PANDORA'S BABY

In vitro fertilization was once considered by some to be a threat to our very humanity. Cloning inspires similar fears

BY ROBIN MARANTZ HENIG

On July 25, a once unique person will turn 25. This nursery school aide in the west of England seems like an average young woman, a quiet, shy blonde who enjoys an occasional round of darts at the neighborhood pub. But Louise Brown's birth was greeted by newspaper headlines calling her the "baby of the century." Brown was the world's first test tube baby.

Today people may remember Brown's name, or that she was British, or that her doctors, Steptoe and Edwards, sounded vaguely like a vaudeville act. But the past quarter of a century has dimmed the memory of one of the most important aspects of her arrival: many people were horrified by it. Even some scientists feared that Patrick Steptoe and Robert Edwards might have brewed pestilence in a petri dish. Would the child be normal, or would the laboratory manipulations leave dreadful genetic derangements? Would she be psychologically scarred by the knowledge of how bizarrely she had been created? And was she a harbinger of a race of unnatural beings who might eventually be fashioned specifically as a means to nefarious ends?

Now that in vitro fertilization (IVF) has led to the birth of an estimated one million babies worldwide, these fears and speculations may seem quaint and even absurd. But the same concerns once raised about IVF are being voiced, sometimes almost verbatim, about human cloning. Will cloning go the way of IVF, morphing from the monstrous to the mundane? And if human cloning, as well as other genetic interventions on the embryo, does someday become as commonplace as test tube baby–making, is that to be feared—or embraced? The lessons that have been

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MICRONEEDLE INJECTS a sperm's package of DNA directly into a human egg, thereby achieving in vitro fertilization (*left*). The first human being born as a result of IVF, Louise Brown was 14 months old when she frolicked on the set of the *Donahue* television program (*right*). With her was Vanderbilt University IVF researcher Pierre Soupart, who predicted that "by the time Louise is 15, there will be so many others it won't be remarkable anymore."

learned from the IVF experience can illuminate the next decisions to be made.

Then and Now

AS IVF MOVED FROM the hypothetical to the actual, some considered it to be nothing more than scientists showing off: "The development of test tube babies," one critic remarked, "can be compared to the perfecting of wing transplants so that pigs might fly." But others thought of IVF as a perilous insult to nature. The British magazine *Nova* ran a cover story in the spring of 1972 suggesting that test tube babies were "the biggest threat since the atom bomb" and demanding that the public rein in the unpredictable scientists. "If today we do not accept the responsibility for directing the biologist," the *Nova* editors wrote, "tomorrow we may pay a bitter price—the loss of free choice and, with it, our humanity. We don't have much time left."

A prominent early enemy of IVF was Leon Kass, a biologist at the University of Chicago who took a professional interest in the emerging field of bioethics. If society allowed IVF to proceed, he wrote shortly after Louise Brown's birth, some enormous issues were at stake: "the idea of the humanness of our human life and the meaning of our embodiment, our sexual being, and our relation to ancestors and descendants."

Now read Kass, a leading detractor of every new form of reproductive technology for the past 30 years, in 2003: "[Cloning] threatens the dignity of human procreation, giving one generation unprecedented genetic control over the next," he wrote in the *New York Times*. "It is the first step toward a eugenic world in which children become objects of manipulation and products of will." Such commentary coming from Kass is particularly noteworthy because of his unique position: for the past two years he has been the head of President George W. Bush's Council on Bioethics, whose first task was to offer advice on how to regulate human cloning.

Of course, IVF did not wind up creating legions of less than human children, nor did it play a role in the disintegration of the nuclear family, consequences that people like Kass feared. And so many newer, more advanced methods of assisted reproduction have been introduced in the past decade that the "basic IVF" that produced Louise Brown now seems positively routine. One early prediction, however, did turn out to contain more than a kernel of truth. In the 1970s critics cautioned that IVF would set us tumbling down the proverbial slippery slope toward more sophisticated and, to some, objectionable forms of reproductive technology—and that once we opened the floodgates by allowing human eggs to be fertilized in the laboratory, there would be no stopping our descent.

