Mammalian Cloning:

An Exciting Technical Advance With Practical And Ethical Considerations

by Teresa R. Strecker

{1}On February 27, 1997, scientists at the Roslin Institute in Edinburgh reported they had successfully cloned a mammal from an adult cell [Nature (1997) 385: 810-813]. The mammary gland of a 6-year old ewe provided a nucleus, which was transplanted into an enucleated, fertilized sheep egg. Two hundred and seventy-seven trials resulted in one viable offspring now known as Dolly.

{2}The successful growth of an animal, whose genetic information was derived from an adult cell, is a major milestone in developmental biology. The failure of earlier attempts at "cloning" had suggested that during differentiation the genetic material (DNA) of an animal undergoes irreversible changes, preventing it from supporting the development of a whole organism. The success of scientists from the Roslin Institute demonstrated that this may not be the case after all.

{3}So why were they successful when so many had failed in the past? The key to their success was making the donated nucleus and recipient egg cytoplasm compatible. By inducing both donor nucleus and host egg to enter a quiescent state, there was sufficient reprogramming of the donor DNA to support the development of a whole organism. The critical nature of this step was evident in the early high attrition in greater than 90% of their trials.

{4}The process by which DNA is regulated during the differentiation of an organism is central to questions addressed today in molecular biology and medicine. Unlocking this mystery lies at the heart of our understanding the molecular basis of cancer and aging. The successful transfer of a nucleus from a differentiated adult cell into an enucleated fertilized egg has opened the door to ways we can understand the regulation of gene expression.

An Immediate Technical Advance for Transgenic Research and Medicine

{5}In addition to its value in basic science, mammalian cloning has direct application to the growing field of transgenics. Transgenic animals are those that have been genetically altered to carry new genes. For example, pigs are being genetically engineered to be acceptable heart donors for human organ transplantation. The major barrier to this trans-species donation has been the rejection of the pig heart by its human recipient. By altering the DNA that encodes cell surface markers, the pig heart can be recognized as "human." Mammalian cloning promises to increase the efficiency of making pig organ donors. Such animals can be cloned and thus save a costly step in their reliable production.

{6}Transgenics also includes the use of animals as living laboratories that yield genetically engineered human proteins. The same biotech company that collaborated in the research responsible for Dolly, PPL Therapeutics, has also produced a human protein, alpha anti-trypsin (AAT), for use in treating cystic fibrosis. This product is

produced in the milk of transgenic sheep who carry the gene that encodes AAT. Cloning sheep that successfully produce this protein would be less expensive and more efficient than having to make more transgenic animals through standard methods of genetic transformation and testing.

Public Reaction to Mammalian Cloning

{7}Despite these obvious and immediate benefits of cloning, the news of Dolly met with loud public outcry, focused solely on the issue of cloning humans. Shortly after hearing of the first successful mammalian cloning in early March, President Clinton barred federal funding of human cloning for 90 days and asked privately funded scientists to abide by a voluntary moratorium while the issue is considered by the National Bioethics Advisory Commission. This panel is examining the legal and regulatory framework for cloning and genetic research, the philosophical and ethical issues, the public policy options and the science of cloning. In addition, twenty European countries have signed the first international agreement to control research in human genetic engineering and cloning.

{8}Clinton's response has been criticized as "knee-jerk" by those who can see the benefits of cloning as a significant technical advancement in organ procurement and transplantation as well as in treating infertility. In contrast, the strongest objections of those outside religious groups to human cloning were the German parliament, which linked the cloning of humans to Nazi eugenics, and the British

physicist Joseph Rotblat, winner of the 1995 Nobel Peace Prize for his work toward nuclear disarmament, who stressed the need for an international committee to address ethical and scientific issues.

How Probable Is Human Cloning?

{9}The common estimate from members of the scientific community is that human cloning will be technically possible in one to ten years. The window in early development during which the genetic material of a donated nucleus has to become reprogrammed after transplantation to a recipient enucleated egg is much shorter in humans, than in sheep. This presents an immediate technical barrier that will have to be addressed before human cloning is possible.

{10}More importantly, the notion of producing exact replicas of ourselves is simply naive. A clone is not the same as an identical twin of the adult who donates a nucleus. A human clone derived from the differentiated cell of an adult would not give rise to an exact copy of its donor for several reasons.

{11}First, body cells from an adult have undergone thousands and thousands of rounds of cell division throughout one's lifetime. During this period cells are exposed to environmental agents that may induce genetic mutations in the DNA. In addition, every time a cell divides, its DNA is replicated by an enzyme that is not perfect in making an error-free copy. Although cellular mechanisms for detecting replication

error or environmentally induced DNA damage exist, the occurrence of error is still measurable, albeit at a low level. What guarantee does one have that the body cell selected to donate a nucleus has not acquired a genetic mutation that will result in disease or a physical disorder in the clone?

{12}In contrast to body cells that undergo many divisions over time, germ cells do not. Germ cells, which give rise to sperm or egg, are set apart from body (somatic) cells early in embryogenesis. This segregation protects them from the signals responsible for directing the differentiation of body cells. In addition, prospective egg cells stop replicating their DNA when the female, herself, is still an embryo. Throughout the rest of development, childhood and early adulthood, eggs reside in the ovary in a quiescent state. Only when an egg is ovulated and fertilized by sperm does it recommence cellular division and DNA replication. The quiescent state of germ cells throughout the lifetime of an individual stands in contrast to the thousands of rounds of cellular division and DNA replication in body cells. In light of these differences, the exchange of an egg nucleus for one from a differentiated body cell may not be as simple as it first appears.

