Chapter Three

Defining Research Bioethics

Introduction

Ethics has traditionally been applied to both health care and scientific research. Over the past forty years, ethics in medicine and science has branched out in numerous directions (genetic ethics, neuroethics, animal ethics, research ethics, legal bioethics, environmental ethics, and life science ethics). While the general term "bioethics" is used to include all these areas, current analyses reveal that each of these areas of study can be viewed as intrinsically different. The first part of this chapter focuses on the need to define research bioethics and when it should be distinguished from medical ethics. The second part of this chapter outlines specific ethical guidelines that address some of the unique characteristics of research bioethics that may differ from classical medical ethics. The conceptualization of research bioethics is designed to link various avenues of science-based research into one ethical discipline that emerges from biotechnology and life-science discoveries.

Bioethics in the Context of Medical Ethics

From the time of Hippocrates until the present day, discussions relating to medical ethics have generally focused on health care professional-patient relationships. Thus, scientific discoveries that directly have an impact on the rights of the patient, the rights and obligations of the physician, and the operations of health care facilities, fall within the domain of medical ethics. Traditional issues in medical ethics include contraception, *in vitro* fertilization (IVF), assisted reproductive technologies, abortion, informed consent, organ transplantation, and end of life issues. In addition, ethical guidelines have been formulated to protect the rights of volunteers participating in clinical or research studies that may lead to new FDA-approved therapies.

Dr. Van Rensselaer Potter (Potter, 1972) was one of the first to define bioethics as "biology combined with diverse humanistic knowledge forging a science that sets a system of medical and environmental priorities for acceptable survival". In this vein, the *Encyclopedia of Bioethics* (1970) defined bioethics as, "the interdisciplinary examination of the moral and ethical dimensions of human conduct in the areas of life sciences and health care. The discipline encompasses the study of medical, legal, scientific, religious, philosophical, moral and ethical issues of life sciences."(Post, 2004).

As discussed in Chapter 2, medical ethicists have developed four general principles or guidelines to provide a framework for discussions and/or resolution of medical ethical dilemmas. They are: 1) *autonomy/respect for persons,* 2)

beneficence, 3) *non-maleficence,* and 4) *justice.* Resolving medical ethics dilemmas often requires balancing conflicting guidelines such as the rights and autonomy of the individual versus the rights of society, the potential benefit versus the risk to the individual, the short-term suffering and pain versus the long term benefits, and the moral versus medical obligations to the patients.

Historically, guidelines in medical ethics were developed in part due to atrocities in ethical conduct of research. Research ethics arose from the ashes of the Holocaust where the Nazi doctors conducted notorious and sadistic medical experiments, characterized by a total lack of voluntary consent and ethical practice as well as a pervasive pseudo-science. These lethal and murderous experiments were intended only to help the German race and German soldiers. In response to these Nazi atrocities, the Nuremberg Code (1948) was drafted by the judges who adjudicated in the Nuremberg Trial of Nazi physicians who were charged with crimes against humanity. The Nuremberg Code outlined some of the fundamental legal guidelines involving voluntary informed consent that subsequently have influenced U.S. regulations governing informed consent.[1]

The next major bioethical document was the National Research Act passed in 1974 in response to the egregious Tuskegee Syphilis Study and the Willowbrook study where mentally retarded children housed at the Willowbrook State School in Staten Island, New York, were intentionally given hepatitis in an attempt to track the development of the viral infection. The United States Public Health Service uncovered that over 400 participants of the Tuskegee Syphilis Study (predominantly African American males) were denied anti-syphilis treatments. The investigation lead to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research whose charge was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects. Furthermore, guidelines were proposed to assure that such human research is conducted in accordance with ethical principles. In 1978, Casper Weinberger, President Gerald Ford's Secretary of Health, Education, and Welfare, drafted the Belmont Report. *This crucial* document outlines the guidelines for protecting human subjects in both clinical and research environments.

Considerable debate has recently emerged, however, regarding whether the principles and guidelines proposed in the Belmont Report adequately addressed the broader ethical issues related to biomedical research in grappling with situations where technology confronts ethics. A number of prominent bioethicists such as Dr. Daniel Callahan, cofounder of The Hastings Center and Gilbert Meilaender, a member of the President's Council on Bioethics, all questioned whether these medical ethical principles that often clashed, could be applied to "real life" bioresearch ethical issues. Even Dr. Thomas Beauchamp,

[1] http://www.ushmm.org/research/doctors/Nuremberg_Code.htm for more information

one of the pioneers in bioethical education, questioned the role of classical ethical theories in resolving modern issues of research bioethics (Beauchamp, 2007).

