Cloning Red Herrings

Why concerns about human-animal experiments are overblown

By David Longtin and
Duane C. Kraemer

In February or March 2002, the U.S. Senate will consider several competing bills that address human cloning, stem cell research, and other issues dealing with reproductive biotechnology. Kansas Republican Sam Brownback has offered some of the most restrictive legislation. He favors a proposal to outlaw the production of cloned human embryos for any purpose. He would ban all attempts to engineer human genes in ways that could be passed on from one generation to the next, partly because he does not want scientists to transfer animal DNA into the human genetic code. He also would forbid researchers from creating human-animal hybrids or chimeras — a term used in mythology to describe a monster made of parts from several animals, but in biological terms, an organism with at least two genetically distinct types of cells. In making these proposals, Brownback has joined a growing number of people on both ends of the political spectrum who voice concerns that bioengineers eventually will pro-

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duce creatures that blur the line between humans and other species.

In a recent article, syndicated columnist Charles Krauthammer argues that many of his fellow conservatives do not recognize the awful power of reproductive technology and how badly it needs to be reined in by the government. He writes: "In 1998 it was reported that a human nucleus had been implanted in a cow egg cell, producing . . . a possible hybrid human-cow creature. It was destroyed in its early embryonic stage, but not before giving us a glimpse of horrors that lie within the reach of the new reproductive biotechnology." Krauthammer suggests that Congress should fund embryonic stem cell research but outlaw the production of cloned human embryos for any purpose. Through such measures, he believes, federal authorities will gain a large degree of control over how such research is conducted, as scientists scramble for government grants.

Francis Fukuyama, a professor of international political economy at the Johns Hopkins School of Advanced International Studies, takes Krauthammer's argument a step further. In a recent op-ed piece in the *Wall Street Journal*, he too mentions the same "hybridization" experiment to justify federal support of embryonic stem cell research. He writes:

> A couple of years ago, a small biotech company named Advanced Cell Technologies [sic] reported that it had successfully implanted human DNA into a cow's egg, and that that egg had successfully undergone a number of cell divisions into a viable blastocyst[1] before it was destroyed. It might come as a surprise to many that biotechnology is in a position to produce creatures that are part human and part animal, and that the law is indifferent as to whether it does so.

Fukuyama believes that Congress should require all scientists who work with embryonic stem cells to obey a set of guidelines recently proposed by the National Institutes of Health, even if those researchers do not receive any government grants. These guidelines, published in the *Federal Register* on August 25, 2000, would allow federally funded scientists to conduct research on stem cells obtained from embryos that had been produced by in vitro fertilization clinics and were slated for destruction. New criteria issued by the Bush administration would require government-backed laboratories to work with 72 existing stem cell lines, but would not change how those cells could be used. Since both sets of rules would bar federally funded scientists from producing cloned human embryos for any reason, they automatically would prevent biologists from doing the kind of research that Advanced Cell Technology conducted. The guidelines also would ban the

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[1]A human embryo reaches the blastocyst stage five or six days after fertilization, just before it implants in the womb. A blastocyst is a sphere made up of about 150 cells. It has a protective outer casing of cells that will help to form the placenta, a fluid-filled cavity, and an inner mass of cells that will become the infant that we would recognize.

creation of human-animal chimeras, but they would do nothing to restrict the insertion of human DNA into other species. Nor do they prohibit the transfer of human fetal stem cells into the fetuses of other animals, as Fukuyama mistakenly claims in the *Wall Street Journal.*

In their descriptions of the cow-egg experiment, Krauthammer and Fukuyama also omit crucial details. In this procedure, scientists first removed the nucleus of a cow egg, taking with it nearly all of the egg's genes but leaving behind the egg's mitochondria. Mitochondria, which possess tiny amounts of their own DNA, are bacteria-like structures that reside in every living cell in the fluid outside the nucleus. Mitochondria allow cells to convert carbohydrates and fats into a usable form of energy. After removing the nucleus, the scientists injected a human skin cell into the gutted cattle egg, thereby refurbishing it with an entire set of human genes. Finally, the researchers used a small electrical pulse to activate the egg, which caused it to start dividing as if it had been fertilized with sperm. During its short existence, the resulting embryo seemed to develop as fully human, despite its minute bovine heritage.

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In June 1999, Neal First at the University of Wisconsin and Tanja Dominko at the Oregon Primate Center published the results of a similar experiment in the journal *Biology of Reproduction.* In this study, they transferred rat, pig, sheep, and monkey nuclei into gutted cow eggs. These rat, pig, sheep, and monkey embryos reached a key stage in their early development — the formation of blastocyst-like structures — within periods of time that were appropriate for their respective species, though not for cattle. This gives us a preliminary indication that the residual bovine DNA had no effect on the young embryos and that animals cloned in this way would not exhibit any hybrid characteristics.

