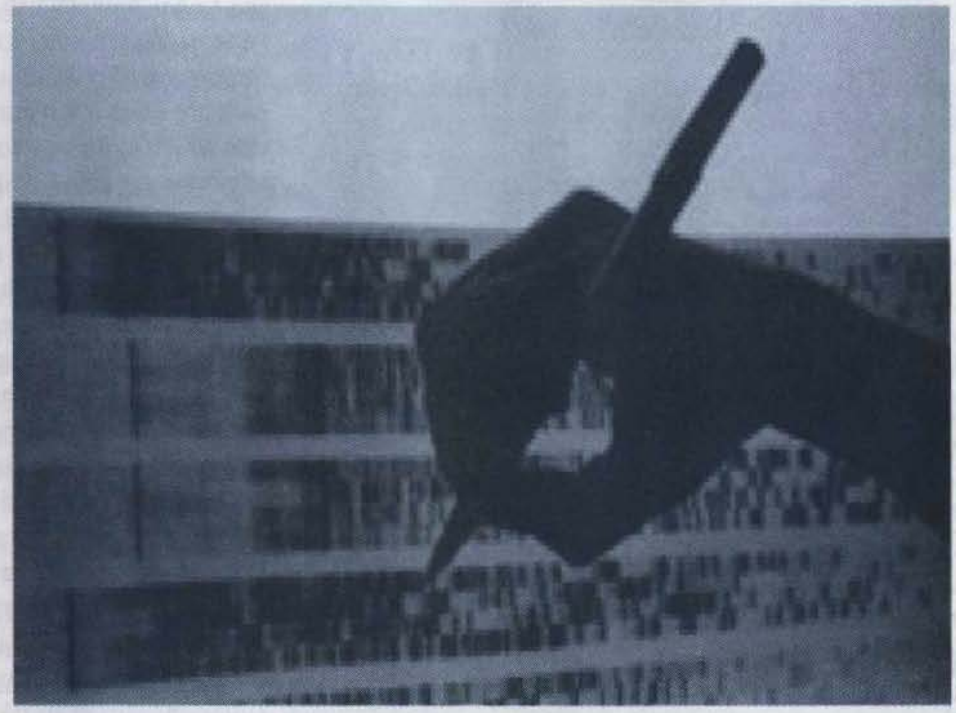
TuftScope

The Interdisciplinary Journal of Health, Ethics, and Policy

May 2001 Volume 1 Number 1



Contents

TuftScope

The Interdisciplinary Journal of Health, Ethics, & Policy

Editors-in-Chief
Bradley Crotty
Katharine McGinigle

Editorial Staff
Rishi Gandhi
Taylor Horst
Jennifer Takigawa
Elizabeth Buchen

Business Affairs
Valentino Caruso
Joanna Christodoulou

TuftScope
Box 108
Mayer Campus Center
Tufts University
Medford, MA 02155

ISSN 1534-7397

Electronic Access
http://www.tuftscope.com

General Inquiries
TuftScope@tufts.edu
Editors@tuftscope.com
Submissions@tuftscope.com

Advertising Information
www.tuftscope.com
advertising@tuftscope.com

TuftScope is published by Charles River Publishers
Boston, MA

TuftScope would like to acknowledge the following organizations for support:
University College of Citizenship & Public Service
Tufts Republicans
Catholic Center at Tufts
Tufts Hillel
Tufts Health Services
Tufts Institute of the Environment
Tufts Post Baccalaureate Program

Editors' Note

Discoveries in biotechnology are made all over the world everyday. In the fast paced era in which we live, information about these discoveries travels very quickly. Information flows at exponential speeds across networks, connecting researchers and propelling discoveries. Due to the plethora of new scientific theories at our fingertips, science is intertwining with political and ethical arenas more so than ever before; therefore, as a society, we must stay informed of the progression of research, protect research subjects and go beyond discussing the bioethics of the matters.

Legal matters usually trail behind scientific advances. As a result, scientists are often unhindered in their research progressions and policy makers and ethicists are often left behind. It is difficult to pass legislation which addresses concerns in a timely manner since advances are often built upon preexisting ones during the review period and the science is difficult for the average constituent to understand.

Certain research has a direct impact on citizens, such as techniques manipulating crops to make them resistant to insect attacks, or cloning cells to create a new human being. Scientists must endeavor to be aware of ethical, social, and political implications of their research as they work. Scientists also have an obligation to discuss social and ethical implications with the community at large. Conversely, citizens must take a proactive approach to learning about new developments, such that social concerns are met satisfactorily.

Active citizenship is crucial to the protection of beliefs and for a true integration with research efforts. *TuftScope* strives to take the first steps towards active involvement. Published semi-annually, the journal prints original articles, research and policy reviews, and letters of bioethics, health policy, and social, ethical, and legal implications of biotechnology.

The audience for TuftScope is broad, as the journal intends to directly link researchers with legislators, economists with physicians, and naturally, students to teachers. We hope that everyone will gain from at least one of the pieces and then will act upon what they have learned from this new journal of health, ethics, & policy.

Brad Crotty Kate McGinigle

TuftScope
The Interdisciplinary Journal of Health, Ethics, and Policy
Volume 1 May 1, 2001 Number 1

THE UNITED STATES V. GENETIC DISCRIMINATION: SECURING OUR RIGHTS IN A BRAVE NEW WORLD

John-Paul A. Ghobrial

The baby's beautiful blue eyes gazed into his mother's heart as if silently inquiring, "What does life hold for me, Mother?" As Joanne left the pediatrician's office, she was too captivated by the newborn wonder she held in her arms to notice the quick scribble placed by the doctor on her Jimmy's medical file. The words were surprisingly legible:

Undersungoboom – Positive

In many ways, those very words decided the fate of much of Jimmy's life. Never allowed to stay at one school for more than a year or so, Jimmy's education had been weak. He regarded the completion of his high-school diploma as a new opportunity to venture out into the workplace. Unfortunately, as soon as any company got hold of his medical records, they immediately refused to hire him. Jimmy could never understand why he had been rejected by schools, employers, and even insurance companies all his life.

Homeless and barely coherent, Jimmy, now 61 years old, passed a Radio Shack. The news program was of little relevance to him, but he watched anyways as the anchor opened with a lead story:

"Biocompany, Inc. has released a statement of apology declaring that one of its tests used over 60 years ago has been determined to be inaccurate. The test, known as UGB 24, was used to check for the presence of the Undersungoboom syndrome in newborn infants. Undersungoboom, as you may know, attacks the synapses of a cell causing the possibility of spontaneous human combustion equal to the magnitude of a car bomb. A class-action lawsuit has been filed by over 2000 individuals claiming that such inaccurate information contained on their medical records has destroyed their lives . . ."

"Poor people," Jimmy thought to himself as he walked away. "At least that never happened to me..."

* * *

The emerging advances in genetic technology have released a virtual Pandora's Box of concerns over the ethical and legal implications of our newfound genetic enlightenment. While Jimmy's story may seem extreme at first, it illustrates the way in which advances in science may have dramatic effects on human life. Having been genetically screened without the consent of himself or his parents, Jimmy leads a difficult life, eternally labeled as something he is not. Schools, insurance companies, and employers refuse to accept Jimmy, fearing that the possibility of spontaneous combustion may threaten productivity and even themselves. The revelation of the test's inaccuracy does little for Jimmy who has already led the life of a leper. However, we should not be quick to assume that improvements in technology are solely responsible for occurrences of genetic discrimination. In fact, recent advances in medical technology, especially the completion of the Human Genome Project (HGP) represent successful moves for civilization.

The Human Genome Project offers innumerable benefits to society, bringing us all closer to more effective approaches to battling a wide range of genetic conditions. The purpose of this article, then, is not to argue against recent advances in science. Rather, we hope to further trumpet the benefits of the Human Genome Project through increased efforts to prevent genetic discrimination. It would be impossible to address the many ethical considerations raised by the HGP. Admittedly, while the project has encountered great success, there remains a long road ahead. With that in mind, many have debated the extent to which genetic tests (i.e. screenings) can be trusted. Still, other groups of individuals accept the accuracy of genetic testing while denouncing the legality of making such information available to insurance carriers and employers. It is to this group that we turn our attention. Only by taking greater steps towards the fight against genetic discrimination is it possible to secure the spoils of genetic research. Recent instances of genetic discrimination are on the rise, creating fear and hysteria in a public that should welcome the HGP for its ability to improve the quality of human life. To protect individuals and create an en-

vironment wherein science can be used effectively to improve human life, we must, through increased and comprehensive legislation, safeguard individuals from the terrors of genetic discrimination.

A close look at the Human Genome Project reveals the many ways in which the mapping of the human genome may prove of great use to combating genetic diseases. The human genome can be likened to a recipe, or set of instructions, that contains all the information necessary for the structures and activities of a human. The genome consists of threads of DNA, which are organized into chromosomes. Chromosomes are the structures that hold genes. On an even deeper level, genes are made up of DNA which, itself, comprises varying sequences of four nitrogenous bases: adenine (A), thymine (T), cytosine (C), and guanine (G). Essentially, DNA provides the blueprint for human life. By mapping out the human genome, scientists predict the possibility of great advances for society. The publicly funded HGP began on October 1, 1990 under the assumption that it would take nearly 15 years to complete the entire project. As recently as 1998, scientists predicted that it would still take more than 7 years to complete the project. However, competition between American and British scientists brought increased attention to the project; the HGP received extra funding. On June 26, 2000, President Clinton announced the completion of "the most important, most wondrous map over produced by humankind."[1] It is important to note the accuracy of President Clinton's description of the value of the value and positive implications of the HGP.