The Need to Redefine Biomedical Research Ethics

Since the 1970s, new biotechnologies in the areas of molecular biology, genomics, and reproductive biology, have been developed, affecting life-science research. These new technologies have challenged the basic definitions of human life, such as when personhood begins and how we define ourselves as an individual species. Embryonic stem cell research and human cloning are important contemporary examples of evolving biotechnologies that require informed discussions about the scientific implications of this research and the bioethical issues that inevitably arise. Recent biotechnological discoveries, such as genetic manipulations, the development of bio-chips, and creating embryos from three genetic parents necessitate the development of a discipline with rules, strategies, and definitions that address the real and never-before-seen bioethical dilemmas that scientists as well as society must confront. The genetic engineering of plants, for example, may not be a relevant problem for the patient-doctor guidelines of medical ethics, but it raises the issue of changing the "natural environmental order."

The first step in differentiating research bioethics from medical ethics is developing an operational definition of bioethics. Today, a broader definition that may better fit contemporary biotechnological innovation is necessary. Bioethics is defined in this book as a broad field of study that examines the ethical issues emerging from biotechnologies that affect human beings, the animal world, the plant kingdom, and the environment. We coin the term *research bioethics* as **the study of ethical dilemmas arising from the acquisition of scientific knowledge and its impact on life forms and the environment.** This definition helps to establish an ethical approach to the acquisition of scientific knowledge as it positively and negatively influences and interacts with human society and the environment at large.

The new definition of research bioethics distinguishes it fundamentally from medical ethics in one critical area. Research bioethics focuses on scientific discoveries that affect human society, animals, plants, and the environment as a whole. In contrast, medical ethics is more circumscribed, and generally focuses on any condition that involves an individual or volunteers participating in medical experimentation or any condition that creates a provider-patient relationship.

If one accepts this definition of research bioethics, then a reformulation of the basic guidelines for research bioethics is required to deal with the specific and unique ethical concerns relating to science, society, and the environment. Historically, scientists who have attempted to apply bioethical-medical ethical principles (as defined by the Belmont Report) (Beauchamp, 2007) to research

settings have discovered that the principles may not provide a useful framework for addressing many relevant ethical **research** concerns. For example, the first Belmont principle, respect for persons (or autonomy), can have a utilitarian, rather than a moral goal. The Belmont Report incorporates John Stuart Mill's utilitarian views of personal autonomy that, "only fully conscious, rational adults capable of acting autonomously are considered moral agents with moral responsibilities" (Callahan, 1994). However, those incapable of acting autonomously (such as infants, comatose patients, or patients with Alzheimer's disease), were defined under the Belmont bioethical principles as non-moral agents and are thus "non-persons" who lack any rights of self-determination. In addition, there are many situations in medical ethics that focus on how the individual infringes on the general welfare of society. Confidentiality and the individual right to privacy in the diagnosis of HIV infection, for example, may compromise public health needs. These needs include surveying the infected in order to protect the uninfected along with notifying individuals of the possible risk of infection.

The second principle, beneficence, incorporates a Hippocratic understanding of beneficence as doing good for the patient. However, the Belmont Report also included a second definition of beneficence that is utilitarian and involves, "one doing good for society at large" (Callahan, 1994). The Belmont Report further declares "citizens have a strong moral obligation to take part in experimental research for the greater good of society." This contradicts the Hippocratic interpretation of beneficence and violates time-honored international medical ethical guidelines such as the Nuremberg Code and the Helsinki Declaration, which oppose physicians experimenting on volunteer subjects unless the subjects **directly benefit** from the procedure.

The third Belmont principle, justice, is also defined in terms of a "fairness" that allocates the benefits and burdens of scientific research equitably across the different social and economic populations. This principle varies a great deal from the classic Aristotelian definition of justice used in medical ethics that emphasizes the fair and just treatment of every human being. Applying fairness in biomedical research is often difficult to ensure. How are decisions made to allocate research funds for Huntington's disease, which affects fewer than a million people around the world, when millions of people are dying of AIDS or malaria? Heart transplants provide another challenge associated with the principle of justice. In the USA about 3,000 heart transplants are performed at a cost of close to 1 million dollars per year per patient. Would this money (three billion dollars) be better allocated to develop new drugs that could benefit the 500,000 people who develop heart problems each year?

Differentiating research bioethics and medical ethics can also manifest into practical ramifications. First, these two disciplines can target two distinctly different participants. The classical audience for medical ethics has been health care providers, clinical researchers, insurance companies, and health care institutions that require guidelines to make complicated decisions regarding the value of human life and patient care. In contrast, biomedical and life science researchers

both in academia and corporate America need ethical guidelines appropriate and relevant for the testing and application of new developing biotechnologies.