In any case, scientists long ago developed other technologies that would stand a far better chance of producing creatures with a genuine mix of human and animal traits — if that is what scientists were really bent on doing.

In 1999, the U.S. Patent and Trademark Office shot down a most unusual request from Stuart Newman and Jeremy Rifkin, two prominent anti-biotechnology activists. Newman, a member of the Council for Responsible Genetics, and Rifkin, president of the Foundation on Economic Trends, had sought a patent on techniques that could be used to create human-animal hybrids and chimeras. Although patent protection is normally intended to foster the exchange of new and useful information, Newman and Rifkin had the opposite intent. They wanted to head off research that they opposed.

Scientists already have inserted small bits of human DNA into pigs, sheep, and other animals, causing their cells to yield medically useful by-products, such as monoclonal antibodies, that can neutralize various infections, tumors, and toxins in human patients. Some monoclonal-antibody drugs are already on the market, such as Daclizumab, which prevents acute rejection of transplanted kidneys. Dozens more are in human clinical trials, and several of them may be approved in 2002 by the Food and Drug Administration. But Newman and Rifkin worry that biologists eventually could transfer even more human genetic material into other species than they previously have. There was nothing original in their proposal, which is one big reason that it failed. The Patent Office also was not prepared to recognize that creatures with substantially human characteristics should be patentable. Newman and Rifkin want to rekindle a debate about how many human genes an animal could receive before we would have to grant it citizenship. But we are a long way from having the capability to transfer such huge quantities of DNA between species. Worrying now about the ethical implications of such technology seems far-fetched.

In the late 1980s, however, Congress considered passing a law that would have addressed this very issue. The attempt failed, partly because legislators had trouble defining what traits would make an animal "human." We have little reason to believe that they would be any more successful today. In 1999, the scientific journal *Nature* quoted Rifkin as saying, "No parliament in the world is going to be keen to debate how much human genetic information [in a hybrid creature] makes up a human being. But we want to force them to do it." Although cross-species research does raise some interesting ethical issues, Rifkin exaggerates the risks and then offers an easy answer. He wants to ban most, if not all, transfers of human genetic material into other animals, despite any medical benefits that may result. Listening to critics like Rifkin, you would think that reproductive biologists are completely unregulated and out of control. Yet these anti-biotech activists ignore many historical, technical, and bureaucratic factors that work against their dire predictions.

The forbidden experiments

MANY BIOTECH OPPONENTS simply refuse to acknowledge that the scientific community has little tolerance for offbeat, ethically challenged cross-species experiments and that its aversion has only grown stronger in the past few decades. Experts have known for years that humans and apes share a large measure of reproductive compatibility, a fact which weakens the view that researchers are on some mad dash to mix our species with other animals. J. Michael Bedford reported in the May 28, 1981 issue of *Nature* that human sperm can penetrate the protective outer membranes of healthy gibbon eggs. This kind of sperm-egg interaction,

which does not occur readily even between mammals as similar as mice and rats, usually indicates that two species are at least close enough to form hybrid embryos. Despite the many provocative questions raised by Bedford's decades-old experiment, no one has ever tested the developmental potential of an ape egg penetrated by human sperm.

Scientists also have long had the ability to produce animal chimeras. In this procedure, biologists can combine the cells of early embryos from two different subspecies or even separate species of mammals. Although the cells from the two embryos remain genetically distinct from each other, they associate randomly to form a single complete individual. In 1961, a Polish embryologist named Kristof Tarkowski first used this technique to produce mice with mixed albino and black fur coats by fusing embryos together in a test tube. Seven years later, British biologist Richard Gardner developed an even more efficient way to make chimeras by injecting cells from one mouse embryo directly into another.

The scientific community has little tolerance for offbeat, ethically challenged cross-species experiments.

From the start, scientists theorized that these procedures might allow them to combine embryos from distantly related species, although they were slow to explore this possibility. In 1980, Canadian embryologist Janet Rossant produced the first cross-species chimeras when she injected embryo cells from Asian wild mice into those of European house mice. These two mouse species occasionally can produce viable hybrids together, but only with great difficulty. Then in 1984, according to a 1986 article in the *Oxford Reviews of Reproductive Biology*, Danish veterinarian Steen Willadsen produced strange creatures composed of tissues from both sheep and cattle, using the same technique that Tarkowski had invented 23 years before.

