From the Writer

For our final assignment, we were given a lot of freedom to choose our own topics. We were asked to analyze a debate over a controversial topic in medicine and provide a commentary on the debate and how it reflects our values as a society. In my initial search for topics, I ran into the topic of chimeras, which immediately sparked my interest. From my background research, it became clear that chimera research had tremendous potential, and that the benefits from studying chimeras would be readily applicable to current problems.

Yet, although I see myself as a very open-minded person, I had an inexplicable disdain of this idea despite knowing the benefits chimeras could bring. Part of what drove me to dig deeper into the subject was to find out what made me feel such an admittedly irrational dislike of such a promising field. In a way, that made the research more personal and helped motivate me throughout my research. Eventually, I started looking into philosophical arguments about ethics and morals and a lot of concepts that I can not really grasp, which was challenging. Eventually, I had to stick to a few simple points that I mostly understood, and that ultimately helped focus my paper and make it easier to read.

— Jielin Yu

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Prize Essay Winner

Rethinking Humanity: the Chimera Debate

For most of history, part-human part-animal beings have always resided in the realm of fiction and folklore. Recently, however, advances in genetic engineering and microsurgery have brought these creatures into existence. Scientists now have created human-nonhuman chimeras—organisms that have both human cells and animals cells in their bodies. These chimeric animals hold enormous potential for the field of medicine as well as basic research into human physiology. Their utility in science lies in their unique biological integration of both human and animal cells, which can give rise to human tissues and even organs within the body of an animal. Useful applications of this technology range from the study of disease, to more accurate testing of drugs and medication, to the possibility of transplants using chimeric organs. Despite its potential, however, chimera research faces significant opposition from a wide spectrum of the population. While scientific and public health concerns exist, the majority of the opposition focus on the violation of current ethical and moral codes that arises from creating and using chimeras. At closer examination, however, all of these objections stem from an unwillingness to surrender society's rigid view of human identity and uniqueness. The debate over chimera research represents the changing perception of humanity and our place in the world.

Chimeras differ from the general perception of the genetically modified organism. Technically, a chimera consists of two genomes in a single body, producing two types of cells that work in conjunction to create a viable organism. It develops from two fertilized eggs that come into contact and combine to form a single embryo, instead of staying separate

and developing into fraternal twins. Chimerism within a species occurs naturally in nearly all animals, including humans. Interspecific chimeras, however, rarely exist in nature due to the unlikelihood of specific conditions required. In 1989, scientists at the University of California, Davis breached this barrier and created the first artificial chimera, a sheep-goat hybrid dubbed the "geep."

Such research into chimeras elicited little public attention and outcry until August 2003, when Hui Zhen Sheng at the Shanghai Second Medical University created the first human-nonhuman chimera. Sheng and his team removed the genetic material from some of the cells in a rabbit embryo and inserted human DNA, creating a human-rabbit chimera.[1]

Sheng's research inspired several subsequent studies that demonstrate the enormous potential of chimeras. By creating animals with human cells, scientists can monitor and track cell differentiation, tissue development, and organ formation without using human infants as subjects. Since chimeras develop from a class of stem cells called nuclear transplant stem cells (ntES), they can be used to study the "molecular mechanisms governing fundamental biological phenomena, such as pluripotency, reprogramming, differentiation, and imprinting."[2] A French team led by Nicole le Douarin at the College de France's Institut d'Embryologie has replaced cells in the vertebrae of a developing cow fetus with human pluripotent stem cells to observe their differentiation and study the development of the spinal cord. This study has already "shed light on the formation of the spinal cord and the integration of the central and peripheral nervous systems in the early stages of development."[3] These results can suggest new procedures in regenerative medicine for patients with spinal cord injuries. Scientists have proposed experiments like le Douarin's to study the many mysteries of human development. With the current state of technology, research using human-nonhuman chimeras provides the most accurate method of observation aside from directly studying human embryos themselves.

Scientists can also use chimeras to study the progress and mechanisms of diseases in live tissues and organs. Chimeras with human tissues offer a fairly accurate substitute for a real human body. A Stanford team is working closely with human-cow chimeras to study how HIV attacks the human immune system.[4] A chimeric pig with mostly human T-cells

was used to model a human immune system, and provided insight into the mechanisms of the virus as well as ways to combat it. Scientists at the University of California, San Diego have used chimeric goats with 40% human livers to study the progress of hepatitis B and hepatitis C.[5] Aideen O'Doherty and a team of scientists in the United Kingdom have used human-mouse chimeras to study the onset of Down syndrome by tracking the differentiation and development of certain human cells. These mice "exhibit behaviors, organ size, and neuronal numbers that mimic the human disease."[6] For many diseases exclusive to humans, such as Down syndrome, using a human-animal chimera may be the only legitimate method of investigation.

