February 17, 2004

Specter of Cloning May Prove a Mirage

By STEPHEN S. HALL

A rose is a rose is a rose, even if — like many commercial plants — it is essentially a clone. But is a normal human blastocyst, a microscopic bubble of proto-life that forms about five days after sperm meets egg, the same as a cloned blastocyst?

That may seem an arcane technical question in the debate about human cloning, reignited last week with the announcement by South Korean scientists that they had cloned a human embryo and harvested embryonic stem cells from it. But scientists, politicians and bioethicists have been grappling for years with the biological and moral subtleties encapsulated by that tiny dot of tissue.

The future of human therapeutic cloning in this country — the laws governing it, the knowledge to be gained from it, the ethical costs of doing it and the medicines it might eventually bestow — may hinge on how society views that question.

In last week's report in the journal Science, researchers at Seoul National University described how they had created some 30 cloned human blastocysts in order to harvest human embryonic stem cells. Such a procedure has raised moral concerns, not only because it requires the destruction of the embryo to gather the cells, but because its mere publication may provide technical guidance to several well-known "cloning entrepreneurs" who have vowed to try human cloning, despite widespread safety and moral concerns.

In response to the South Korean experiment, Dr. Leon R. Kass, chairman of the President's Council of Bioethics, said, "The age of human cloning has apparently arrived: today, cloned blastocysts for research; tomorrow, cloned blastocysts for baby-making." Dr. Kass urged Congress to pass a ban or moratorium on all forms of human cloning. Several lawmakers

called for just such a ban on all human cloning research.

But it's unclear how imminent that "tomorrow" actually is. While the South Korean paper offers a new technical trick for creating a cloned human blastocyst, it does not resolve any questions about how robust that blastocyst may be for generating a healthy, normal human being.

"There's no doubt that there's still an awful lot of work to be done before anybody would feel comfortable that it could be done safely," said Dr. George Daley, a stem cell researcher at Children's Hospital in Boston.

The South Korean group did not try to create a baby. The promise of therapeutic cloning, still theoretical, derives from the following premise. By introducing the DNA of an adult human cell into a human egg whose nucleus has been removed, the resulting hybrid cell can be induced to behave like a fertilized egg. Like a normal embryo, it begins its development as a single cell, but it contains the genetic payload — and, presumably, the immunological identity — of the adult patient. Treatment, not children, is the ultimate point of the exercise.

But cloned embryos may not be genetically equivalent to normal embryos. Dr. Rudolf Jaenisch, an expert on the genetics of animal cloning at the Whitehead Institute for Biomedical Research in Cambridge, Mass., has published studies showing that cloned mice are riddled with genetic abnormalities. Those glitches suggest that a cloned embryo would have "little if any potential to ever develop into a normal human being."

When an egg cell reprograms the DNA of an adult cell during a cloning experiment, Dr. Jaenisch said, the process is probably incomplete — raising the possibility that genes in the cloned embryo are not activated (or "expressed") at the right time, in the right amount, and properly suppressed when not needed.

Gene regulation of this sort is especially significant in a class of genes known as imprinting genes, which play a crucial role in fetal development. "We think that 30 to 50 percent of imprinted genes are not properly expressed in clones," Dr. Jaenisch said, "and imprinting genes are mostly important for pre-natal development."

As a result, he said, the South Korean approach may be "useful for therapy, but not useful for cloning." Dr. Daley, who with Dr. Jaenisch published one of the first animal experiments suggesting the promise of

therapeutic cloning, said, "All of the concerns and risks of mammalian reproductive cloning have not changed with this paper."

Paradoxically, however, scientists working in the area believe that the same genetic glitches that might prevent an embryo from growing into a genetically normal organism are unlikely to compromise the quality of stem cells that might be harvested for medical use. "Cloned tissues are not likely to have the same problems," Dr. Daley said, "but that's yet to be proven."

In addition to being a notoriously inefficient procedure, animal cloning has produced many animals with conspicuous developmental problems, like respiratory illnesses and overly large placentas. Dolly the cloned sheep suffered from premature arthritis before dying last year. Such genetic dysfunction is one reason for nearly unanimous scientific opposition to reproductive cloning. As Dr. Daley put it: "As a scientist, I would be willing to support a ban on reproductive cloning, if it allows us to pursue legitimate therapeutic research. That is the most rational way of approaching the debate."

But Dr. Jaenisch also made a distinction between cloned embryos and the kind of blastocysts formed during normal reproduction, including embryos fertilized in vitro. "When you really think about an I.V.F. embryo that rests in a deep freeze, it only has three fates," he said. "It can be destroyed, it can be implanted into a woman or it can be converted into embryonic stem cells. When you make embryonic stem cells, you do destroy an embryo, and that is an ethical issue.

"Cloned embryos also have three fates. "They can be destroyed, they can be used to make normal embryonic stem cells tailored to the needs of patients, but they cannot make a normal baby. In my opinion, the destruction of a cloned embryo to make embryonic stem cells poses less ethical problems than the destruction of frozen embryos in the I.V.F. clinic."

Dr. Thomas H. Murray, president of the Hastings Center in Garrison, N.Y., says this scientific distinction has moral import. "What are the ethical implications if embryos created in this way are not viable, or severely impaired?" he asked. "If Rudy Jaenisch is right, if embryos created by cloning are a fairly abnormal ball of cells, that would compel us to think very hard about what moral meaning to attach to such an entity."

Such a scientific distinction, Dr. Murray also noted, could "complicate" a split in the anti-abortion movement that emerged several years ago during the debate over stem cell research and cloning. Several prominent abortion opponents, including Senator Orrin G. Hatch, Republican of Utah, supported federal financing for stem cell research; Mr. Hatch has also co-sponsored legislation allowing therapeutic cloning while prohibiting reproductive cloning.

In fact, the biological distinction between cloned embryos and normal embryos came up for discussion two years ago at the President's Council on Bioethics. Dr. Paul McHugh, the former head of psychiatry at Johns Hopkins University School of Medicine, floated the notion that a cloned embryo was distinct — in creation, composition and reproductive intent — from a normally formed embryo. He coined the word "clonote" to distinguish it from "zygote," the single-celled embryo that results from fertilization.

"If you take the point that the clonote is something different, it's something manufactured rather than begotten, then you would want to study, use its best potentials for humankind and not let its potentials for error and slavery appear," he said at the time.

Despite the renewed calls last week for a ban on all forms of cloning, including therapeutic cloning for medical research, even the Bush bioethics council split sharply on the issue. In discussions leading up to the panel's July 2002 report, "Human Cloning and Human Dignity: An Ethical Inquiry," the committee failed to muster a majority in favor of a blanket ban on both therapeutic and reproductive cloning. Only 7 of 17 voting members supported a complete ban; 3 others supported a moratorium. Indeed, the panel's public discussion leading up to the report revealed considerable sentiment in favor of therapeutic cloning, as long as it was properly regulated.

The most provocative aspect of the South Korean research, in Dr. Daley's opinion, was something that was not even included in the paper, but was revealed by several of the scientists at a news conference last Thursday. Dr. Woo Suk Hwang and Dr. Shin Yong Moon said that when the researchers tried to use the DNA from male adult cells or cells from females unrelated to the egg donors, they failed to create any embryos. The only successes in their cloning experiments came from the use of so-called cumulus cells, the adult cells that typically surround a maturing egg cell in a woman's ovarian follicles.

The failure of the other cells to work, Dr. Jaenisch said, merely underscores how much research remains to figure out the best adult cells to use for therapeutic cloning. Whether making human medicines or human babies through cloning, in other words, "tomorrow" may still be a long way off.