One Hereford, Two Hereford, Three Hereford, Four Will Cloning Make GENETICS SOAR?

by Lisa Bryant

Can the same technology that produced Dolly the Ewe develop a "super steer?"

You've heard of Dolly, the lamb cloned by Scotland's Roslin Institute and PPL Therapeutics. You've heard of super tomatoes. Will the same cloning technology bring a new generation of superior cattle to our dinner table?

Although Dolly's arrival shook the world and generated an enormous amount of speculation and questions, Dolly is not the first clone. Both livestock and plants have been cloned for years. Potato growers cut up the eyes of potatoes and develop new plants — that's cloning. Colorado State University and a handful of breeders have cloned Herefords.

Dolly is different because she was derived from a non-embryonic cell with no reproductive function. Previously cloned livestock resulted from an embryo splitting process. Dolly's arrival finally proved that a mature mammal cell could be taken from another source — the udder of a 6-year-old ewe.

Scottish scientists used a new approach. Remember the discussion of DNA in the O.J. Simpson trial? California state attornies hoped this tiny genetic code material would convict O.J. because of its uniqueness to an individual. Scientists isolated a cell containing DNA in Dolly's donor ewe and removed it. A second ewe provided an unfertilized egg. The scientists physically fused the donor cell with the unfertilized egg with an electrical process. The egg began dividing as a fertilized egg would, and became an embryo. The reconstructed eggs that contained a full set of paired chromosomes were inserted into a recipient. Exactly like an embryo transfer at this point, the recipient accepted the egg and carried it to term, resulting in an "identical twin" to the donor ewe.

This brings endless applications of cloning to the drawing board. It may be practical to produce two prototypes for cattle — one excelling in carcass quality and the other in breeding and reproductive traits. Or perhaps scientists can now modify the genetic material to delete or substitute specific genes to produce a superior animal, or eliminate many genetic diseases or abnormalities.

ABS Global Inc. is well on its way to discovering the possibilities. With the announcement of a healthy, 9-month-old Holstein bull calf named Gene, ABS initiated a branch (Infigen Inc.) to specialize in cloning applications. "We can make an unlimited number of cells, freeze them for any amount of time, then thaw them and make identical animals possessing a desired trait," said Michael Bishop, vice president of research for Infigen. "Cells from cattle containing unique, favorable traits can be stored indefinitely, essentially preserving them for the future."

ABS also reports that cloning could allow advanced research in feed efficiency and other economically important traits. Using cloned animals in research eliminates genetic variability and allows focus on the actual factors being tested. Using genetic identicals could predict environmental effects on production. True genetic merit could then be evaluated.

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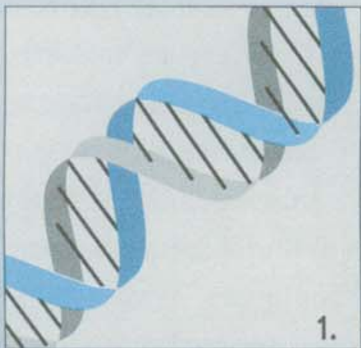
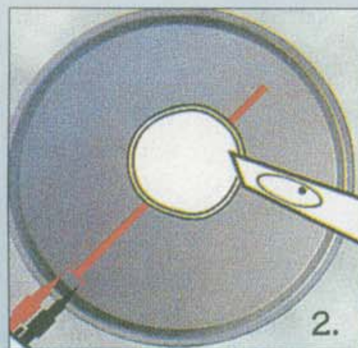
George Seidel, professor of physiology at Colorado State University (CSU), believes cloning will provide the beef industry a practical, profitable method to increase

Recipe to Make a "SUPER STEER"

Although some variations in cloning exist, one example is outlined.

