Where Do We Draw the Line?

Researchers duplicate a human embryo, provoking cries that technology has gone too far

By PHILIP ELMER-DEWITT

When it finally happened—after years of ethical hand wringing and science-fiction fantasy—it was done in such a low-key way by researchers so quiet and self-effacing that the world nearly missed it. The landmark experiment was reported by Jerry Hall at a meeting of the American Fertility Society in Montreal three weeks ago. Afterward, colleagues came up to congratulate him and say “Nice job.” Others voted to give his paper, written with his supervisor, Dr. Robert Stillman, the conference's first prize. But nobody seemed to want to pursue the one fact that made his little experiment—in which he started with 17 microscopic embryos and multiplied them like the Bible’s loaves and fishes into 48—different from anything that had preceded it. Hall flew back to George Washington University, where he is director of the in-vitro lab and where Stillman heads the entire in-vitro fertilization program, reassured that people would view his work as he saw it: a modest scientific advance that might someday prove useful for treating certain types of infertility.

How wrong he was. When the story broke last week—on the front page of the New York Times under the headline SCIENCE

TIST CLONES HUMAN EMBRYOS, AND CREATE AN ETHICAL CHALLENGE—everybody focused on the one thing the scientists seemed willing to overlook: the cells Hall had manipulated came not from plants or pigs or rabbits or cows, but from human beings.

Once it was out, the news that human embryos had been cloned flew around the world with the speed of sound bites bouncing off satellites. That afternoon the switchboard at George Washington logged 250 calls from the press. By the next day more calls and faxes were flooding in from as far away as Spain, Sweden, South Africa and Australia. A spokesman for the Japan Medical Association found the experiment “unthinkable.” French President François Mitterrand pronounced himself “horrified.” The Vatican’s L’Osservatore Romano warned in a front-page editorial that such procedures could lead humanity down “a tunnel of madness.”

It was the start of the fiercest scientific debate about medical ethics since the birth of the first test-tube baby 15 years ago. A line had been crossed. A taboo broken. A Brave New World of cookie-cutter humans, baked and bred to order, seemed, if not just around the corner, then just over the horizon. Ethicists called up nightmare visions of baby farming, of clones cannibalized for spare parts. Policymakers pointed to the vacuum in U.S. bioethical leader-
Test-Tube Reproduction

**1938** Pregnancy reported from artificial insemination

**1944** First attempt at in-vitro fertilization

**1949** Researchers discover glycercol can be used to freeze sperm for later use

**1951** First successful transfer of an embryo from one cow to another

**1952** First calf produced using frozen semen

**1952** Frogs cloned from the cells of tadpoles

**1953** Live rabbit offspring from in-vitro fertilization

1978 First offspring from artificial insemination

The experiment at the center of the controversy seems, in many ways, unworthy of the hoopla. It is not the Jurassic Park-type cloning that genetic material from a mature individual—or DNA from an extinct dinosaur—is nurtured and grown into a living replica of the original. This is far beyond the reach of today’s science. There is a vast difference between cloning an embryo that is made up of immature, undifferentiated cells and cloning adult cells that have already committed themselves to becoming skin or bone or blood. All cells contain within their DNA the information required to reproduce the entire organism, but in adult cells access to parts of that information has somehow been switched off. Scientists do not yet know how to switch it back on.

Nor does the Hall-Stillman experiment involve genetic engineering—the cutting and splicing procedures by which DNA strands within the nuclei of cells are mixed and matched. In one kind of genetic engineering, scientists have inserted human genes into the DNA of bacteria in order to mass-produce insulin and other human proteins. They have also experimented with therapies that involve replacing genes in human patients who either lack those genes or whose genes are defective. The George Washington research required none of that. The cells were just copied with their genes intact—a far simpler process. Simple enough, in fact, that agricultural researchers have used it to clone embryos from cattle, pigs and other animals for more than a decade.

What brought the research into the human arena was the rapidly developing field of in-vitro fertilization. In clinics popping up around the world, couples who have trouble conceiving can have their sperm and eggs mixed in a Petri dish—and the resulting embryos transferred to the mother’s womb. The process is distressingly hit-or-miss, though, and the odds of a successful pregnancy go up with the number of embryos used. In a typical in-vitro procedure, doctors will insert three to five embryos in hopes that, at most, one or two will implant.

But some couples cannot produce more than one embryo, perhaps because the man’s semen is in short supply or the woman’s ovaries are running out of eggs or do not respond well to hormone treatments designed to stimulate them into superovulating (producing large numbers of eggs on demand). A woman with only one embryo has about a 10% to 20% chance of getting pregnant through in-vitro fertilization. If that embryo could be cloned and turned into three or four, the chances of a successful pregnancy would increase significantly.

