatments for diseases. These include the lack of informedness in the consent, especially about the potential economic benefits, the commodofication of our bodies, which is somewhat distasteful and the nations of exploitation and bribery in getting samples from developing countries. There is also the question of the meaning of access to the results of the intervention.

Evers, K. (2002). "European perspectives on therapeutic cloning." N Engl J Med 346(20): 1579-82.

The author, an ethicist, proposes extensive international regulations to protect individuals from potential abuse as a consequence of experiments in therapeutic cloning. Therapeutic cloning most likely will involvesomatic cell nuclear transfer and thus lots of donated ova. She worries about the commodification of human reproductive tissues, but does not come down for or against their use.

Fischbach, G. D. and R. L. Fischbach (2004). "Stem cells: science, policy, and ethics." J. Clin. Invest. 114(10): 1364-1370.

Human embryonic stem cells offer the promise of a new regenerative medicine in which damaged adult cells can be replaced with new cells. Research is needed to determine the most viable stem cell lines and reliable ways to promote the differentiation of pluripotent stem cells into specific cell types (neurons,

muscle cells, etc.). To create new cell lines, it is necessary to destroy preimplantation blastocysts. This has led to an intense debate that threatens to limit embryonic stem cell research. The profound ethical issues raised call for informed, dispassionate debate.

Foubister, V. (2000). Gene therapy group adopts stringent rules on financial ties. American Medical News: 10-11.

Frankel, M. S. and A. R. Chapman (2001). "GENETIC TECHNOLOGIES: Facing Inheritable Genetic Modifications." Science 292(5520): 1303-.

This policy forum approaches the question of inherited genetic modification, not only to eliminate serious medical problems but proceeding into the realm of improving human beings, perhaps to produce distinctly superior humans. They point out that the fertility industry is not regulated at all and because of this socially unacceptable activity could be carried out without anyone even knowing about it. The propose that there be a policy discussion and regulation of these activities.

Hall, S. S. (2002). "HUMAN CLONING: President's Bioethics Council Delivers." Science 297(5580): 322-324.

This news report details the stem cell report that proposed a ban on reproductive cloning and a four-year moratorium on research cloning. The sharp divisions within the Council made it possible for its proposals not to be enacted. It is a very good summary.

Jones, S. (2000). Genetics in Medicine: Real Promises, Unreal Expectations, Milbank Memorial Fund.

This commissioned report based on meeting of those who purchase health care in the US and Gt. Britain raises doubt about the relevance of genetics as then understood to the delivery of health care. As the summary stated, “the new genetics is no more than another form of high-tech medicine of crucial importance to a few but irrelevant to the many. At present it suffers from too much publicity and too few results.” I think that this article by very practical people is important reading and highly relevant to the changed situation as we see it today.

Knoppers, B. and R. Chadwick (1994). "The Human Genome Project: Under and International Ethical Microscope." Science 265: 2035-5.

This very brief paper outlines the ethical issues associated with research and care in human genetics. Five principles, autonomy, privacy, justice, equity and quality are discussed, with appropriate references. These same principles operate to ensure ethical use of genetic materials today.

Koerner, B. (2002). "Embryo Police." Wired February: 52-57.

This reportorial piece highlights HFEA, Britain’s Human Fertilization and Embryology Authority, which is responsible for regulating what is permissible to do with reproductive tissues and monitoring the field. The author reviews all the kinds of research that could result in a variety of experiments, including those leading to human- other chimeras. The conclusion is that all nations will have to regulate reproductive science and practice intensely.

Kulynych, J. K., David (2002). "Use and Disclosure of Health Information in Genetic Research: Weighin the Impact of the New Federal Medical Privacy Rule." American Journal of Law and Medicine 28(2, 3): 309-324.

This careful paper details the changes in definitions and outlines the rules associated with the HIPAA act, which had not been operationalized at that time.

Lanza, R., J. Cibelli, et al. (2001). "The ethical reasons for stem cell research." Science 292(5520): 1299.