Scientists have conducted this type of research primarily in an attempt to save endangered species. To speed up the breeding of rare zoo animals, reproductive biologists sometimes transfer the embryos of these endangered species into surrogate mothers from other closely related but more plentiful domestic species. This technique already has been performed successfully on endangered mammals such as wild cattle, zebras, and exotic cats by transferring their embryos into domestic cows, horses, and house cats, respectively. In many other cases, however, cross-species embryo transfers do not work so well, possibly because the foreign embryo does not implant properly in the host female's womb or because the surrogate's immune system rejects the alien fetus growing inside her.

Because chimeras were composed of embryo cells from two distinct species, they showed scientists how to overcome these reproductive barriers. Several days after fertilization, a young embryo has two basic parts: an inner mass of cells that will become the animal we would recognize, and an outer

casing of cells that helps to form the placenta. It is the outer casing that determines whether the embryo will implant properly in the womb and keeps the mother's immune system from rejecting the fetus. Biologists discovered that they could inject the inner cell mass of an Asian mouse embryo into the gutted outer casing of a European mouse embryo. After they transferred the reconstructed blastocyst into a European mouse female, she gave birth to a pure Asian mouse pup. This technique, a spin-off of the experiments with chimeras, eventually may allow scientists to transfer the embryos of endangered species into other distantly related mammals. But by the early 1990s, researchers stopped producing cross-species chimeras, having learned all they could from these strange creatures.

In his 1998 book *The Biotech Century*, Rifkin suggests that biotech companies one day might revive this old technique to produce human-chimpanzee chimeras and then use these hapless creatures as organ "donors." Aside from the all-too-obvious ethical difficulties that such a venture would pose, there are a host of technical problems that Rifkin ignores. Because most of the organs harvested from such chimeras would contain an unpredictable mix of human and ape tissues, they would not be much more compatible with the human body than organs taken from pure chimpanzees. The mass production of such chimeras also would be highly inefficient and prohibitively expensive. Biotech companies would find it easier to insert small bits of human DNA into chimpanzee embryos, producing apes whose tissues would be more compatible with the human immune system. Unlike the chimeras, these genetically engineered chimpanzees would be indistinguishable from other members of their species. They also would have the ability to pass their human DNA on to future generations of apes through traditional breeding, something that chimeras could never do. At the moment, however, it seems improbable that biotech companies will pursue either of the scenarios that we have just mentioned.

A slippery slope?

WHILE NO ONE will ever produce a human-ape chimera, some bioethicists are concerned that researchers might cross the human-animal divide in other less dramatic ways. Thomas Murray, director of the Center for Biomedical Ethics at Case Western Reserve University, argues that cross-species research is "a classic slippery slope." He told a *Washington Post* reporter in 1998, "If we put one human gene in an animal, or two or three, some people may get nervous but you're clearly not making a person yet. But when you talk about a hefty percentage of cells being human . . . this really is problematic. Then you have to ask these very hard questions about what it means to be human." Indeed, to a casual observer, it might appear as if scientists already have performed experiments that raise such questions.

Biologists recently demonstrated that human neural stem cells can integrate themselves into the brain of a monkey fetus and contribute to its development. This research, published in the September 7, 2001 issue of the journal *Science*, was performed by Vaclav Ourednik at Harvard Medical School, W. Michael Zawada at the University of Colorado, and their colleagues. In accordance with strict federal guidelines, these scientists obtained human neural stem cells from a 15-week-old fetus after the mother had sought an elective abortion. They then injected the human cells into the brains of three bonnet monkeys that were still in the womb. Normally, when human tissues are grafted into adult animals, their bodies quickly reject the transplanted material unless they receive potent immunosuppressive drugs. In this experiment, however, the fetal monkeys' immune systems were too young to recognize the human cells as foreign and instead became acclimated to their presence. When the researchers aborted the primate fetuses a month later, they found that the human stem cells had helped not just to construct the monkeys' brains but also to form a pool of stem cells from which new brain cells could possibly be derived throughout adulthood. Because the transplanted cells appeared to function normally in the monkeys' brains, this experiment bolsters the idea that neural stem cells someday could prove useful in correcting various human brain diseases such as Parkinson's, Huntington's, and Alzheimer's.

Receiving their cues from the surrounding tissues, foreign cells take on a form and function appropriate for their adopted species.

Before stem cells can be used in human patients, however, they will have to be tested in monkeys suffering from equivalent neurological afflictions. Primates offer the best animal model in this case because their brains are structurally most similar to ours. Scientists must make sure that human neural stem cells, once introduced into a person's body, will not become cancerous. They also must develop better ways to keep a patient's immune system from rejecting the transplanted cells, a problem that stands out most clearly when human stem cells are transferred into other species. Last, researchers need a primate model to determine whether enough stem cells can be delivered into a patient's brain to make a therapeutic difference.