A second ramification of the differentiation between research bioethics and medical ethics relates to education via case studies. Medical ethics case studies are generally obtained from real-life situations. Seeing the patient in the health care facility is essential to resolving and/or managing medical ethical issues. In contrast, real-life situations in bioethics are less opportune when the technology is still under development. Society and government are hesitant to allow research with novel biotechnologies to progress without discussing end results. Consequently, bioethical dilemmas are often hypothetical with regards to patient applications. For example, no accessible research facilities are currently engaged in human reproductive cloning to provide a real situation where bioethicists can assess the health and behavior of a cloned human. Furthermore, new biotechnologies are often introduced in a corporate setting where governmental access is also limited.

The third ramification relates to the different compositional structures of regulatory agencies dealing with medical ethics versus bioethics. Medical ethics committees are typically composed of individuals involved in health care including practicing physicians, nurses, other health care professionals, hospital administrators, medical ethicists, insurance experts, theologians, and lawyers. Medical ethics committees often focus on the influence of managed care with respect to the patient's best interest or deal with issues that may interfere with the daily operations of health care or medical institutions. In contrast, research bioethics committees should also include basic research scientists, physician-scientists, bioethicists, political analysts, environmentalists, and sociologists. An example of this type of committee is the President's Council on Bioethics that focused on human cloning and stem cell research. While the recommendations of the council have been controversial and may never be implemented as originally designed, the Commission was thorough in dissecting the ethical issues and arguments relevant to these technologies.[2] Many Institutional Review Boards (IRBs) established in universities, are expanding their focus to include bioethical issues emerging from new biotechnologies.

The final distinction between medical ethics and research bioethics includes the time frame that is necessary to propose practical ways to resolve the ethical dilemmas. In cases involving patient - health care medical ethics, there is a more immediate need for resolution. The classical case-study whether a neurologically brain dead patient should be removed from a respirator or whether a terminal cancer patient should be denied the option of euthanasia requires an immediate response. In contrast, many bioethical dilemmas related to embryonic stem cell

[2] http://bioethics.georgetown.edu/pcbe/reports/cloningreport/ and http://bioethics.georgetown.edu/pcbe/reports/stemcell/.

research, reproductive cloning, or genetically modified organisms have been debated over the last decade, often without the need for immediate resolution.

Translational Science and Bioethics

Translational science is a relatively new concept (Hostiuc, 2016) that can be divided in two categories, translational medicine and translational research. Translational medicine is to a practical, outcome-oriented research and can be viewed as research on human specimens, whose findings may inform basic science research and lead to a transfer of the results towards clinical therapeutics. It starts with fundamental research (genes, molecular processes, biochemical pathways) and ends at a macro level (social healthcare, access to healthcare, and access to education. Translational research is the application of basic scientific research to non-medical applications. An example of translational science is synthetic biology where scientists have created two new DNA base pairs. In this new system the DNA is now composed of six base pairs. While its application to medicine and health care remains to be defined, it is being applied to enhance the power of DNA-based chip technology in biocomputers.

As discussed below, the bioethical assessment of translational medicine and research can be different especially in establishing the hierarchy of bioethical guidelines. In medicine, one could argue that autonomy may be the most important guideline. In research, on could argue that non-maleficence may be the most important ethical guideline. The new research in synthetic biology that may allow scientists to rewrite the genetic code can elicit fear that tampering with the Holy Grail, DNA, may lead to disastrous consequences. The application of gene drive technology to eradicate Zika born mosquitos, discussed in Chapter 9, may have severe ecological consequences that we will not detect for decades.

Four Additional Principles for Research Bioethics

The following four additional research bioethical guidelines are proposed to regulate the pursuit of scientific inquiry: 1) respecting the value of human life and balancing the needs of the society versus the needs of the individual; 2) Respect for the bio-environment; 3) using scientific research to alleviate specific bioethical concerns; and 4) the “yuck factor” where a technology is deemed unethical for intuitive, rather than logical, reasons.

Human Dignity: At times, respecting human dignity or the value of human life and balancing the needs of society versus the needs of the individual has been invoked in contemporary bioethics regarding issues of human genetic enhancement as well as the generation of human-nonhuman chimeras (de Melo-Martin, 2008; Loike and Tendler, 2008). Regarding this guideline there are two controversial parameters that must be delineated. The first is to define human dignity and the second is to

identify cases when it is appropriate to apply this principle.

