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Written by Judith L. Fridovich-Keil
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Dolly In 1996 Dolly made history as the first successfully cloned mammal. She is pictured standing in her pen at the Roslin Insti...(more)

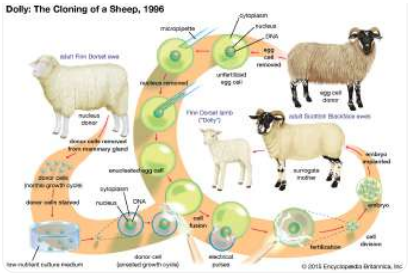
Dolly, female Finn Dorset sheep that lived from 1996 to 2003, the first clone of an adult mammal, produced by British developmental biologist Ian Wilmut and colleagues of the Roslin Institute, near Edinburgh, Scotland. The announcement in February 1997 of Dolly's birth marked a milestone in science, dispelling decades of presumption that adult mammals could not be cloned and igniting a debate concerning the many possible uses and misuses of mammalian cloning technology.

The concept of mammalian clones, even humans, was not new at the time of Dolly's birth. Among mammals, naturally occurring genetic clones, or individuals genetically identical to one another, had long been recognized in the form of monozygotic (identical) twins. Unlike Dolly, however, such clones are derived from a single zygote, or fertilized egg, and thus they are clones of one another, rather than clones of another individual. Moreover, clones had been generated previously in the laboratory, but only from embryonic cells that were either undifferentiated or only partially differentiated. In animals, the production of clones from fully differentiated (adult) cells (e.g., skin or muscle cells) had been carried out successfully only in lower species, such as frogs.

For decades, scientists had tried and failed to clone mammals from existing adults. The repeated failures led scientists to speculate about the significance of the timing and process of cell differentiation in the developing mammalian embryo. Of particular interest were changes that occurred to DNA during an animal's development, whereby patterns in gene expression were altered as cells became increasingly specialized in function. It was realized that, through the process of differentiation, adult mammalian cells lose totipotency—the ability to become any of the different cell types required for making a complete and viable animal. It was presumed that the process was irreversible. The successful production of Dolly, however, proved otherwise.

Dolly was cloned from a mammary gland cell taken from an adult Finn Dorset ewe. Wilmut and his team of researchers at Roslin created her by using electrical pulses to fuse the mammary cell with an unfertilized egg cell, the nucleus of which had been removed. The fusion process resulted in the transfer of the mammary cell nucleus

into the egg cell, which then began to divide. In order for the mammary cell nucleus to be accepted and functional within the host egg, the cell first had to be induced to abandon the normal cycle of growth and division and enter a quiescent stage. To accomplish that, researchers deliberately withheld nutrients from the cells. The importance of the step had been determined experimentally, though an explanation for its necessity was lacking. Nevertheless, starting with a collection of mammary cell nuclei and host egg cytoplasms derived from Scottish Blackface ewes, a number of fused couplets successfully formed embryos. The reconstructed embryos were transferred to surrogate Scottish Blackface ewes. Of 13 recipient ewes, one became pregnant, and 148 days later, which is essentially normal gestation for a sheep, Dolly was born.



How was Dolly cloned? Dolly the sheep was successfully cloned in 1996 by fusing the nucleus from a mammary-glan...(more)

Dolly remained alive and well long after her birth, with a functional heart, liver, brain, and other organs, all derived genetically from the nuclear DNA of an adult mammary gland cell. The technique used to produce her later became known as somatic cell nuclear transfer (SCNT). SCNT has since been used to generate a wide variety of mammalian clones, from different types of adult cells; its success in producing clones of primates, however, has been notably limited.

On February 14, 2003, Dolly was euthanized by veterinarians after being found to suffer from progressive lung disease. Her body was preserved and displayed at the National Museum of Scotland in Edinburgh.

Judith L. Fridovich-Keil

cloning

genetics

Also known as: reproductive cloning

Written by Michael Rugnetta
Fact-checked by The Editors of Encyclopaedia Britannica

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Dolly the sheep Dolly the sheep, the first clone of an adult mammal, at the Roslin Institute, near Edinburgh.

Key People: Steen Willadsen • Gordon L. Woods • John Gurdon • Robert P. Lanza

Related Topics: biotechnology • nuclear transfer • clone • science

cloning, the process of generating a genetically identical copy of a cell or an organism. Cloning happens often in nature—for example, when a cell replicates itself asexually without any genetic alteration or

recombination. Prokaryotic organisms (organisms lacking a cell nucleus) such as bacteria create genetically identical duplicates of themselves using binary fission or budding. In eukaryotic organisms (organisms possessing a cell nucleus) such as humans, all the cells that undergo mitosis, such as skin cells and cells lining the gastrointestinal tract, are clones; the only exceptions are gametes (eggs and sperm), which undergo meiosis and genetic recombination.