If Ourednik and his colleagues had decided not to abort the monkey fetuses used in their experiment, the newborns would have looked like monkeys, but their brains would have possessed a large percentage of human cells. Would these creatures have started to think like people? The best evidence says no. When neural tissue from aborted mouse fetuses is grafted into the visual cortexes of kittens, or when human neural stem cells are

transferred into the brains of mice, the foreign cells essentially go native. Receiving their cues from the surrounding tissues, they take on a form and function appropriate for their adopted species. The animals that receive these types of cross-species transplants also show no signs of unusual behavior, unlike the full-fledged chimeras that we described earlier.

Current technology, therefore, appears to leave bioengineers with a rather stark choice. If they were to inject cells from an early human embryo into an equally young chimpanzee embryo, they would produce a creature with an unpredictable mix of human and ape characteristics. As we mentioned before, this is an experiment that no one will ever do. Alternatively, scientists could inject cells from an early human embryo into an older chimpanzee fetus. In this context, the human cells would be redirected by the surrounding tissues, producing an animal that would probably look and think like an ordinary ape. Between these two extremes, there seems to be no unhappy medium.

Current ethical safeguards

Fukuyama argues in the *Wall Street Journal* that, while bioengineers have the ability to produce creatures that would be part human and part animal, the law is powerless to stop them. He writes:

> Such rules as exist . . . have focused on federally funded research. This was fine in an age when the NIH funded the vast majority of biotech research. But today, there is a huge private biotech industry and hundreds of millions of loose research dollars seeking all sorts of morally questionable objectives.

But Fukuyama oversimplifies the issue. Most scientists seem to agree that federally funded research receives a higher level of scrutiny now than it did 20 years ago. In 1977, for example, when Bedford injected human sperm into the fallopian tube of a healthy adult gibbon, he did so under an NIH grant. We doubt that such a bold experiment would attract government money today.

Moreover, even though federal law does not spell out precisely which types of cross-species experiments private laboratories may or may not conduct, existing government regulations would make it difficult for any scientist to produce creatures with substantially human characteristics. In 1985, Congress amended the Animal Welfare Act, requiring all research facilities that work with higher mammals to establish Institutional Animal Care and Use Committees (IACUCS), whether or not those facilities receive federal money. Any IACUCS established on behalf of a private company must register with the Animal and Plant Health Inspection Service (APHIS) at the U.S. Department of Agriculture (USDA) and meet certain minimal criteria to stay

in operation. These oversight bodies function somewhat like trial juries, reviewing all experiments that are to be performed at their institutions. According to the law, IACUCs are supposed to "represent society's concerns regarding the welfare of animal subjects" used in research. While their main task is to alleviate the animals' physical suffering, many of these committees routinely take other ethical issues into account. Whenever an experiment is likely to cause the animals involved unnecessary pain or distress, the law requires scientists to consider more humane alternatives. On this basis alone, IACUC members would have good reason to challenge the creation of a human-ape chimera.

Each IACUC must have at least three members: a chairperson, a veterinarian, and an outside individual who is not affiliated with the facility beyond his or her service on the committee. Although both the chairman and the veterinarian are employed by the institution itself, they may not have any direct involvement in the research projects that they are evaluating. They also must have other jobs at the facility and may not receive any compensation above their regular salaries. Presumably, they would have a vested interest in preventing their companies from performing ethically challenged experiments that might scare away investors and invite congressional scrutiny. The unaffiliated member must not be closely related to anyone on staff at the institution and may not receive payment other than a modest travel stipend. A local clergyman or a professor of bioethics typically fills this volunteer position.

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The secretary of agriculture can levy stiff fines against private laboratories that ignore the judgments of their IACUCs: $2,750 per day for every violation of the Animal Welfare Act that she uncovers. By necessity, any attempt to produce a human-ape chimera would take at least nine months and would use a large number of animals as egg donors and surrogate mothers. If a biotech company were to perform such an experiment without the approval of its IACUC, the secretary theoretically could impose several million dollars in penalties on that facility and perhaps even put it out of business.