Human dignity can be viewed either within a secular or religious perspective. Immanuel Kant proposed a secular definition that human dignity is associated with the capacity to think for oneself and direct one's actions. Using a Kantian moral framework of human dignity, human beings possess an unconditional and incomparable worth that is independent of metaphysical or religious precepts (Macklin, 2003; Karpowicz et al., 2005). According to Kant, human beings have dignity because of their reasoning faculties, which give them the freedom and ability to distinguish moral from immoral actions. Using this Kantian definition; however, some scholars have argued that not all human beings have dignity. The Kantian principle suggests that patients in a permanent vegetative state, for example, who have irreversibly lost their autonomy may no longer have dignity (Loike and Tendler, 2011).

In contrast to this secular definition of human dignity, a theologically-based definition formulates or characterizes human dignity as an inviolable right invested by God in all human beings including fetuses, comatose patients, and patients in a permanent vegetative state (Kass, 2006; Loike and Tendler, 2011). In its simplest religious formulation, human dignity can be equated with the sanctity or infinite worth of human life and assumes that there is something uniquely valuable about human life. From a religious Judeo-Christian view, human dignity emanates from the first chapter of Genesis that records how human beings were uniquely fashioned and divinely created (Soloveitchik, 1983). Several Biblical scholars comment that the Bible describes that God created human beings using two different processes (Soloveitchik, 1983). The first process was biological/genetic as indicated by the fact that human beings were created on the same day as other animals. The second process was metaphysical as God infused into human beings a spiritual entity that differentiates human beings from all other creatures. This metaphysical, and almost divine quality of human beings confers a sanctity that exists within each human being from the beginning of life as a zygote until natural death.

Irrespective of the origins of respecting human dignity, there are moral virtues, such as courage, compassion, and altruism that people often consider as being good. Without implement such moral virtues within a cooperative platform, a society cannot survive.

If one accepts the principle and outcomes of human dignity, then it is appropriate to examine the role human dignity may play in bioethics. On the one hand, bioethicists, such as Ruth Macklin, point out that respecting human dignity is a vague restatement of other bioethical guidelines, beneficence or autonomy, and brings no significant value or greater understanding to bioethical dilemmas (Macklin, 2003). Ruth Macklin states,

> "[Human] dignity is a useless concept…A close inspection of leading examples shows that appeals to dignity are either vague restatements of

> other, more precise, notions or mere slogans that add nothing to an understanding of the topic."

In addition, Dr. Macklin presents other philosophical arguments that weaken the validity of the principle of respecting human dignity (Macklin, 2003).

Other scholars and bioethicists (Kass, 2006; Loike and Tendler, 2011) argue from a secular and religious perspective the paramount importance of applying the principle of respecting human dignity in bioethical matters. Francis Fukuyama (Fukuyama, 2002) blends a secular approach of human dignity with the distinct nature of the human species.

> "[Fukuyama] He defines human nature as "species-typical traits" of human beings (such as language and cognition, which provide the grounds for feelings such as pride, anger, shame, and sympathy), arising from genetic factors. …. these species-specific traits of humans differentiate us from all other nonhuman species, and this differentiation constitutes the basis of human dignity. The reduction of shared traits among humans will result, in the degradation of human dignity (Bhuiyan, 2009)."

Under what situations should respect for human dignity be applied? Research programs, for example, designed to examine whether cows can be genetically altered to develop human uteri and serve as surrogate incubators for human embryos should not receive priority over programs engaged in examining artificial incubators for premature babies. Ethicists will argue that gestating human embryos in cows raise the issue of respecting human dignity and should not receive government funding or support. In another situation publicized in April 2008, British researchers claim to have created human embryos using human cells and the egg cells of cows. The researches stated that they had hollowed out egg cells obtained from cattle and inserted human DNA into the hollowed cells to create a growing embryo for the purposes of later isolation of human embryonic stem cells.[3] A final example involves transplanting precursor human astrocytes into mouse embryos to reconstitute human astrocytes into the brains of mice. Such human-chimeras have been reported to be more intelligent than normal mice raising the issue whether it is ethical to create mice that express genes that are associated with human intelligence?

There is also an intimate connection between respecting human dignity and infringing individual rights. For example, obtaining the genetic fingerprint of every individual in a population for the purpose of crime control or prevention of terrorist attacks infringes on the individual's right to privacy and confidentiality; however, it may be a practical method to reduce or solve crimes. Genetic profiles and fingerprints of potential criminals or terrorists have been shown to help manage crime control and potential terrorist attacks and may serve to improve the safety of society in general (Barber and Foran, 2006; Berger, 2006). Another example involves the genetic testing of newborns or adults. Currently, New York State