{13}Another reason a clone is not an identical twin of the donor is that the donor and clone may not possess the same mitochondria. Mitochondria are membrane-bound sub regions in each cell that are responsible for providing the chemical energy necessary to support life. Mitochondria contain their own genetic

material and are inherited maternally. Mitochondrial DNA encodes enzymes necessary for carrying out critical steps in metabolism, responsible for converting nutrients into chemical energy. Unless the donor and clone come from the same maternal line, the clone and donor will possess different mitochondrial DNA.

{14}Finally, geneticists are becoming increasingly aware of the role of environment on the expression of certain genetic traits. While an individual's DNA may provide the predisposition to develop a certain trait or disease, one's environment is thought to play a critical role in the expression of a genetic condition. For example, nutrition affects whether an individual will reach full adult height. Similarly, environmental factors may play a role in the manifestation of diseases such as Alzheimer's in individuals who possess certain susceptibility genes.

Ethical Concerns of Human Cloning

{15}In addition to practical concerns, there are also ethical considerations regarding human cloning. There is consensus that human life should not be used strictly as a means to an end, regardless how beneficial a medical goal or research objective. An example of violating this principle would be cloning human infants as organ donors. Currently, several hundred newborns die each year due to a lack of donated vital organs. Cloning human infants could be justified on utilitarian grounds since organs from one donor could save the lives of several infants. Donor infants would be conceived solely for the purpose of organ procurement, possibly using

sperm and egg donors and surrogate mothers. Thus, these individuals would never be intended to live as autonomous human persons, but would be conceived to serve the common good.

{16}Far fetched, you say? In 1995, the Council on Ethical and Judicial Affairs of the American Medical Association recommended the use of infants born with anencephaly, a congenital defect resulting in the absence of the higher brain or cerebrum, as live organ donors [JAMA (1995) 273: 1614-1618]. This decision differed from an 1988 ruling of the same council, when they declared it was ethically acceptable to remove the organs from the anencephalic infant only after his or her death, as defined as the cessation of either cardiac or whole brain function.

{17}What happened between 1988 and 1995 that led these physicians to no longer view the infant born with anencephaly as protected by the Uniform Anatomical Gift Act (UAGA) and the Uniform Determination of Death Act (UDDA)? During this period, physicians involved in neonate organ transplant research tried to procure organs from anencephalic infants within the boundaries of the law. They discovered it was not technically possible to harvest usable organs from deceased infants with anencephaly. This failure precipitated the 1995 AMA recommendation to use the anencephalic infant as a live organ donor. In so doing, the AMA justified removing the anencephalic infant from the protection of laws that govern organ donation on the grounds that he or she is a non person that could better serve the interests of others.

{18}This conditional depersonalization of individuals establishes an ethically compromising precedent for human cloning. It suggests that on utilitarian grounds one may be exempt from the respect and dignity due a human person, and thereby, one may become an object to be used for another's gain. How does this relate to human cloning? To answer this question let's look at a more immediate case in which human cloning may be used.

{19}Consider a single parent who has suddenly and tragically lost her only healthy child in an automobile accident. The child's father died years earlier. Human cloning would enable her to restore their lost son. If she acts as the donor of the enucleated egg used in this cloning procedure, her new child will have both the nuclear and mitochondrial DNA of the deceased.

{20}Is it ethical for the mother to clone her dead son? Some would argue it would be unethical to prevent her from doing so, assuming it was technically possible. Does cloning the deceased child violate the respect and dignity due a human person? That depends entirely on what it means to be a clone. Is he a mere extension of the deceased's life or will he be respected as an autonomous individual?

{21}The significance of what it means to be a clone becomes clear in light of the technical uncertainties of human cloning. "For example, the donor nucleus taken from the lung of the deceased child in our scenario may contain genetic mutations resulting from environmental agents the child had been exposed to earlier in life"

(e.g., cigarette smoke). Due to mutation(s) in the body cell that contributes the donor nucleus, the clone may develop anomalies or diseases that were not manifest in the original child. If the intent of cloning was to restore the original child, would a less than "perfect" replica be rejected as a medical failure or will he still be respected as a unique individual? For example, if the clone was born with an unforeseen congenital anomaly, he may be used for other medical purposes if the sole intent of his life was to be an exact replica of the deceased child. On the other hand, if the clone is respected as a unique individual, the presence of differences between the new and deceased child could not be used as a basis for treating the clone as an object to serve the interests of others.

{22}Human cloning does not remove the uncertainty inherent in human life. There is no way at this time to guarantee a clone will be an exact replica of its donor. In fact, a clone may be significantly different. Projecting the expectation of the "perfect" clone immediately limits and defines one's purpose, and potentially dehumanizes the individual in the process. Human beings are not laboratory animals. Any human being that arises from the application of human cloning should be respected as a unique and autonomous individual.

{23}Before we argue that human cloning is our right, there are clearly serious issues that must be fully considered before this technology can be realistically recommended. Any recommendation must be made with the knowledge that respect

and dignity of human beings in our society has already become conditional. Therefore, the application of new technical advances to human reproduction calls for restraint and reflection, as we clarify what it means to be human, apart from considering only the medical, scientific and personal interests of others. To forge ahead with technology simply because it can be done promises to further confuse and potentially diminish the respect and dignity we all depend on as human beings.

Teresa R. Strecker, Ph.D.
Southern Methodist University
Biological Sciences Department

Date of BLT Publication: April 1997