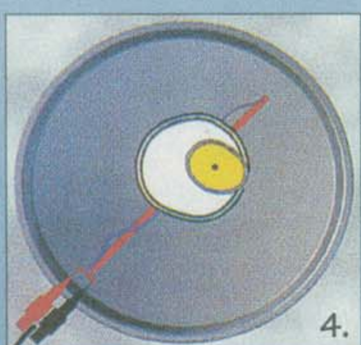


Cells containing genes from the donor's DNA are isolated and removed.

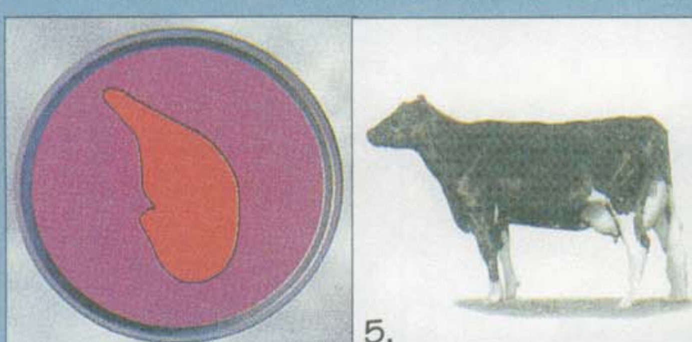


An unfertilized egg is removed from a second donor, and the nucleus is removed.

Scientists use a tiny glass needle under a microscope to inject the cells containing the donor DNA into the unfertilized egg.



The DNA and egg are fused to produce an embryo.



The embryo is inserted into a recipient cow that accepts the embryo and gestates 283 days.

A cloned calf such as ABS' Gene is born. The resulting calf is a genetic match to the donor.

predictability and uniformity in the future. He said embryo splitting provides a viable means of getting more calves from a valuable animal. "It makes great sense if you've got a cow whose offspring will be valuable."

Cloning could speed up the time required to transfer genetic progress from elite herds to the average commercial rancher. Although A.I. is accomplishing genetic progress to some extent, only half of the genes are transferred. With the dairy industry's widespread A.I. use, the Roslin Institute estimates the average cow to be some 10 years behind that of the best cows. Cloning could boost genetic improvement within one generation.

In addition to the opportunities in the livestock industry, this "nuclear transfer" in livestock could revise the world of human medicine. Seidel said this was the purpose of creating Dolly and will be the driving force to first apply cloning. Scientists estimate that using animals for producing human pharmaceuticals is five to ten times more economical in the long term and two to three times less expensive in start-up costs than cell culture production methods.

- Transgenic sheep, goats and cattle are already producing human proteins in milk to treat cystic fibrosis.
- Due to a shortage of suitable human donor organs, transgenic pigs are being developed that contain human proteins to coat their tissues. The human proteins reduce the immediate rejection of a transplanted kidney or heart. By breeding pigs with replaced DNA, pig proteins responsible for

rejection could automatically be replaced with human counterparts.

• Premature infants are unable to use cow's milk. With gene targeting, a cow's normal proteins could be replaced by human proteins. The improved nutritional qualities could meet the advanced needs of these special consumers.

• Treating some diseases, such as leukemia and Parkinson's disease, requires cells from close relatives. Dolly's arrival brings the possibility of using a patient's own cells to derive a treatment. By removing cells from the patient, scientists could convert the cells to the desired type and reinsert them into the patient for treatment.

• During pregnancy, most cells divide and multiply at least 20-30 times. Somatic mutations resulting from small mistakes in the replication of DNA are thought to cause an increased risk of cancer and aging conditions when we get older. Future technology could help reduce the incidences of these replication mistakes.

However, the process is not faultless. Dolly's birth resulted from almost 300 eggs prepared and placed in ewes. Only one of these resulted in a live lamb. Only two to three percent of eggs produce cloned animals, and only a portion of those express the added gene needed in medicine at sufficiently high levels. If the cloned cells could be produced in a culture medium, more substitution, deletion or addition of selected genes could be possible. Laboratories could reduce their costs and the numbers of experimental animals used now.