In biomedical research, cloning is broadly defined to mean the duplication of any kind of biological material for scientific study, such as a piece of DNA or an individual cell. For example, segments of DNA are replicated exponentially by a process known as polymerase chain reaction, or PCR, a technique that is used widely in basic biological research. The type of cloning that is the focus of much ethical controversy involves the generation of cloned embryos, particularly those of humans, which are genetically identical to the organisms from which they are derived, and the subsequent use of these embryos for research, therapeutic, or reproductive purposes.

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Hwang Woo Suk and Gerald Schatten South Korean cloning and stem cell researcher Hwang Woo Suk (le...(more)

Will cloning bring the woolly mammoth back to life? Woolly mammoths became largely extinct about 10,000 years ago...(more)

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Early cloning experiments

Reproductive cloning was originally carried out by artificial “twinning,” or embryo splitting, which was first performed on a salamander embryo in the early 1900s by German embryologist Hans Spemann. Later, Spemann, who was awarded the Nobel Prize for Physiology or Medicine (1935) for his research on embryonic development, theorized about another cloning procedure known as nuclear transfer. This procedure was performed in 1952 by American scientists Robert W. Briggs and Thomas J. King, who used DNA from embryonic cells of the frog *Rana pipiens* to generate cloned tadpoles. In 1958 British biologist John Bertrand Gurdon successfully carried out nuclear transfer using DNA from adult intestinal cells of African clawed frogs (*Xenopus laevis*). Gurdon was awarded a share of the 2012 Nobel Prize in Physiology or Medicine for this breakthrough.

How Dolly the sheep was cloned Overview of somatic cell nuclear transfer (SCNT). In 1996 the first clone of an adult mamm...(more)

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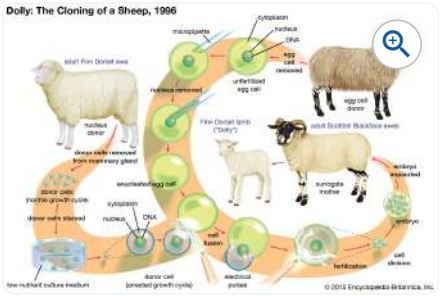
Advancements in the field of molecular biology led to the development of techniques that allowed scientists to manipulate cells and to detect chemical markers that signal changes within cells. With the advent of recombinant DNA technology in the 1970s, it became possible for scientists to create transgenic clones—clones with genomes containing pieces of DNA from other organisms. Beginning in the 1980s mammals such as sheep were cloned from early and partially differentiated embryonic cells. In 1996 British developmental biologist Ian Wilmut generated a cloned sheep, named Dolly, by means of nuclear transfer involving an enucleated embryo and a differentiated cell nucleus. This technique, which was later refined and became known as somatic cell nuclear transfer (SCNT), represented an extraordinary advance in the science of cloning, because it resulted in the creation of a genetically identical

clone of an already grown sheep. It also indicated that it was possible for the DNA in differentiated somatic (body) cells to revert to an undifferentiated embryonic stage, thereby reestablishing pluripotency—the potential of an embryonic cell to grow into any one of the numerous different types of mature body cells that make up a complete organism. The realization that the DNA of somatic cells could be reprogrammed to a pluripotent state significantly impacted research into therapeutic cloning and the development of stem cell therapies.

CC, the first cloned cat The first cloned cat, named CC (or Copy Cat), was born on December 22, 2001, to her surrogate r...(more)

Soon after the generation of Dolly, a number of other animals were cloned by SCNT, including pigs, goats, rats, mice, dogs, horses, and mules. Despite those successes, the birth of a viable SCNT primate clone would not come to fruition until 2018, and scientists used other cloning processes in the meantime. In 2001 a team of scientists cloned a rhesus monkey through a process called embryonic cell nuclear transfer, which is similar to SCNT except that it uses DNA from an undifferentiated embryo. In 2007 macaque monkey embryos were cloned by SCNT, but those clones lived only to the blastocyst stage of embryonic development. It was more than 10 years later, after improvements to SCNT had been made, that scientists announced the live birth of two clones of the crab-eating macaque (*Macaca fascicularis*), the first primate clones using the SCNT process. (SCNT has been carried out with very limited success in humans, in part because of problems with human egg cells resulting from the mother's age and environmental factors.)