If you consider all the techniques that might soon be available to manipulate a developing embryo, it could appear that the IVF naysayers were correct in their assessment of the slipperiness of the slope. After all, none of the genetic interventions now being debated—prenatal genetic diagnosis, gene insertions in sex cells or embryos to correct disease, the creation of new embryonic stem cell lines and, the elephant in the living room, cloning—would even be potentialities had scientists not first learned how to fertilize human eggs in a laboratory dish.

But does the existence of a such a slippery slope mean that present reproductive technology research will lead inevitably to developments that some find odious, such as embryos for tissue harvesting, or the even more abhorrent manufacture of human-nonhuman hybrids and human clones? Many people clearly fear so, which explains the current U.S. efforts to

Overview/*In Vitro Veritas*

- Many arguments against in vitro fertilization in the past and cloning today emphasize a vague threat to the very nature of humanity.
- Critics of IVF attempted to keep the federal government from supporting the research and thus ironically allowed it to flourish with little oversight.
- Because of the lack of oversight, it is only in the past few years that the increased rate of birth defects and low birth weight related to IVF have come to light.

PASCAL GOETGHELUCK *Science Photo Library* (*left*); RAY FOLI *Corbis-Bettmann* (*right*)

WILLIAM PLOWMAN *Getty*

MEMBERS of the Christian Defense Coalition and the National Clergy Council protest Advanced Cell Technologies's human cloning research outside the biotechnology firm's headquarters in Worcester, Mass., on November 30, 2001. Similar protests against IVF occurred in the 1970s.

WILLIAM PLOWMAN Getty

curtail scientists' ability to manipulate embryos even before the work gets under way. But those efforts raise the question of whether science that has profound moral and ethical implications should simply never be done. Or should such science proceed, with careful attention paid to the early evolution of certain areas of research so that society can make informed decisions about whether regulation is needed?

IVF Unbound

THE FRENZY TO TRY to regulate or even outlaw cloning is in part a deliberate attempt not to let it go the way of IVF, which has been a hodgepodge of unregulated activities with no governmental or ethical oversight and no scientific coordination. Ironically, the reason IVF became so ubiquitous and uncontrolled in the U.S. was that its opponents, particularly antiabortion activists, were trying to stop it completely. Antiabortion activists' primary objection to IVF was that it involved the creation of extra embryos that would ultimately be unceremoniously destroyed—a genocide worse than at any abortion clinic, they believed. Accordingly, they thought that their best strategy would be to keep the federal government from financing IVF research.

A succession of presidential commissions starting in 1973 debated the ethics of IVF but failed to clarify matters. Some of the commissions got so bogged down in abortion politics that they never managed to hold a single meeting. Others concluded that IVF research was ethically acceptable as long as scientists honored the embryo's unique status as a "potential human life," a statement rather than a practical guideline. In 1974 the government banned federal funding for fetal research. It also forbade funding for research on the human embryo (defined as a fetus less than eight weeks old), which includes IVF. In 1993 President Bill Clinton signed the NIH Revitalization Act, which allowed federal funding of IVF research. (In 1996, however, Congress again banned embryo research.) The bottom line is that despite a series of recommendations from federal bioethics panels stating that taxpayer support of IVF research would be acceptable with certain safeguards in place, the government has never sponsored a single research grant for human IVF.

This lack of government involvement—which would also have served to direct the course of IVF research—led to a funding vacuum, into which rushed entrepreneurial scientists supported by private money. These free agents did essentially whatever they wanted and whatever the market would bear, turning IVF into a cowboy science driven by the marketplace and undertaken without guidance. The profession attempted to regulate itself—in 1986, for example, the American Fertility Society issued ethical and clinical guidelines for its members—but voluntary oversight was only sporadically effective. The quality of clinics, of which there were more than 160 by 1990, remained spotty, and those seeking IVF had little in the way of objective information to help them choose the best ones.