This letter to the editor supports stem cell research in the face of political opposition. They make three ethical points. 1) unregulated private organizations will supplant the government in doing this research without the appropriate controls and ethical guidelines 2) embryos will be destroyed in the same numbers 3) the negative viewpoint is limited to a small minority of Americans who shouldn’t be allowed to dictate policy.

Magnus, D. and M. K. Cho (2005). "ETHICS: Issues in Oocyte Donation for Stem Cell Research." Science 308(5729): 1747-1748.

Malakoff, D. (2003). "Human cloning. New players, same debate in Congress." Science 299(5608): 799.
This brief news report describes the Congressional debate surrounding a four year ban on all therapeutic stem cell research as suggested by the President's Commission. While the tide seems to have turned, this gives the players and the arguments.

Marshall, E. (1999). "GENETIC TESTING: Beryllium Screening Raises Ethical Issues." Science 285(5425): 178b-179.
This report discusses the use of genetic screening to deny certain jobs encountering beryllium exposure by the Department of Energy because of a demonstrated genetic susceptibility to berylliosis, a severely debilitating and lethal pneumoconiosis. It focuses on an existing practice but the ethical issue in considering genetic screening as consideration for certain lines of work runs counter to public policies insisting that discrimination on the basis of a disability is illegal and immoral. We have learned to accept these protections in relation to college and professional school admission and most employment. Is the beryllium case the camel's nose in the tent? Very worthwhile reading.

Marshall, E. (2000). "BIOMEDICINE:Gene Therapy on Trial." Science 288(5468): 951-957.
This news article reviews the Jesse Gelsinger case before all the data were in and interviews a number of people in the gene therapy field as well as detailing the corporate connections of the gene therapy establishment. A most interesting quote was obtained from Arthur Caplan indicating that Wilson did not have a conflict of interest.

Marshall, E. (2002). "Clinical research. Gene therapy a suspect in leukemia-like disease." Science 298(5591): 34-5.
This news report describes the situation involving the first leukemia patient who developed leukemia in the course of a gene therapy trial to treat combined immunodeficiency disease.

Marshall, E. (2003). "GENE THERAPY: Second Child in French Trial Is Found to Have Leukemia." Science 299(5605): 320-.
With the development of leukemia in a second child in the French combined immunodeficiency trial, gene therapy studies in humans ground to a halt except for a few cancer studies.

McCabe, L. (1996). "Efficacy of a targeted genetic screening program for adolescents." Am J Hum Genet. 59(4): 762-3.
The author discusses an article on genetic screening in which a population of school children was invited to be tested for beta-thalassemia or Tay Sachs heterozygosity depending on their backgrounds. Both parent and child had to sign informed consents after a session in which they were taught about the diseases and their inheritance. The article points out that studies such as this might give pause to those who consider the risk of genetic testing to be greater than possible benefits. A persuasive argument for genetic testing for specific conditions is given.

Lebacqz, K, Mendiola, M., T. Peters, et al. (1999). "Research with human embryonic stem cells: ethical considerations. By Geron Ethics Advisory Board." Hastings Center Report 29(2): 31-6.
Geron was successful in developing immortalized human embryonic stem cells and convened an ethics advisory board to delineate appropriate ethical practices. They consisted of six points that are elaborated in this document. Paraphrased, they state that 1) the blastocyst must be treated with appropriate respect; 2) Those donating embryos should give full and informed consent; 3) no reproductive cloning; 4) acquisition or development of the feeder layers should not violate norms for human or animal research; 5) such research should be done with concern for global justice; 6) such research should be approved by an independent ethics advisory board in addition to an IRB. These considerations were core to the conclusions of the National Academy of Sciences Committee and have been applied to the regulations of the California Institute for Regenerative Medicine. This is a very worthwhile read.

Merz, J. F. (1999). "Disease Gene Patents: Overcoming Unethical Constraints on Clinical Laboratory Medicine." Clin Chem 45(3): 324-330.