In addition to helping the study of disease, chimeras also offer a safer and more ethical method of testing for new drugs. FDA regulations require new drugs to undergo extensive pre-clinical studies to examine their absorption, distribution, metabolism, and toxicity before clinical tests on human subjects. Current procedures rely mostly on animal testing, which at best gives scientists an estimation of the drug's effect on a human. Testing on animals such as the common lab mouse provides inaccurate results due to the large differences in physiology and biochemistry. Greater accuracy requires testing on animals similar to humans, such as primates, which raises ethical and financial challenges. Human-animal chimeras provide a loophole through this dilemma by creating a lower animal that has human cells in the organs and system targeted by the drug. This method of testing not only reduces the risk to clinical trial subjects, but also helps make new medications available to patients sooner by speeding up the testing procedure.

Another application of chimeras lies in the field of xenotransplantation, or transplantation using animal organs. The world currently faces a shortage of organs for patients who need transplants. Many die while waiting, while many more venture abroad to seek alternative sources of organs in the less developed countries. The extensive use of chimeras can potentially remedy the situation. Theoretically, cells or pure genetic material can be inserted into an animal embryo or fetus to create a human-animal chimera that has organs made of the patient's cells. These organs can then be transplanted to the patient without risk of rejection or autoimmune complications. Current research focuses heavily on pigs and sheep due

to similarities in the size of organs and has yielded encouraging results. Jeffrey Platt at the Mayo Clinic Transplantation Biology Program has produced pigs that produce human hemoglobin and have lungs that can pump human blood, which is a step towards the possibility of complete lung transplants.[7] Esmail Zanjani at the University of Nevada has created a fetal sheep with organs that were 15% human, and provoked no immune response from the human immune system.[8] These have led to further experiments to enhance the feasibility of xenotransplantation through chimeras. If successful, this procedure can provide a safe and cost-effective solution to one of the most debilitating shortcomings of the medical system.

Despite its promises, chimera research poses scientific, religious, and ethical problems. The scientific concerns mostly involve the public health consequences of the spreading of disease between species. Many of the deadliest diseases, such as AIDS, have only recently spread from animals to humans. The recent scares of avian and swine influenzas have demonstrated that diseases usually spread across species through constant, close contact. In this regard, a chimera provides the perfect vessel for diseases to overcome the species barrier, because cells from two different species are integrated in the same body. Cases of porcine virus infecting human cells in human-pig chimeras have already been observed.[9] The possibility of the interspecific transmission of disease constitutes a legitimate concern. Similar threats, however, exist for nearly all topics of research involving infectious biological agents. The set of safety procedures developed for them can be applied with equal effectiveness to experiments involving chimeras. To further mitigate the threat to public health, the Centers for Disease Control and Prevention has pushed for a rule to require potential human-nonhuman chimeras to be handled in Biosafety Level 4 facilities, the highest security level reserved for biological agents such as the smallpox virus and the 1918 Spanish influenza virus, both diseases with proven deadliness.[10] Thus, from the public health perspective, the possibility of spreading disease across species barriers via chimeras calls for heightened caution and strict regulations, rather than an end to this area of science.

Chimera research also faces staunch opposition from many religious groups. Many Hindus disdain chimeric research involving cows, the sacred animals that are to be treated with the same respect "as one's

mother." For the opposite reason, chimeric research involving many lower animals, especially pigs, disagrees with the beliefs of Judaism, Islam, and sects of Christianity like the Seventh-day Adventists. Pigs are deemed unclean, and the eating of pork is forbidden. Creating a part-pig, part-human creature, therefore, is obviously sacrilegious. A common Christian objection arises from the idea that "your body is a temple of the Holy Spirit within you, whom you have from God. You are not your own"(1 Corinthians 6:19).[11] In 2005, the Pontifical Council for Health stated the Catholic Church's stance on the subject, saying that human genes "embody the characteristic uniqueness of the person, which medicine is bound to protect," an opinion echoed by the council of the bishops of England and Wales in 2007.[12]

Besides the religious opposition, ethical challenges also exist. One argument asserts that the artificial creation of chimeras constitutes an unnatural breach of the species barrier. The act transgresses the laws of nature and produces an organism "against its natural evolutionary will," according to Dr. Bernard Dixon, a HealthWatch Award recipient.[13] He argues that creating a human-animal chimera would be akin to creating an evolutionary intermediate between humans and animals that never existed. Many oppose chimeric research based on this idea of backwards evolution and breaching the evolution lineage.

