Breakthroughs IN BIOSCIENCE

Cloning: Past, Present, and the Exciting Future

by Marie A. Di Berardino, Ph.D.

The not-too-distant future

Jimmy walks into the neighborhood pharmacy to fill his prescription for a protein he was born without. He lacks the gene for blood clotting factor IX and relies on the local drugstore for his medicine. Jimmy pulls open the bag that contains his 90-day supply of patches, removes the old patch from his chest, and attaches a new one. He adjusts his jersey and heads out to meet his buddies for a game of touch football. Even though he is hemophiliac, Jimmy isn't worried about the bruises and scrapes he is sure to get.

Similarly,

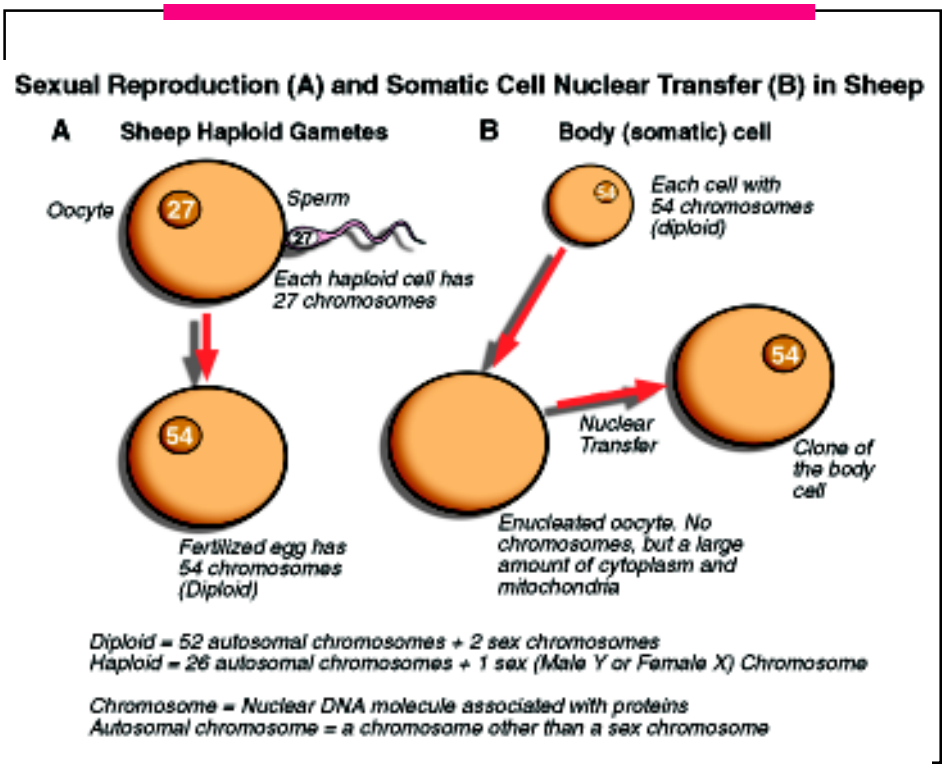
- Christine is scheduled to have her *own* genetically reprogrammed skin cells transplanted to replace her severely damaged heart cells.
- Margo, who has Parkinson's disease, receives special nerve cells. She is not concerned about tissue incompatibility and rejection, because these cells are her own genetically reprogrammed skin cells.
- Patients routinely buy anti-cancer or anti-viral drugs in large quantities to treat their conditions.

This is the future. It is what Dolly so wondrously has wrought. Born July 1996, she is the first mammal successfully cloned from an adult cell, one taken from a ewe's mammary gland.

Nuclear transfer

Dolly was not created in the ordinary way. Typically, a lamb is the product of natural reproduction—two germ cells, a sperm from an adult male and an egg (oocyte) from an adult female, fuse at fertilization. Each of these germ cells (the sperm and the oocyte) contributes half the chromosomes needed to create a new individual. Chromosomes are found in the cell's nucleus and they carry the DNA, which is the genetic blueprint for an individual.