Perhaps the largest concern voiced is the ethical aspect. Some question whether cloning is contrary to fundamentals of life. Is it right to intervene in nature's selective breeding? Religious leaders are asking if science is taking technology too far and exploiting the animal kingdom.

Of course, animal rights activists are questioning if the animals are mistreated. Although it was not the intention of the study, early DNA manipulation produced some devastating effects in hogs designed for growth. With little control on the growth genes, hogs not prepared for the added weight and stress developed arthritis and gastric ulcers.

Seidel said they have experienced occasional, sporadic objections at CSU. But if CSU has the opportunity to explain, most people think the research sounds reasonable.

The cloned animals have shown some faults as well. Just as identical twins aren't necessarily identical, cloned animals may not be physically identical. Although CSU has split embryos since the 1980s, Seidel said cloning embryos isn't a guaranteed winner. "You don't know what sort of animal it's going to develop into." The new technology of cloning adults lends another story, Seidel said. "If you have a good adult animal that was performing well, it would be quite useful to make a copy."

Some studies found the cloning process caused delayed birth of calves as well as some extreme weights and cesarean deliveries.

Seidel said CSU encountered some abnormalities with calves in their studies. "Occasionally, there are some limb deformities that often are correctable or correct themselves," he said. With cloning by nuclear transplantation, a process that removes the nucleus from the embryo and places it into another egg, CSU experienced some calves that are metabolically abnormal, and they tend to die easily. "It's not so unusual to lose 20-30% of your calves with the methods used in the past."

Although the calves were abnormal at birth, Seidel said if kept alive, they actually turn into normal calves within a couple of days. "For example, if you have them born in a warm room and put a blanket on them, give them oxygen if they're not breathing well, give them glucose if their blood sugar is low, if you treat them as an intensive care patient, they survive pretty well." He said once the calves live past this stage, they are genetically normal and do not transmit any problems to their offspring. But success rates must be increased, abnormalities erased and costs decreased before cloning becomes worth the time and effort involved.

With these disadvantages, cloning may not be worth the advantages. Today's cloning technology presents limited value for most breeding programs. Some major barriers must be overcome before the application is practical. The benefits must prove to be cost-efficient.

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Genetic models are already determining the possible benefits, but further research must identify the risks. Scientists also question how old Dolly is — one or seven? Will the now-pregnant ewe age prematurely? More research with shorter-lived species, such as mice, will determine these answers.

A non-surgical method of transfer must be developed for on-farm use. Splitting embryos was more popular five or six years ago, Seidel said. The technique takes extra time that may not be practical if splitting the embryos on the farm. If manpower and time are plentiful, embryo splitting works well.

For those who don't have that much labor, breeding companies would probably sell the cloned embryos much the same way they sell semen now. Farmers could select the embryos from a list describing genetic merit. Even sex could be selected and guaranteed. The cloned embryo would be delivered to the farm in similar fashion to that of semen straws.

Cloning has the potential to lose genetic diversity. If this happened, an entire line could be wiped out by a virus or a less-than-desirable characteristic could appear along with the desired trait. Embryo banks and freezing could provide a safety net. Breeding companies that sell cloned embryos could also limit the number of particular clones to a breeder.

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Seidel said the problems with cloning will eventually be solved. He believes it could be a practical animal breeding tool in the next 7-10 years. However, at the slow pace with which technologies diffuse through herds, it will be a long time before it is widespread. "For a comparison, A.I. is used for about five percent of beef cattle. It's a rather simple technique that doesn't cost very much. It's a very good technique genetically. And if only five percent of the cows seem worth breeding A.I., it will be a lot less for cloning because it's a lot more complicated.

"There will be a lot of time to think about it, to work out problems. And we should be thinking about those things from an ethical standpoint, from a practical standpoint and from an animal welfare standpoint. People are doing that."

Cloning technology is far from the grill in producing "super steer." Only the next century holds the answer for cattlemen and scientists. HW