[3] http://www.sciam.com/article.cfm?id=scientists-make-human-cow

screens every newborn for cystic fibrosis and several other genetic disorders. This appears to reduce the number of children born with these diseases. However, additional genetic screening for certain types of cancers or neurological diseases is more controversial, especially when these tests may not medically benefit the individual research subject. Sometimes, such results could harm research subjects who are not properly educated or prepared to handle the psychological implications of the results of the screening. Should the results of genetic testing done within the context of a research study be shared with the volunteer subjects participating in the study? A great deal of time and effort would be required to properly educate the volunteers about the nature of these genetic exploration studies. Identifying the gene for Familial dysautonomia (Anderson et al., 2001) was clearly accelerated by using a DNA database established exclusively to screen for Tay Sachs disease. Those individuals who originally provided samples for the Tay Sachs database were never informed that their DNA samples would be used for other research purposes. Were the scientists justified in using this database? What protective measures of confidentiality or informed consent were implemented for this study? Is it justified to screen for new disease markers utilizing genetic data banks that were obtained from other studies without obtaining permission (informed consent) from the donors? The underlying justification for such screening is the belief that the more genetic information obtained regarding a disease process, the greater that possibility is that scientists will be able to design more effective future therapies. The countervailing opinion is that individuals may choose not to engage in certain genetic testing for a variety of personal motivations including prescribing to the idea that their life unfolds in a predestined manner. Moving forward, it is clear that it is important to obtain permission from donors to extend the use of their genetic material in other genetic research studies that examine any disease markers, not only the ones that they signed an informed consent for.

A final example relates to the ongoing debate over how to handle the publication of scientific research findings that could threaten national security (see Chapter 14). 'Publish or perish' has always been a guiding characteristic of the academic life of investigators in the sciences. However, since the Anthrax mail attacks of 2001, there have been debates regarding which results of biological research should be published. Similarly, there is concern that research in synthetic biology in which scientists are attempting to build all-new life forms from artificial DNA may pave the way to create new powerful bioterrorist weapons. There is a fear that publishing the underlying methods behind these types of scientific projects could fall into the hands of terrorists, possibly jeopardizing national security.

Policies should be established enabling the scientists to publish research without revealing details that could endanger the safety of the nation. Who should oversee exactly what information is published: governmental agencies, authors, research institutions, journals, or some combination? Policy guidelines should establish strategies for preventing the misuse of biotechnology while preserving scientific inquiry and the dissemination of appropriate scientific data.

In summary, this first additional guideline assumes that all human beings have infinite or immeasurable value and that saving lives is a significant long-term objective of current scientific research activity. Thus, a primary objective of research must be to utilize and develop new life-science technologies to improve health care, disease treatment, and disease prevention. In fact, the recent roadmap proposed by the National Institutes of Health[4] reflects these objectives. Biological research with unclear societal applications should not receive equal priority as research with clear societal applications.

Respect for the bio-environment and biological order: Respecting the environment is a critical concern for bioethics, but is not typically relevant in discussions of medical ethics. The use of biotechnology to improve the color, taste, nutrition, and production of food began in ancient times, when farmers first cross-bred different plant strains and realized that they could produce varieties with the optimal characteristics of both of the original plants. Today about 2-4% of farmlands are planted with genetically modified (GM) crops and most of these GM crops are planted on US soil.[5] In addition, GM plants can serve as a source for manufacturing recombinant proteins to be used for therapeutic purposes. Plant-based production of therapeutic proteins is predicted to cost 4-5 times less than production by classical cell culture techniques. However, the general concern over any genetically modified plant or organism is that transgenes will spread through the environment and ultimately affect non-targeted organisms. In addition, there is a fear that introducing genetically modified organisms could disturb the ecological balance of other plants and animals including humans. Scientists have only begun broadly examining the effects of genetically modified plants on the environment as recently as the 1990s. Finally, as of 2016, there is still considerable debate whether GM plants actually improve yield and reduce the use of pesticides.[6]

This guideline (respect for the bio-environment) would ensure that research into GMOs incorporates safety measures in addition to studying the possibilities of how a genetically modified organism could affect factors of the bio-environment such as the consumer, other plant life or insect habitats. In 2003 and 2008, The Food and Drug Administration (FDA) concluded that meat from **cloned** animals is as safe as conventionally bred animals. Clones are genetic copies of donor animals; unlike genetically modified animals, their DNA is not changed, but used to introduce desirable traits into herds. In contrast, Australia's current policy is that cloning is restricted to breeding stock cattle and sheep that are not entering the

[4] http://bioethics.georgetown.edu/pcbe/bookshelf/

[5] http://www.newscientist.com/channel/life/gm-food; http://www.ers.usda.gov/publications/err-economic-research-report/err162.aspx

[6] http://www.nytimes.com/topic/subject/genetically-modified-food and https://www.geneticliteracyproject.org/2016/10/31/danny-hakims-new-york-times-gmo-expose-misleads/

food supply. It is unclear why such a statement was issued without the appropriate scientific studies justifying such a conclusion. Just as new drug investigations require safety controls, research that involves GMOs should include appropriate safety tests. Such safety controls should be instituted regardless whether the GMO is developed by industry or academic institutions. The fact that most European countries are considering, or have, a ban of GMOs highlights the difficulty in scientifically assessing their environmental impact.