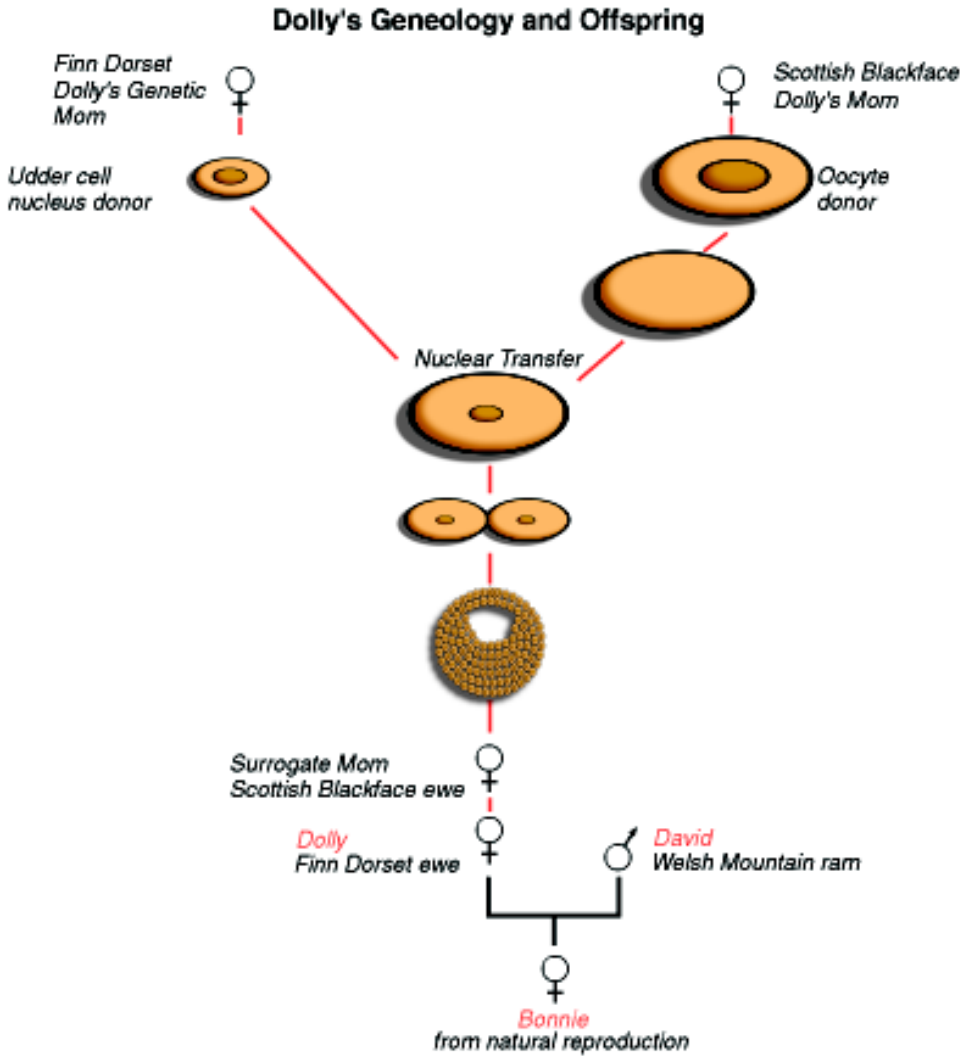
The process that produced Dolly differs from ordinary reproduction in two major ways. First, body (or somatic) cells from an adult ewe's udder (this is the donor) were placed in a culture dish and allowed to grow. The nutrients were then removed from the culture, which stopped the cells' growth. One of these non-growing cells was then fused (by electric jolts) with another ewe's oocyte from which the nucleus had been previously removed (i.e.,



enucleated, so it had no chromosomes). This procedure is known as 'somatic cell nuclear transfer'. Within a day the fused cells began to divide in the culture dish. After several divisions, the early embryo was transferred to the uterus of a surrogate mother and allowed to develop.

Second, unlike the sperm and the egg, each of which contributes half the number of chromosomes at fertilization, each body cell contains twice the number of chromosomes in each germ cell. So fusion of a sperm and an egg forms an individual whose full genetic composition is unique to that individual. On the other hand, the embryo cloned from somatic cell nuclear transfer begins development with the diploid (double) number of chromosomes, all derived from one somatic cell (adult udder) of a single individual. This embryo has the same nuclear genetic composition as the donor of the somatic cell.