It is impossible to deny the value of the HGP as a means of improving the quality of human life. Even those that fear the uncurbed nature of science must admit that the HGP could provide a crucial link in fighting against all kinds of diseases. By identifying the existence and location of a certain gene, scientists may be able to find new ways to fight the effects of that gene's presence. For example, recent studies have shown the existence of a gene whose presence indicates a higher risk for breast cancer. The Human Genome Project provides a crucial means of combating the effects of the cancer gene. Perhaps, future scientists may discover ways of "turning off" the gene or even removing it in future generations. Doctors can begin to look beyond the symptoms of a disease and focus on the true cause. Apart from helping the fight against various diseases, the knowledge gained by the HGP could also help extend people's lives through increased understanding of organ transplants and the effects of environmental surroundings. Imagine a gene for "youthfulness" that could extend the duration of an individual's life. One last benefit of the HGP comes in its usefulness to the legal system. Advances in the HGP will allow improvements in the science of DNA forensics. Such increased reliability in the science of DNA may prevent innocent individuals from being convicted while guilty persons will be faced with justice. Clearly, the benefits of the Human Genome Project are many. An increased understanding of the human genome may improve the lives of humans in ways never imagined. It is for this reason that we must seek to create a safe society wherein individuals need not fear the concept of genetic testing. Attempts to restrict science may prove a detriment to society. Rather, we must focus our efforts on ways to regulate the dissemination of private genetic information.

The ethical implications of the HGP are most evident when considering the ways in which access to an individual's genetic information may affect that individual's life. If someone is identified as having a certain genetic condition, she may be discriminated against because of this information. For example, an insurance company, aware of a woman's genetically higher risk of developing breast cancer, may be more likely to deny that woman a new policy. Similarly, employers will be weary to hire someone who has been identified with XYY syndrome. Even if that individual does not exhibit the aggressiveness normally demonstrated by XYY males, the employer may refuse him a position merely because of the risks associated with because of his genetic condition. By evaluating the XYY male's capabilities in light of his genetics and not his performance on the job, the employer becomes guilty of genetic discrimination. The situation becomes even more complex in light of errors in genetic testing that may mistakenly identify the presence of a genetic defect that is not really there. A woman may inadvertently abort a healthy child if she is informed that that child may have a defect. As we have seen in the story of Jimmy, such questions of the reliability of genetic tests may alter an individual's life entirely.

Recent developments in science have inaugurated a new era of increasing genetic intolerance. It would be impossible to touch upon every case within the constraints of this article, yet it is important to bring attention to the extent to which genetic discrimination is occurring. A recent survey by the Shriver Center for Public Health in Massachusetts revealed that "doctors and genetic testing centers reported 582 cases of people who were turned down for jobs or health insurance because of 'flaws' discovered in their genes."[2] The

same article mentions the case of "a 40-year-old woman with an exemplary employment record [who] agreed to take part in a genetic research survey and tested positive for BRAC1, a gene linked to some breast and ovarian cancers. Despite having preventive surgery she lost her health insurance and then her job." Even Dr. Francis Collins, the head of the HGP, warned against the possibility of genetic discrimination in hiring and insurance decisions.[3] The incidents of discrimination are not relegated merely to adults. Merely the possibility of a genetic defect has resulted in discrimination against unborn babies and their families. Delivering a speech on the ethical considerations of the HGP, Sharon Davis, Ph.D. described "a case in which a pregnant woman whose fetus tested positive for cystic fibrosis was told that her health maintenance organization (HMO) would be willing to cover the cost of an abortion but would not cover the infant under the family's medical policy if she elected to carry the pregnancy to term."[4] Christine Dent, a woman who was forced to "surrender her dream of becoming a U.S. Army officer and leave a subsequent job at a municipal water department" best illustrates the way in which genetic discrimination can ruin someone's life. When searching for a health insurance policy, Dent describes how "You're on the phone with them and they are all excited, and then they find out you're gene positive, and they hang up."[5] Clearly, genetic discrimination is not some abstract threat of a *Brave New World* future. Rather, it is taking place in our world today. With that in mind, the need to combat such discrimination becomes all the more important.

While recent legislation has aimed to prevent genetic discrimination, there still remains a great need to create new legislation that will more effectively protect individuals from genetic discrimination by schools, insurance companies, employers, and other institutions. Although most existing anti-discrimination legislation protects against disability-related genetic discrimination, the majority of existing federal legislation fails to address actual genetic information. The Americans with Disabilities Act of 1990 (ADA) protects individuals with visible genetic disabilities, yet it ignores genetic conditions that are unexpressed (i.e. risk of cancer). The HGP itself notes that "unaffected carriers of recessive and X-linked disorders, [and] individuals with late-onset genetic disorders who may be identified through genetic testing or family history as being at high risk of developing the disease are not covered by the ADA."[6] With respect to discrimination by insurance companies, the most important piece of existing legislation is the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). Interestingly, the HIPAA remains the only piece of federal legislation to address genetic discrimination based on genetic information. Yet, the HIPAA merely provides protection to those who receive employer-based insurance or commercial group policies. Thus, the HIPAA provides no protection to private individuals in search of health insurance.

It is remarkable to think that so many opportunities for discrimination continue to exist in the workplace considering the great efforts that have been made to stop discrimination of other forms. Even more surprising is that such few effective accomplishments have been made in regulating the insurance companies, who seem to have enormous influence on our lives through their access to the Medical Information Bureau (MIB). State legislation seems to have taken a more aggressive role in fighting genetic discrimination. The target of state anti-discrimination legislation has been the insurance industry. Forty-two states provide some level of legislative protection from genetic discrimination by insurance companies whereas only twenty-one protect individuals in the workplace.[7] Most recently, the Genetic Nondiscrimination in Health Insurance and Employment Act was introduced to Congress. In light of recent cases that have demonstrated the ineffectiveness of the ADA and HIPAA in fighting genetic discrimination, many hope that this new act will solidify America's fight against genetic discrimination.

The debate over the relationship between the HGP and genetic discrimination continues to exist across the nation. In spite of the many obvious examples of genetic discrimination, some still maintain that the likelihood of genetic discrimination becoming a widespread phenomenon is doubtful. Hank Greely, a Stanford law professor, asserts that the public hysteria over advances in genetics has little to do with discrimination. "I think a lot of people find genetic testing frightening for reasons that don't necessarily have anything to do with insurance," Greely said. "It may have to do with, 'How am I going to feel if I pass this on to my kids? What's my relationship with my mother going to be like if she passed it on to me? Will my spouse begin to distance himself or herself emotionally from me? Will he or she leave? How will I take this information myself?'"[8] Regardless of the true source of such anxieties, as the science of genetics continues to advance, the process of genetic testing will probably become less and less expensive, making it more accessible to the population. More and more individuals will be faced with the decision of whether or not genetic testing is right for them. These people should not be forced to give up an opportunity to share in the

rewards of the HGP merely out of fear of discrimination. The key to protecting such individuals lies in increased awareness and stronger legislation that will make it much more difficult for an employer or insurance company to discriminate against someone based on their DNA.

In some ways, the success of the Human Genome Project seems only possible with the approval of fate or some higher power. How else could humans, merely one step away from primates, have achieved such divine endeavors? Just like the caveman may have feared the burn of the newly discovered flame, many fear the consequences of recent advances in technology. Yet, in order to truly benefit from the Human Genome Project, we must create a safe society in which individuals are free to embrace the flame of genetics without the fear of getting burnt by genetic discrimination. Perhaps, such a world can only be found in books, but stronger anti-discrimination legislation may play a crucial role in making this story a reality.

Author Biography

JP Ghobrial, LA '02, is from Los Angeles, CA. He is double majoring in International Relations and French and intends to persue graduate studies in international law. He is primarily interested in questions of identity with regards to the development of more effective human rights legislation.

References

[1] Weiss, Rick, and Justin Gillis. "Teams Finish Mapping Human DNA." The Washington Post 27 June 2000: final ed.: A1.

[2] Borger, Julia. "Who's Testing Our Genes – and Why?" The Guardian 19 Sep. 2000: 15.

[3] Vergano, Dan. "Collins Warns of Dangers." USA TODAY 27 June 2000: 10D.

[4] Davis, Sharon. "The Human Genome Project: Examining The Arc's Concerns Regarding the Project's Ethical, Legal, and Social Implications." DOE Human Genome Program Contractor-Grantee Workshop VI. 12 Nov. 1997.

[5] Austin, Marsha. "The Enemy Within." The Denver Post 2 July 2000: 2nd ed.: J1.

[6] United States. The Human Genome Project. *Genetics Privacy and Legislation* <http://www.ornl.gov/hgmis/elsi/legislat.html#I>.

[7] Council for Responsible Genetics Programs. "Genetic Discrimination Legislation in the United States." August 2000. < http://www.genewatch.org/programs/GD_onepage_00.html>.

[8] Allen, William. "Experts Say Fears About Biased Use of Genetic Testing are Exaggerated." The St. Louis Post-Dispatch 25 Oct. 1999: A1.

