Human Embryo Cloning Reported

Cloned human embryos have potential applications in in vitro fertilization, but before that can happen some serious ethical issues will have to be addressed

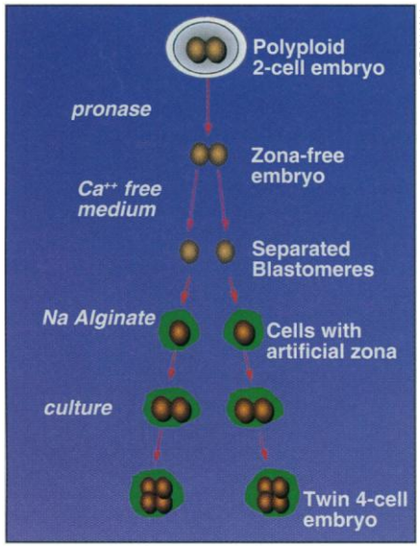
The prospect of cloning human embryos conjures up visions of a Brave New World, in which masses of identical people become automatons functioning for the benefit of the state. Given the sensitivity of the subject, it's surprising that the first public report of cloning human embryos, which was made earlier this month at the American Fertility Society's annual meeting in Montreal, slipped by—at least for a while—with none of the screaming headlines that might have been expected. But the work, done without use of federal funds, by a team led by Jerry Hall, director of the In Vitro Fertilization and Andrology Laboratory at George Washington University School of Medicine in Washington, D.C., was destined not to remain obscure for long. *The New York Times*, among others, has since weighed in with stories.

The achievement has caused excitement not so much for its scientific interest—similar embryo cloning procedures have been used on mammals such as sheep and cattle for several years—but because it seems certain to stir up an intense ethical debate. Although some may say this is "an emotional over-reaction," says bioethicist Margaret Somerville, director of the McGill Center for Medicine, Ethics, and Law in Montreal, "what we are talking about is the ability to mass-produce humans."

Hall himself is certainly aware of the concerns, so much so that one of his main reasons for performing the experiment was to stimulate an ethical discussion of whether human embryo cloning should be allowed to proceed. "It was clear that it was just a matter of time until someone was going to do it, and we decided it would be better for us to do it in an open manner and get the ethical discussion moving," Hall says. There are also reasons to think that embryo cloning might help improve in vitro fertilization (IVF) procedures. Indeed, Hall's peers at the fertility society meeting were sufficiently impressed by his presentation that they awarded it the "general program prize" for the best paper there.

Hall's reason for thinking that some research group would soon try to clone human embryos was a technical advance that took place about 2 years ago. In older procedures for cloning animal embryos, researchers would fuse individual embryonic cells with unfertilized eggs from which the nuclei had been removed (*Science*, 29 January 1988, p. 463). That helped to ensure that each new embryo would have an intact zona pellucida, a clear, jelly-like covering necessary for implantation and development, as well as enough nutrients to support the embryonic cell divisions. But that procedure isn't practical for human embryo cloning because of the unavailability of human eggs. Then, in 1991, Hall and his George Washington colleague Sandra Yee showed that it was possible to coat separated embryonic cells with a synthetic zona pellucida, opening the way to human embryo cloning.

For their current work, Hall, Robert Stillman, also of George Washington, and their colleagues began with 17 two- to eight-cell embryos that had been fertilized in the George Washington IVF clinic, but were considered unfit for implantation because they had been penetrated by multiple sperm and therefore had extra sets of chromosomes. After separating the individual embryonic cells, called blastomeres, and coating them with the artificial zona pellucida, Hall and his colleagues placed the blastomeres in nutrient solutions where they could begin dividing again. The result: 48 new embryos, an average of three for each original embryo, although in the culture conditions most did not develop to the point where they would be capable of implanting in the uterus.



JERRY HALL

Test-tube twinning. The diagram shows how the human embryos were cloned.