In the end, three sheep contributed to the production of a single lamb clone: a Finn Dorset sheep donated her udder cells for culture; a Scottish Blackface sheep donated the enucleated oocyte (with its nucleus removed, thus losing its own genetic identity in the process); and a Scottish Blackface sheep became the surrogate



Timeline

This illustrated timeline shows essential milestones in basic research that led to the cloning of Dolly and beyond, and some benefits derived from that research. Some of the initial hypotheses have been refuted by later studies.

1880s

Wilhelm Roux and August Weismann independently propose the germ plasm theory: The egg and sperm contribute chromosomes equally to the zygote (fertilized egg). The chromosomes are carriers of the hereditary potentials, and the germ cells (gametes) of the embryo are the only ones to carry the complete set of hereditary potentials (nuclear determinants), whereas each somatic (body) cell type contains only part of these potentials required for the specific cell type.

1888

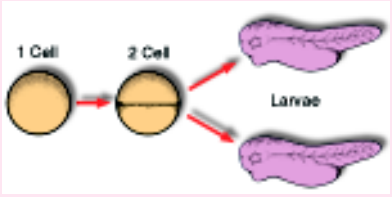
Wilhelm Roux performs the first test of the germ plasm theory: Destruction of one cell of the 2-cell frog embryo with a hot needle results in development of a half-embryo, supporting mistakenly the Roux-Weismann theory.

1894

Hans Dreisch isolates blastomeres of 2- and 4-cell embryos of sea urchins and observes development of blastomeres into small but complete larvae. These and other experiments disprove the Weismann-Roux theory.

1901

Hans Spemann splits a 2-cell newt embryo into two parts, successfully producing two larvae.



mother, carrying the embryo to birth. The clone (Dolly) was easily identified because she had the physical traits of the Finn Dorset sheep that donated the udder cells and differed from the traits of the Scottish Blackface sheep used as the surrogate mother and the oocyte donor.

And now Dolly herself is a mother—the old-fashioned way—by mating with David, a Welsh mountain ram, and giving birth to Bonnie. In fact, Bonnie now has other siblings.

Can Dolly help Jimmy, Christine, and Margo?

Imagine herds of female sheep, cattle, and goats producing large quantities of human proteins in their milk, an ideal place for those proteins to be harvested and used to treat patients like Jimmy, the hemophiliac, whose blood cannot clot. We can realize this dream today—one step at a time, because the process that produced Dolly also can be used to produce the transgenic (one species carrying another species' genes) clones.

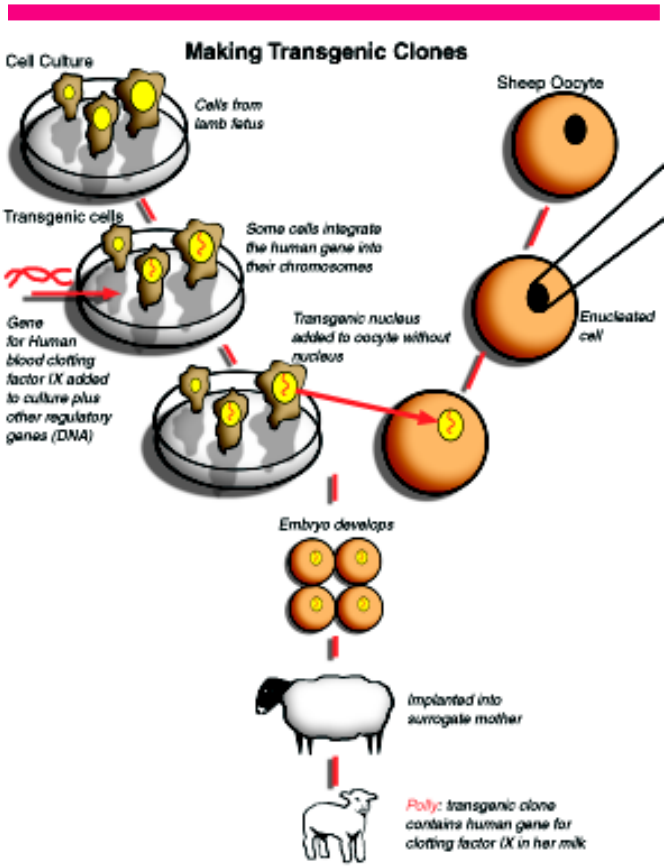
Scottish scientists first removed cells from a fetal lamb and grew them in a culture dish. Multiple copies of fragments of DNA (deoxyribonucleic acid, which holds genetic information) containing the human gene for blood clotting factor IX were added to the dish and coaxed into the cells. Some cells incorporated the human DNA into their chromosomes, thus becoming 'transgenic cells', or cells containing a transferred gene.