TuftScope
The Tufts University Journal of Health, Ethics, and Policy
Volume 1 May 1, 2001 Number 1

THE ETHICAL ASPECTS OF EMBRYONIC STEM CELL RESEARCH

Jennifer Takigawa

Introduction

In November 1998, John Gearhart of Johns Hopkins University School of Medicine and James Thomson of the University of Wisconsin Medical School published reports of the first successful isolation and culturing of cell lines of human embryonic stem (ES) cells. They can be obtained from either human fetal tissue of aborted fetuses or from preimplantation human embryos. ES cells are just one of many types of stem cells found in the human body. Unlike stem cells which remain as stem cells to allow for the daily functioning of our bodies, ES cells have the ability to differentiate into most specialized cells and tissues such as blood cells, nerve cells, and liver cells.[1] The potential benefits of ES cell research include possibly finding treatment and cure for injuries or diseases such as Alzheimer's disease, Parkinson's disease, heart disease and kidney failure.[2] ES cell research, however, poses a burden that cannot be minimized or eliminated: the derivation of ES cells causes the death of a preimplantation embryo. Is it Ethically justifiable to sacrifice the life of an embryo for the benefit of humankind?

This paper suggests three concepts as a starting point in dealing with the ethical dilemmas that arise from conducting ES cell research. First, there is a need to establish the moral status of a preimplantation embryo. Since embryos are incapable of giving informed consent, embryos maybe classified as a vulnerable population. On ethical grounds, vulnerable population should be respected and research on a vulnerable population should be justified. Secondly, the right to autonomy must be granted to the women/couples who donate their embryos for research. Lastly, there is a need to understand individuals as part of a larger community. This last suggestion is especially important because neither the embryos nor their donors receive any benefits for participating in ES cell research.

History

Prior to the discovery of the capability of ES cells, the use of fetal tissue in transplantation led to the formation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974 and the National Institute of Health (NIH) Human Fetal Tissue Transplantation Panel in the late 1980's. Both groups set up guidelines to prevent the sale of fetal tissue for profit, to require informed consent from all participants of the research as well as to insure that a woman's choice to terminate her pregnancy is not influenced by her desire to donate fetal tissue for research. Despite the guidelines, the Bush Administration maintained the moratorium on the federal funding of human fetal tissue transplantation believing that research may coerce women to terminate her pregnancy. The moratorium on federally funded research of human fetal tissue transplantation was lifted on President Clinton's first day in office.[3]

In 1993, the Clinton administration also removed the requirement of an Ethics Advisory Board (EAB) approval for federal funding of embryo research. The EAB was appointed by the Secretary of Health, Education, and Welfare to provide guidance on federal funding of research involving in-vitro fertilization. The NIH then set up a Human Embryo Research Panel (HERP) to recommend guidelines for federal funding of embryo research. Although the HERP's report in 1994 supported the use of preimplantation embryos for ES cell research, Congress did not grant federal funding of any research with human embryos.[4]

Since the discovery of the promise of ES cells, the National Bioethics Advisory Commission (NBAC) was formed in 1995 whose role will be discussed later in this paper.

The New NIH Guidelines

The NIH formally adopted new guidelines on federal funding on ES cells in August 25, 2000. The NIH guidelines embody ethical principles to help protect the autonomy and self-determination of the women/couples who donate their embryos as well as to establish moral responsibilities of publicly funded researchers.

The NIH guidelines require publicly funded re-

searchers to obtain their ES cells (without federal funds) from aborted fetuses or from frozen embryos that were left over after fertility treatments. Embryos donated for research must be frozen in order to ensure that potential donors were given time since the conception of the embryo to think and make a decision on whether or not to donate the embryo. In order to ensure that the decision to donate frozen embryos is a voluntary decision made by the couples, the guidelines forbid fertility specialists from using any form of incentives or coercion (e.g. financial reward, ability to specify recipients of the ES cells). When couples have an excess supply of embryos, couples are usually given the option of either storing unused embryos, donating them to another woman, or discarding them. Couples are asked to donate their embryos for research only after making the decision to discard the embryo.[5]

Following former President Clinton's request to the National Bioethics Advisory Commission (NBAC) to conduct a review of the issues involved with ES cell research in November 1998, the NBAC reported that "if the decision to discard the embryos precedes the decision to donate them for research purposes, then the research determines only how their destruction occurs, not whether it occurs."[2]

The new NIH guidelines were written by lawyers who work for the NIH in order to attain legal permission for the government to be able to conduct ES cell research.[6] The guidelines still uphold the 1998 law which prohibits federal funding for the creation of a human embryo for research purposes or for "research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to the risk of injury or death."[1] The legal argument is that ES cells are neither an embryo nor a human being, and therefore, any research on ES cells shall not be considered as human embryo research.[3] The NBAC believes that the 1998 law "conflicts with several of the ethical goals of medicine and related health disciplines, especially healing, prevention, and research. These goals are rightly characterized by the principles of beneficence and nonmaleficence, which jointly encourage pursuing social benefits and avoiding or ameliorating potential harm."[2]

Nonmaleficence: Do No Harm

What does "harm" mean when used in the context to describe the principle of nonmaleficence? Is "harm" applied to the damaged embryo after its ES cells have been removed? This question deals with the issue of the moral status of an embryo and whether or not an embryo should be considered as a person. If an embryo does not have any moral status, no "harm" is done by sacrificing the life of an embryo unless the damaged embryo is transferred to a woman's uterus. "The embryo is an organism with human origins but not yet sentient or having a set of interests. Physical harm could only be done to an embryo itself after implantation, gestation, and in the context of rudimentary sentience."[7]

Moral Status of a Preimplantation Embryo

Determination of whether benefits are outweighing the risks, therefore, depend on one's understanding of an embryo, more specifically, a preimplantation embryo. When human germ cells or embryonic/fetal tissues are outside of their ordinary environments, the cells take on a different meaning. For example, "frozen sperm become property in divorce settlements" and "frozen embryos are made available for adoption." Therefore, McGee and Caplan believe that a preimplantation embryo has less moral status than an embryo inside a woman's body.[8]

Views Supporting ES Cell Research

Embryos are morally considered in hopes of determining the degree of social protection that should be given to embryos. There are opposing arguments on whether an embryo shall be considered as a person with rights and interests. Biological arguments that reason the embryo's lack of moral status include how the embryo from in vitro cannot develop any of its organs or particular tissues unless it is implanted into a woman's uterus.[6] Others hold the development of the "primitive streak" (the precursor to the spinal cord of an individual fetus) as the threshold for moral status.[9] Such views raise little ethical concern about having to protect the embryo or to limit its use in research because if the embryo has no moral status to begin with, it will not be diminished by the embryo's use for research.

The nature of the disagreements over the moral status of an embryo lies not only on contending biological interpretations but on theological and religious considerations as well. According to Rabbi Tendler, "the Judeo-biblical tradition does not grant moral status to an embryo before 40 days of gestation." ES cells have to be removed from the embryo about four to seven days after conception. Tendler characterizes such embryos as having "the same moral status as male and female gametes, and its destruction prior to implantation is of the same moral import as the 'wasting of human seed'." Furthermore, Tendler equates the purpose of ES cell research with the paramount ethical principle in biblical law, the moral obligation to save human lives. "Life-saving abortion is a categorical imperative in Jewish biblical law. Mastery of nature for

the benefit of those suffering from vital organ failure is an obligation."[10] The moral status of the embryo, therefore, "is of secondary importance to the question of the life-saving consequences" of ES cell research.[11] Therefore, the Jewish tradition is in accord with the developmental view held by HERP. Meaning, an embryo is not guaranteed of its full moral status at conception, but an embryo gradually obtains such a status during the development of the embryo. The HERP notes:

Among the qualities considered under a pluralistic approach are those mentioned in single-criterion views: genetic uniqueness, potentiality for development, sentience, brain activity, and degree of cognitive development. Other qualities often mentioned are human form, capacity for survival outside the mother's womb, and degree of relational presence (whether to the mother herself or to others). Although none of these qualities is by itself sufficient to establish personhood, their developing presence in an entity increases its moral status until, at some point, full and equal protectability is required.[9]

The discussion on the moral status of the embryo, however, shall not ignore the relationship between the parents and their embryos or the "interests that potential parents and society bring to procreation and reproduction." "An embryo has moral standing not so much for what is (at conception or later) but because it is the result of procreative activity."[12]

Views Against ES Cell Research

Edmund Pellegrino, a Roman Catholic, believes that an embryo deserves full moral status at any stage in the development of the embryo and rejects the idea of using embryos as means to an end.[13] People who support Pellegrino's beliefs generally argue that the embryo's potential to become a fetus once implanted into the uterus ought to confer the fetus's status as a person.[4]

Respect for Embryo Donors

The discussion on the moral status of the embryos, however, is not to undermine women/couples who donate their embryos. The fundamental interest of couples to conceive a child can be damaged if ES cell research is carried out in morally unjustifiable manner. Although the NIH guidelines require that the fertility specialist who harvests the embryo cannot be the same person who destroys the embryo to remove ES cells, will fertility specialists ever feel pressured to make "spare embryos?" Meaning, some fertility specialists may advise couples to create more embryos than the standard with the hidden intention of giving the excess embryos to researchers.