To be sure, the IACUC system is not perfect. Scott Plous at Wesleyan University and Harold Herzog at Western Carolina University reported in the July 27, 2001 issue of *Science* that these oversight boards often differ in their criticisms of the experiments they are reviewing. Plous and Herzog asked 50 IACUCs from U.S. universities and colleges to send in three research protocols each that they had recently examined. All of the protocols involved studies of animal behavior. After any information identifying the

scientists and their institutions was removed, each of the protocols was assigned randomly to another committee for review. Plous and Herzog found that the first and second IACUCs differed 79 percent of the time on which research to approve or on what modifications were needed to make the experiment acceptable. Of the 118 cases in which the two committees disagreed in their protocol reviews, the second committee was more negative than the first committee 101 times. Most of the unfavorable responses (84 of 118) resulted from calls for more information, which suggests that these IACUCs may have been a little disoriented when trying to second-guess research proposals from unfamiliar institutions. Nevertheless, Plous and Herzog raise some troubling questions. Like trial juries, IACUCs frequently reach different conclusions from the same evidence. But we still believe that the creation of a human-ape chimera would be so far beyond society's ethical limits and so devoid of genuine scientific merit that no oversight board would ever approve such an experiment.

Possible regulatory improvements

THE USDA IS studying ways that it might update its regulations to cope more effectively with the ethical issues raised by new reproductive technologies. In December 2001, APHIS hired a full-time veterinarian — a specialist in laboratory animal medicine — to head this effort. Congress also could amend the Animal Welfare Act for the same reason. This law has only a few criminal penalties. One such provision states that if an IACUC member knowingly discloses trade secrets to a rival company, that person may face a maximum of three years in jail and a $10,000 fine. We believe that a similar punishment should be imposed directly on any scientists who transfer human DNA into other animals without the approval of their oversight committees, in addition to the civil penalties that may be assessed against their companies today.

At present, federally funded laboratories must register their IACUCs with the Department of Health and Human Services (HHS), which imposes much stricter membership requirements on these committees than does the USDA. Instead of having a minimum of three participants, IACUCs that operate under HHS guidelines must have at least five members, including a veterinarian, an outside individual not affiliated with the institution, a scientist experienced in animal research, and another person whose primary concerns are in a nonscientific area.

We believe that corporate IACUCs should stay under USDA jurisdiction. But at the same time, Congress could stipulate that whenever private companies conduct experiments involving the transfer of human DNA into other species, their IACUCs also would have to meet the HHS membership criteria. To a large extent, such a measure would be symbolic, because many corporate IACUCs already have more than enough personnel to meet this stan-

dard. Yet it would send a message that these oversight boards must exercise special care when dealing with animals that possess human genes, without forcing legislators to spell out precisely how these committees should do their jobs.

The existing regulatory system is highly adaptable and has worked fairly well since 1985. With minor adjustments, it should continue to function for years to come. Scientists have not shown any interest in creating human-ape chimeras nor in producing human infants with animal DNA inserted into their genes. At best, therefore, proposals to ban such research are merely gratuitous. Jeremy Rifkin's call for an urgent debate about how much human DNA we should allow biologists to transfer into other animals is also premature. Our knowledge of genetics is still too primitive to write such laws intelligently. Moreover, we do not yet have the ability to move huge quantities of DNA between species. For the moment, it would be better to let Animal Care and Use Committees make such decisions on a case-by-case basis as this nascent technology develops.

In 1870, Jules Verne wrote his classic novel *Twenty Thousand Leagues Under the Sea*, in which he vaguely predicts the advent of nuclear-powered submarines. If, upon reading that book, parliaments around the world had set out to make laws governing the ethical use of military submarines for all time, we would see their efforts today as quaint, futile, and perhaps even dangerous. For the foreseeable future, current U.S. laws would allow scientists to pursue promising avenues of biomedical research, while ensuring that society's ethical concerns about cross-species experimentation are respected. After making a few improvements in the IACUC system, Congress should consider leaving well enough alone.

The GOP's California Blues

By BILL WHALEN

NINETEEN EIGHTY-EIGHT is the answer to two California trivia questions: It's the last time the Dodgers won in the post-season and also the last time a Republican won either a presidential or Senate election in the Golden State. The baseball metaphor is appropriate: If the big leagues ran the state parties, the California GOP, with few wins, a fractious roster, and a market that seemingly cares little for the Republicans' product, would seem an inviting target for either relocation or consolidation.

It's the new reality of the land that gave birth to the Reagan Revolution. Republican folklore has long honored California as a kingmaker and a wellspring of Republican ambition. In eight of the 10 presidential elections from 1948 to 1984, at least one California Republican — Earl Warren, Richard Nixon, Ronald Reagan — was on the Republican ticket. California's Orange County, home of John Wayne Airport, remains the spiritual homeland of paleoconservatives, a place where you can occasionally still find an "AuH_2O" bumper sticker. But California is fast becoming a graveyard for Republican fortunes.

Dating back to 1996, California has gone Democratic in each and every presidential, gubernatorial, and U.S. Senate election — while Texas has done

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