This is the reason Hall and Stillman began experimenting with cloning. But they weren’t trying, in their initial effort, to produce clones that would actually be implanted in their mothers and later born. The scientists said they just wanted to take the first step toward determining if cloning is feasible in humans as it is in cattle. Working in George Washington’s in-vitro fertilization clinic, they selected embryos that were abnormal because they came from eggs that had been fertilized by more than one sperm; these flawed embryos were destined for an early death whether or not they were implanted. Thus Hall and Stillman saw nothing unethical about experimenting with them, and they got permission to do so from the university.

When one of those single-celled embryos divided into two cells, the first step in development, the scientists quickly separated the cells, creating two different embryos with the same genetic information. (This sometimes happens naturally inside a mother, and the result is identical twins.) In the process, though, the researchers had to strip away an outer coating, called the zona pellucida, that is essential to development. Then came the trickiest part of the procedure. Over the years, Hall had been working with a gel derived from seaweed that could serve as a substitute for the zona pellucida. When Hall put the artificial coating around the cloned embryos, they began to grow and develop. The experiment was a success.

The scientists replicated their procedure many times, producing 48 clones in all. That was the entire experiment. None of the clones grew for more than six days. The scientists had no intention of starting an embryo factory, selling babies or doing anything else that ethicists worry about.
In fact, Hall and Stillman were totally taken aback by the furor they created. TIME correspondent Ann Blackman asked Hall if he feared that his work would create a backlash against this kind of research. "I revere human life," said Hall, his voice choking with emotion. "I respect people's concerns and feelings. But we have not created human life or destroyed human life in this experiment." To Hall and Stillman, human cloning is simply the next step in the logical progression that started with in vitro fertilization and is driven by a desire to relieve human suffering—in this case, the suffering of infertile couples.

That is certainly the least controversial of the technology's potential applications. In the TIME/CNN poll, Americans were evenly split on whether they approved or disapproved of cloning for this purpose. If it works—and that is still a big if—it could probably find a market among infertility patients who have tried everything else. "It's pretty scary," said Barbara Tilden, a 39-year-old Illinois woman who has gone through eight different infertility treat-

![Diagram of cloning process]

ments in the past 10 years. "But I'd probably consider it as a desperate last attempt!"

Arthur Caplan, director of the Center for Bioethics at the University of Minnesota, could conjure up several equally defensible ways in which cloning human embryos might be medically appropriate. Suppose, for example, a woman knew she was about to become sterile, either because of chemotherapy or through exposure to toxic substances. She might consider having an embryo cloned for future use. Or suppose a couple knew that their children had a chance of inheriting hemophilia or cystic fibrosis. Researchers have developed DNA-analysis techniques to screen embryos for such disorders, but the procedures require snipping cells off embryos, a process that sometimes kills them. In such situations, having a couple of extra clones around could mean the difference between passing on a defective gene or giving birth to a perfectly healthy child.

Even these uses of cloning are fraught with ethical difficulties—not the least of which is the assumption that a defective embryo will be discarded, an action that most right-to-life advocates equate with murder. Medical ethicists have worried for some time that advances in reproductive technology in the U.S. are proceeding in an ethical vacuum, one created not by the technology but by the politics of abortion. "Congress and our state legislatures are fearful of anything that gets them near the abortion debate," complained Caplan. "As a result, we have had no systematic discussion of surrogacy, of what to do with frozen embryos when parents die, of who can operate a fertility clinic. And we have had no systematic discussion of cloning."

As soon as Caplan heard the news from the American Fertility Society meeting, he phoned Gina Kolata, the reporter at the New York Times who broke the story. As a result, Caplan helped shape the discussion that followed. For example, although Hall's technique cannot produce more than two
They Clone Cattle, Don’t They?

Want to peek into a crystal ball and glimpse at the future of cloning? One way might be to look at the livestock industry, the proving ground for reproductive technology. More than a decade has passed since the first calves, lambs and piglets were cloned, and yet there are no dairy herds composed of carbon-copy cows, no pigpens filled with identical sows. While copying particular strains of valuable plants such as corn and canola has become an indispensible tool of modern agriculture, cloning farm animals, feasible as it may be, has never become widespread. Even simple embryo splitting, the technique used by the George Washington University researchers on human cells, is too expensive and complicated to take off commercially. “Cloning,” says George Seidel, an animal physiologist at Colorado State University, “remains very much a niche technology.”

But people have certainly tried to turn livestock cloning into a booming branch of agribusiness in the U.S., and they’re still trying. Wisconsin-based American Breeders Service, a subsidiary of W.R. Grace & Co., now owns the rights to cattle-cloning technology developed by Granada Biosciences, a once-high-flying biotech firm that went out of business in 1992. The process calls for single cells to be separated from a growing calf embryo. Each cell is then injected into an unfertilized egg and implanted in the womb of a surrogate cow. Because the nucleus of the unfertilized egg is removed beforehand, it contains no genetic material that might interfere with the development of the embryo. In theory, the method of cloning does not seem much better than embryo splitting, which typically produces twins and sometimes triplets. There have been other problems as well. Some of the calves produced have weighed so much at birth that they have had to be delivered through caesarean section. “I think we have a right to see the difficulties they think a child ought to be from what he or she actually is. That difficulty would be compounded—for both the parent and the child—if an exact template for what that child could become in 10 or 20 years were before the mind in the form of an older sibling. “I think we have a right to our own individual genetic identity,” said Daniel Callahan, director of the Hastings Center, an ethics-research organization in Briarcliff Manor, New York. “I think this could well violate that right.”