Right to Privacy

A more imminent concern is whether or not donors will be able to maintain their right to privacy. It is likely that the tissue from which the ES cells are derived maybe used to test for genetic diseases to assure the safety of the recipients of the ES cells. The consequence of such tests is that they may reveal information about the genetic makeup of the donors which may pose a psychological burden to the donors. The new NIH guidelines state that donors must be notified when giving their informed consent whether or not identifiers ("any information from which the donor(s) can be identified") will be retained or not.[5]

Informed Consent

Before any embryos are frozen, the parents of the embryos must give informed consent on what they want done with the frozen embryos if the parents were to divorce, die or change their minds about having children. The parents are usually given three choices: termination, donation to another couple, or donation for research purposes. In other words, requiring parents to give further informed consent about the use of their embryos for ES cell research upon choosing the termination option suggest that such an option is now questionable. In addition, "the embryos already in storage under a general research authorization should not be used for ES cell research without making an attempt to recontact the couples for specific consent. The new possibility of ES cell research is sufficiently different from the types of research that couples assumed would be done one the embryos at the time the couples donated them that recontact seems prudent."[14]

Although many people who support ES cell research share a common belief that fewer ethical dilemmas are involved if ES cells are obtained from aborted embryos, is a woman who decided to have an abortion an appropriate person to give a proxy consent for research on the aborted embryo? By aborting the embryo, is the woman demonstrating her ability to act in the embryo's best interest? The woman's right to abortion shall not be demeaned because the right to abortion is a woman's right to liberty and bodily integrity.

In general, how valuable is informed consent in justifying research involving human embryos? Robertson is probably right in stating that most of the egg donors in the future will be those who have unused embryos from undergoing in-vitro fertilization or those who donate eggs for infertile couples.[4] Robertson fails to mention that there may be monetary incentives involved in the latter group's decision to donate their eggs in the first place,

and therefore, some aspect of coercion should be weighed in with the donor's informed consent.

Beneficence: The Obligation to Do Good

Although human embryos deserve respect as a form of human life, the scientific and clinical benefits of ES cell research should not be forgone. Last spring, approximately 90 potential recipients of ES cell treatment formed the Coalition for Urgent Research or CURE which includes members like Christopher Reeve and Michael J. Fox.[15] According to the coalition's estimate, approximately 128 million Americans may be saved from diseases using stem cell therapies when they become available. Roche and Grodin believe that "we have a moral imperative to do what we can to alleviate suffering and improve the human condition and we cannot ignore that obligation simply because no clear, unconventional path to that goal is apparent."[6]

Societal Issues

Aside from issues primarily dealing with the moral status of the embryo, there are also societal issues at stake. For example, the decision to fund ES cell research must be weighed against other demands for governmental financial support. Federal funds are scarce resources, and therefore, the government must decide on the portion of federal money that will go towards ES cell research as opposed to preventive medicine, drug rehabilitation, assisted reproductive technology and more.[10]

The question that arises then is whether ES cell research should be performed because it is neither a necessity nor a last resort. There are alternatives to ES cells that would not involve the termination of life such as adult stem cells. Although the ethical concerns involving the derivation of adult stem cells should not be undermined, ethical concerns such as protecting the rights and the well-being of the donors of adult stem cells are more routine.[6]

In addition, because private companies are already committed to supporting ES cell research, failure to federally fund ES cell research will not lead to its termination. If the government does not fund ES cell research, however, private companies will patent its discoveries which will restrict free access to such discoveries and slow additional discoveries from taking place.

Robertson believes that the NIH guidelines are already impeding the speed of progress of ES cell research by not spending federal money to obtain ES cells. First, ES cells are sensitive to the conditions in which they were derived, and therefore, separation between the derivation and use of ES cells may have negative consequences on the quality of the research being done.[16] Secondly, under the current NIH guidelines, publicly funded researchers must face "intellectual property and other barriers to obtaining privately-derived ES cells. Those barriers may deter some researchers from undertaking ES cell research and thus slow the pace of progress in the field."[4]

Publicly Funded Research vs. Privately Funded Research

Currently, the only provider of ES cells in the U.S. is the University of Wisconsin. Furthermore, these cells are the property of Geron Corporation, the company that funded Thomson and Gearhart's research.[15] Although Geron did say that it will provide its cells only to researchers Geron believes will conduct research in a morally appropriate way, Geron severely restricts access to the cells.[17] Furthermore, Geron holds the rights to any discovery that was made utilizing those cells. The University of Wisconsin also has the power to order researchers at any time to destroy the ES cells and to terminate ongoing research.[15] Some researchers believe that by limiting publicly funded research, vital research will be performed under private companies which have no obligations to release information about such research. Without published research, both progress and success of the research involving ES cells will be limited.[15]

Federally funded research may also better protect the right to autonomy of women and couples because of the difference in nature of federally-funded and privately-funded research. The year Gearhart and Thomson published their discovery, Geron Corporation created its own Ethics Advisory Board (EAB). It works independently of the corporation, and it serves to offer advice on the ethics regarding the work Geron sponsors. The EAB established conditions to conducting ES cell research which Geron may or may not decide to enforce.

How do the conditions set forth by the Geron EAB differ from those of the NIH guidelines? First, Geron EAB does not specifically prohibit the use of monetary incentives to get women/couples to donate their embryos. The women/couples donating embryos "should understand whether there are commercial implications and if so, whether they hold any propriety rights in the tissue lines developed from embryonic cells."[9] Second, the EAB conditions do not stipulate that the embryos must be frozen in order to give ample time for women/couples to think about their decision to donate their embryos. Meaning, donators are in a less vulnerable state as more time elapses since the embryos were fertilized,

and hence, donors will be able to give a viable informed consent. The EAB, on the other hand, demands that the researchers be sensitive to the vulnerable state of donators. "The IVF process is often physically painful, emotionally burdensome, and financially costly. These factors may make IVF patients particularly vulnerable. Such possible vulnerability demands careful and consistent efforts on the part of researchers..."[9]

Looking at the Future

The NBAC raised concerns about the possibility of not having enough embryos for research from infertility treatments in the future and "the recognition that some research requires embryos that are generated particularly for research and/or medical purposes."[2] Currently, there are at least 100,000 IVF embryos kept frozen and the number of frozen embryos is increasing at a rate of nearly 19,000 per year.[14] The success of ES cell research depends on finding ways to immunologically alter the cells or tissues produced from ES cells to prevent rejection by the immune system of prospective patients. John Robertson suggests that human embryos may need to be created for research purposes in order to develop a large library of ES cell genotypes that encode different transplantation antigens and thus, create a library in which we know which ES cells to use for different individuals. Furthermore, Robertson goes on to say that ES cells may be obtained from embryos created by cloning the patient's own cells to insure compatibility. He even claims that women should be allowed to donate her eggs for research purposes and "undergo ovarian hyperstimulation and egg retrieval in order to get eggs for research." George Annas, Arthur Caplan, and Sherman Elias would argue that such treatment of women would put them at great risk and would offer no direct benefits to the women. Robertson justifies his views by equating the need of egg donors for infertile couples to the need of egg donors for ES cell research.[4]

Extreme measures as those described by Robertson may or may not be avoided in the future if human embryos are generated asexually be somatic cell nuclear transfer (SCNT).[18] Scientists in the future may be able to clone the DNA in the embryo to develop perhaps five or ten nuclear-transfer-derived embryos consisting of the same DNA that makes up the original embryo. That DNA is not lost when ES cells are derived, and thus, the "identity" of the embryo will not be lost.[19] This approach to deriving ES cells is currently not included in the NIH guidelines.[18] Such a method does not cause additional harm to women who are potential egg donors, but SCNT will promote the creation of embryos for research which is not allowed by the NIH guidelines. In 1998, President Clinton stated that SCNT should not be used to produce embryos for reproduction, but should be used to produce embryos for research. Further federal regulations will be necessary when more information on SCNT becomes available in order to prevent researchers from abusing SCNT by altering the genetic code of our future children.[20]

Conclusion

ES cell research is justifiable only if ES cells are derived from aborted embryos or excess preimplantation embryos destined to be discarded. It would make no moral sense to say that the social benefits of ES cell research outweighs the death of embryos because they should be treated with respect. The potential benefits of ES cell research, however, are so immense that perhaps there is harm if ES cell research is not performed. At the same time, the sacrifice of thea lives of embryos seems unjust because they never benefited from other people's involvement in research. Perhaps with the development of biotechnology, the principle of justice in public health will be altered from the general belief of how we, as members of the community, should all contribute to the common good. Meaning, the definition of "we" may not only refer to the people that make up a community, but also incorporate whole banks of cells, tissues and embryos.

Finally, both the moral and societal issues involved with conducting ES cell research are discussed in this paper because justifying ES cell research on the basis of its benefits makes moral sense only if people in need actually have access to those benefits.

Author Biography

Jennifer Takagawa, LA '03, is from Rye, NY. She is majoring in Internation Relations and is a participant in the Community Health Program. *She would like to thank Charlene Galarneau for her contributions to the paper.*

References

[1] Stephenson, Joan. "Green Light for Federally Funded Research on Embryonic Stem Cells." The Journal of the American Medical Association 11 Oct. 2000: 1773-1774.