The development of genetically modified organisms should include a comprehensive survey of potential environmental impacts. One could envision that routine test phases could be implemented, similar to the test phases implemented with the development of new therapies. Phase I development would examine the effects of GMOs within a test field that examines other plants, whereas phase II development would include the effects of GMOs on larger farms and fields and a study of their impact on insects, animals, humans and other plants.

Another generally adhered component of this guideline is to provide health care and ethical treatment of animals used for scientific research. This issue is becoming more difficult, owing to the fact that as we learn more about animal behavior, science recognizes that many animals exhibit social skills and characteristics that resemble human behavior. As the complexities of animal behavior are revealed, distinctions that differentiate human beings from animals become blurred. In fact, several countries, such as Argentina, confer “personhood” status to certain non-human primates.

Does a "legal person" need to be human, or even alive? American courts routinely extend personhood rights to nonhumans: to corporations, municipalities, and even ships. Therefore, there is a greater need today for scientists to: a) evaluate whether research can only be accomplished using animal models, such as non-human primates, rather than cell models, and b) consider the degree of animal suffering and sacrifice within each experimental design.

Respecting biological order also falls within the second guideline and is rooted in the diverse religious and cultural backgrounds of human beings. A variety of religious groups and cultures believe that while the pursuit of scientific knowledge is valuable, there may be areas where humans should not “play God” by engaging in activities that do not reflect the natural order of life. Examples of inappropriate or low priority scientific investigations may include: research into male pregnancy (e.g., uterine transplants), the creation of two-headed animals, or creating chimeras where human embryonic stem cells are transplanted into mice or chimps to reconstitute part of a human brain in these animals (see Chapter 8), and using germ line gene therapy when research into somatic gene therapy has not been fully developed.

Many cultures believe that some higher power is responsible for creation of the world and that there is a valid reason behind biological order. Other cultures believe that natural evolution has ultimately resulted in a functional biological order that operates efficiently in this world. Therefore, technologies that alter this

biological order are viewed with great skepticism; the fear is that these technologies will destroy humanity or the environment. For example, there is currently a heated debate over whether it is ethical for scientists to create artificial organisms using commercially available DNA. A group led by J. Craig Venter has reportedly created an artificial virus with the identical genetic code of a simple virus already known to infect and kill bacterial cells.[7] The researchers hope that this type of technology will help create genetically-based solutions for treating diseases or dealing with environmental challenges.

There are also significant concerns that scientists do not know enough about the effects of synthetic organisms on biodiversity, the environment, or society. Moreover, there is a fear that this technology could be used to create bioterrorist organisms that are even more destructive than anthrax or smallpox. Developing such technologies should take into consideration that sometimes the unknown may lead to undesired paths.

A major question facing scientists related to this guideline is whether and what types of limitations should there be to scientific research. For example, transplanting human embryonic stem cells containing specific genetic predispositions for disease into mouse embryos creates a mouse model for human diseases. However, examining whether transplanting human brain cells into mice to study human behavior or mental capacity raises issues of animal welfare concerns and whether such a mouse would have human-like consciousness. Clearly, there are many factors that must be considered. Is creating such human-mouse chimeras the only way to examine neuro-biological questions (see Chapter 8)? Does this type of research show disrespect for biological order?

Use of scientific research to alleviate bioethical concerns. The third guideline reflects a current trend in research bioethics. There are times when bioethical concerns appear to be irresolvable. The contentious debate over when a pre-embryo or embryo attains human status or personhood has been ongoing for many decades, restraining the progression of embryonic stem cell research, which is influenced by how one views the beginning of human life (see Chapter 7). The scientific community has responded to this apparently irresolvable issue by trying to utilize creative science to circumvent or defuse the bioethical concerns. For example, research on de-differentiating an adult cell to a pluripotent stem cell or obtaining embryonic stem cells from a morula without destroying the pre-implanted embryo is not as ethically troubling as conventional therapeutic cloning using embryonic stem cells.

The Asilomar Conferences of 1973 and 1974 highlight a unique situation in which life science research was restricted. The first conference was organized in response to the research program of Dr. Paul Berg to determine if the simian virus 40 (SV40) could be used to transfer a foreign gene into a common bacteria found in the human intestine. In 1971, Dr. Robert Pollack contacted Dr. Berg to discuss the safety issues related to Dr. Berg's proposal. One safety issue was the fear that

[7] http://www.economist.com/science/displayStory.cfm?story_id=2224008).

transfecting a common bacteria with SV40 might potentially expose millions of people to this virus, resulting in an increase in the incidence of cancer. Thus, the overall bioethical issue discussed at the first conference was determining the risks of joining DNA from animal viruses with DNA from bacteria. In 1974, a second conference was called when it became possible to safely splice and recombine different DNAs and join DNA from animal viruses with DNA from bacteria.

