ANIMAL CLONING

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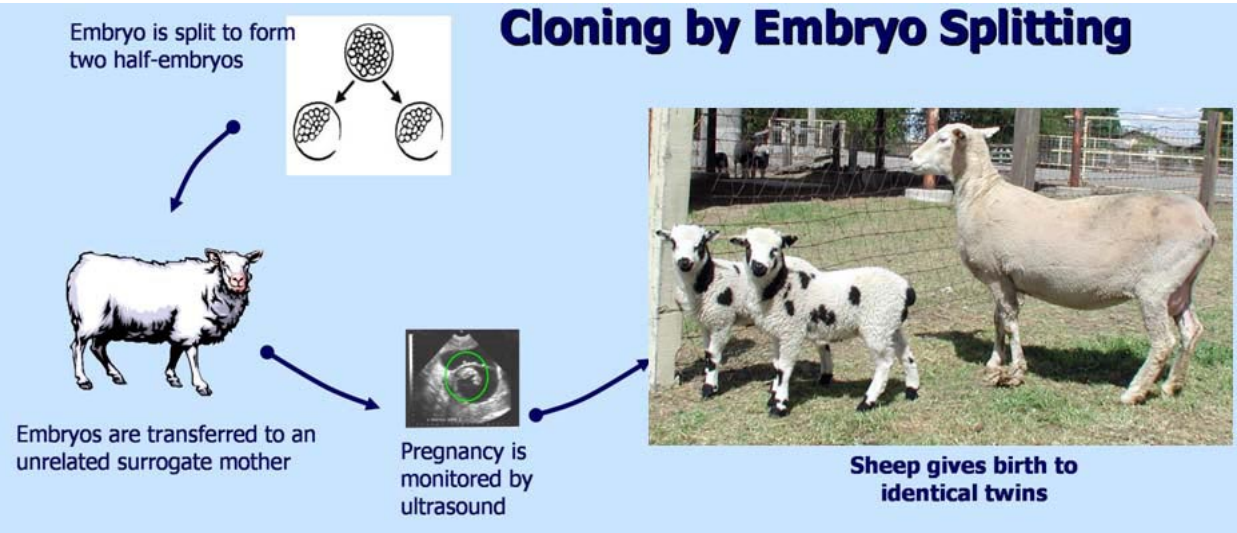
The birth of Dolly in 1996, the first animal cloned from an adult cell, was not universally celebrated. Critics of biotechnology worried that genetically modified livestock would fill the supermarket with identical copies of someone's idea of unnatural perfection. In fact, cloning does not alter the genetic makeup of an animal, and is unlikely to be extensively used in animal agriculture due to the cost associated with making a clone. The cost to clone a cow is around $15,000, much more than the value of most commercial cows, and it will most likely be used only to reproduce elite breeding stock.

Q: What is a clone?

A: A clone is an organism that is descended from — and is genetically identical to — a single common ancestor. Cloning involves making genetically identical copies of a plant or animal, using asexual reproduction. Many common fruits and vegetables (e.g., pears, apples, oranges and potatoes) are clones, and cloned livestock have been a part of animal agriculture for over 20 years. Animals can be cloned by two different methods: mechanical embryo splitting or nuclear transfer.

Embryo splitting involves bisecting the multi-cellular embryo at an early stage of development to generate clones or "twins." A 32-cell embryo, for example, might be bisected into two 16-cell twins. This type of cloning occurs naturally (human identical twins result from this process, but fraternal twins do not), but it can also be performed in a laboratory where it has been successfully used to produce clones from a number of different animal species. This technique was first used in agriculture to replicate valuable dairy breeding animals in the 1980s. The Holstein Association USA registered their first embryo split clone in 1982, and more than 2300 had been registered by October 2002[1]. This method has a practical limitation in cattle[2] and sheep[3], in that a maximum of four clones can be produced from each embryo.