[2] United States. National Bioethics Advisory Com mission. "Ethical Issues in Human Stem Cell Research: Executive Summary." Sept. 1999. 1 Nov. 2000 <http://bioethics.gov/stemcell_exec_intro.htm>.

[3] Edwards, Brian E., John D. Gearhart, and Edward

E. Wallach. "The Human Pluripotent Stem Cell: Impact on Medicine and Society." Fertility and Sterility July 2000: 1-7.

[4] Robertson, John A. "Ethics and Policy in Embryonic Stem Cell Research." Kennedy Institute of Ethics Journal June 1999. 29 Oct. 2000. <http://muse.jhu.edu/journals/kennedy_institute_of_ethics_journal/v009/9.2robertson.html>.

[5] United States. National Institutes of Health. "National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells." 25 Aug. 2000 (corrected 21 Nov. 2000). 29 Nov. 2000. <http://www.nih.gov/news/stemcell/stemcellguidelines.htm>.

[6] Roche, Patricia A. and Michael A. Grodin. "The Ethical Challenge of Stem Cell Research." Women's Health Issues May-June 2000. 15 Nov. 2000.<http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TD8-40BG4JS8&_user=201547&_coverDate=06%2F30%2F2000&_alid=7986200&_rdoc=50&_fmt=full&_orig=search&_cdi=5192&_sort=d&_st=0&_acct=C000014058&_version=1&_urlVersion=0&_userid=201547&md5=a4d3635e6636490c150c1173d075cb21>.

[7] Fletcher, John C. "Deliberating Incrementally on Human Pluripotential Stem Cell Research." United States. National Bioethics Advisory Commission. Ethical Issues in Human Stem Cell Research: Volume II Commissioned Papers. Sept. 1999. 28 Nov. 2000 <http://bioethics.gov/stemcell2.pdf>.

[8] McGee, Glenn, and Arthur Caplan. "What's in the Dish?" Hastings Center Report 29, no. 2 (1999): 36-38.

[9] Geron Ethics Advisory Board. "Research withHuman Embryonic Stem Cells: Ethical Considerations." Hastings Center Report 29, no.2 (1999): 31-36.

[10] Tendler, Moshe Dovid. National Bioethics Advisory Commission. Ethical Issues in Human Stem Cell Research: Volume III Religious Perspectives. June 2000. 28 Nov. 2000. < http://bioethics.gov/stemcell3.pdf>.

[11] Zoloth, Laurie. National Bioethics Advisory Commission. Ethical Issues in Human Stem Cell Research: Volume III Religious Perspectives. June 2000. 28 Nov. 2000. < http://bioethics.gov/stemcell3.pdf>.

[12] Annas, George J., Arthur Caplan and S Elias. "Ethics, Public Policy, and Human Fetal Tissue Transplantation Research." New England Journal of Medicine 334 (1996): 1329-1332.

[13] Pellegrino, Edmund D. United States. National Bioethics Advisory Commission. Ethical Issues in Human Stem Cell Research: Volume III Religious Perspectives. June 2000. 28 Nov. 2000. < http://bioethics.gov/stemcell3.pdf>.

[14] Andrews, Lori B. "State Regulation of Embryo Stem Cell Research." United States. National Bioethics Advisory Commission. Ethical Issues in Human Stem Cell Research: Volume II Commissioned Papers. Sept. 1999. 28 Nov. 2000 <http://bioethics.gov/stemcell2.pdf>.

[15] Allen, Arthur. "God and Science." The Washington Post 15 Oct. 2000. 18 Oct. 2000. <http://www.washingtonpost.com/ac2/wp-dynA615872000Oct12?language=printe>.

[16] Harris, Lisa H. "Ethics and Politics of Embryo and Stem Cell Research: Reinscribing the Abortion Debate." Women's Health Issues May/June 2000. 15 Nov. 2000. <http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TD8-40BG4JS&_user=201547&_coverDate=06%2F30%2F2000&_alid=7986200&_rdoc=51&_fmt=full&_orig=search&_cdi=5192&_sort=d&_st=0&_acct=C000014058&_version=1&_urlVersion=0&_userid=201547&md5=d3390301bd06c8103720e5bc1c364b9f>.

[17] Knowles, Lori P. "Property, Progeny, and Patents." Hastings Center Report 29, no.2 (1999): 38-40.

[18] Friedrich, M.J. "Debating Pros and Cons of Stem Cell Research." The Journal of the American Medical Association 9 Aug. 2000: 681-682.

[19] McGee, Glenn, and Arthur Caplan. "The Ethics and Politics of Small Sacrifices in Stem Cell Research." Kennedy Institute of Ethics Journal June 1999. 29 Oct. 2000. <http://muse.jhu.edu/journals/kennedy_institute_of_ethics_journal/v009/9.2mcgee.html>.

[20] Parens, Erik. "Embryonic Stem Cells and the Bigger Reprogenetic Picture." Women's Health Issues May/June 2000. 15 Nov. 2000. <http://www.sciencedirect.comscience?_ob=ArticleURL&_udi=B6TD840BG4JS4&_user=201547&_coverDate=06%2F30%2F2000&_alid=7986200&_rdoc=49&_fmt=full&_orig=search&_cdi=5192&_sort=d&_st=0&_acct=C000014058&_version=1&_urlVersion=0&_userid=201547&md5=9f21b951459f68cae1cb942681d93719>.

TuftScope
The Interdisciplinary Journal of Health, Ethics, and Policy
Volume 1 May 1, 2001 Number 1

POSSIBLE ETIOLOGY OF SEASONAL AFFECTIVE DISORDER

CO_2 -> MYOGLOBIN -> O_2 CHEMORECEPTORS -> ACTH, MELATONIN

Daniel Kleinman

Abstract

In winter months, bonding between CO and myoglobin increases. This is due to a slowly raised level of CO_2, which lowers blood pH, increasing the affinity of myoglobin for CO. The lower pH environment also causes myoglobin to be more rapidly autoxidized, irreversibly bonding to oxygen. Furthermore, when myoglobin is bombarded with light, it releases CO. Less light exposure during the winter does not disrupt CO-Mb bonding, as it does during summer months.

With greater CO bonding to myoglobin and autoxidation taking place, the protein is less able to deliver oxygen to muscle cells for aerobic respiration. In effect, this causes local hypoxia. Oxygen sensing mechanisms begin a signal cascade in the corotid body, triggering a sympathetic reaction, releasing neural hormones.

These oxygen chemosensors cause the release of beta-endorphins, corticotrophin (ACTH), and cortisol through a chain of reactions centered in the hypothalamus and pituitary glands. Endorphins are responsible for easing pain and positive stimuli. Cortisol affects the release of glucose to cells for the production of energy. Corticotrophin signals for cells to create the enzyme adenylate cyclase, which changes ATP into cyclic-AMP (cAMP). cAMP causes the breakdown of glycogen for more energy production.

Additionally, norephinephrine (NE) release has also been specifically shown to increase during general hypoxia. It stimulates greater production of melatonin, a hormone responsible for regulating sleep duration.

Overall, the breaking down of increased levels of glucose, due to cortisol and corticotrophin, causes the body to crave carbohydrates. The raised level of beta-endorphins creates a situation in which receptors shut off, disabling positive stimuli. The increased synthesis of melatonin causes extended sleep time. Thus, SAD sufferers crave carbohydrates, experience depression, and feel perpetual exhaustion.

Introduction

An estimated 10% of people living in the northern United States suffer from some form of SAD, affected by depression only during winter months. Estimated rates of SAD sufferers throughout the country range from 1.4% of Florida residents to 35% of nonnative Alaskans.[1] General symptoms include irritability, carbohydrate craving, weight gain, increased sleep time, and general sadness. In addition, SAD patients are known to have elevated levels of corticotrophin releasing hormone/factor (CRH/CRF), adrenocorticotrophic hormone (corticotrophin)(ACTH), beta-endorphins, cortisol, and melatonin.

The relationship between levels of light exposure and SAD is almost unquestioned. Treatment of the disorder has generally been limited to exposing patients to increased levels of light during the winter through the use of a 10,000-lux lightbox, positioned about 45 cm from the subject's face for a period of time ranging from 30 to 45 minutes each day. The current hypotheses for the cause of SAD have generally centered on the reduced levels of serotonin due to lowered levels of light reaching the subject. However, researchers, since the defining of SAD in 1984 by Norman Rosenthal, have hypothesized that the disorder could be totally psychological, arise from the ophthalmic function (primarily retinal sensitivity to light), center on delayed circadian rhythms, or concern the over-secretion of melatonin. None of these theories comes to any satisfactory conclusion in explaining the symptoms of SAD. To come to a stronger understanding of the mechanism by which the disorder takes its course, it is necessary to observe the situation from a broader vantage point and combine research that has been done thus far with outside studies to explain each of the symptoms experienced by sufferers. Though it has not previously been theorized, this paper will present the hypothesis that SAD is caused by a pattern of interrelated chemical imbalances stemming from the failure of myoglobin (Mb) to effectively deliver oxygen at low pH.