These transgenic cells were then separated from those without human DNA and used to create Polly, the transgenic sheep that today produces the human clotting factor IX in her milk. Purposely, scientists genetically designed the transgenic sheep clones so that the human gene would function only in the mammary gland.

It will soon be possible for the human clotting factor IX protein to be routinely harvested and purified from the sheep milk. Obviously, researchers still need to conduct controlled clinical studies before this protein is available for hemophiliacs like Jimmy, but they have already made an astonishing breakthrough.

Transgenic clones

The importance of the transgenic clones is that biotechnology is now being extended to produce different human proteins like insulin (diabetes), interferon (viral infections), clotting



1914

Spermann conducts early nuclear transfer. By using a strand of baby hair, he partially constricts a newly fertilized egg cell (zygote), forcing the nucleus to one side and only cytoplasm to the other. As the nucleus side of the cell divides successively to the16-cell stage, a nucleus slips over to the cytoplasm on the other side. Cell division starts on this side also, and the hair knot is tightened, preventing further nuclear transfer. Twin larvae develop, one slightly older (the side with the initial nucleus) than the other (the side with the initial cytoplasm). This proved that the nucleus from a 16-cell stage could direct the growth of another larva.

factor VIII (hemophilia), and tissue plasminogen activator (dissolving blood clots). In other words, female clones of such animals as cattle, sheep, and goats are being genetically designed to be dairy/pharmaceutical producers, a virtual living bio-pharmaceutical industry. Transgenic clones of mammals are a major advance in biotechnology because they can synthesize, in large quantities, complex molecules critically required for patient care. The current recombinant DNA technology in bacteria is capable of synthesizing only simple proteins, but not the complex molecules that sheep can produce in large quantities in their milk. Indeed, Jimmy will be able to wear his patch very soon.

While these advances are on the horizon for us, beneficial applications to agriculture are already being implemented. Transgenic cloning can be used for the genetic improvement of livestock related to milk production, quality of meat, growth rate, reproduction, nutrition, behavioral traits, and/or resistance to diseases. This cloning process simply accelerates the older, slower, and less predictable methods of crossbreeding and hybridization.

Strictly speaking, clones obtained from nuclear transfer are not exact copies of the donor. A clone like Dolly produced by oocyte-somatic cell fusion is a mosaic—a mixture of the oocyte and body cell. In addition to the nucleus, the donor cell contributes a tiny amount of cytoplasm and cell membrane to the oocyte, but the egg cell contributes an enormous amount of cytoplasm and cell membrane to the fused product. In fact, virtually all mitochondria (the organelles in the cytoplasm that are the major source of cell energy and contain DNA of their own) are derived from the oocyte cytoplasm. So cloning of multicellular organisms is not equal to true cellular cloning that results from asexual reproduction, when a one-celled organism like the amoeba divides and clones itself.

Similarly, plants clone themselves when they reproduce by budding or sprouting new shoots. The agricultural industry has intentionally propagated—by cloning—bananas, grapes, apples, sugar cane, pineapples, potatoes, asparagus, and many other plants. Identical twins and triplets that occur among many multicellular animal species including humans, are derived by a cloning process. A cell, isolated from other cells growing in a culture dish, gives rise after cell division to a clone. All these examples include the exact duplication of the whole body cell, including the nucleus, cytoplasm, and cell membrane.

We are only beginning to understand the molecular changes involved in nuclear reprogramming, yet this line of basic research may result in some of the most beneficial applications to humans. It might permit us to de-differentiate mature cells and re-differentiate them into specific cell types required for tissue repair.

Why is this such a big deal?

Dolly has debunked a long-held, generally accepted biological concept: Adult cells have their fate sealed; put another way, once an udder cell, always an udder cell. This means that the genetic status of the adult donor nucleus had to be reprogrammed, and that the oocyte cytoplasm seems to contain the appropriate molecules to trigger this reprogramming. The value of cloning from an adult cell is that we can predict that the clone will be very much like the donor animal, whereas we cannot do so when the clone is derived from an embryonic or fetal cell. Even when the parents of embryos and fetuses are known, we cannot yet foretell exactly the physical traits of their offspring; they are a combination of traits from both parents. Additional variations occur

1940s – 1950s

Various species of mammalian embryos are cloned by embryo splitting, but success is limited to splitting of embryos at stages prior to implantation to the uterus.