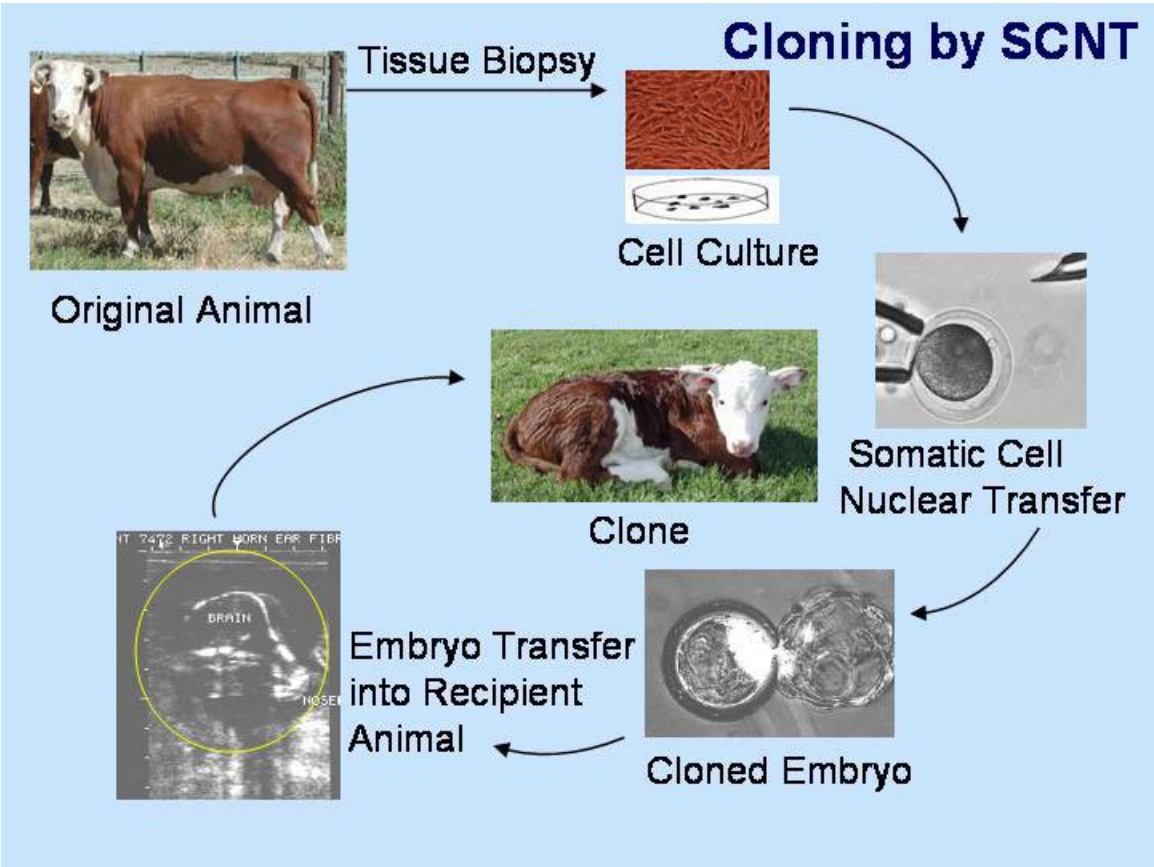


Cloning can also be done by nuclear transfer, where the genetic material from the nucleus of one cell is placed into a “recipient” unfertilized egg that has had its genetic material removed by a process called enucleation. In order to begin the development process, the donor nucleus must be fused with the egg through the administration of a brief electrical pulse or a chemical fusion process, after which the embryo starts to divide as if it had been fertilized. In the case of mammals, the embryo is then placed into a surrogate mother where it will develop until birth, at which point it will be delivered in the same way as any newborn.

