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My attempt to patent a human-animal chimera

In 1997, with the support of the social critic Jeremy Rifkin of the Foundation on Economic Trends in Washington, D.C., Professor Stuart A. Newman undertook to apply for a patent on embryos and full-term creatures containing human along with nonhuman cells – so-called "chimeras" that he had no intention of producing...

Stuart A. Newman*

In 1997, with the support of the social critic Jeremy Rifkin of the Foundation on Economic Trends in Washington, D.C., I undertook to apply for a patent on embryos and full-term creatures containing human along with nonhuman cells – so-called "chimeras". The public had only just learned (to widespread surprise) about the cloning of Dolly the sheep and the announcement of the production of versatile and controversial embryonic stem (ES) cells from human embryos was still a year in the future. In those innocent days less than a decade ago the prospect of fabricating creatures that were part-human and part-beast would have appeared to most people like something out of Greek mythology or the pages of a fantasy novel. Indeed, it had been a century since the British writer H.G. Wells had published "The Island of Dr. Moreau", the story of a visionary scientist whose well-motivated experiments along these lines led to death and destruction. Still, in the last years of the 20th century, such quasi-humans were unknown outside of works of fiction.

Nonetheless, as a developmental biologist whose work requires close tracking of the scientific literature, I knew that such things were feasible. Specifically, in 1984, two research groups reported in the journal *Nature* the production of viable goat-sheep chimeras – "geeps" – and their growth to healthy adult animals (1-2). Such interspecies embryo chimeras are different from hybrids – organisms such as mules resulting from the reproductive mating of two different species. Interspecies embryo chimeras are produced by aggregating early embryo cells or ES cells of two or more different species and implanting them in the uterus of a surrogate mother drawn from one of the species. Whereas each cell of a fully developed hybrid contains DNA from both species, in chimeras the species identities of the descendents of the embryonic cells are maintained. The fully developed chimera is thus a mosaic of the originating species, an unprecedented life form that could not be achieved without technological intervention. As was the case with the geep, a chimera constructed of human and chimp cells, for example, would have recognizable resemblances to both originating species, perhaps stronger and hairier than a human, with mental qualities of both person and ape.

I also anticipated more than a decade ago that producing chimeras and other part-human entities might eventually be contemplated by scientists and physicians. Along with other observers of biomedical science, I noted the rapidity with which new "breakthroughs" in reproductive or reparative biology were being turned into business models, often accompanied by extravagant promises of cures. In the United

States, this latter situation was a consequence of two changes in the legal environment that had occurred in 1980: the U.S. Supreme Court decision in *Diamond v. Chakrabarty* (3), which permitted the patenting of living organisms and their descendants, and the passage of the *Bayh-Dole Act* (4) by the U.S. Congress, which enabled university investigators and their institutions to commercialize research that was the fruit of Federally-funded grants and contracts. It was therefore clear to me that medical applications of human cloning, human ES cells (known by scientists in the mid-1990s to be just around the corner), and even human-animal chimeras, were things the public would eventually be presented with and asked to get used to, regardless of how bizarre-sounding they were in 1997.

In filing this patent application, I had no intention of producing human-animal chimeras, nor does U.S. patent law require that an actual prototype for an invention be supplied: it only needs to be demonstrated to be feasible, novel, useful, and, according to U.S. law, appropriate subject matter for patenting. While the 1980 *Chakrabarty* decision approvingly quoted a 1952 Congressional report that held statutory subject matter to "include anything under the sun that is made by man" (3), in 1987 the Patent and Trademark Office (PTO) qualified this with the statement that "[a] claim directed to or included within its scope a human being will not be considered to be patentable subject matter" (5).

As a scientist who came of age in the 1960s, I had witnessed the damage that could be wrought by using the products of research and technology without appropriate constraints. The list is long and includes the development and proliferation of nuclear and chemical weapons, the transformation of the climate by greenhouse emissions, problems of nuclear waste disposal, and destruction of ecosystems by agriculture and development. My objective in filing the application was to help alert a wider public to what was coming down the road in terms of human applications of developmental biology. In a society with democratic values it should be inarguable that those who pay for scientific research and will eventually experience its effects should be informed of what is in store while there is still a chance to discuss its objectives and influence its course. As a researcher myself, moreover, I was not oblivious to the possibility of a backlash against my field if it was seen to have violated the social trust.

Given the state of the law, was my fear that developmental biology could stir up social disquiet and anti-science sentiment warranted? It might be imagined that in the United States, a country in which the right to abortion has always been controversial and where it is currently being rolled back at both the state and Federal levels, there would be strict governmental restrictions on research using human embryos. This is not the case, however. The wide acceptance of in vitro fertilization across the political landscape, the iconic status of the for-profit medical system by the right, and the unwillingness to entertain any embryo-valuing legislation by the left, have all conspired to make human embryo research in the U.S. (albeit without Federal funding), perhaps the least-regulated anywhere on earth. This is in sharp contrast to Canada, Japan and most of Europe, where there are strict regulations on such activities, and the prospect of obtaining a patent on human-nonhuman chimeras would be almost nil.

