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## Cloning Creates Human Embryos

By GINA KOLATA

**S**cientists in South Korea report that they have created human embryos through cloning and extracted embryonic stem cells, the universal cells that hold great promise for medical research.

Their goal, the scientists say, is not to clone humans but to advance understanding of the causes and treatment of disease.

But the work makes the birth of a cloned baby suddenly more feasible. For that reason, it is likely to reignite the fierce debate over the ethics of human cloning.

The work was led by Dr. Woo Suk Hwang and Dr. Shin Yong Moon of Seoul National University and will be published tomorrow in the journal *Science*. The paper provides a detailed description of how to create human embryos by cloning. Experts in the field not involved with the work said they found the paper persuasive.

"You now have the cookbook, you have a methodology that's publicly available," said Dr. Robert Lanza, medical director of a company, Advanced Cell Technology in Worcester, Mass., that had tried without success to do what the South Koreans did.

Although the paper, written in dense jargon and summarizing its findings by saying, "We report the derivation of a pluripotent embryonic stem cell line (SCNT-hES-1) from a cloned human blastocyst," its import was immediately clear to researchers.

"My reaction is, basically, wow," said Dr. Richard Rawlins, an embryologist who is director of the assisted reproduction laboratories at the Rush University Medical Center in Chicago. "It's a landmark paper."

It is what patients with diseases like Parkinson's and diabetes had been waiting for, the start of so-called therapeutic cloning. The idea is to clone a patient's cells to make embryonic stem cells that are an exact genetic match of the patient. Then those cells, patients hope, could be turned into replacement tissue to treat or cure their disease without provoking rejection from the body's immune system.

Even though the new work clears a significant hurdle, scientists caution that it could take years of further research before stem cell science turns into actual therapies.

Even before the publication — reported last night by a South Korean newspaper, one day ahead of the embargo imposed by *Science* — the research was criticized by cloning opponents.

Dr. Leon R. Kass, chairman of the President's Council on Bioethics, called for federal legislation to stop human cloning for any purpose.

"The age of human cloning has apparently arrived: today, cloned blastocysts for research, tomorrow cloned

blastocysts for babymaking," Dr. Kass wrote in an e-mail message. "In my opinion, and that of the majority of the Council, the only way to prevent this from happening here is for Congress to enact a comprehensive ban or moratorium on all human cloning."

The House has twice passed legislation that would ban all human cloning experiments, most recently in February 2003. But the bills have foundered in the Senate, where many members who oppose reproductive cloning do not want to ban it for medical research.

Dr. Hwang said he knew that the work would elicit strong responses but that the research was so important it should be done anyway, adding that there was strict oversight by an ethics committee.

"Of course," he said, "we acknowledge that there will be controversy. But as scientists, we think it is our obligation to do this."

The paper describes the successful process in detail, with precise information on how to start the embryos growing and what solutions are best to nourish them. That recipe appears to advance the likelihood of reproductive cloning. When fertility laboratories fertilize eggs, grow embryos to the same developmental stage as the embryo clones and implant them in a human uterus, 40 to 60 percent end up as babies.

The scientists stress that all the research was in the laboratory, in petri dishes. No embryo was implanted in a woman. The women who provided unfertilized eggs that were needed to start the cloning process were not paid.

The research was financed by the government of South Korea, where cloning to create a baby is illegal.

Dr. Hwang is an expert in animal cloning, and Dr. Moon is a medical doctor who trained in the late 1980's at a leading American fertility center, the Jones Institute for Reproductive Medicine at the Eastern Virginia Medical School in Norfolk. That is one of the very few places where researchers have extracted human stem cells from embryos that were made the usual way, by using sperm to fertilize eggs.

Until now, no one had even come close to using cloning to create a human embryo or even a monkey embryo, to say nothing of extracting stem cells from one.

Stem cells are the research prize. They appear after an embryo has grown for five or six days, its cells subdividing within the hard casing of the egg. Although the embryo at this stage contains about 100 cells, it is still no bigger than the original egg, nearly invisible to the naked eye.

"If it was floating in water with light underneath, it might look like a speck of dust," said Dr. William Gibbons, a professor of obstetrics and gynecology at Eastern Virginia.

The defining feature of a blastocyst is that it has a real structure, made of a ball of cells, the inner cell mass, encased in a sphere. The sphere becomes the placenta if the blastocyst is implanted in a woman's uterus, and the inner cell mass becomes the fetus.

