

## The Legacy of Doctor Moreau

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H.G. Wells along with Jules Verne firmly established science fiction and made it seem real to many. Their pioneering works paved the way for all those who followed, including this scary edition of our favorite magazine you are now holding in your hands. Many of the SF tropes we all now take for granted were invented by the minds of those two innovators. And as we all know as time passes what was innovated then becomes the scientific reality of tomorrow. With enough time the imagination becomes reality and sooner or later tomorrow becomes today. It is a long list of fictional inventions Wells and Verne created on the page that have become real in our everyday lives and I suspect there will be more to come.

In H.G. Wells' 1896 novel, *The Island of Doctor Moreau*, the main protagonist, Doctor Moreau, is a single minded scientist intent in making the world a better place by understanding the genetic principles of what makes man, man. As the Wells story goes, a survivor of an accident at sea is stranded on Moreau's island and comes to believe the doctor's work, of turning animals into man and man into animals, called "manimals", is blasphemous. Moreau does his work in his "House of Pain", the nickname his beasts call his lab. Eventually, the manimals mutiny and destroy Moreau.

The term, "humanized animals" or manimals was coined by Wells. As Wells portrayed him, Doctor Moreau is a very curious scientist and he indulged deeply in that curiosity. He crossed that proverbial SF line of "things man should leave alone" when he created his island of beasts. Such curiosity-driven research dominates much of SF cinema and our favorite mad and annoyed scientists are indeed obsessively curious. And if you wait long enough then science will catch up to science fiction where facts and fiction converge and blur. The age of Moreau's manimals is now upon us.

We are fortunate to have three filmed versions of Wells' story. The first and certainly the best, *ISLAND OF LOST SOULS*, and starring Charles Laughton, a vile and cunning protagonist, was filmed in 1933. The second version titled, *THE ISLAND OF DR. MOREAU*, was filmed in 1977 and starred Burt Lancaster as the good doctor. The weakest of the three, filmed in 1996 and also titled, *THE ISLAND OF DR. MOREAU*, starred Marlon Brando. It is easy to dislike both the Laughton and Brando Moreaus but harder with the Lancaster Moreau simply because he seems to be a likeable protagonist.

We can see an interesting progression of science from these films. In 1933, the date of the first film, the real function of DNA was unknown though the ideas of “germ plasm”, “vital humor”, and “glands” were popular. There were actually ads in the pulp magazines of the day advertising the use of “gland extracts” to essentially cure all ills. Also, many remedies were touted to be useful for all those “gland problems” everyone seemed to be having at the time. By the second film in 1977 the ability to manipulate DNA and genes (gene cloning) was underway in many research labs throughout the world and by the third film in 1996 high school students have been cloning DNA in their classrooms. And now, in the second decade of the 21<sup>st</sup> Century, the ability to do exactly what Moreau was doing is here. Advances in genetics and stem-cell science could help to create animals with quintessentially human characteristics. Wells’ concept of manimals and how they are created is no longer a stretch of the imagination and in reality is not that far away. These advances in genetic and stem-cell technologies could now, in theory, create the manimals that Wells imagined in his story. What this means is the mixing of species is certainly possible and, as blasphemous as it sounds, scientists can now create species faster than God.

To keep all of you gentle readers up to date there currently is an ethical debate going on amongst scientists and some policy makers about the nature of blending different species to create hybrids or what are called, chimaeras that are human-animal hybrids. Well, shades of Doctor Moreau and his manimals. Quite amazing that H.G. Wells foresaw the day when literally any gene or combination of genes can be inserted into an animal. Even a document, “Animals Containing Human Material” (ACHM), recently prepared by the Academy of Medical Sciences in the United Kingdom, addresses many concerns of this field of study. Are man-beasts or “Sayers of the Law” that far behind? As the Lugosi Sayer of the Law intones in the 1933 film, “We are not men! We are not beasts! We are things!” What rights should such manimal things have?