Another argument focuses on the moral confusion caused by the creation of human-nonhuman chimeras. Currently, society's moral and ethical framework calls for a distinct separation between humans and animals. A part-human, part-animal organism, therefore, creates a significant moral challenge, in that "the moral status of nonhuman animals, unlike that of human beings, invariably depends in part on features other than species membership, such as the intention with which the animal came into being. With human beings the intention with which one is created is irrelevant to one's moral status."[14] As a society, our moral obligations towards animals of the same species are contingent on our purpose for breeding them, whether it is for food, labor, research, or companionship. Humans are not, however, created with a purpose in the same sense as animals are, and thus a human being's purpose does not factor at all in his or her moral standings. Human-nonhuman chimeras sit astride this clear dichotomy in the basis of moral status: they are created for a clear purpose,

and they are also partially human. This "dual-citizenship" presents a crippling problem to a moral code that has no experience in dealing with such a case. While few believe that the possession of human cells alone warrants human species membership and consideration, many believe that certain chimeras share enough in common with humans to deserve human treatment. This approach, however, still involves a separation between humans and nonhumans. With our current understanding of human consciousness and identity, however, society can only draw an arbitrary line that determines the fate of possibly human organisms.

Some bioethicists also argue that even if a chimera receives human treatment and consideration, being a chimera still jeopardizes its personhood. Personhood deals with the concept that our cognitive ability grants us a certain level of self-consciousness and autonomy. The problem arises when chimeric animals may have enough cognitive ability to be granted partial personhood. Experiments conducted by Irwin Weissman at Stanford University have produced mice with nearly all human neurons in their brains.[15] While most scientists agree that the small size of the mouse brain limits mental capabilities, the experiment does raise the issue of whether their cognitive abilities make them somewhat human. Bioethicist Ralph Buchsbaum asserts that the possibility of creating a human-like sapience trapped within an animal's body constitutes a violation of human rights, and makes research with chimeras unethical.

An argument similar to personhood deals with the idea of human dignity, a term often mentioned in debates against practices such as cloning, torture, and abortion. Despite its common usage, the concept is surprisingly vague. The term suggests an innate right to respect an ethical treatment that is exclusive to humans and different from animal dignity. Indeed, the Second World Conference on Bioethics, held 2002 in Spain, stated that "full dignity is an attribute of humankind, and that its recognition is a fundamental right of each and every individual which must be respected and protected."[16] The conference, however, left the source of human dignity, whether it is biological, mental, or divine, unclear. A human-animal chimera can potentially have a high enough biological or mental resemblance to humans to have full dignity. There also exists the horrifying prospect that a human can have chimeric parents. An experiment in Brazil, conducted by Irina Kerkis, produced chimeric mice with

human gametes.[17] She had hoped to discover a treatment for infertility in men. Her experiment, however, opens the possibility of a human having mice parents, for if male and female chimeric mice mated, the zygote produced would be entirely human. Possibilities like this cause many to consider any type of chimeric research an affront to human dignity.

These problems all arise from the distinct separation between animals and humans in our current system of ethics. A few fundamental, and outdated, ideas underlie its inability to cope with this promising field of research. The first flaw regarding bioethics comes from an understandable perception that species boundaries are rigidly defined and unchanging, especially with regards to higher primates and human beings. The arguments based on the unnaturalness of breaching species barriers all stem from this idea. In reality, the definition of a species is rather arbitrary in itself. The usual list of criteria includes physiological differences, reproductive incompatibility, and genomic differences. Yet, nature provides several examples that defy these standards. A 2006 study by Dr. David Reich suggests that the earliest *Homo habilis*, our direct ancestors, mated frequently with other apes for over two hundred thousand years before our lineages diverged.[18] Thus, the unnaturalness argument against chimeric research is a manifestation of the desire to maintain the current taxonomy and order of life.