Reproductive cloning



Dolly the sheep and her cloning Dolly the sheep was cloned using the process of somatic cell nuclear transfer (SCNT). T...(more)

Reproductive cloning involves the implantation of a cloned embryo into a real or an artificial uterus. The embryo develops into a fetus that is then carried to term. Reproductive cloning experiments were performed for more than 40 years through the process of embryo splitting, in which a single early-stage two-cell embryo is manually divided into two individual cells and then grows as two identical embryos. Reproductive cloning techniques underwent significant change in the 1990s, following the birth of Dolly, who was generated through the process of SCNT. This process entails the removal of the entire nucleus from a somatic (body) cell of an organism, followed by insertion of the nucleus into an egg cell that has had its own nucleus removed (enucleation). Once the somatic nucleus is inside the egg, the egg is stimulated with a mild electrical current and begins dividing. Thus, a cloned embryo, essentially an embryo of an identical twin of the original organism, is created. The SCNT process has undergone significant refinement since the 1990s, and procedures have been developed to prevent damage to eggs during nuclear extraction and somatic cell nuclear insertion. For example, the use of polarized light to visualize an egg cell's nucleus facilitates the extraction of the nucleus from the egg, resulting in a healthy, viable egg and thereby increasing the success rate of SCNT.

Reproductive cloning using SCNT is considered very harmful since the fetuses of embryos cloned through SCNT rarely survive gestation and usually are born with birth defects. Wilmut's team of scientists needed 277 tries to create Dolly. Likewise, attempts to produce a macaque monkey clone in 2007 involved 100 cloned embryos,

implanted into 50 female macaque monkeys, none of which gave rise to a viable pregnancy. In January 2008, scientists at Stemagen, a stem cell research and development company in California, announced that they had cloned five human embryos by means of SCNT and that the embryos had matured to the stage at which they could have been implanted in a womb. However, the scientists destroyed the embryos after five days, in the interest of performing molecular analyses on them.

Therapeutic cloning

Therapeutic cloning is intended to use cloned embryos for the purpose of extracting stem cells from them, without ever implanting the embryos in a womb. Therapeutic cloning enables the cultivation of stem cells that are genetically identical to a patient. The stem cells could be stimulated to differentiate into any of the more than 200 cell types in the human body. The differentiated cells then could be transplanted into the patient to replace diseased or damaged cells without the risk of rejection by the immune system. These cells could be used to treat a variety of conditions, including Alzheimer disease, Parkinson disease, diabetes mellitus, stroke, and spinal cord injury. In addition, stem cells could be used for in vitro (laboratory) studies of normal and abnormal embryo development or for testing drugs to see if they are toxic or cause birth defects.

Although stem cells have been derived from the cloned embryos of animals such as mice, the generation of stem cells from cloned primate embryos has proved exceptionally difficult. For example, in 2007 stem cells successfully derived from cloned macaque embryos were able to differentiate into mature heart cells and brain neurons. However, the experiment started with 304 egg cells and resulted in the development of only two lines of stem cells, one of which had an abnormal Y chromosome. Likewise, the production of stem cells from human embryos has been fraught with the challenge of maintaining embryo viability. In 2001 scientists at Advanced Cell Technology, a research company in Massachusetts, successfully transferred DNA from human cumulus cells, which are cells that cling to and nourish human eggs, into eight enucleated eggs. Of these eight eggs, three developed into early-stage embryos (containing four to six cells); however, the embryos survived only long enough to divide once or twice. In 2004 South Korean researcher Hwang Woo Suk claimed to have cloned human embryos using SCNT and to have extracted stem cells from the embryos. However, this later proved to be a fraud; Hwang had fabricated evidence and had actually carried out the process of parthenogenesis, in which an unfertilized egg begins to divide with only half a genome. The following year a team of researchers from the University of Newcastle upon Tyne was able to grow a cloned human embryo to the 100-cell blastocyst stage using DNA from embryonic stem cells, though they did not generate a line of stem cells from the blastocyst. Scientists have since successfully derived embryonic stem cells from SCNT human embryos.

Progress in research on therapeutic cloning in humans has been slow relative to the advances made in reproductive cloning in animals. This is primarily because of the technical challenges and ethical controversy arising from the procuring of human eggs solely for research purposes. In addition, the development of induced pluripotent stem cells, which are derived from somatic cells that have been reprogrammed to an embryonic state through the introduction of specific genetic factors into the cell nuclei, has challenged the use of cloning methods and of human eggs.