There are three primary sources of CO production

within the body. The breakdown of heme endogenously (within cells) accounts for the majority of CO normally found. However, CO is a neurotransmitter and anaerobic microbes (methanogenic archaea and acetongenic bacteria) produce carbon monoxide during carbon dioxide fixation. For bacteria, as described by Javier Seravalli, CO production is the intermediate step in the fixation of CO_2 by the Wood-Ljungdahl pathway ending in the formation of acteyl-CoA. Although a channeling effect has been suggested to keep CO from completely dispersing into the body, as much as 66% of CO produced by bacteria has been found to bond to heme proteins.[2]

The ability of myoglobin to distinguish between toxic CO and oxygen is central to the existence of life. CO affinity for free heme in solution is around 20,000 times that of oxygen. However, the affinity of CO for myoglobin is only 25 times that of O_2, making it possible for myoglobin to store and deliver oxygen.[3] This affinity is thought to be the result of the low-energy hydrogen-bond (8kJ/mol) between myoglobin's distal histidine (His 64 amino acid) and CO in contrast with the high-energy hydrogen-bond (32 kJ/mol) between His 64 and O_2. The 24 kJ/mol energy gap partially explains the favoring of O_2.[4]

A steric mechanism may also have a hand in the discrimination between CO and O_2. The bond angle formed between the iron atom of the heme and the CO ligand is nearly linear, 160-173 degrees (Figure 1). This allows for greater steric interaction, weakening the bonding between them. There is less steric hindrance with the approximately 120 degree bond angle between the heme iron and O_2.[5]

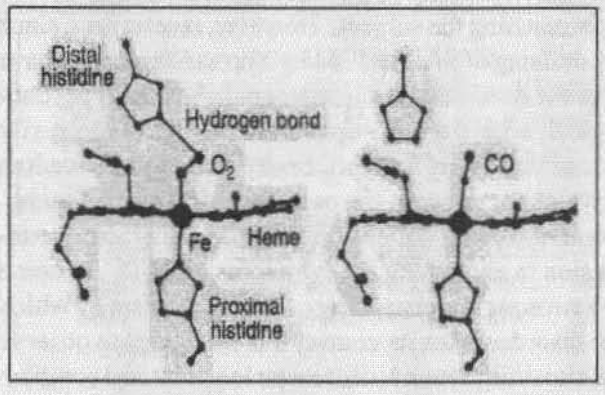


Figure 1
Hydrogen bonding between distal histidine and ligands.[3]

This steric hindrance could account for 0.5 to 7.0 kJ/mol of discrimination. Electrostatic interactions may account for 12-17 kJ/mol of discrimination between O_2 and CO. However, the sum of these three energy figures taken from several sources is far larger than the estimated 17 kJ/mol that would account for the theorized level of discrimination[4]. Nevertheless, we can be confident that each of these factors has a role in discrimination, hydrogen-bond energies being the most significant.

During winter months, the probability that CO will bond with myoglobin increases. In the winter, people stay in confined spaces for longer periods of time, allowing CO_2 build up. The increased burning of fuels also exposes us to higher levels of CO_2. In response to rapid changes in level CO_2, the body enters a stress reaction, increasing breath rate. However, the change that we are looking at takes place so gradually that the stress reaction does not occur. Instead, a buffer system maintains homeostatic levels of CO_2, by adjusts the physiological pH.

$$CO_2\,(g) \rightleftharpoons CO_2\,(aq) \qquad (1)$$

$$CO_2\,(aq) + H_2O \rightleftharpoons H_2CO_3\,(aq) \qquad (2)$$

$$H_2CO_3\,(aq) \rightleftharpoons HCO_3\,(aq) + H^+\,(aq) \qquad (3)$$

Increased concentration of H^+ ion lowers the blood pH. Myoglobin has been found to absorb oxygen at higher rates at higher pH levels.[6] Thus in winter, higher levels of carbon dioxide slightly lower the physiological pH, causing myoglobin to have a lower affinity for oxygen.

This phenomenon is likely explained by a change of the distal histidine (His 64) amino acid in response to pH. The side chain of His 64 has a pKa of 6.10. When the difference between pH and pKa is greater than one, 95% of the side chain will remain in its conjugate base form (figure 3). However, if the difference becomes less than one, 90% of the side chain takes on the conjugate base form.[8] The charged side chain severely lowers the strength of the hydrogen bond between His 64 and the ligand. Because the energy of the CO-His 64 hydrogen-bond, as stated before, is lower to begin with (8kJ/mol), it is more likely to be affected than the O_2-His 64 bond (32 kJ/mol).

In addition, slight pH changes greatly affect the rate at which myoglobin autoxidizes. Autoxidation occurs when oxygen binds with Mb in a way that it cannot release. As a result, when the pH drops, myoglobin becomes inactive at a much greater rate.[6]

Central to the success of SAD light therapy, unlike Hemoglobin, when bombarded by light, myoglobin releases its hold on CO, but not oxygen.[8] Recent research done by Tsu-Yi Teng explains that light ruptures the

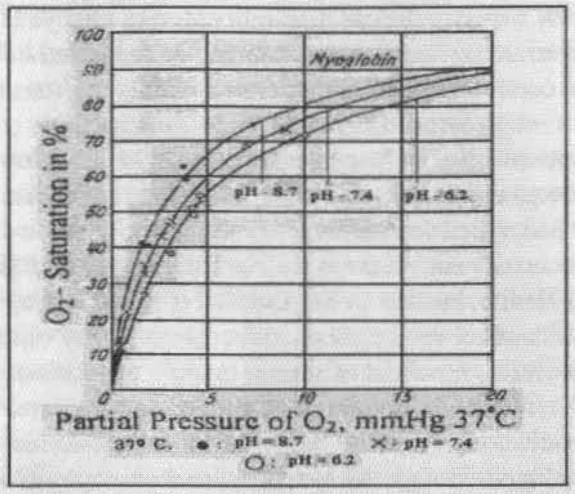


Figure 2
Percent oxygen saturation of myoglobin vs. partial pressure at varying pH

Normal physiological pH of blood is between 7.45 and 7.35. Normal partial pressure in muscles is around 20 mmHg.[15]

Fe(III)-CO bond, causing the ligand to move to two possible outer sites of the heme pocket. Longer exposure time forces the CO molecule farther from the heme of the myoglobin.[10]

The release of CO is best explained by the change in energy of the hydrogen-bond between the His 64 and CO when it is no longer connected to the iron atom. The CO-histidine hydrogen-bond has an energy of less than 5 kJ/mol as opposed to the suggested 8 kJ/mol energy of the Fe (III)CO- histidine 64 hydrogen bond[4]. Thus myoglobin is freed from CO when exposed to light.

The depth of light traveling through muscle tissue has been theorized through Monte Carlo simulations, which project photon trajectories. Monte Carlo simulations done by Gandjbakhche "indicate that in the 510- to 590-nm range [upper range of visible light] the mean path length within the myocardium for diffusely reflected light varies from 1.4 to 1.2 mm... [and] will show spectral features uniquely associated with myoglobin and cytochrome c... The maximum path length was set to 2 cm."[10] This supports the theory, suggesting that significant levels of light do enter muscle tissue.

Figure 3
pH = 7.4 ~ 95% Conjugate Base
Lower pH ~ Lower % Conjugate Base
A. Positive charge lowers the strength of hydrogen bonds with ligands

Overall, during the winter we are exposed to less light due to shorter days and by remaining indoors. Again, we are also exposed to higher levels of CO_2 by remaining in enclosed spaces and due to increased combustion for heating purposes. This slowly lowers our physiological pH. Less light and lowered pH increase the bonding of CO to myoglobin and the rate at which myoglobin autoxidizes. Myoglobin is unable to deliver oxygen as efficiently, causing local hypoxia around muscle tissue.

Local hypoxia may begin a signal cascade in the carotid body, triggered by PO_2-dependent chemoreceptors. These likely work through NADPH oxidase, H_2O_2 (a product of NADPH), protein kinase c (PKC), or a theorized heme protein similar to cytochrome c. Evidence for a heme protein may come from the role which myoglobin plays in this process. Despite debate over oxygen sensing mechanisms, it is generally agreed that potassium ion (K^+) channels are closed under hypoxic conditions. O'Kelly found that, "Graded hypoxia caused graded inhibition of whole cell K^+ currents."[12] Closing potassium currents results in depolariztion of type I cells. Lahiri found, examining the rat carotid body, that "This closing is followed by an influx of calcium through voltage-dependent calcium (Ca^{2+}) channels and liberation of transmitters. The latter generate action potentials in synaptically apposed nerve endings that travel via the corotid sinus nerve to the brainstem to regulate respiration and circulation... Because the light effects on CO-bound heme protein are fast, it suggests they are located in the sinus nerve endings."[13]

In response to these signals of changes in PO_2 and CO_2, the body first produces corticotrophin releasing hormone / factor (CRH/CRF) in the hypothalamus. CRH causes the increased release of beta-endorphins and adrenocorticotrophin hormone (corticotrophin) (ACTH). They are released equimolarly from the pituitary gland, and are found at elevated levels in SAD patients.[14] Endorphins generally act as positive stimuli to the brain and ease pain. A constant base level could causes endorphin receptors to shut off, decreasing positive stimuli. ACTH causes the hypersecretion of cortisol in the adrenal glands, which serves to increase the release of glucose to cells.[7]

Corticotrophin (ACTH) also directly changes the production of energy within the cell. It bonds with a receptor site on the cell membrane, activating the en-

zyme adenylate cyclase. Adenylate cyclase changes ATP into cyclic-AMP (cAMP), which acts as a secondary messenger in the regulation of glycogen. It acts through a protein kinase, stopping the production of glycogen and beginning the "degradation" or splitting apart of glycogen for energy. Glycogen is an energy storage molecule less efficient than fat, but can release energy quickly.[7] The body only stores a day supply of glycogen within cells, as opposed to about a month supply of fat. Thus, the continued presence of cAMP quickly depletes glycogen levels, which causes the body to constantly crave carbohydrates to replenish lost nutrients.