Those who control patents on genes that relate to specific disorders or susceptibilities are maintaining monopolies over genetic testing for those genes. This results in diminished availability of the tests and monopoly prices. This interferes with the ability of physicians to diagnose and treat their patients. Unless the patent office requires compulsory licensing of genetic patents that it grants, this situation could become much worse as noted by the American Association for Clinical Chemistry in 1999. This is balanced by the need to maintain very high testing standards for complex assays. I do not believe that much progress has been made to make testing more available or cheaper.

Morella, C. A. (2001). "Stem Cell Research Needs United Support." Science 293(5527): 47b-.

This letter by Congresswoman Morella indicated that the scientific community would have to unite and lobby hard to get their views on stem cell research heard and listened to.

Motulsky, A. G. (1999). "If I had a gene test, what would I have and who would I tell?" Lancet 354(suppl I): 35-37.

This brief paper by one of the leaders in genetics over the twentieth century asks a series of critical questions about genetic screening. He points out, for example that testing for something for which there is no treatment or effective preventive seems inappropriate. He also notes that non-genetic tests for susceptibilities are sometimes more effective in that many genes could produce the same adverse physiological state. While it doesn't deal directly with research ethics, it is worth our attention.

Noguchi, P. (2003). "Risks and benefits of gene therapy." N Engl J Med 348(3): 193-4.

The author, from the FDA, reviews leukemia, the serious adverse event associated with gene therapy for combined immunodeficiency disease, a lethal genetic disorder of the immune system. After a special committee review the study was limited to patients failing bone marrow transplantation, but with the subsequent identification of more cases the trial was stopped completely. This paper gives the arguments for continuing the study in a limited way.

Nowlan, W. (2002). "HUMAN GENETICS: A Rational View of Insurance and Genetic Discrimination." Science 297(5579): 195-196.

The author, an insurance executive, give arguments to reassure the body politic that insurance companies are motivated to insure people not to deny them insurance. They further should have the right to charge in accordance with the appropriate actuarial risk. His most cogent argument is that insurers can't insure on the basis of genetic tests that will not lead to a disease for years. Since most individual health insurance policies last only a few years, the companies have little motivation to deny coverage unless there is established illness. He indicated that states have enacted numerous anti-discrimination laws, and that he believes that these are counterproductive. This "other view" is well worth reading because no matter what the future may bring, there is little evidence of insurance discrimination to date.

Okie, S. (2005). "Stem-Cell Research -- Signposts and Roadblocks." N Engl J Med 353(1): 1-5.

Parens, E. and E. Juengst (2001). "Inadvertently Crossing the Germ Line." Science 292(5516): 397-.

This editorial reflects on the successful pregnancies resulting from transfer of ooplasm from donors to eggs of women whose infertility was due to ooplasmic defects. This process resulted in mitochondria and mitochondrial DNA being transferred. The authors worry about the lack of controls over non-federally funded inherited genetic modifications.

Reich, J. G. (2002). "EMBRYONIC STEM CELLS: The Debate in Germany." Science 296(5566): 265-.

Robinson, G. E. (2004). "GENOMICS: Beyond Nature and Nurture." Science 304(5669): 397-399.

Rothenberg, KH, Terry, SF. (2002) Before it's too late – Addressing Fear of Genetic Information. Science,297:196-7.

The fears of uninsurability and employment discrimination are widespread as the possibility of meaningful genetic screening approaches reality. While a melange of laws have been passed in state legislatures, this national problem needs a uniform national solution they claim
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Sade, R. M. (1994). "Issues of social policy and ethics in gene technology." Methods Find Exp Clin Pharmacol 16(7): 477-89.