The procedure worked best, Hall says, with blastomeres from the smallest embryos. Blastomeres from eight-cell embryos developed only to the eight-cell stage. Blastomeres from four-cell embryos made it to 16-cells. But only blastomeres from two-cell embryos reached the 32-cell stage, which is when embryos would normally implant. Despite their abnormal chromosome composition, Hall says, these embryos "looked wonderful."

Since none of the embryos were implanted in human recipients, it's not known whether any of those that stopped dividing before the 32-cell stage would have developed further under more natural conditions. But if only two-cell embryos have the capacity to grow to the stage where implantation occurs, Somerville's prediction of mass-produced humans is unlikely to come true. Moreover, Hall has no plans to implant any of the cloned embryos or attempt any other potential clinical applications. "We won't," he says, "until the American Fertility Society establishes some guidelines. In this study, we were just answering a basic research question."

If such guidelines were formulated and the procedure approved, one potential application of human embryo cloning would be generating multiple embryos for implantation after IVF. To raise the chances of success, physicians ordinarily implant three to five embryos in a women seeking to conceive by IVF procedures. But not every couple can produce so many genetically distinct embryos, and cloning one or two embryos might be a way to get around this problem. This may be the easiest application to justify ethically since all the embryos would have a chance at developing. "We're already implanting multiple embryos and nobody has any questions about that," notes Joe Massey, an infertility specialist with Reproductive Biology Associates in Atlanta.

But even if the procedure were to be deemed ethical, it may not have the desired biological results, says Lucinda Veeck, director of embryology at the Jones Institute for Reproductive Medicine in Norfolk, Virginia. "If the originating pre-embryo is unhealthy, will increasing the number to three or four unhealthy pre-embryos be truly helpful?" she asks. Still, Veeck notes that the new technology will be "invaluable" for studying early embryonic development. It might help to understand, for example, how different components of the cytoplasm influence embryogenesis.

Another potential application of human embryonic cloning would be in screening IVF embryos for genetic defects. That is now

done by removing one cell from an embryo created in vitro and using gene amplification techniques to produce enough DNA for analysis. But that method fails in about one-third of the cases, and better results might be obtained by using a cloned two- or three-cell embryo copy for analysis.

But opinions divide sharply about whether this application would be ethical in view of the fact that one clone would be destroyed by the analysis. "You'd essentially have the situation of one identical twin being sacrificed for the sake of the other," says Somerville. The president of the American Association of Bioethics, Arthur Caplan of the University of Minnesota in Minneapolis, also finds the idea disturbing, saying that the idea of "creating embryos solely for the purpose of genetic diagnosis is morally suspect." In contrast, another bioethicist, John Robertson of the University of Texas, Austin, who's a member of the American Fertility Society's ethics committee, says he thinks the idea of using two- or three-cell clones for diagnosis is not much different from taking a single embryonic cell.

For the present, there seem to be no regulations or guidelines that could help researchers navigate these ethically treacherous waters. The United States has not had a bioethics commission since 1989 when the congressionally appointed Biomedical Ethics Advisory Committee expired in political disarray without ever issuing a report. At Congress's request, however, the Office of Technology Assessment has prepared a report reviewing past efforts, with an eye to setting up a new ethics commission. (The report, "Biomedical Ethics in U.S. Public Policy," was released on 14 October.) If Congress does establish such a commission, human embryo cloning would presumably come under its purview.

But for now, the fertility society comes the closest to having guidelines, although they deal with "pre-embryo research," rather than with human embryo cloning and its applications. They stipulate that researchers can experiment with pre-embryos not intended for implantation if they are exploring an issue of clinical importance and obtain clearance from their institutional review boards. Hall obtained such clearance, and his experiments did appear to comply with the fertility society's current guidelines, says Edward Wallach of Johns Hopkins University School of Medicine, who chairs the society's ethics committee. Wallach also says that his group will likely develop more specific guidelines for embryonic cloning in an ethics report expected in January. In view of the Brave New techniques reported at the Montreal meeting, January will be none too soon.