Mammals were first cloned via nuclear transfer during the early 1980s, almost 30 years after the initial successful experiments with frogs[4]. Numerous mammalian clones followed — including mice, rats, rabbits, pigs, goats, sheep[5], cattle[6], and even two rhesus monkeys named Neti and Detto[7] — all as a result of nuclear transfer. The Holstein Association USA registering their first embryo nuclear transfer clone in 1989, and approximately 1,200–1,500 cows and bulls were produced by embryonic cell nuclear transfer in North America in the 1980s and 1990s[8]. However all of these clones were produced from the transfer of nuclei derived from early (8-32 cell) embryos, and therefore a theoretical maximum of only 32 clones could be produced from each individual embryo. And then in 1996, along came Dolly.

Q: What was so special about Dolly?

A: Dolly the sheep, was the first animal to be cloned via nuclear transfer from a cultured somatic cell derived from an adult[9]. This process, known as SCNT (for somatic cell nuclear transfer) cloning, allows cloning to be performed on a potentially unlimited number of cells from an adult animal whose performance and traits are well known. This allowed cloning technology to be extended to make copies of elite breeding animals with well established breeding superiority based on their own performance records, and those of their offspring.



A diverse range of species have now been successfully cloned from adult tissues using SCNT including cattle[10], mice[11], pigs[12], cats[13], rabbits[14], horses[15], goats[16], dogs[17], rats[18], and zebra fish [19]. It was estimated in October 2007 that there were 500-600 SCNT livestock clones in the United States (Barbara Glenn, Biotechnology Industry Organization, personal communication). Very few of these valuable clones will themselves enter the food supply, rather food products will likely be milk and meat derived from the sexually produced offspring of these SCNT clones.

Q. Why is cloning inefficient?

A: The proportion of adult somatic cell nuclei that successfully develop into live offspring, after transfer into an enucleated egg, is very low[20]. High rates of pregnancy loss have been observed after transfer of the eggs containing the adult cell nuclei into recipient animals[21]. On average, only 9% of transferred embryos result in calves; with efficiencies ranging from 0 to 45% depending upon the type of somatic tissue from which the transferred nucleus was derived[22]. The problems associated with the cloning process are not unique to SCNT cloning, and all have been observed in animals derived via other commonly-used assisted reproductive technologies (e.g. embryo transfer, in vitro fertilization), and even natural mating[23]. However, the frequency of problems tends to be higher in SCNT clones.

Q. Are clones and their progeny healthy?

A: Various abnormalities such as such as 'large offspring syndrome' (where cloned lambs and calves are often large at birth), placental abnormalities, edema, and perinatal deaths have been observed in cloned animals, with frequencies that are at least partially dependent upon the type of somatic tissue from which the transferred nucleus was derived. On average, 42% of cloned calves die between delivery and 150 days of life[24]. Although cloning poses no risks that are unique and distinct from those encountered in animals involved in modem agricultural practices, the frequency of the risks is increased in cattle during the early portions of the life cycle. However, adult cloned cows have been observed to have normal breeding and calving rates and cloned bulls produce good quality semen and have normal fertility when used for artificial insemination or natural mating. To date, there has been no evidence of clone-associated abnormalities being passed on to their offspring following sexual reproduction. This suggests that abnormalities seen in clones are not heritable and appear to be corrected during gametogenesis (the formation of eggs and sperm).

Q: Is the milk or meat from clones safe? Is it the same?

A: Studies examining the composition of food products derived from clones have found that they have the same composition as milk or meat from conventionally-produced animals [1,8,25-32]. Milk and meat from clones produced by embryo splitting and nuclear transfer of embryonic cells have been entering the human food supply for over 20 years with no evidence of problems. However, in 2001 the Center for Veterinary Medicine at the FDA determined that it should undertake a comprehensive risk assessment to identify hazards and characterize food consumption risks that may result from SCNT animal clones[33] and therefore asked companies not to introduce these cloned animals, their progeny, or their food products (e.g. milk or meat) into the human or animal food supply (http://www.fda.gov/cvm/CVM_Updates/clones.htm). As there is no fundamental reason to suspect that clones will produce novel toxins or allergens, the main underlying food safety concern was whether the SCNT cloning process results in subtle changes in the composition of animal food products [34]. They asked companies and producers to adhere to a voluntary moratorium not to introduce SCNT cloned animals, their progeny, or their products into the human or animal food supply during the multiyear duration of the risk assessment.