Technical developments in the last ten years have made possible mapping and sequencing of the entire human genome, along with the possibility of treating genetic disorders by manipulating DNA. A variety of issues regarding potential uses and abuses of these technologies have become apparent. They relate to both genetic screening and gene therapy. Problems facing individuals and their families mostly revolve around rights of self-determination and of confidentiality. Health care professionals will need to design optimal systems to provide genetic counseling and to protect confidentiality of DNA data bases. Society and social institutions will need to develop policies and laws that protect the privacy of individuals whose DNA is stored in data banks. Patenting of the results of gene research remains controversial internationally. Moreover, there is concern in many quarters about society's potential abuse of gene technology for eugenic purposes. Gene therapy is now a reality. There is little disagreement on the use of gene therapy to treat genetic diseases in individuals by somatic cell therapy. There is much controversy, however, over the use of germ-line cell therapy. Gene technology has contributed to the growth among a small group of influential people of the Post-Modern Movement, which is strongly antiscience and antitechnology. This movement may pose a long-term threat to future technological advances and should not be ignored. There is much outside of the laboratory that scientists, particularly molecular biologists, can do to assure a secure place for science and technology in our culture.

Sankar, P. and M. Cho (2002). "Genetics. Toward a new vocabulary of human genetic variation." Science 298(5597): 1337-8.

This very thoughtful piece deals with genetic variation in ethnic populations that are being discovered at a rapid rate. Do these findings permit one to use the discredited word “race” for closely related populations? Race has been reconceptualized as a social construct separate from genetic background, but is that actually appropriate? The authors suggest that the word race be defined carefully any time it is used in scholarly publications.

Shapiro, H. T. (1999). "Ethical dilemmas and stem cell research." Science 285(5436): 2065.

This brief editorial describes societal dilemmas associated with embryonic stem cell research and how the National Bioethics Advisory Commission addressed them. Essentially, they supportedhe Federal funding of research using of embryonic stem cells under certain conditions.

Szebik, I. and K. Glass (2001). "Ethical issues of human germ-cell therapy: a preparation for public discussion." Acad Med 76(1): 32-8.

At this point debate on the transfer of heritable elements to sperm or egg, thus changing the individual’s genome had not been discussed very much although scientific progress was dramatic. The authors, in an attempt to stimulate discussion do a philosophical analysis of the arguments. They claim that because germ-cell therapy affects future generations, its moral status differs from that of somatic-cell therapy. They discuss the concepts of “playing God”, moving in the direction of “human enhancement” and, of course ending up with new genomes for the future. They indicate that humanity is already subject to many influences that alter the human gene pool including of course abortion and that human activity already produces irreversible changes. Their most cogent point is that discussion is needed.

Temple, L., R. McLeod, et al. (2001). "Essays on science and society. Defining disease in the genomics era." Science 293(5531): 807-8.

Vogel, G. (2001). "BIOMEDICAL POLICY: Bush Squeezes Between the Lines on Stem Cells." Science 293(5533): 1242-1245.

This thorough news focus article describes in detail the Bush decision regarding the Federal support of stem cell research. It also describes the search for lines that fulfill the requirements announced by the President.

Vogel, G. (2001). "EMBRYO RESEARCH: British Parliament Approves New Rules." Science 291(5501): 23a-.

This reporter discusses the overwhelming passage by the British parliament of rules supporting research using embryonic stem cells and somatic cell nuclear transfer.

Vogel, G. (2001). "Stem cell policy. Can adult stem cells suffice?" Science 298(5523): 1820-2.

This news report describes the discussion over whether adult stem cells can take the place of embryonic stem cells either in research or in clinical promise. We know that to study development embryonic stem cells are better. Five years later, the data remain out on the relative roles of the two types of cells in therapeutics.

Vogel, G. (2005). "STEM CELLS: Collaborators Split Over Ethics Allegations." Science 310(5751): 1100

This news report discusses the beginning of the unraveling of the Huang empire..

Weiss, R. (2002). Resumption of Gene Therapy Urged. Washington Post. Washington, D.C.: A17. October 11, 2002,

Weissman, I. (2002). "Stem cells--scientific, medical, and political issues." N Engl J Med 146(20): 1576-9.

This stem cell researcher and stem cell research advocate argues that the current embryonic stem cell lines will be inadequate to fulfill the needs for understanding human development. Further, he argues that cell lines developed from discarded embryos from fertility clinics will not be effective in studying specific diseases. He proposes ways to accomplish this while banning reproductive cloning. This is a brief and useful statement that was taken very seriously by the people of the state of California.