1952

Robert Briggs and Thomas J. King transplant a nucleus from a frog embryo somatic cell into an unfertilized, enucleated oocyte. These injected eggs developed into tadpoles and many metamorphosed into juvenile frogs. This technique, nuclear transplantation (nuclear transfer) becomes the prototype experiment for cloning multicellular organisms.

1961-62

John B. Gurdon and Robert G. McKinnell, by using the nuclear transfer method on different species of frog (*Xenopus* and *Rana*, respectively), obtain adult frogs that produced normal progeny. This demonstrates totipotency of embryonic nuclei.

1962-65

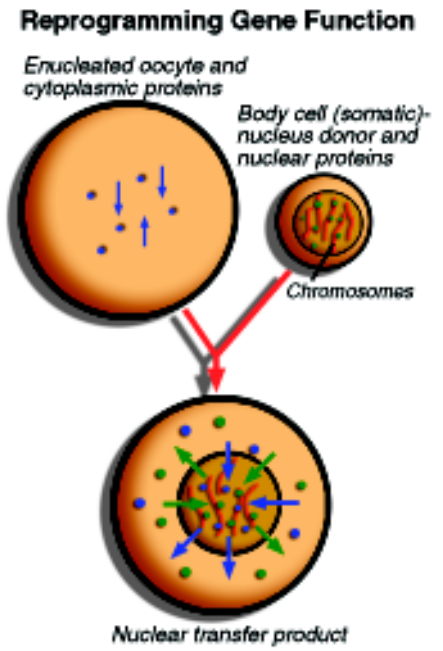
Robert G. McKinnell, Thomas J. King, and Marie A. Di Berardino obtain swimming larvae from enucleated oocytes injected with adult frog kidney carcinoma cell nuclei. This demonstrates that some cancer cells can be controlled by the differentiation process, and that inducing cancer cells to differentiate may stop the cancer process.

because, during the maturation of the parents' sperm and egg before fertilization, the genes are randomly distributed to sperm and egg cells. Thus, offspring cloned from adult cells are more similar to their donor than are offspring that result from sexual reproduction, i.e., a combination of sperm and egg. There is, however, no guarantee that an exact copy will evolve, because variations in the physical traits of the donor may result from environmental influences during pre- and postnatal development and, in some cases, from the mitochondrial DNA of the oocyte.

Totipotency

Animal cloning began more than a century ago when scientists wondered how an initially formless mass of cells, the blastocyst, develops into a structured organism composed of separate skin cells, blood cells, muscle cells, brain cells, stomach cells, and so on. They specifically wanted to know whether these many different cell types were irreversible or whether these differentiated cells could reverse and express again the totipotency of the early embryo.

Early Embryonic Cells Are Totipotent—By using an early version of the nuclear transfer technique in their initial studies, scientists established that nuclei from early embryonic cells were indeed totipotent; that is, they could develop into complete fertile organisms, with all the cell types and organs of an adult. These studies showed that frogs, salamanders, insects, fish, and mammals (mice, rats, rabbits, pigs, goats, cattle, and sheep) could be produced by this process. Furthermore, many of these species were fertile. (The only primates to have been cloned by nuclear transfer thus far are two Rhesus monkeys produced from the nuclei of an eight-cell stage embryo.)



Few Nuclei Remain Totipotent throughout Development—Scientists now know that the older the donor cell from which the nucleus is transplanted, the more likely it is that the injected oocyte will develop abnormally. In fact, only a few tadpole nuclei from frogs have been shown to be totipotent, and those may have come from immature cells. When fully differentiated cell types (pigment, skin, red and white blood cells) from adult frogs were used as donors, their nuclei gave rise to tadpoles but not to fertile frogs. In mammals, very few *fetal* cell nuclei (approximately 0.3-2%) from sheep and cattle led to the normal development of living newborn animals. Dolly, produced from an *adult* cell, represents only a 0.2% cloning success. The inability to clone most nuclei from advanced stages probably results from protein changes that occurr in the chromosomes during cell differentiation, changes that will have to be identified and controlled in the future.