On January 15th, 2008 the FDA published its final 968-page risk assessment on animal cloning which examined all existing data relevant to 1) the health of clones and their progeny, or 2) food consumption risks resulting from their edible products, and found that no unique food safety risks were identified in cloned animals. This report, which summarizes all available data on clones and their progeny, concludes that meat and milk products from cloned cattle, swine and goats, and the offspring of any species traditionally consumed as food, are as safe to eat as food from conventionally bred animals (http://www.fda.gov/cvm/CloneRiskAssessment_Final.htm).

Q. Are the progeny of clones safe to eat?

A: There have been a limited number of peer-reviewed studies on the offspring of clones, three in pigs[29,35,36], and three in cattle[24,37,38]. This is perhaps not surprising given that it is estimated that at the current time there are only 500-600 SCNT livestock clones in the United States (Barbara Glenn, Biotechnology Industry Organization, personal communication). The largest study of the progeny of clones compared the quality and composition of meat derived from the progeny of cloned swine and non-cloned swine. That study was carried out by ViaGen (www.viagen.com), a company that provides animal cloning services, and reported data on 404 swine: 242 clone progeny and 162 comparators. The composition of meat samples from these two groups was indistinguishable[29]. After reviewing this large data set, the FDA concluded that all of the blood values, overall health records, and meat composition profiles of the progeny of clones were in the same range as for very closely related conventionally bred swine.

Although the amount of data describing the health of the progeny of clones is more limited than the amount describing the health of animal clones themselves, there is an underlying biological assumption behind the predicted health and resultant food safety of the sexually-produced progeny of clones. The genetic remodeling process that occurs during gametogenesis (i.e. the production of eggs and sperm), is thought to naturally reset any epigenetic anomalies that might result from the cloning process. In other words, sexual reproduction effectively corrects any programming errors that may have been introduced into the cloned parent's DNA, thereby resulting in the production of normal gametes and offspring. This assumption is supported by peer-reviewed studies in mice where it has been observed that abnormalities present in cloned mice are not passed on to their sexually-derived progeny[39]. In addition, observations on the relatively small number of progeny of bovine and swine clones that have been born support the premise of normal development. Sexually-produced progeny of clones show no evidence of the developmental abnormalities that are sometimes observed in cloned animals themselves.

Are other regulatory authorities confident that the progeny of cloned animals are safe to eat?

The FDA's assessment that the progeny of SCNT clones are not likely to pose food safety concerns is shared by the National Academy of Sciences[40], and international food safety authorities including the European Food Safety Authority which recently released a report stating that "*it is very unlikely that any difference exists in terms of food safety between food products originating from clones and their progeny compared with those derived from conventionally bred animals,"* [i] and Food Standards Australia New Zealand (FSANZ) which concluded that "*there are well founded scientific reasons, supported by a mounting body of experimental evidence, to confidently expect that the health profile of any offspring, produced by natural mating, would be entirely normal."* [ii] The FDA is not recommending any additional labeling or withholding of milk or meat from the progeny of clones. In a stakeholder teleconference on January 15th, 2008, the USDA stated that "based on the findings that the FDA has shown, it would not be necessary to continue with the moratorium on the progeny." This effectively opened the way for milk and meat from the progeny of clones to enter the food supply.

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[i] **http://www.efsa.europa.eu/EFSA/DocumentSet/sc_opinion_clon_public_consultation.pdf**
[ii] **http://www.foodstandards.gov.au/_srcfiles/Cloning_Review_Final_June%202003.pdf**

U.S. Food and Drug Administration Information on Animal Cloning

- http://www.fda.gov/cvm/CloningRA_FAQConsumers.htm
- http://www.fda.gov/cvm/CloningRA_Primer.htm
- http://www.fda.gov/cvm/CloningRA_Myths.htm

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