But at the blastocyst stage, the inner cell mass consists of cells that are still indeterminate, not yet committed to becoming any particular cell type. They are the stem cells, which can in theory develop into any of the body's tissues and organs. Stem cells from a clone would be genetically identical to the person who contributed cells to make the embryo.

Some scientists want to use stem cells to study how genes cause disease. Others say they may one day use stem cells to grow replacement tissues that are identical to the patient's own cells.

But while most expected that cloning would one day be used to create human embryos for harvesting stem cells, the South Korean research elicited amazement from experienced investigators.

They were particularly surprised that the researchers had managed to assemble so many unfertilized human eggs, 247 in all.

Advanced Cell Technology, the lone American company that has tried to conduct similar research, went through a long and arduous debate with its ethics board before recruiting young women to donate eggs. The board eventually decided that a fair payment for a woman's time and effort would be \$4,000.

To donate eggs, women have to inject themselves with hormones to stimulate their ovaries, be monitored with ultrasound to see when the eggs are ready to emerge from the ovaries and then allow doctors to extract the eggs with a thin needle. Advanced Cell Technology advertised for donors and paid them the fee, but ended up with just 19 eggs. The company restarted its program in June, Dr. Lanza said, with "just a few donors."

In South Korea, Dr. Moon said in a telephone interview, there was no advertising for egg donors and no payments. The 16 women who donated the 242 eggs were "personal contacts," he said, declining to elaborate.

The Koreans are to discuss their findings today in Seattle, at the annual meeting of the American Association for the Advancement of Science.

The investigators selected 176 eggs that were in a developmental stage that made success seem most likely. To start the cloning, the team removed the genetic material from the eggs and replaced it with genetic material obtained from cumulus cells, the adult cells that cling to eggs. Cloning experiments with mice had indicated that the cells were especially amenable to the process.

Dr. Moon explained, "The cumulus cell is easy to get," because it is on the surface of the egg.

The abundance of eggs enabled the scientists to experiment with ways of having the egg cells start to divide and of growing the embryos in the laboratory.

"They had an incredible amount of eggs and an opportunity to perfect the protocols," said Dr. Jose B. Cibelli, formerly with Advanced Cell Technology and now a professor of animal biotechnology at Michigan State University. "They tried 14 different protocols."

Dr. Cibelli consulted with the Koreans toward the end of their work and is listed with them as an author of the paper in *Science*.

The researchers experimented with different timing, between adding the cumulus cell to an egg and activating the egg, making it start to divide with its cumulus cell genes.

"If they waited four hours instead of two hours, it didn't work," Dr. Hans Schöler, a professor of reproductive medicine at the University of Pennsylvania, said.

All along the way, Dr. Schöler added, such small variations in the procedure had marked effects.

"Marginal differences made it work," he said. "If you stepped a little bit to the right or a little bit to the left, it didn't work."

The resulting method yielded blastocysts 26 percent of the time. "That's amazing," Dr. Schöler said.

Eventually, Dr. Hwang, Dr. Moon and their colleagues ended up with 30 blastocysts, from which they were able to extract 20 inner cell masses. One grew into a line of stem cells.

The next step, Dr. Schöler said, will be to improve the success rate of obtaining stem cell lines from blastocysts.

Dr. Ron McKay, a stem cell scientist at the National Institute of Neurological Disorders and Stroke, said the work suggested that it might be easier than anyone thought to make cloned human embryos and extract stem cells from them.

"The next question takes you to the heart of the whole discussion," Dr. McKay said. "Why do it anyway? What's the point? Is there any point?"

Dr. McKay said that for him the point was that such cells could provide a unique opportunity to study human disease. He spoke of a scientist who had died in her 40's from breast cancer. What if her cells had been cloned to make embryonic stem cells and those cells had been directed to turn into breast tissue? That might give scientists a chance to examine how genes for breast cancer altered the cells' susceptibility and might explain how and why the cancer developed in the first place.

Dr. McKay said learning to make embryo clones for research could help people who want to make babies that are clones. But he added that scientists did not always do everything that is possible.

"I really don't want to comment on the slippery slope," he said.

Dr. Cibelli, too, focused on the Koreans' report.

"Now you have the demonstration that everyone was waiting for," he said. "Whether this approach will be applicable to making babies, I don't know. And I hope I never find out."