Genetic reprogramming

Scientists found that cloning actually reprograms nuclear function and returns some nuclei to an undifferentiated state. This discovery followed a line of basic research that may result in some of the most beneficial applications to humans.

Soon after a nucleus is transferred to an egg, there occurs a two-way transfer of specific proteins between the nucleus and cytoplasm. This transfer causes modifications in chromosomal proteins, resulting in

1964

F.C. Steward grows a complete carrot plant from fully differentiated carrot root cell. This and the previous amphibian experiments led some scientists to believe that cloning from differentiated animal cells was possible.

1966

John B. Gurdon and V. Uehlinger succeed in growing adult frogs from injection of tadpole intestinal cell nuclei into enucleated oocytes.

1970s

By using nuclear transfer, researchers obtain pre-feeding larvae from nuclei of differentiated frog skin (J.B. Gurdon, R.A. Laskey, O.R. Reeves) and lymphocytes (M.R.Wabl, R.B. Brun, and L. Du Pasquier).

1983

James McGrath and Davor Solter develop nuclear transfer technology for mammalian embryos. Fertile mice were obtained when a nucleus surrounded by minute amount of cytoplasm from a 1-stage fertilized egg was fused with another enucleated fertilized egg.

nuclear DNA synthesis, and later in the expression of a new set of genes. These and other changes reflect reprogramming of nuclear function by chemicals in the oocyte cytoplasm. When investigators identify the role of these proteins, we will understand how to convert a nucleus from a differentiated adult cell type into one that is relatively immature. This might permit us to actually *reprogram* mature cells and turn them into specific cell types required for tissue repair. By doing this, we could potentially replace damaged heart or brain cells by reprogramming the patients' own skin cells into heart muscle cells and nerve cells (for people like Christine and Margo).

Dolly is only the first!

Dolly is no longer unique, although she always will be the first animal cloned from an adult cell. Being the result of a nuclear transfer between an adult ewe udder cell and an enucleated oocyte, she showed that an adult mammalian cell could be reprogrammed genetically to be totipotent and give rise to an entire individual that grew to maturity and gave birth to offspring of her own. Soon after Dolly was born, a set of triplet transgenic calves bearing a foreign gene was cloned from fetal cells, all sharing the same nuclear genes. This indicates the feasibility of producing herds of sheep and cattle capable of producing the same protein.

In Hawaii, 17 months after the announcement of Dolly's birth, 32 mice were cloned from cumulus cells (i.e., cells that surround the developing oocytes in the ovaries), confirming successful cloning from adult cells. Ten of these clones have themselves produced normal progeny, and some of the 31 clones themselves came from clones, demonstrating the feasibility of augmenting the number of clones. In December 1998, eight calves were cloned from a single adult cow's cumulus and oviductal cells (cells lining the tubes of the oviduct that transport oocytes to the uterus). These studies showed that not only adult cells could be reprogrammed, but also that some differentiated cells (such as cumulus and oviductal cells) had the same capability. Keep in mind that not all adult cells are differentiated; for example, undifferentiated cells are found in bone marrow, the intestinal lining, etc., of adults.

Direct advantages

Transgenic clones can be directly beneficial to humans, other animals, and agriculture in additional ways.

- They may be developed for tissue and organ transplantation. Although not yet a reality, there is promise that large animals can be genetically designed and cloned so that their tissues and organs will not trigger immunological responses in the recipient and cause them to be rejected. Recently, muscle rigidity and tremors in parkinsonian rats were improved by transplanting cloned transgenic bovine neurons into their brains. This research, called xenotransplantation, is one of the many avenues being pursued in an attempt to alleviate the desperate shortage of human tissues for transplantation.
- Domestic animals can be genetically designed to express a certain human disease and therefore serve as models for the study and treatment of human illnesses. Although many mouse models of human diseases are available today, such models in large domestic animals physiologically more similar to humans are sparse and critically needed.
- Somatic cell nuclear transfer might help preserve endangered species such as pandas that have low reproductive rates.

Indirect advantages

Two other significant gains from clones are worth mentioning.