Weissman, I. L. (2005). "Medicine: Politic stem cells." Nature advanced online publication.

Kennedy, D. (2006). "Editorial Retraction." Science 311(5759): 335b-.

This formally retracts the editorial about human stem cell cloning previously published in Science.

Normile, D., G. Vogel, et al. (2006). "CLONING: South Korean Team's Remaining Human Stem Cell Claim Demolished." Science 311(5758): 156-157.

This news report in Science describes in some detail the investigation of Dr. Hwang's research and the conclusion that human stem cell lines did not exist but that the cloning of a dog did take place.

Stem Cells

Lo, B., P. Zettler, et al. (2005). "A New Era in the Ethics of Human Embryonic Stem Cell Research." Stem Cells **23**(10): 1454-1459.

The authors from UCSF discuss, well in advance of any clinical opportunities, the ethical concerns surrounding the injection of stem cells in a Phase I trial in humans. The issues they consider include updating the scientists on the health profile of the donor -- you would not want to introduce a genetic disease -- and making sure that the subjects understand what the research entails in terms of, among other things, remote risk and lifelong follow up.
http://stemcells.alphamedpress.org/cgi/content/full/23/10/1454

Walters, L. (2004). "Human embryonic stem cell research: an intercultural perspective." Kennedy Inst Ethics J **14**(1): 3-38.

This report reviews positions, formal and informal, adopted by various religions or spokespersons for non-monolithic religions regarding human embryonic stem cell research. It also reviews policies that have been developed in four regions of the world. An excellent compilation.

Pullman, D. and A. Latus (2003). "Clinical trials, genetic add-ons, and the question of benefit-sharing." The Lancet **362**(9379): 242.

The authors consider whether those contributing genetic material for research that would yields profitable results should receive some benefit from their contribution. They note that groups contributing to

genetic studies can sometimes be expected to benefit and they suggest that individuals should have the same possibility. They propose a way to accomplish this.

Guenin, L. M. (2004). "The morality of unenabled embryo use--arguments that work and arguments that don't." Mayo Clin Proc **79**(6): 801-8.

This very thoughtful philosophical piece dissects arguments for and against the use of about to be discarded embryos for the production of lines to carry out research. He comes up with formulation justifying their use for research purposes. This is a really sound paper and well worth reading carefully

Park, S., S. Orkin, et al. (2006). "Reactions to the Hwang Scandal." Science **311**(5761): 606-7.

These are 4 thoughtful letters in reaction the Hwang scandal. The Park letter apologizes for Korean science. The Orkin letter discusses the negative impact on stem cell research. The Martin letter criticizes the editors of Science. The Kwok letter emphasizes the importance of protecting whistleblowers.
http://www.sciencemag.org/cgi/content/full/311/5761/606b

Dickenson, D. (2004). "CONSENT, COMMODIFICATION AND BENEFIT-SHARING IN GENETIC RESEARCH." Developing World Bioethics **4**(2): 109-124.

This is a very thoughtful and interesting paper. It deals with the issues surrounding getting blood or tissue samples for genetic diagnostics. and for the development of treatments for diseases. These include the lack of informadness in the consent process, especially about the potential economic benefits, the commodification of our bodies, which is somewhat distasteful, and the notions of exploitation and bribery in getting samples from developing countries. There is also the question of the meaning of access to the results of the intervention.
http://www.blackwell-synergy.com/doi/abs/10.1111/j.1471-8731.2004.00087.x

Macklin, R. (2003). "Bioethics, Vulnerability, and Protection." Bioethics **17**(5-6): 472-486.

The author deals with vulnerable populations, exploitation, and harm, which are independent variables. She defines exploitation as occurring when the wealthy or powerful take advantage of the poverty powerlessness or dependency of others to serve their purposes. She points out that people can be harmed even if not exploited in clinical research.
http://www.blackwell-synergy.com/doi/abs/10.1111/1467-8519.00362