The second flaw lies in our current dichotomy of ethics towards humans and animals, a relic of the "Great Chain of Being" theory. For animals, ethical consideration increases linearly with cognitive abilities and mental functions—apes receive better treatment than pigs, who receive better treatment than lab mice. The trend ends abruptly with humans, where all members of the species receive the same ethical status. Thus, a severely handicapped human being with inferior mental capabilities nonetheless receives better treatment than a smarter chimpanzee. This privileged status leads to our exclusion from the mental capabilities and ethics relationship, which in turn causes conflicts between our personal morals and the ethics system of our society. The conflict is similar to that of a lawyer who is ethically bound to defend his client to the best of his ability, even if it contradicts his moral sense of justice. Morally, we have an obligation to give equal, if not better, treatment to animals with equal capabilities and capacity to suffer as severely mentally handicapped people, yet our

code of ethics orders us to do otherwise. Chimeras, being part-human and part-animal, force society to think critically of current bioethics and finally bring them into alignment with our morality. This restructuring inevitably comes at the cost of losing our coveted position at the top of all life. However, to ban chimera research and delay the progress of medicine merely to defend our pedestal seems utterly unjustifiable.

Yet, despite the benefits, most nations have started legal movements to outlaw the creation of human-nonhuman chimera. In the United States, Senators Brownback and Landrieu have introduced the Human-Animal Hybrid Prohibition Act of 2009, which makes chimera research bureaucratically and financially challenging. Today, the United Kingdom stands as the only nation to have legalized human-animal chimeras for medical research, a decision that has drawn harsh criticisms and cries of alarm from Germany and the rest of the European Union.[19] The unpopularity of chimera research is understandable, as is the general feeling of revulsion and fear towards such creatures. To many, chimeras present a threat to our biological uniqueness in the world. In an age when astronomers and cosmologists continue to discover how small and inconsequential we really are, biology stands as the last bastion in defense of our significance and superiority. And this bastion is on the verge of being overrun by surreal part-human animals.

Notes

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2. Ibid. 252.
3. M. Teillet and N. Le Douarin, "Experimental Analysis of the Migration and Differentiation of Neuroblasts of the Autonomic Nervous System and of Neuroectodermal Mesenchymal Derivatives Using a Biological Cell Marking Technique." *Developmental Biology* 41, no. 1 (1974): 162–184.
4. B. Ogle et al., "Spontaneous Fusion of Cells between Species Yields Transdifferentiation and Retroviral Transfer." *The Federation of American Societies for American Biology Journal* 18, no. 3 (2004): 548–550.
5. C.T. Scott, "Chimeras in Crosshairs." *Nature Biotechnology* 24, no. 5 (2006): 487–490.
6. A. O'Doherty et al., "An Aneuploid Mouse Strain Carrying Human Chromosome 21 with Down Syndrome Phenotypes." *Science* 309, no. 5743 (2003): 2033–2037.
7. Scott, "Chimeras in Crosshairs," 487–490.
8. Ibid.
9. Ogle, "Spontaneous Fusion," 548–550.
10. Center for Disease Control and Prevention, "Biosafety in Microbiological and Biomedical Laboratories" 5th (2009). http://www.cdc.gov/biosafety/publications/bmbl5/index.htm
11. 1 Corinthians 6:19
12. J. L. Allen, "Human, Animal Mix: Chimeras, Created in Laboratories, Raise Ethical Concerns. *National Catholic Reporter* (2007): 4.
13. Bernard Dixon, "Engineering Chimeras for Noah's Ark." *The Hastings Center Report* 14, no. 2 (1984): 10–12.
14. F. Baylis and J. S. Robert, "Crossing Species Boundaries," *The American Journal of Bioethics* 3, no. 3 (2003): 1–13.
15. Agnieszka Czechowicz et al., "Efficient Transplantation via Antibody-Based Clerance of Hematopoietic Stem Cell Niches," *Science* 318, no. 5854 (2007): 1296-1299.
16. International Society of Bioethics. "Universal commitment to the dignity of the human being." II World Conference on Bioethics, Spain, (2002).
17. J. Leake and S. Templeton, "Mice Produce Human Sperm to Raise Hope for Infertile Men." *The Times*, July, 6, 2008. http://www.timesonline.co.uk/tol/news/science/article4276551.ece
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19. *Deutsche Well* Staff (jen), "British Nod to Embryo 'Chimeras' Raises Hackles in Germany." *Deutsche Well*, May 21, 2008. http://www.dw-world.de/dw/article/0,,3351368,00.html

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