First, inducing cancer cells to differentiate is a useful type of therapy. We know that many types of cancer cells are less specialized than their normal counterparts. For this reason investigators suspected that the precursors of cancer cells could be immature cells or stem cells that fail to complete differentiation. If this is

1983-86

Marie A. Di Berardino, Nancy H. Orr, and Robert McKinnell obtain pre-feeding and feeding tadpoles from transplanting nuclei of adult frog erythrocytes (unlike humans, frog mature red blood cells contain nuclei).

1986

Steen Willadsen clones lambs by fusing a nucleus of an 8-cell embryo to enucleated oocyte. An electrical impulse usually was used for the oocyte fusion and activation process. Other researchers subsequently succeeded in producing full-term cattle, sheep, pigs, goats, and rats by using a similar approach, as long as the blastomere nuclei were obtained from embryos prior to implantation.

so, then by using information gained from nuclear transfer technology, we may be able to induce the cells to mature and stop making tumors. Previous studies have demonstrated that we can control at least some cancer cells by using the differentiation process.

Second, aged cell nuclei can be rejuvenated. People and other organisms change as they age. Environmental insults and diseases cause these changes; others are intrinsic to the organism. Studies using cell culture have shown that body cells grow and divide normally in culture for awhile, but eventually stop dividing, become senescent, and die. An exception was seen in aged frog red blood cell nuclei (human red blood cells lack nuclei): After their transfer into enucleated oocytes, frog red blood cell nuclei were rejuvenated. They carried out the formation of tadpoles that survived almost a third of the way to metamorphosis. The oocyte cytoplasm contains an abundance of chemicals that promote DNA synthesis and cell division after normal fertilization. We believe that these substances also rejuvenate aged cell nuclei and turn non-cycling frog red blood cells into active ones. If we could isolate these substances, we might be able to alleviate—or reverse—senescence.

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Perils

Although Dolly, mice, and calves have been the first animals cloned from adult cells, the low efficiency in producing them negates attempts to clone humans. The Dolly experiment began with 434 attempts to fuse a mammary gland cell to an oocyte, and ended with only a 0.2% success rate; the remaining attempts resulted in death either during fusion or in various developmental stages. Moreover, the 1-2% success rate with mouse and 1-5% with calf cloning from adult cells are equally low. And high frequency of fetal (approximately 60%) and neonatal (approximately 50%) deaths are common. In a real sense, cloning is a roulette game.

Even if cloning from adult cells did become efficient, there still would be serious hazards.

- Donor cells could suffer mutations from radiation, chemicals, aging, and/or errors in DNA replication during the lifetime of the donor, which would be transferred to the clone.
- Mutations could arise in donor cells during cell culture, not an unusual event, and there is no way of distinguishing a normal donor cell from a mutant one.
- The embryo may be a mosaic of cells, some with apparently normal chromosomes and others with abnormal ones. So far, the prospects for identifying an abnormal embryo prior to transfer to the uterus are poor.

And there are other scientific concerns:

- the life span of the clone is unknown, as is
- the compatibility between the genetic products in the cytoplasm of the oocyte and the donor cell, and
- during the normal process of sexual reproduction, there is a natural selection of the fittest germ cells in fertilization. Although this process is not perfect (i.e., it fails to eliminate some harmful mutations), it does not exist in cloning.

So we can see that it is unlikely that cloning of a human being from any donor age will happen any time soon. Indeed, the scientific community was so strongly opposed to the production of a human being by cloning techniques that the Federation of American Societies for Experimental Biology and other professional organizations representing more than 67,000 scientists have issued a voluntary moratorium against such an act. The groups endorsing this position included those scientists most capable of performing this type of work.

Although these scientists believe that cloning a human being is unethical and reprehensible, they are still concerned that some of the anti-

1993

M. Sims and N.L. First report for the first time production of calves by transfer of nuclei from cultured embryonic cells.

1997

Dolly, the first mammal cloned from an adult cell, is produced in Scotland. Ian Wilmut and colleagues report the birth of a lamb derived from the transfer of a nucleus obtained from an adult ewe udder cell into an enucleated oocyte that was then implanted into a surrogate mother.

Primate cloning: Two Rhesus monkeys are the first and only primates thus far cloned by nuclear transfer from the 8-cell stage—Don Wolf's laboratory at Oregon Regional Primate Research Center.

1998

The Honolulu group, led by Teruhiko Wakayama, reported the production of a large number of live mice from injecting nuclei taken from adult ovarian cells into enucleated oocytes. These investigators also report success in recloning efficiently the first clones.