Today, in what appears to be an effort to avoid the mistakes made with IVF, the federal government is actively involved in regulating cloning. With the announcement in 1997 of the birth of Dolly, the first mammal cloned from an adult cell, President Clinton established mechanisms, which remain in place, to prohibit such activities in humans. Congress has made several attempts to outlaw human cloning, most recently with a bill that would make any form of human cloning punishable by a $1-million fine and up to 10 years in prison. (The House of Representatives passed this bill this past winter, but the Senate has yet to debate it.) Politicians thus lumped together two types of cloning that scientists have tried to keep separate: "therapeutic," or "research," cloning, designed to produce embryonic stem cells that might eventually mature into specialized human tissues to treat degenerative diseases; and "reproductive" cloning, undertaken specifically to bring forth a cloned human being. A second bill now

THE AUTHOR

ROBIN MARANTZ HENIG has written seven books, most recently *The Monk in the Garden: The Lost and Found Genius of Gregor Mendel*. Her articles have appeared in the *New York Times Magazine*, *Civilization* and *Discover*, among other publications. Her honors include an Alicia Patterson Foundation fellowship and a nomination for a National Book Critics Circle Award. She lives in New York City with her husband, Jeffrey R. Henig, a political science professor at Columbia University; they have two nearly grown daughters. Her next book, entitled *Pandora's Baby*, is about the early days of in vitro fertilization research.

From Outrage to Approval

THE STORY of Doris Del-Zio demonstrates the ironies resulting from society's changing attitude toward IVF in the 1970s. After years of failure to conceive a child, Del-Zio and her husband turned to Landrum Shettles of what is now known as the Columbia Presbyterian Medical Center. In the fall of 1973 Shettles prepared to attempt a hasty IVF procedure on the couple. The operation was abruptly terminated by Shettles's superior, Raymond Vande Wiele, who was outraged at Shettles's audacity and who questioned the medical ethics of IVF. Vande Wiele confiscated and froze the container holding the Del-Zios' eggs and sperm. As far as the Del-Zios were concerned, Vande Wiele had committed murder: they sued him and his employers for $1.5 million.

By coincidence, the Del-Zios' case against Vande Wiele was finally brought to trial in July 1978, the same month that Louise Brown was born. The birth of the world's first test tube baby put Shettles's early IVF attempt in a different light. After Brown's appearance, most people—including the two men and four women on the Del-Zio jury—seemed much more inclined to think of IVF as a medical miracle than as a threat to civilized society.

The trial lasted six weeks, each side making its case about the wisdom, safety and propriety of IVF. In the end, Vande Wiele was found to be at fault for "arbitrary and malicious" behavior, and he and his co-defendants were ordered to pay Doris Del-Zio $50,000.

IVF developed rapidly after the trial, and 200 more test tube babies—including Louise Brown's sister, Natalie—were born over the next five years. (Natalie is now a mother, having conceived naturally, and is the first IVF baby to have a child.) Seeing so many healthy-looking test tube babies worldwide changed Vande Wiele's opinion, a change that paralleled the transformation in feeling about IVF that was occurring in the public at large. When Columbia University opened the first IVF clinic in New York City in 1983, its co-director was Raymond Vande Wiele. —*R.M.H.*

COURTING JUSTICE: Doris Del-Zio and her attorney, Michael Dennis, outside U.S. district court in New York City on July 17, 1978, after a session of jury selection. Del-Zio and her husband, John, sued physician Raymond Vande Wiele for derailing their early attempt at in vitro fertilization.

AP PHOTO

before the Senate would explicitly protect research cloning while making reproductive cloning a federal offense.

IVF Risks Revealed

ONE RESULT OF the unregulated nature of IVF is that it took nearly 25 years to recognize that IVF children *are* at increased medical risk. For most of the 1980s and 1990s, IVF was thought to have no effect on birth outcomes, with the exception of problems associated with multiple births: one third of all IVF pregnancies resulted in twins or triplets, the unintended consequence of the widespread practice of implanting six or eight or even 10 embryos into the womb during each IVF cycle, in the hope that at least one of them would "take." (This brute-force method also leads to the occasional set of quadruplets.) When early studies raised concerns about the safety of IVF—showing a doubling of the miscarriage rate, a tripling of the rate of stillbirths and neonatal deaths, and a fivefold increase in ectopic pregnancies—many people attributed the problems not to IVF itself but to its association with multiple pregnancies.