Many of the uses envisioned for cloning are not particularly farfetched compared with things that are already happening. A few years ago, a California couple made a remarkable decision when faced with the news that their daughter was dying of leukemia. The father braved a vasectomy reversal and the mother a pregnancy at 43 to have a new child born for the express purpose of providing the bone-marrow transplant that saved the older child’s life. Husband and wives who have been through in-vitro fertilization with some embryos left over have had to wrestle with
the fact that they have a potential human being stored on ice. There are already 10,000 frozen embryos floating around in liquid-nitrogen baths in the U.S., stuck in a kind of icy limbo as their would-be parents sort out the options. Do they let the embryos thaw out and die? Do they give them away? Do they have the right to sell embryos to the highest bidder? And who gets custody—or the cash—in a divorce?

When the profit motive enters into the equation, ethical considerations tend to be forgotten. And private profit drives the infertility business in the U.S. "We are one of the few countries in the world where you can sell sperm and eggs," said George Annas, a medical ethicist at Boston University. There are already catalogs that list the characteristics of sperm donors—including one made up of Nobel prizewinners. Without regulation, it will only be a matter of time, said Annas, before some entrepreneur tries to market embryos derived from athletes Michael Jordan or model Cindy Crawford.

"This is the dawn of the eugenics era," declared Jeremy Rifkin, founder of the Foundation on Economic Trends, a biotechnology-watchdog group in Washington. Painting a dark picture, Rifkin organized protests last week outside George Washington University and other U.S. reproductive-research institutions.

Rifkin, however, was the exception. Few people seemed to be thinking of the Bush New World visions in which a totalitarian government creates whole subclasses of clones designed expressly for particular tasks. As Annas pointed out, there are better ways to create a back U.S. Navy SEAL team or an astronaut corps than to clone the appropriate mix of sperm and egg and wait 20 years. "Maybe if this were Nazi Germany, we would worry more about the government," said Annas. "But we're in America, where we have the private market. We don't need government to make the nightmare scenario come true."

Most people seemed to respond to the idea of human cloning at a more fundamental level. In the TIME/CNN poll, 58% said they thought cloning was morally wrong, while 63% said they believed it was against God's will. "It's not that anyone thinks there is a commandment 'Thou shalt not clone,'" said Margaret O'Brien Steinfeld of Catholic Commonweal magazine. "But there are limits to what humans ought to be thinking about doing." For many, the basic sanctity of human life seemed to be under attack, and it made them angry. "The people doing this ought to contemplate splitting themselves in half and see how they like it," said Germaine Greer, a professor of Christian ethics at Mount Saint Mary's College in Emmitsburg, Maryland.

The reaction from around the world was, in may ways, even more heated. "This is not research," snapped Dr. Jean-François Mattei of Timone Hospital in Marseilles, France. "It's aberrant, showing a lack of a sense of reality and respect for people." In Germany, Professor Hans-Bernhard Wuermeling, a medical ethicist at the University of Erlangen, was equally repelled by the notion of producing clones for spare parts, calling it "a modern form of slavery."

German officials were quick to point out that the experiment Hall and Stillman conducted—cloning a human embryo—would have been considered a federal offense in Germany, punishable by up to five years in prison. "The Americans do not even have our scruples," complained Rudolf Dressler, deputy whip of the Social Democratic opposition in the Bundestag. "They simply go ahead with research, cost what it may." More than 25 countries have commissions that set policy on reproductive technology. In Britain, cloning human cells requires a license the government simply cuts off funding to projects the U.S. Congress finds offensive. But that wouldn't work in this case since there is no federal funding for embryo research; experiments are financed largely by private money, much of it derived from the booming business of in-vitro fertilization.

"This is the dawn of the eugenics era," said Rifkin, calling for a ban on embryo'splitting.

MAKING MATTERS EVEN more complicated, there is no federal body charged with setting artificial-fertilization policy in the U.S. The last congressional commission empowered to debate the new technology was disbanded in 1989. Instead, policy is set by a patchwork of state laws, professional societies and local review boards, like the one at George Washington that gave the go-ahead to Hall and Stillman.

Two weeks ago, a report by the congressional Office of Technology Assessment presciently recommended that the government step in. In the past, bioethical policy could have been addressed by any one of a series of federal boards. Perhaps the best was a presidential commission established under President Carter that developed broad policy guidelines on some of the most controversial issues in medicine, such as deciding when brain death has occurred or whether it is ethically correct to use a do not resuscitate order. The commission was disbanded in 1983. Last week's debate made it likely that some kind of national board will be established during President Clinton's watch. It had better be