No doubt some sort of legislation will be proposed that will attempt to regulate the mixing of human DNA with animals. However, not all human DNA is the same because some DNA genes are more important than others. But which ones? Such legislation, unless it is carefully considered, may unfortunately block important research that could impact on diseases with no known cures. It should also be pointed out that no matter the level of legislation, a single-minded scientist, on his own island, would have no legal interference to create such manimals, nor the scruples to worry about such interference. Why he would want to do that is not the point. Its just that if he really wanted to he could. And that is enough to scare anyone, even the readers of this article.

The ACHM document prepared by the Academy of Medical Sciences says that genetic and stem cell technologies are so advanced that the creation of ‘Sayers of the Law’ are certainly possible and some forms of this technology should be

outright banned. This then brings up the issue of which traits should be banned (for example, a primate with a brain composed entirely of human neurons). Many lay people think that the mixing of some genes between species is acceptable but work that introduces key human traits (brains, reproduction, physical appearance) would not receive public support and would be considered unethical and therefore banned. Another example of work cited in this ACHM document that should be banned is generating human sperm and egg cells in an animal capable of fertilization and bringing the resulting fetus to term. In the 1996 Moreau film version there is a graphic scene of a seemingly female-like human giving birth to...something. This smacks that idea right in the face.

Over the years in many biomedical labs throughout the world many human genes have been inserted into the DNA of lab mice to study their effects. These human gene-bearing lab mice are called transgenic mice or sometimes “humanized mice”. Many thousands of these transgenic rodents, expressing all sorts of human genes and others grafted with human tissues, have been created worldwide. These mice have been genetically engineered to specifically express human genes. One such example of humanized mice are those containing a fully functional human immune system in which all the human genes necessary for a functional immune system have been inserted. This gives scientists the ability to study the human immune response without actually using humans. This research definitely paved the way for creating new therapies and the understanding of deadly diseases. These humanized animals enable research on *in vivo* human biology that would otherwise not be possible due to ethical, logistical, or technical constraints. Such transgenic lab mice, though possessing a few human genes, nevertheless still look very much like and act like lab mice so no real ethical boundaries have been crossed. A hairless lab mouse that has skin resembling human skin would be very useful in researching skin diseases. However, the sight of such an animal could bring about disgust and may even be frightening to others. And taken to the extreme and inserting many human genes, if not entire chromosomes, into transgenic mice (or other animals for that matter) may result in creatures that do indeed bring about revulsion and disgust. Like Moreau’s manimals. We do indeed see such transgenic species in all three filmed versions of Wells’ story and some of the manimals are visually unappealing and bring about revulsion and disgust. A man’s face with a pig’s snout or a rat’s nose are examples. Also, others seem quite reasonable like a human-leopard face and under the right circumstances may make good pets.

In addition to transgenic rodents, scientists have also created transgenic sheep and goats that manufacture human proteins in their milk. For example, human enzymes in the milk of a transgenic goat are being used to combat diarrhea-causing bacteria. Transgenic pigs containing human genes are being developed for study in transplant surgery. Transgenic animals are here to stay so how far should this work go and where does an animal stop being an animal and become a manimal? This is essentially the gray zone of thinking that the above mentioned ACHM document is attempting to address.

In my own research I have created many rodent-human hybrids at the cellular level (its easier that you think). A simple chemical, polyethylene glycol (a polymer of ethylene glycol which is car radiator fluid), is used like a glue to literally fuse rodent and human cells together thereby mixing their DNA and all cellular components. Each species, the rodent cell and the human cell, do intermix and form entirely new molecules and proteins in the hybrid or chimaeric cell. It is an effective way to study the effects of genes on each other. If you will, you could call these cellular manimals. However, it should be obvious that single celled manimals are not fully functioning beings and should not be considered as such.