The Asilomar Conferences proposed a set of scientific guidelines for recombinant DNA research that incorporated safeguards into this technology. The most important guideline proposed was to establish biological and physical safeguards to restrict the viability of these new recombinant organisms within a laboratory environment. The biological barriers mandated the use of bacterial hosts that could not survive outside the laboratory and that physical barriers such as gloves, hoods and filters were required to ensure that recombinant organisms never left the laboratory. The third safety net prohibited the use of highly pathogenic organisms until more knowledge was gained. The Asilomar Conferences challenged the autonomy of biological science and showed that scientists and the public must share the responsibility of preventing the negative effects of scientific research on society in general. Moreover, the proposed guidelines worked as so far, no pathological organism has ever been released from such research. In December of 2015, a summit convened experts from around the world to discuss the scientific, ethical, and governance issues associated with human gene-editing research.[8] Unlike the Asilomar conferences, the there was more cautionary statements than guidelines issued by the organizers of the summit.

In some situations, there is a lack of consensus regarding how research should be regulated. Research involving the genetic alterations of pathogens may be important in creating new vaccines but also may offer new approaches to create bioterror weapons (see chapter 14). Other examples include the creation of the first synthetic life form made entirely with pieces of lab-assembled DNA (Moore, 2012), and the creation of a living organism that can grow and reproduce using DNA base pairs that aren't found in nature (Malyshev et al., 2014). Scientists inserted an unnatural base pair, marked X-Y, into the sequence of a plasmid of E. coli. The resulting bacterium is the first organism able to stably maintain DNA comprised of 3 types of base pairs. This scientific accomplishment raises the possibility that scientists might be able to retool nature to create new forms of proteins for therapeutic and other uses. The move from creating new proteins to creating new life seems only a small step away from a long-standing dream, or nightmare, of creating artificial life.

The "yuck factor" in bioethics. Originally termed by Dr. Arthur Caplan, the "yuck factor" was popularized by Dr. Leon Kass in 1997 when he described his position against cloning human beings. Dr. Kass defined the bioethical "yuck factor" as being an unethical technology based on an intuitive negative response rather than

[8] http://www.nationalacademies.org/gene-editing/Gene-Edit-Summit/index.htm

on concrete ethical or moral values. The yuck factor has been applied to other biotechnologies as well, such as generating mice that produce human sperm or eggs, creating cows with a human uterus, or using stem cell technology to produce consumable human hamburgers (See Chapters 8 and 15).

History can serve as a master teacher about research bioethics.

The development of in vitro fertilization (IVF) and embryonic stem cell research raise similar bioethical issues regarding the initiation of human life (see Chapter 8). As IVF became a more accepted treatment for infertile couples, these ethical concerns declined in importance for the American public. One might extrapolate this observation and predict that if embryonic stem cell research or gene editing technologies develop into an accepted therapy, the bioethical issues of whether a pre-implanted embryo is considered a human being or "playing God with our genetic code" will be less of a concern to society in general.

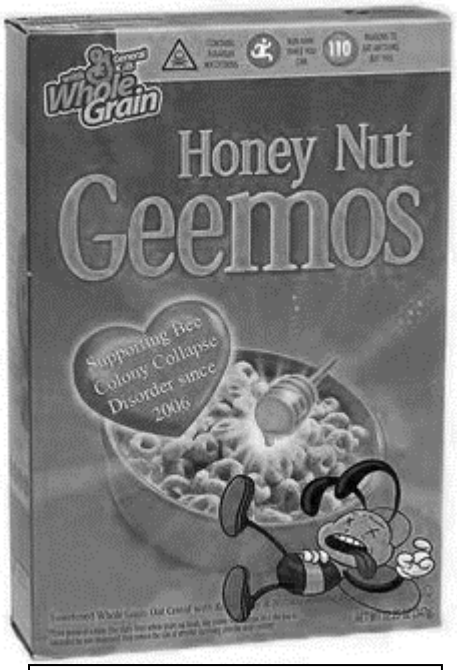
Unfortunately, historical lessons cannot always provide insight into the resolution of bioethical issues. The court of law may not be an effective forum for resolving bioethical issues. Consider the 1973 Supreme Court's *Roe v. Wade* decision regarding a woman's right to abortion. In the majority opinion written by Justice Blackmun, the court granted the right to early term abortions by balancing the interests of the fetus and the mother, during the early term of a pregnancy the woman's right to an abortion outweighed the embryo's/fetus' right to continued existence. Considering this decision, an interpretation of the Court's ruling in *Roe v. Wade* would indicate there should be no law banning or restricting embryonic stem cell research. Similarly, various interpreters of the U.S. Constitution believe that the ability to reproduce is a fundamental human right (See Griswold v. Connecticut, Planned Parenthood v. Casey). Within this context, infertile couples should be allowed to engage in reproductive cloning as long as the medical risks are minimal. Nonetheless, reproductive cloning is not as yet considered acceptable by either the research community or society.