Ethical controversy

Human reproductive cloning remains universally condemned, primarily for the psychological, social, and physiological risks associated with cloning. A cloned embryo intended for implantation into a womb requires thorough molecular testing to fully determine whether an embryo is healthy and whether the cloning process is complete. In addition, as demonstrated by 100 failed attempts to generate a cloned macaque in 2007, a viable pregnancy is not guaranteed. Because the risks associated with reproductive cloning in humans introduce a very high likelihood of loss of life, the process is considered unethical. There are other philosophical issues that also have been raised concerning the nature of reproduction and human identity that reproductive cloning might violate. Concerns about eugenics, the once popular notion that the human species could be improved through the selection of individuals possessing desired traits, also have surfaced, since cloning could be used to breed "better" humans, thus violating principles of human dignity, freedom, and equality.

Can cloning save endangered species?
Overview of the potential use of cloning in conservation of species.

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There also exists controversy over the ethics of therapeutic and research cloning. Some individuals and groups have an objection to therapeutic cloning, because it is considered the manufacture and destruction of a human life, even though that life has not developed past the embryonic stage. Those who are opposed to therapeutic cloning believe that the technique supports and encourages acceptance of the idea that human life can be created and expended for any purpose. However, those who support therapeutic cloning believe that there is a moral imperative to heal the sick and to seek greater scientific knowledge. Many of these supporters believe that therapeutic and research cloning should be not only allowed but also publicly funded, similar to other types of disease and therapeutics research. Most supporters also argue that the embryo demands special moral consideration, requiring regulation and oversight by funding agencies. In addition, it is important to many philosophers and policy makers that women and couples not be exploited for the purpose of obtaining their embryos or eggs.

There are laws and international conventions that attempt to uphold certain ethical principles and regulations concerning cloning. In 2005 the United Nations passed a nonbinding Declaration on Human Cloning that calls upon member states "to adopt all measures necessary to prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life." This does provide leeway for member countries to pursue therapeutic cloning. The United Kingdom, through its Human Fertilisation and Embryology Authority, issues licenses for creating human embryonic stem cells through nuclear transfer. These licenses ensure that human embryos are cloned for legitimate therapeutic and research purposes aimed at obtaining scientific knowledge about disease and human development. The licenses require the destruction of embryos by the 14th day of development, since this is when embryos begin to develop the primitive streak, the first indicator of an organism's nervous system. The United States federal government has not passed any laws regarding human cloning due to disagreement within the legislative branch about whether to ban all cloning or to ban only reproductive cloning. The Dickey-Wicker amendment, attached to U.S. appropriations bills since 1995, has prevented the use of federal dollars to fund the harm or destruction of human embryos for research. It is presumed that nuclear transfer and any other form of cloning is subject to this restriction.

genetic engineering

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genetically engineered salmon A genetically engineered salmon (top) and a natural salmon of the same age. The a...(more)

Key People: Ian Wilmut • George Ledyard Stebbins, Jr.

Related Topics: recombinant DNA • genetically modified organism • gene editing • three-parent baby...*(Show more)*

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genetic engineering, the artificial manipulation, modification, and recombination of DNA or other nucleic acid molecules in order to modify an organism or population of organisms. The term *genetic engineering* is generally used to refer to methods of recombinant DNA technology, which emerged from basic research in microbial genetics. The techniques employed in genetic engineering have led to the production of medically important products, including human insulin, human growth hormone, and hepatitis B vaccine, as well as to the development of genetically modified organisms such as disease-resistant plants.

Historical developments

The term *genetic engineering* initially referred to various techniques used for the modification or manipulation of organisms through the processes of heredity and reproduction. As such, the term embraced both artificial selection and all the interventions of biomedical techniques, among them artificial insemination, in vitro fertilization (e.g., “test-tube” babies), cloning, and gene manipulation. In the latter part of the 20th century, however, the term came to refer more specifically to methods of recombinant DNA technology (or gene cloning), in which DNA molecules from two or more sources are combined either within cells or in vitro and are then inserted into host organisms in which they are able to propagate.

genetically modified humans CRISPR and genetically modified humans.

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The possibility for recombinant DNA technology emerged with the discovery of restriction enzymes in 1968 by Swiss microbiologist Werner Arber. The following year American microbiologist Hamilton O. Smith purified so-called type II restriction enzymes, which were found to be essential to genetic engineering for their ability to cleave a specific site within the DNA (as opposed to type I restriction enzymes, which cleave DNA at random sites). Drawing on Smith’s work, American molecular biologist Daniel Nathans helped advance the technique of DNA recombination in 1970–71 and demonstrated that type II enzymes could be useful in genetic studies. Genetic engineering based on recombination was pioneered in 1973 by American biochemists Stanley N. Cohen and Herbert W. Boyer, who were among the first to cut DNA into fragments, rejoin different fragments, and insert the new genes into *E. coli* bacteria, which then reproduced.