In addition, for an increase in hypoxia there is an increase in the neurological release of norepinephrine (NE) from the adrenal gland, which is the principal neurotransmitter in the production of melatonin, responsible for regulating sleep time.[15] NE triggers the cAMP-signaling pathway of the pineal gland, which activates the CREM gene responsible for encoding transcription factor (TF). The CREM transcription factors, CREB and inducible cAMP early repressor (ICER), control the amplitude and rhythmically of arylalkylamine-N-acetyl transferase (AA-NAT). AA-NAT is the rate-limiting enzyme of melatonin synthesis.[16,17] Changes in AA-NAT result in increased secretion of melatonin. When levels of melatonin rise, a subject will feel exhaustion and sleep longer, as seen in SAD patients.

This system is able to account for all symptoms experienced by SAD sufferers. Increased levels of CRH, ACTH, beta-endorphins, cortisol, and melatonin have each been accounted for. The carbohydrate craving experienced by SAD patients is caused by a combination of cortisol increasing the release of glucose to the cells and corticotrophin increasing the consumption of glycogen, causing the body to believe it needs to replenish lost energy. Weight gain is caused by the increase in food consumption, combined with a lack of physical exercise partially brought on by exhaustion due to higher levels of melatonin. Longer sleep time is simply caused by higher melatonin levels as well. Irritability is best explained by a higher base level of beta-endorphins, shutting of receptors, making one less responsive to positive stimuli. Constant exhaustion and lower energy production also contribute to general sadness and irritability. Through this system, most symptoms of SAD have been accounted for.

Discussion of SAD Research

The majority of SAD studies, regardless of their area of concentration, support the myoglobin-CO theory, in part. Among these are the many investigations into the ophthalmic function and its relation to SAD. It has been widely believed that light entering the eye is the determining factor in SAD, due to its suspected role in the control of circadian rhythms. Preliminarily, researchers suggested that SAD patients either were "subsensitive" or "supersensitive" to light due to low intraocular pressure, had a faulty blink rate mechanism, or had retinal dopaminergic abnormality.[18-20] However, a team of researchers at the National Institute of Mental Health, headed by Dr. Dan Oren, found, "[No] differences between patients and controls in any of these measures, no effect of season on dark adaptation, and no effect of light therapy on intraocular pressure. [In conclusion] while the action of light in SAD may be mediated through the eye, the casual photophysiology does not appear to reside in ocular abnormalities."[20] This brought into question the site of action in light therapy, leading back to the theory that effects of light on SAD may not act through the eye, as had previously been proposed in at least one report.[21]

Several studies concerning light exposure provide evidence for the myoglobin-SAD theory. The type of light used for SAD treatment has been found of little significance, as no benefit was seen in light treatment including UV-A exposure.[22] This would be expected, as the breaking of the Fe (III)-CO bond is not dependent on UV-A light. Also, the time of day at which light treatment was administered was found to be insignificant. Those undergoing standard light therapy in the daytime improved just as those treated in the evening.[23] This also seems logical, as the time of day at which the iron-CO bond is broken should be irrelevant. An investigation into the effects of SAD light treatment intensities found that 10,000 lux is more effective than 2,500 lux in alleviating SAD symptoms.[24] However, another study found that an intensity of 6,000 lux has similar effects to that of 400 lux, with the exception that patients exposed to the 400 lux were more prone to relapse into depression.[25] This simply suggests that greater intensity allows more light to reach the iron-CO bond, freeing more myoglobin.

To the contrary, an experiment investigating the site of action of light therapy concluded that light therapy directed at the eyes was much more effective than therapy directed at the skin.[26] This would go against the myoglobin-CO theory; however, this study has largely been discarded due to the placebo effect and because it was never replicated.[20] It should be noted that muscle tissue associated with the corotid body is likely the site of action. Furthermore, the face has substantial muscle tissue close to the skin where light could act.

Lastly, researchers have noted anecdotal evidence from SAD sufferers, experiencing substantial, antide-

pressive mood improvement after visits tanning salons.[27] This would be expected and possibly an effective treatment for SAD sufferers.

In general, the diagnosis of the effects of treatments on SAD patients is difficult to fully document. Each of the studies mentioned above involving patients' reactions to a stimulus, which did not solely involve the observation of hormone levels, was based on a system where a patient rated himself or a physician rated the subjects' mood according to numerical scales. This is not a perfectly reliable way of studying the significance of a stimulus. However, there is really no other way to document change in overall feelings. Also, in every SAD study, researchers have had a difficult time controlling variables. Several studies have admitted to being insecure in their conclusions due to anything from an unusually sunny winter to an inability to control variables in their subjects' daily lives. Yet, despite unavoidable gray areas in research and the strong presence of the placebo effect, a majority of SAD studies are supportive of the CO-myoglobin theory.

If this theory is correct, it raises the question of why do all people not suffer from SAD. The likely answer is because of varying lifestyles, physical and emotional ability to deal with stress, and varying times at which the stress reaction takes place. A person who stays inside often is more likely to be exposed to higher levels of carbon dioxide and receive lower exposure to light. Thus they become more likely to suffer from SAD. Exercise habits may play a strong role as they could potentially change the threshold at which the sympathetic or stress reaction is triggered. People who frequently put themselves into controlled anaerobic respiration and lower their pH through exertion may raise the threshold at which the nervous system reacts. Smoking may have similar effects as people are artificially exposing themselves to increased CO_2.

Therefore, we may all theoretically be susceptible to SAD, however some may be more likely to develop symptoms due to lifestyle, a genetically or acquired lower threshold for stress, or other variation. With this in mind, the best cure for the disorder would simply be light therapy and reduction of carbon dioxide intake - both accomplished by spending more time outside.

In conclusion, although researchers have delved deeply into SAD, they have concentrated on the relationship between the ocular mechanism, circadian rhythms, and the hypothalamus. It is by looking at SAD research alongside outside studies that we can connect mechanisms with levels of hormones released in SAD patients, coming to a stronger understanding of Seasonal Affective Disorder. Nevertheless, further research is necessary to confirm and assess the extent to which these mechanisms act.

Author Biography

Danny Kleinman, LA '04, is from Bethesda, MD. His inspiration for the paper came from a 1997 article in a National Institute of Health newsletter on photographing myoglobin.

References

[1] Rosenthal, Norman E. MD, "Diagnosis and Treatment of Seasonal Affective Disorder." JAMA, December 8, 1993b - Vol. 207, No. 22

[2] Seravalli, Javier et. al., "Channeling of Carbon Mon oxide during Anaerobic Carbon Dioxide Fixation." Bio chemistry, January 20, 2000 - 39 (6), 1274-1277

[3] Borman, Stuart A. Instrumentation in Analytical Chemistry. American Chemical Society: June 1986

[4] Sigfridsson, Emma and Ryde, Ulf, "On the signifi cance of hydrogen bonding for the discrimination be tween CO and O2 by myoglobin." JBC, July 7, 1998- 4:99-110

[5] Kachalova, Galina S. et. al. "A Steric Mechanism for Inhibition of CO Binding to Heme Proteins." Science, 16 April 1999- Vol. 284

[6] Shikama, Keiji, "The Molecular Mechanism of Au toxidation for myoglobin and Hemoglobin: A Vener able Puzzle." Chemistry Reviews, April 8, 1998 - 98, 1357-1373

[7] Krochwitz, Jacqueline I. and Melvin Winkour. Chem istry General, Organic, Biological. Second Edition. McGraw-Hill, Inc.: New York, 1990.

[8] Brown, William. Intro to Organic and Bio Chemistry. USA: PWS Publishing, 1981.

[9] Contie, Victoria L. "Molecular Movies: Using X Rays To Study Motion." NCRR Reporter May/June 1997

[10] Teng, Tsu-Yi et. al., "Initial Trajectory of Carbon Mon oxide after Photodissociation from myoglobin at Cryo genic Temperatures." Biochemistry, May 15, 1997 - 36 (40), 12087-12100

[11] Gandjbakhche, Amir H. et. al. "Visible-light photon migration through myocardium in vivo." AJP – Heart and Circulatory Physiology. August 1999 – 277(2): H698-H704.