Conclusions

The acquisition of scientific knowledge is a fundamental characteristic of human society and can generate a variety of ethical issues that differ in principle from medical ethics. Thus, the call to conceptually differentiate these two disciplines is the focus of this chapter. The reformulated definition for research bioethics serves as the fulcrum for developing the four principles of bioethics described here. As in any moral and ethical system, there may be clashes between the four principles proposed for research bioethics. Nonetheless, these guidelines are designed to ensure the ethical pursuit of scientific inquiry and to establish a structural framework in research bioethics in order to develop appropriate applications of scientific technologies to society.

The aforementioned guidelines are valid only if they enable ethicists and scientists to respond to bioethical issues related to new biotechnologies in a more effective way than prior medical ethics or bioethical conceptualizations. In this period of economic uncertainty, research bioethical guidelines establish priorities regarding which research activities should be pursued by evaluating how the research will benefit the public or the environment.

In the final analysis, research bioethics is inclusive enough to incorporate genetics ethics, environmental ethics, and neuroethics, among other fields. Bioethics in general would then be the overall subject covering both research bioethics and medical ethics. Despite the differences in philosophical focus between the two, there is a common thread underscoring both life-science research and clinical research that can best be summarized by a famous Hippocratic aphorism: "Life is short, the art long, experience fleeting, experiment perilous, and judgment uncertain."[9]



Obtained from NIH.GOV

[9] Hippocrates. Aphorisms. http://classics.mit.edu/Hippocrates/aphorisms.html

References

Anderson, S. L., et al., "Familial dysautonomia is caused by mutations of the IKAP gene." Am J Hum Genet, 68(3):753-758, 2001.

Barber, A. L. and Foran D. R., "The utility of whole genome amplification for typing compromised forensic samples." J Forensic Sci, 51(6):1344-1349, 2006.

Beauchamp, T. L. The 'four principles' approach to health care ethics." Principles of health care ethics, 3-10, 2007.

Berger, M. A., "The impact of DNA exonerations on the criminal justice system." J Law Med Ethics, 34(2):320-327, 2006.

Bhuiyan, M. "Imagining the Consequences of Human Biotechnology." Journal of Health Politics, Policy and Law 34: 829-839, 2009.

Callahan, D., "Bioethics: private choice and common good.", Hastings Center Report, 24: 28-31, 1994.

de Melo-Martin, I. "Chimeras and human dignity." Kennedy Inst Ethics J 18(4): 331-346, 2008.

Fukuyama, F. (Our posthuman future : consequences of the biotechnology revolution. New York, Farrar, Straus and Giroux, 2002.

Karpowicz, P., et al. "Developing human-nonhuman chimeras in human stem cell research: ethical issues and boundaries." Kennedy Inst Ethics J 15(2): 107-134, 2005.

Kass, L. R., Life, Liberty, and the Defense of Dignity: The Challenge for Bioethics. San Francisco, Encounter Books, 2006.

Loike, J.D., and Tendler, M.D. Reconstituting a Human Brain in Animals: a Jewish Perspective on Human Sanctity and Chimera Research. Kennedy Institute of Ethics Journal, 18:347-367, 2008.

Loike, J. D. and Tendler, M. D. "Halachic Bioethics Guidelines." Journal of Halacha in Contemporary Society 16: 92-118, 2011.

Macklin, R. "Dignity is a useless concept." BMJ 327(7429): 1419-1420, 2003.

Malyshev, D. A., et al. "A semi-synthetic organism with an expanded genetic alphabet." Nature 509: 385-388, 2014.

Moore, W., "Application of Modern Moral Theories in Medical Ethics." in Proceedings of the XXII World Congress of Philosophy, 3:69-74, 2012.

Post, S., Encyclopedia of Bioethics. New York, Macmillan Press, 2004.

Potter, V. R., "Bioethics for whom?" Ann N Y Acad Sci, 196(4):200-205, 1972.

Soloveitchik, J. B. Halakhic man. Philadelphia, Jewish Publication Society of America. 1983.