Furthermore, despite the specter raised by the *Chakrabarty* decision and the 1987 PTO codicil to it, the U.S. Congress had drawn no line that would preclude a pre-term human embryo, if appropriately modified, from being patented, nor had it indicated how many human genes or cells an animal would have to contain before it could *not* be patented by virtue of Constitutional protections pertaining to humans. It thus seemed clear that while there would be variability concerning which applications of the new developmental biology-based technologies would trouble which particular members of society, taken far enough, some of these applications were bound to violate the value systems of virtually everyone. And while a decision as to patentability by the U.S. Patent and Trademark Office (PTO) would not determine the legality of producing human-animal chimeras or other types of biologically manipulated humans, I reasoned that the public and scholarly discussion that might arise from the attempt to patent such entities could inform legislative deliberations.

The articles reporting the production of geeps provided detailed instructions for making interspecies chimeras which, because of the similarity of all mammals at the early embryonic stages, justified my assertion that my invention was feasible despite my not having implemented it. But because the technology for making such chimeras had already been published, the claim of novelty was not directed to methodology, but rather was in the introduction of a "new composition of matter", earlier publications having neither reported nor mentioned a human component in any interspecific embryo chimeras. Composition of matter is a standard category of patentable invention, pertaining, for example, to inventions of new alloys, plastics, etc. This was the basis on which the post-*Chakrabarty* U.S. PTO granted patent protection for the Oncomouse (6), a genetically engineered strain of rodent, but which the Canadian Supreme Court judged inapplicable to "higher life forms" in 2002 (7).

The claim that the invention was useful, the third hurdle it needed to clear for patentability, was presented in the form of proposals to use part-human embryos to test drugs and chemicals for toxicity, and fully developed part-human animals as sources of transplantable organs for human patients. It is clear from such scenarios, offered in the spirit of the 18th century satirist Jonathan Swift (8), that biotechnology is capable of producing items that, while legal and useful, would nonetheless be considered immoral and undesirable by many people.

The initial publicity in 1998 around the chimera patent application was met with skepticism and accusations of bad faith by a Patent Commissioner, and some biotechnology executives and scientists. The developer of the Oncomouse, Dr. Philip Leder of Harvard Medical School, for example, stated that "[t]he creation of chimeras is an outlandish undertaking. No one is trying to do it at present, certainly not involving human beings") (9). Since then, however, the University of Massachusetts, in association with the biotechnology company Advanced Cell Technology, has filed a patent application for a technique for creating cloned embryos produced from human cell nuclei and cow eggs (10). And because of the intense activity around the possibility of using human ES cells for organ and tissue repair, the discourse around making human-animal chimeras has shifted. In 2001, a Stanford University researcher proposed introducing human ES cells into mouse embryos at an intermediate stage of development so as to produce mice in which all the brain cells are of human origin (11), and in late 2002, a Rockefeller University scientist announced his intention to inject human ES cells into mouse embryos in order to explore the developmental fate and therapeutic potential of such cells (12). This latter experiment would produce embryo chimeras of undefined species identity, precisely as I had described in the 1997 application.

The chimera patent initiative had the effect I had hoped for, spawning consideration of these issues in scores of newspaper and magazine articles, several television documentaries and radio features, and, importantly, dozens of law review articles which dealt with implications of human-animal chimeras in arenas ranging from human rights to international trade. Nonetheless, the PTO ultimately rejected my chimera patent application. The rejection was based, in part, on various technical grounds, many of which I was able to overcome in successive refilings. And while rejection of a patent application by the PTO does not set any legal precedent, and therefore someone with an improved description could, in principle, reapply and satisfy all the technical criteria for patentability, the public nature of my initiative has essentially disqualified any human-animal chimera with respect to the "novelty" standard.

But over the course of eight years of responses and revisions the main sticking point was always the question of whether a human-nonhuman chimera, which in different embodiments could contain variable proportions of human cells, was appropriate subject matter for patent protection. In rejecting the application on this ground, the PTO appealed to what it considered the intention of the U.S. Congress, but, as noted above, Congress has given no guidance on this question. Nor, despite several attempts to formulate legislation that would exclude human-nonhuman chimeras, could they do so in a satisfactory

manner if they continue to accept the premise (rejected by the Canadian Supreme Court) that animals can be inventions. Given the common evolutionary heritage and biological continuity of all organisms on Earth — we share more than 98 percent of our DNA sequence with chimpanzees, for example — the best solution, from both moral and practical viewpoints, would seem to be to begin reversing the drive, which has accelerated over the past quarter century, to privatize all aspects of our lives. We can begin with our fellow organisms.

**Professor of Cell Biology and Anatomy, New York Medical College, Valhalla, NY.*

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