With all the advances in genetics and stem-cell technology currently available then animals could now be created that more and more resemble humans and have certain human characteristics and behaviors. Science is catching up to science fiction. Extensive humanization of a primate brain may have certain ethical issues and a self-aware primate may have trouble expressing itself which could be agonizing for the animal. Transgenic animals with human brain material could be useful in studying neurodevelopmental disorders (like schizophrenia) by understanding how normal brain development and function occurs. And the development of embryos that mix human DNA with non-human primates will bring about other issues. Perhaps this is how the original Planet of the Apes primates started.

In putting human DNA into animals, transgenic mice are at one end whereas at the opposite pole are blurred human-primate transgenic species (such as in the 1941 film, THE MONSTER AND THE GIRL, where a human brain is transplanted into the skull of a gorilla) that are ethically untenable and no one should have a problem in banning this work. However, it is the middle ground that is currently under debate. As mentioned above, how about human-skinned animals, useful for studying various skin diseases and disorders? No one would have a problem with that. However, it is the creation of hybrid embryos, relatively easy with current genetic and DNA technologies, that are being hotly debated. Do you bring these embryos to term or destroy them before? Definitely a topic for society to debate. And when does a transgenic embryo (a manimal embryo?) cross a line and become predominantly human? And once a manimal embryo has been declared predominantly human (or even marginally human) then a whole different set of laws come into effect that are scientific, medical, ethical, social, and theological. Quite a mess ol' Doctor Moreau created. And no really easy answers either.

An example of some of the Moreau-like procedures current scientists are struggling with are the introduction of human stem cells into animals that would then integrate into the animal's body resulting in the formation of chimeras or hybrid animals. The formation of chimeras would take place at the embryo stage where the DNA of the two species could mix together and then randomly form

some sort of new creature or hybrid. Embryo ethics is at the center of much of this debate. Are hybrid embryos and chimeric animals something society wants to have around? How hybrid and chimaeric do they have to be in order to be considered human or quasi-human? What this all comes down to is the controlling of certain human genes (note, however, that not all genes need to be controlled) or combination of certain human genes and how they are integrated into another species. How many genes does it take to cross that proverbial line of “doing things man should leave alone”? No one really knows.

Stem cells have the ability to change into virtually any cell in the body. This is a natural process and all animals have stem cells. Scientists are now learning how to steer the stem cells into becoming any cell of choice. The possibility of using human stem cells to replace damaged organs is at the forefront of current biomedical research and the technical problems are quickly being solved. For example, mouse stem cells have been converted to sperm cells which in turn were able to successfully fertilize a mouse egg resulting in the delivery of normal pups. This effectively demonstrates that stem cells can be programmed to become any cell in the body and since sperm cells are the most complicated of cells this proves how sound the technology really is. An infertile man could have his stem cells converted to sperm cells which in turn can fertilize a human egg or conversely, an infertile woman could have her stem cells converted to egg cells that can be fertilized. Also, human stem cells have been introduced into goat fetuses that produce animals with organs containing functioning human cells. With these real possibilities, this then leaves all the ethical issues and the moral values for us to think about and ponder. To be sure, these ethical issues are complex. All of this started from the imagination of H.G. Wells. The ethical questions he raised in his story are just as valid and real today, maybe even more so, as when first published over a century ago.

Areas under debate by the scientific community and part of the ACHM document mentioned above have focused on three main areas of “manimal research” that should be banned outright. One is the modification of an animal brain that will lead to human cerebral function; how much cerebral function is a moving target and no one really knows for sure. The second is to establish functional human sperm and egg cells in an animal that could be fertilized. The third is to create a manimal that has human features such as facial shape, skin texture, or speech. Quite frankly, all three of these areas certainly lack scientific justification so there should be no problem in banning them. Unless, of course, you happen to be a scientist like Doctor Moreau with your own island at your disposal away from the scrutiny of all those pesky lawmakers. Many of his manimals do indeed express all of the above banned features to one degree or another.

