Inc., based in Houston, were going great guns using nuclei from very early embryos to clone hundreds of calves to make large herds of genetically superior beef cattle. But by 1991, Granada had shut its doors. "We couldn't make as many calves as we wanted to," recalls Bondioli, who worked there. And too often, calves were oversized and unhealthy, with lungs that were not fully developed at birth.

Researchers see the same trends in the few cows and sheep produced by the newer cloning procedures. Large numbers of deaths occur around the time of birth. For example, PPL and Roslin lost eight of 11 lambs in their first experiment with transgenic clones. But it's not the nuclear transfer procedure itself that's at fault, says Robl. Animals produced by in vitro fertilization and other procedures involving the manipulation of embryos have similar problems, albeit at a lower frequency.

"Something that you do to the embryo ... leads to a problem 9 months later," says George Seidel Jr., a physiologist at Colorado State University in Fort Collins. His data and other observations suggest that in problem calves the placenta does not function as it should. As a result, cloned calves have too little oxygen and low concentrations of certain growth factors in their blood.

While some researchers are experimenting with different nutrient solutions or making other subtle changes in their nuclear transfer techniques to make embryos and newborns thrive, others are frantically trying to hone the genetic manipulation techniques. Researchers currently have no control over where the foreign genes end up in the chromosomes or how many copies of the gene become part of that cell's genetic repertoire.

Developing that control would enable them to knock out specific genes, say the one encoding the pig protein that elicits a strong, immediate rejection response to pig organ transplants. "The Holy Grail for many is finding a way of getting targeted disruption of genes in livestock as we have in mice," explains Colman, who is confident that even this tough molecular biology problem will be solved quickly. "I expect we'll have targeting solved by next year," he predicts.

Such confidence is required in this fast-moving field, in which progress generally comes through trial and error. Understanding how it all works, say these scientists, will come later. "[There] clearly is at this point in time a pushing forward of the technology," says Alexion's Bondioli. "Have we learned any more biology? Probably not. But [we] have opened up a means to study [it]."

–Elizabeth Pennisi

XENOTRANSPLANTS

No Moratorium on Clinical Trials

U.S. health officials last week said they will allow limited clinical trials of animal-to-human transplantation to proceed, even though some researchers argue that such work poses a risk to public health and should not be permitted without further study. At a meeting on 21 and 22 January, officials from the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) outlined plans to allow this research to go forward under stringent safeguards that are now being finalized. They intend to impose rigorous standards to maintain disease-free donor animals, create a national registry of organ recipients, and establish both a tissue bank of samples from both donor animals and recipients and a national policy advisory committee.

Xenotransplantation, which once seemed an implausible alternative to human organ donation, is now being tested as a real possibility. Diabetes patients have received encapsulated pig pancreas cells, and fetal pig brain cells have shown some success in Parkinson's disease therapy. Although previous attempts to transplant whole organs from animals into people have failed when the patient's immune system attacked the organ, clinicians hope to overcome these problems with new immunosuppressive drugs and genetically engineered animals whose organs masquerade as human tissue (see previous story).

But even if it succeeds, xenotransplantation carries some unusual risks. Implanting living cells into an immunosuppressed host gives microorganisms—especially viruses that would not ordinarily leap from an animal into a human—a way past the body's first lines of defense. Once inside, an invader might adapt to its human environment and infect other people.

Those fears were heightened last spring, when researchers discovered that a pig retrovirus could infect human cells. Pigs had been the favored donor animal, in part because scientists thought their diseases would be less likely to infect humans than primate diseases. In October, the FDA ordered a halt to all clinical trials with pig tissues until a test was available to detect the virus in patients. So far, all patients have tested negative for the pig virus, and the FDA has permitted several trials, including tests of therapies for Parkinson's disease and epilepsy, to resume.

SCOTT BAUER

Potential donor. Pigs may provide organs for patients.

Some scientists say the FDA may have moved too hastily, however. In last week's issue of *Nature* and next month's *Nature Medicine*, a team of nine scientists—led by xenotransplantation researcher Fritz Bach and health policy expert Harvey Fineberg, both of Harvard University—call for a moratorium on clinical trials pending a broad public debate.

The Department of Health and Human Services, meanwhile, is proposing a new committee to address such concerns, said Mary Groesch, an NIH staffer. The panel would function like NIH's Recombinant DNA Advisory Committee, she said, sponsoring public workshops and offering advice, but leaving regulatory decisions to the FDA. Groesch said the current situation is "strikingly similar" to the apprehension about potential ecological disasters that caused a moratorium on recombinant DNA research in the 1970s.

The plan to allow this research to continue while experts monitor and discuss the risks won support from some meetinggoers. But others remained skeptical. Bach, for example, said that while he is "comforted" by the plans for a national advisory committee, he would prefer human trials to be halted until the committee is in place. Virologist Jonathan Allan of the Southwest Foundation for Biomedical Research in San Antonio, who opposes the use of nonhuman primates as donors, said he was "baffled, absolutely baffled," that the agencies have left open the possibility of transplanting material from such primates. "You're playing Russian roulette," he warned. If a new retroviral disease emerges, he says, there would be no ready treatment. But CDC epidemiologist Louisa Chapman said the guidelines will impose a practical ban on the use of primates, because they require that donor animals be free of specific diseases known to infect humans—a standard nearly impossible for primates to meet. Officials say they will take such criticism into account over the next few months as they prepare a set of final guidelines for publication—they hope—sometime this summer.

–Gretchen Vogel