[12] O'Kelly, Ita et. al., "O2 Sensing by Airway Chemoreceptorderived Cells: Protein Kinase Activa tion Reveals Functional Evidence For Involvement Of NAPDH Oxidase." J Biol Chem, 17 March 2000 275(11): 7684-7692

[13] Lahiri, Sukhamay et. Al. "Chemoreceptor discharges and cytochrome redox changes of the rat corotid body: Role of heme ligands." Physiology, 3 August 1999 - 96 (16): 9427-9432

[14] Akil. H et. al., "Multiple HPA Profiles in Endogenous Depression: Effects of Age and Sex on Cortisol and

Beta-Endorphins." Biol Psychiatry, 1993 - 33:73-85
[15] Kummar, Ganesh K et. al., "Release of dopamine an dnorepinephrine by hypoxia from PC-12 cells." AJP Cell Physiology. June 1998 – 274(6): C1592-C1600
[16] Foulkes, NS et. al., "Rythmic transcription: the mo lecular basis for circadian Melatonin synthesis." Bio Cell, November 1997 - 89(8):487-484.
[17] Sassone-Corsi P, "Coupling gene expression to cAMP signaling: role of CREB and CREM." Int. J. Biochem. Cell Biol., Jan 1998 - 30(1):27-38
[18] Stojek, A et. al., "Low interaocular pressure in sea sonal affective disorder." Lancet. 1990 - 336:1443-1444.
[19] Dupue, RA et. al., "Seasonal Independence of low prolactin concentration and high spontaneous eye blink rate in unipoar and bipolar II seasonal affective disor der." Arch Gen Psychiatry. 1990 - 47:356-364.
[20] Oren, Dan A. et. al., "An Investigation of Ophthalmic Function In Winter Seasonal Affective Disorder." De pression, 1993 - 1:29-37
[21] Foster, RG et. al., "Circadian photoreceptor in the retinally degenerated mouse (rd/rd)." J Comp Physiol A. 1991 - 169:39-50.
[22] Lam, Raymond W. MD, "Seasonal Affective Disor der: Current Opinion in Psychiatry" "http:// www.mentlahealth.com/book/p40-sad.html" www.mentlahealth.com/book/p40-sad.html. January 1994
[23] Wirz-Justice, A et. al., "Ligth therapy in seasonal affective disorder is independent of time of day or circadian phase." Arch Gen Psychiatry. 1993- 50:929-937.
[24] Terman, JS et. al., "Efficancy of brief, intense light e exposure for treatment of winter depression." Psychopharmacol Bull. 1990 - 26:3-11.
[25] Rosenthal, Norman E. MD, et. al. "A Multicenter Study of the Light Visor for Seasonal Affective Dis order: No Differences in Efficacy Fround Between Two Different Intensities." Neuropsychopharmacology 1993a, 8:151-160.
[26] Wehr, TA et. al., "Eye versus skin phototherapy of seasonal affective disorder." Am J Psychiatry. 1987 -144: 753-757.
[27] Rosenthal, Norman E. MD, "Possible Benefits of UV Light in Seasonal Affective Disorder." NIH Confer ence Abstract. September 1998

Information for Authors

Scope of Journal

Promoting a well-rounded discussion of health and health issues in today's society, TuftScope accepts submissions on public & community health, government policy, health economics, clinical and research ethics, medical education, and the influence of technology. The format of these submissions should be essay or opinion/editorial.

TuftScope also accepts research submissions in any of the fields mentioned above, or any reviews of current medical or scientific research.

How to Submit

Address an e-mail message to Submissions@tuftscope.com. Attach your work in proper file format to the e-mail and in the body of the e-mail, place the authors, title, affiliation, and the address of the corresponding author. Omit all identifying information from your attached submission

Letters & Correspondence

Address all letters to the same e-mail address above, using "Letter" in the subject heading of the message.
If you wish to submit a rapid letter for the online edition at http://www.tuftscope.com, please indicate so in the body of the message.

Guidelines for Authors

Submissions must be submitted in a word processing program. File must be Microsoft Word with *.doc extension, or text with *.txt, or *.rtf file extensions.

Do not format end notes and foot notes with word processing formatting. Please use standard MLA notation for citations, and include the reference list on an attached page.

No set length limit exists. TuftScope, however, reserves the right to edit submissions for length. In the event that a submission must be edited, it will be sent to the author for approval before publication.

Include a Title Page with Authors names, affiliations, site of research (if applicable), sponsor of research (if applicable), title, corresponding author's mail and e-mail address

Special Considerations for Research Authors

Include an abstract, less than 250 words

Check to be sure that the title page contains project sponsor information, author affiliations, all authors, and site of research

TUFTS
University College of Citizenship and Public Service

UCCPS

education for active citizenship

"Tufts students are renowned for their volunteer spirit. I have been volunteering at soup kitchens and homeless shelters since high school. UCCPS has encouraged me to stop and think for the first time, 'What can I do so that these facilities won't be necessary in the future?'"

Greg Propper, A01

Internships
TEACH
Omidyar Scholars
Student Advisory Council
Active Citizenship Summers

We can make a difference!

The University College of Citizenship and Public Service seeks to educate a new generation of committed and engaged citizens who will ensure that the American model of participatory democracy continues to flourish.

The **New York Times** calls it "the most comprehensive example" of higher education re-emphasizing "public service as a core tenet of the curriculum."

University College of Citizenship and Public Service

Tufts University ¥ Lincoln Filene Building ¥ Medford, MA 02155 ¥ 617-627-3453

find out more online at http://UCCPS.tufts.edu

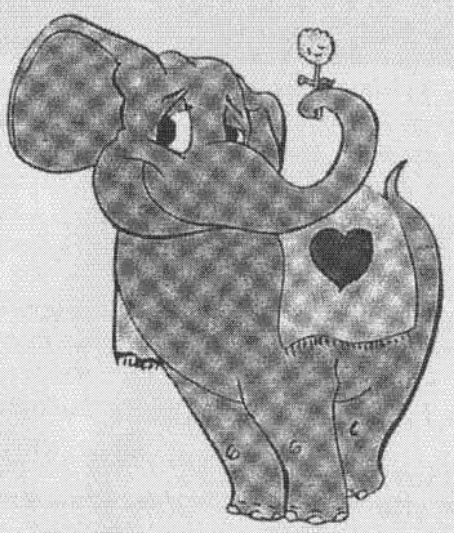
Graduation Shabbat

at Hillel

Friday, May 18, 2001

Services at 6:00pm

Dinner at 7:15pm



Dinner reservations required. $18 per person.

For more information or to reserve dinner call Hillel at 627-3242.

It's never too late to be a pre-med student at Tufts...

As an undergraduate, you already know the benefits of a Tufts education. You've grown accustomed to the friendly and supportive nature of this academic community. You know it has a diverse curriculum taught by exceptional faculty. And, it's close to Boston.

You like it here.

Are you just coming to the realization that medicine is **where you want to be?** Do you want to pursue a career that not only challenges you academically, mentally, and emotionally, but can **make a real difference** in people's lives? Did you think it was too late to change gears this far into your undergraduate education?

It's not too late. Tufts has a Post-Bac Premed Program suited to your individual needs, and we'd like to tell you more about it.

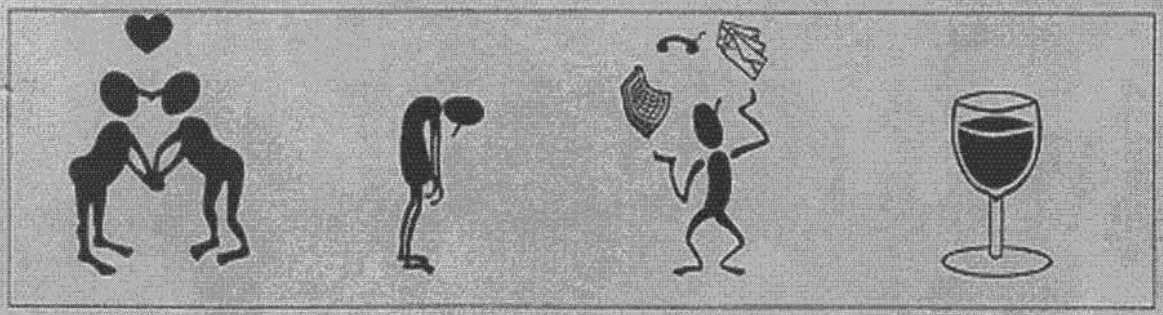
Find out how — in as little as one year — you can complete the science prereqs for medical, dental, and veterinary schools, as well as other health professions.

For a program brochure contact:

Graduate and Professional Studies

(617) 627-3395

Or drop by our office at Ballou Hall, 1st floor, Medford campus.
You can also make an appointment with Carol Baffi-Dugan,
Tufts Program Director for Health Professions Advising,
located at Dowling Hall, Medford campus.



You don't need to have a sprained ankle, mono, or a sore throat to come to Tufts Health Service!

You can talk to us and use us as resources regarding:

- **Physical symptoms of stress, anxiety and depression**
- **Support and referral for sexual assault**
- **HIV/AIDS and STDs**
- **Emergency contraception**
- **Concerns about alcohol and/or other drugs**
- **Relationship issues**
- **Birth control (we carry many brands of pills for $5/pack)**
- **Eating concerns & other nutrition issues**
- **Dealing with violence in relationships**
- **Sleep problems**

Tufts Health Service

627-3350

We care about the issues you care about. We care about you!

Should

Tufts Institute of the Environment

sponsor

A BioEthics Speaker Series?

We are looking for students with:

- Interest in bioethics
- Issue and discussion suggestions
- Speaker suggestions

to help plan and coordinate a speaker series during fall 2001.

All students are welcome to participate in this process. Please contact us below.

Phone: 617-627-3645
Fax: 617-627-6645

Email: tie@tufts.edu

Tufts Institute of the Environment, Miller Hall, Tufts University, Medford, Massachusetts 02155

TuftScope
Mayer Campus Center
Tufts University - Medford - Massachusetts - 02155