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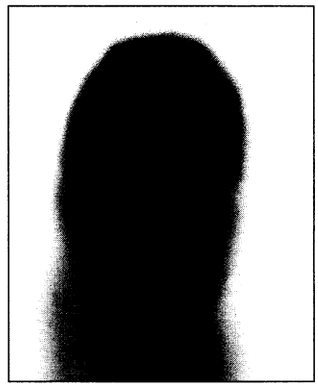
DEVELOPMENTAL BIOLOGY

New Protein Appears to Be Long-Sought Neural Inducer

Some of the most critical events in our lives happen before we are even born. Take for example gastrulation, when the ball-shaped embryo buckles, and cells stream inward to form three layers which respond to a myriad of chemical signals that tell them which mature tissues to become. Most of our tissues and organs—including the brain and nervous system—have their origins in this key event. In the case of the nervous system, part of the top cell layer, called the ectoderm, follows orders to become a plate of neural tissue that later folds inward to form the spinal cord and brain. This "neural induction" was discovered more than half a century ago, and although biologists have repeatedly searched for the molecular signal that triggers it, they have always come up empty-handed.



What noggin does. The dark areas show regions of a tadpole head where noggin turns on a gene indicating neural tissue is being formed.

Now, on page 713 of this issue, developmental biologist Richard Harland and his co-workers at the University of California, Berkeley, report finding that an embryonic protein they discovered last year, called "noggin," acts as a neural-inducing signal in frog embryos. The noggin gene has been found in rodents as well, suggesting it may perform similar functions in mammals. "It's an exciting result," says Salk Institute developmental biologist Chris Kintner. "It brings a phenomenon [neural induction] that has been known for many years to a better molecular understanding." Adds developmental biologist Jonathan Cooke of the National Institute for Medical Research in London: "Lots of people are interested in noggin....It is the only protein that has been found that is a bona fide direct neural inducer."

It's not only developmental biologists who are excited. Noggin has also been found in the brains of adult rats, raising some neuroscientists' hopes that the molecule may be a new type of chemical signal, with multiple roles in nervous system development and function. If that is the case, noggin might someday prove useful as a treatment for nerves damaged by disease or trauma, a possibility that has at least one biotech company interested. But in spite of the manifest enthusiasm, researchers caution that much more work is needed before they accept definitively that noggin is a player in either neural development or the adult brain.

Still, Harland's results already represent the solution to a mystery that began with experiments—some dating to the early decades of this century—in which researchers transplanted pieces of tissue from one developing embryo into new locations in another and watched to see what happened. These transplants revealed that the yolky bottom half of the embryo, known as the vegetal hemisphere, produces a chemical signal that tells a band of cells at the embryo's equator to become mesoderm, the tissue that streams inward at gastrulation, and later forms muscle, blood, and bones.

The transplantation work also showed that the mesoderm releases a welter of chemical signals. Even before gastrulation begins, one patch of mesoderm—called the "Spemann organizer" after its discoverer, German embryologist Hans Spemann—begins sending signals that tell part of the mesoderm to make dorsal, or back-of-the-body, structures such as the vertebral column, as well as signals that tell the adjacent part of the ectoderm to form the neural plate.

Researchers lost no time in starting to look for the molecules that determine mesoderm formation and the subsequent events, but for many years their efforts were unsuccessful. The hunt for the neural inducing factor proved particularly confusing—not because there were no results, but because the work produced an embarrassment of riches. Indeed, a long list of compounds, most of them biologically irrelevant, could trigger ectoderm to become neural tissue in the newt and salamander embryos commonly studied at that time. Even though those experiments were done in the 1930s and '40s, they had a lasting—and chilling—effect on the field, says developmental biologist Jonathan Slack of the Imperial Cancer Research Fund at the University of Oxford. "Even when I came in, in the mid-1970s, people said neural induction is completely nonspecific, you can't do anything with it."

It wasn't until the late 1980s that researchers began finding a way out of this