The Japanese group, led by Yoko Kato, produced eight calves from cumulus and oviductal cells derived from one adult donor.

cloning legislation designed to prevent the cloning of a human being contains language that also will prohibit vital biomedical research that can lead to the repair of diseased and damaged human tissues and organs, and to possible treatments and cures for diabetes, cancer, Parkinson's disease, and other neurodegenerative diseases.

Other nations have found a successful balance between these two concerns. Many European countries have outlawed attempts to clone humans, while preserving the freedom of scientists pursuing cloning studies in non-human organisms because of the potential benefits. In the United States, the National Bioethics Advisory Committee recommended an "imposed period of time in which no attempt is made to create a child using somatic cell nuclear transfer." In their 1997 statement, the committee cautioned, "Any regulatory or legislative actions undertaken to effect the foregoing prohibition on creating a child by somatic cell nuclear transfer should be carefully written so as not to interfere with other important areas of scientific research."

Knowledge: threat or promise?

When scientists first discovered anesthesia, atomic energy, and recombinant DNA, we did not know if these breakthroughs might lead to deleterious applications. The choices we make for the application of knowledge reside in ethical decisions by humans. Animal cloning, like other research, was initiated to seek fundamental knowledge for the benefit of humankind. In addition to expanding the knowledge base in cellular, developmental, and molecular biology, as well as in cancer and aging, cloning has now been applied to enhance medicine and agriculture. Presently, hospital committees in the United States bar attempts to clone humans because of clinical, safety, and ethical concerns. Cloning is only one of many discoveries in which society will have to choose which applications are ethical and which ones are not.

Suggested Readings

For the original report on Dolly, see I. Wilmut et al. (1997) Viable Offspring Derived from Fetal and Adult Mam-malian Cells. *Nature*, **385**:810-813.

For a general treatment of cloning, see I. Wilmut (1998) Cloning for Medicine. *Scientific American*, December 58-63.

For the original report on transgenic lamb clones, see A. E. Schnieke et al. (1997) Human Factor IX Transgenic Sheep Produced by Transfer of Nuclei from Transfected Fetal Fibroblasts. *Science*, **278**:2130-2133.

For the original report on transgenic calf clones, see J. B. Cibelli et al. (1998) Cloned Transgenic Calves Produced from Nonquiescent Fetal Fibroblasts. *Science*, **280**:1256-1258.

For the original report on cloning mice from adult cells, see T. Wakayama, A.C.F. Perry, M. Zuccotti, K.R. Johnson and R. Yanagimachi (1998). Full-term development of mice from enucleated oocytes injected with cumulus cell nuclei. *Nature*, **394**:369-374.

For the original report on cloning from adult cow cells, see Kato, Y., Tani, T., Sotomaru, Y., Kurokawa, K., Kato, J., Doguchi, H., Yasue, H., and Tsunoda, Y. (1998) Eight calves cloned from somatic cells of a single adult. *Science*, **282**:2095-2098.

For the original article on treating parkinsonian rats, see W. M. Zawada et al. (1998) Somatic cell cloned transgenic bovine neurons for transplantation in parkinsonian rats. *Nature Medicine*, **4**:569-574.

For original articles on cloning cancer cell nuclei, see T. J. King and M. A. Di Berardino (1965) Transplantation of nuclei from the frog renal adenocarcinoma. I. Development of tumor nuclear-transplant embryos. *Ann.N.Y.Acad.Sci.* **126**:115-126 and R.G. McKinnell, B.A. Deggins and D.D. Labat (1969). Transplantation of pluripotential nuclei from triploid frog tumors. *Science* **163**:394-396

For an article on cloning red blood cell nuclei, see M.A. Di Berardino and N. Hoffner Orr (1992) Genomic potential of erythroid and leukocytic cells of *Rana pipiens* analyzed by nuclear transfer into diplotene and maturing oocytes. *Differentiation* **50**:1-13.

For a thorough coverage of the science and history of animal cloning, see Marie A. Di Berardino (1997) *Genomic Potential of Differentiated Cells*, Columbia University Press, N.Y.

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Science editor for this article was Ida Chow, Ph.D., a natural clone herself (her identical twin sister is a physicist living in Brazil). She is the Executive Officer of the Society for Developmental Biology. Her research is on cell-cell interaction during vertebrate development.