POLICY FORUM: DEVELOPMENTAL BIOLOGY

Don't Clone Humans!

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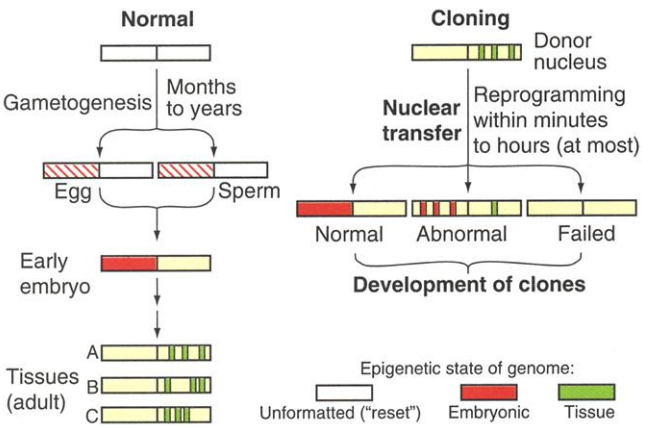
The successes in animal cloning suggest to some that the technology has matured sufficiently to justify its application to human cloning. An in vitro fertilization specialist and a reproductive physiologist recently announced their intent to clone babies within a year's time (*1*). There are many social and ethical reasons why we would never be in favor of copying a person. However, our immediate concern is that this proposal fails to take into account problems encountered in animal cloning.

Since the birth of Dolly the sheep (*2*), successful cloning has been reported in mice (*3*), cattle (*4*), goats (*5*), and pigs (*6*, *7*), and enough experience has accumulated to realize the risks. Animal cloning is inefficient and is likely to remain so for the foreseeable future. Cloning results in gestational or neonatal developmental failures. At best, a few percent of the nuclear transfer embryos survive to birth and, of those, many die within the perinatal period. There is no reason to believe that the outcomes of attempted human cloning will be any different. The few cloned ruminants that have survived to term and appear normal are often oversized, a condition referred to as "large offspring syndrome" (*8*). Far more common are more drastic defects that occur during development. Placental malfunction is thought to be a cause of the frequently observed embryonic death during gestation. Newborn clones often display respiratory distress and circulatory problems, the most common causes of neonatal death. Even apparently healthy survivors may suffer from immune dysfunction, or kidney or brain malformation, which can contribute to death later. So, if human cloning is attempted, those embryos that do not die early may live to become abnormal children and adults; both are troubling outcomes.

The fetal abnormalities and abnormalities in those few clones that are born live are not readily traceable to the source of the donor nuclei. The most likely explanation may be failures in genomic reprogramming. Normal development depends upon a precise sequence of changes in the configuration of the chromatin and in the methylation state of the genomic DNA. These epigenetic alterations control tissue-specific expression of genes. For cloning technology, the crucial question is a simple one: Is the configuration of chromatin changes acquired by a donor nucleus in the injected oocyte functionally identical to that resulting from gametogenesis and fertilization?



Reprogramming in normal development renders the egg and sperm genome competent to express embryonic genes (red box). During differentiation, tissue-specific genes are activated (small green boxes in tissues A, B, C). Cloning of a somatic nucleus (tissue A) may lead to three outcomes: no reprogramming (no activation of embryonic genes and early death—"failure"); partial reprogramming (some embryonic genes are activated—"abnormal" development); complete reprogramming (faithful activation of embryonic genes—"normal" development).

Epigenetic reprogramming is normally accomplished during spermatogenesis and oogenesis, processes that in humans take months and years, respectively. During nuclear cloning, the reprogramming of the somatic donor nucleus must occur within minutes or, at most, hours between the time that nuclear transfer is completed and the onset of cleavage of the activated egg begins. Prenatal mortality of nuclear clones could be due to inappropriate reprogramming, which could lead in turn to dysregulation of gene expression. Some long-term postnatal survivors are likely to have subtle epigenetic defects that are below the threshold that threatens viability.

Circumstantial evidence begins to hint at defects in programming of gene expression in cloned animals (*9*, *10*). Expression of imprinted genes was significantly altered when mouse or sheep embryos were cultured in vitro before being implanted into the uterus (*11*, *12*). Thus, even minimal disturbance of the embryo's environment can lead to epigenetic dysregulation of key developmental genes. Also, preliminary observations suggest that widespread gene dysregulation in cloned mice is associated with neonatal lethality (*13*).

There is every reason to think that the human cloning experiments announced by P. Zavos and S. Antinori will have the same high failure rates as laboratories have experienced when attempting animal cloning. Zavos tried to reassure the public by saying that: "We can grade embryos. We can do genetic screening. We can do quality control." (*1*). The implication is that they plan to use the methods of routine prenatal diagnosis employed for the detection of chromosomal and other genetic abnormalities. However, there are no methods available now or in the foreseeable future to examine the overall epigenetic state of the genome.

Public reaction to human cloning failures could hinder research in embryonic stem cells for the repair of organs and tissues. Research is being conducted into programming these cells to turn into specific tissues types, which could (for example) be used to regenerate nerve cells and those in the heart muscle, benefiting patients with Parkinson's, Alzheimer's, and heart disease. The potential benefit of this therapeutic cell cloning will be enormous, and this research should not be associated with the human cloning activists.

We believe attempts to clone human beings at a time when the scientific issues of nuclear cloning have not been clarified are dangerous and irresponsible. In the United States, the National Bioethics Advisory Commission (*14*) reached that conclusion 5 years ago, "At present, the use of this technique to create a child would be a premature experiment that would expose the fetus and the developing child to unacceptable risks." All the data collected subsequently reinforce this point of view.

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References and Notes

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