So, back to the movies, the legacy of Doctor Moreau in the 1933 film is one primarily of hormones, small biological molecules, like insulin, growth hormone, or testosterone, that he used to create his manimals. Surgery was performed on his beasts but the main driving force was hormones. What is interesting about

hormones is they work in a transient or temporary way and they must constantly be used to maintain their effects (think of a diabetic who must take the hormone, insulin, every day). Which is why Lota, Laughton Moreau's "most nearly perfect creation", did revert back ("stubborn beast flesh...creeping back") to her natural state when the hormone treatments stopped. And hormones also played a significant role in the 1977 film too. The changes brought about by the Lancaster Moreau are just as transient and temporary as his Laughton predecessor. To keep the beasts changing Moreau needed to keep injecting hormones. In the 1996 film the Brando Moreau uses gene therapy to transform and control his manimals. At least the gene therapy procedures, if successfully carried out, would indeed result in permanent changes and not the temporary changes his hormone-using predecessors tried. And this is where the lines of science and fiction are converging in this field making the boundaries blurry instead of sharper and more defined. The world has moved from one of hormones, a transient control system, to a more fundamental control, namely that which controls all life, DNA. And when you control DNA then you effectively control life and all its forms.

For proper function Moreau's manimals need to have homeostasis, a consistency in normal internal physiology, for both brain and body functions. For this dynamic equilibrium to work some highly responsive networks are involved in normal body homeostasis such as the nervous and immune systems and muscle coordination. In the world of manimals, those physiological benefits of animals, such as fur and the ability to regulate their body temperatures (think hibernation), may be at odds as each is struggling to maintain its individual homeostasis. In this way, the two species of cells are at war with each other. The animal has his own traits and the human also has his own traits and often times these two are at opposite poles. In the 1977 film Moreau began to change Braddock, the man lost at sea, from a human to an animal and during the transformation Moreau says, "Your mental processes are changing. The way you think is changing. You're beginning to think in images, concrete images. Hot, cold, light, dark, food, hunger, pain. Words becoming meaningless to you, except for the most elementary command. You've lost control. You are becoming an animal." And these possibilities are exactly what current scientists want to legislate to prevent. It should also be pointed out that the ethical issues in the ACHM document pertain to converting animals into humans and NOT the conversion of humans into animals. The ACHM document considers that angle to be so outre that it does not merit discussion.

Creating transgenic animals, ACHMs, or manimals with quintessentially human characteristics is technically relatively straightforward. Those of you who use computers to write will readily understand the simple principles involved. Think of an animal's DNA or genes as a large word document like you have in your computer that is broken down into chapters, subheadings, paragraphs, etc. Inserting DNA genes into an animal is like inserting new text into your word document. For word documents, you use your cursor, locate the area you want

to insert the text, then hit the “paste” command. Depending upon what text you inserted it could either blend in seamlessly, seem somewhat awkward with maybe a misspelling or bad grammar, or be totally unrelated to either the before or after the surrounding text (or maybe even in a different language). This is the same with inserting DNA genes into animals. You select the area of the genome (an animal’s chromosomes) you want to insert the DNA, then using a series of enzymes you literally paste the new DNA gene right into the genome text. When this new text or gene is read it can then have the same sort of effects as with word processing. The new gene (or genes) could have minimal effects or change something significant that could dramatically alter homeostasis and result in something like Moreau’s manimals. It really is technically that simple. However, it’s the results that are now being ethically and morally debated. If there is a real medical benefit then this research will move forward and society will readily accept it. If the risks out weigh the benefits then manimals will remain part of our cinema legacy and go no further than that. I suspect that over time the fine line between fact and fiction will slowly blurr and future societies may come to embrace the legacy of Doctor Moreau. This then brings up an interesting image of people taking their pet manimals out for their morning walk. And after an evening out for dinner you no longer need a doggie bag for leftovers but, rather, a manimal bag!

Thank you for reading. It’s back to the lab for me. Stay healthy and eat right.