By last year, however, IVF's medical dark side became undeniable. In March 2002 the *New England Journal of Medicine* published two studies that controlled for the increased rate of multiple births among IVF babies and still found problems. One study compared the birth weights of more than 42,000 babies conceived through assisted reproductive technology, including IVF, in the U.S. in 1996 and 1997 with the weights of more than three million babies conceived naturally. Excluding both premature births and multiple births, the test tube babies were still two and a half times as likely to have low birth weights, defined as less than 2,500 grams, or about five and a half pounds. The other study looked at more than 5,000 babies born in Australia between 1993 and 1997, including 22 percent born as a result of IVF. It found that IVF babies were twice as likely as naturally conceived infants to have multiple major birth defects, in particular chromosomal and musculoskeletal abnormalities. The Australian researchers speculate that these problems may be a consequence

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THE DAY AFTER her 20th birthday, Louise Brown poses at home with her parents.

ADRIAN ARBIB *Corbis*

of the drugs used to induce ovulation or to maintain pregnancy in its early stages. In addition, factors contributing to infertility may increase the risk of birth defects. The technique of IVF itself also might be to blame. A flawed sperm injected into an egg, as it is in one IVF variation, may have been unable to penetrate the egg on its own and is thus given a chance it would otherwise not have to produce a baby with a developmental abnormality.

Clearly, these risks could remain hidden during more than two decades of experience with IVF only because no system was ever put in place to track results. "If the government had supported IVF, the field would have made much more rapid progress," says Duane Alexander, director of the National Institute of Child Health and Human Development. "But as it is, the institute has never funded human IVF research of any form"—a record that Alexander calls both incredible and embarrassing.

Although the medical downsides of IVF are finally coming to light, many of the more alarmist predictions about where IVF would lead never came to pass. For example, one scenario was that it would bring us "wombs for hire," an oppressed underclass of women paid to bear the children of the infertile rich. But surrogate motherhood turned out to be expensive and emotionally complex for all parties, and it never became widespread.

Human cloning, too, might turn out to be less frightening than we currently imagine. Market forces might make reproductive cloning impractical, and scientific advancement might make it unnecessary. For example, people unable to produce eggs or sperm might ponder cloning to produce offspring. But the technology developed for cloning could make it possible to create artificial eggs or sperm containing the woman's or man's own DNA, which could then be combined with the sperm or egg of a partner. In the future, "cloning" might refer only to what is now being called therapeutic cloning, and it might eventually be truly therapeutic: a laboratory technique for making cells for the regeneration of damaged organs, for example. And some observers believe that the most common use of cloning technology will ultimately not involve human cells at all: the creature most likely to be cloned may wind up being a favorite family dog or cat.

The history of IVF reveals the pitfalls facing cloning if decision making is simply avoided. But despite similarities in societal reactions to IVF and cloning, the two technologies are philosophically quite different. The goal of IVF is to enable sexual reproduction in order to produce a genetically unique human being. Only the site of conception changes, after which events proceed much the way they normally do. Cloning disregards sexual reproduction, its goal being to mimic not the process but the already existing living entity. Perhaps the biggest difference between IVF and cloning, however, is the focus of our anxieties. In the 1970s the greatest fear related to in vitro fertilization was that it would fail, leading to sorrow, disappointment and possibly the birth of grotesquely abnormal babies. Today the greatest fear about human cloning is that it may succeed. SA

MORE TO EXPLORE

Moving toward Clonal Man: Is This What We Want? James D. Watson in *Atlantic Monthly*, Vol. 227, No. 5, pages 50–53; May 1971.

The Frankenstein Myth Becomes a Reality: We Have the Awful Knowledge to Make Exact Copies of Human Beings. Willard Gaylin in *New York Times Magazine*, pages 12–13, 41–46; March 5, 1972.

The Embryo Sweepstakes. David Rorvik in *New York Times Magazine*, pages 17, 50–62; September 15, 1974.

Remaking Eden: How Genetic Engineering and Cloning Will Transform the American Family. Lee M. Silver. Avon Books, 1998.

The Clone Age: Adventures in the New World of Reproductive Technology. Lori B. Andrews. Henry Holt and Company, 1999.

Free to Be Me: Would-Be Cloners Pushing the Debate. Rick Weiss in *Washington Post*, page A1; May 12, 2002.

ENDPOINTS

Pandora's Baby
IN REVIEW

TESTING YOUR COMPREHENSION

1] A "test tube baby" is produced through the process of
- a] in vivo fertilization.
- b] in vitro fertilization.
- c] therapeutic cloning.
- d] reproductive cloning.

2] When was the first person born as a result of an in vitro fertilization procedure?
- a] 1862
- b] 1953
- c] 1978
- d] 1992

3] Today there are about _____ people who were born as a result of an in vitro fertilization procedure.
- a] 0
- b] 100
- c] 10,000
- d] 1,000,000

4] Today there are about _____ people who were born as a result of human cloning.
- a] 0
- b] 100
- c] 10,000
- d] 1,000,000

5] For most of the last 25 years, what has been the U.S. federal policy on IVF research?
- a] All research on IVF was banned.
- b] The federal funding of IVF research was banned.
- c] The federal government funded IVF research but failed to regulate it.
- d] The federal government funded and carefully regulated IVF research.

6] The type of cloning that intends to produce a new living human is called
- a] therapeutic cloning.
- b] reproductive cloning.
- c] in vitro cloning.
- d] in vivo cloning.

7] The type of cloning that intends to produce embryonic stem cells is called
- a] therapeutic cloning.
- b] reproductive cloning.
- c] in vitro cloning.
- d] in vivo cloning.

8] What is the current U.S. federal policy on human reproductive cloning research?
- a] All research on human reproductive cloning is banned.
- b] The federal funding of human reproductive cloning research is banned.
- c] The federal government funds reproductive cloning research but fails to regulate it.
- d] The federal government funds and carefully regulates human reproductive cloning research.

9] Why do IVF procedures increase the chance of multiple births?
- a] IVF embryos are often cloned, producing multiple embryos.
- b] Women undergoing IVF have closer medical supervision than other women.
- c] More IVF-created embryos survive than naturally created embryos.
- d] IVF usually involves the implantation of six or more embryos at once.

10) Which of the following statements about the safety of IVF is most correct?

a) No convincing data has ever been collected indicating that IVF babies have an increased health risk.

b) From the beginning of IVF research, it was clear that IVF babies have a small but significant increased health risk.

c) Recent evidence suggests that IVF babies do have increased risk of low birth weight.

d) Recent studies have found that the increased risks for IVF babies include low birth weight and major birth defects.

BIOLOGY IN SOCIETY

1) If you were asked to testify before a congressional hearing on cloning research, what would be your opinion about federal funding of therapeutic cloning? Do you think the government should fund and/or oversee such research? What about for reproductive cloning? Would you testify differently about therapeutic and reproductive cloning? Why? What regulations or safeguards would you recommend be put into place?

2) Do you think that insurance companies should pay for infertile couples to have an IVF procedure? Why or why not? What about for non-infertile couples?

3) Present three arguments in favor of human reproductive cloning. Present three arguments against it. Which do you consider more convincing and why?

THINKING ABOUT SCIENCE

1) On page 16, the author describes two studies published in 2002 about the risks of IVF. For each study, rephrase the information presented in terms of the scientific method. For each of the two studies, write a hypothesis that could have served as the basis of the experiment. Next, describe the method used and the data collected. What conclusions were drawn from that data? What possible sources of error were there in the experimental design? Can you think of a way (real or hypothetical) to get around those sources of error?

2) How might the procedures of human gene therapy and human therapeutic cloning be combined to cure a child born with a hereditary immune defect? Design a series of hypothetical procedures that might be effective.

WRITING ABOUT SCIENCE

Write an essay that imagines a future society where human cloning is as widespread and accepted as IVF is today. What problems might such a society face? What benefits?

Testing Your Comprehension Answers:
1b, 2c, 3d, 4a, 5b, 6b, 7a, 8a, 9d, 10d.