Designer Babies

Human cloning is a long way off, but bioengineered kids are already here.
By Shannon Brownlee

In the mid-1990s, embryologist Jacques Cohen pioneered a promising new technique for helping infertile women have children. His technique, known as cytoplasmic transfer, was intended to "rescue" the eggs of infertile women who had undergone repeated, unsuccessful attempts at in vitro fertilization, or IVF. It involved injecting the cytoplasm found inside the eggs of a fertile donor, into the patient's eggs.

When the first baby conceived through cytoplasmic transfer was born in 1997, the press instantly hailed Cohen's technique as yet another technological miracle. But four years later, the real story has proven somewhat more complicated. Last year, Cohen and his colleagues at the Institute for Reproductive Medicine and Science of St. Barnabas, a New Jersey fertility clinic, set off alarm bells among bioethicists with the publication of a paper detailing the genetic condition of two the 17 cytoplasmic-transfer babies born through the clinic to date. The embryologists reported that they had endowed the children with extra bits of a special type of genetic material, known as mitochondrial DNA, or mtDNA, which came with the cytoplasm transferred from the donor eggs to the patient's.

That meant the resulting children had three genetic parents: mother, father, and mtDNA donor. It also meant that female children would transmit their unorthodox combination of mitochondrial DNA to their own offspring (mtDNA is passed down only through eggs), with unknown implications. In effect, Cohen had created the first bioengineered babies. As Cohen's group noted, their experiment was "The first case of human [inheritable] genetic modification resulting in normal, healthy children."

Just how normal those children will turn out to be is anybody's guess. At a recent meeting in Europe, the New Jersey researchers reported that one of the children conceived through cytoplasmic transfer has been diagnosed with "pervasive developmental disorder," a catch-all term for symptoms that range from mild delays in speech to autism. Cohen's group maintained that it is extremely unlikely that cytoplasmic transfer and the resulting mishmash of mtDNA is to blame.

But geneticists have only begun to trace the connections between mtDNA and a host of diseases ranging from strange metabolic ailments to diabetes and Lou Gehrig's disease, and some experts argued that the child's disorder may well be caused by a mismatch between the donor and mother's mtDNA. As Jim Cummins, a molecular biologist at Murdoch University in Western Australia, put it: "To deliberately create individuals with multiple mitochondrial genotypes without knowing the consequences is really a step into the dark."

Welcome to the murky world of "reprogenetics," as Princeton biologist Lee Silver has dubbed the merger between the science of genetics and the fertility industry. While much of the nation's attention has been focused on human cloning, a possibility that is still largely theoretical, a massive, uncontrolled experiment in bioengineering humans is well underway in the Wild West of American fertility clinics, as Cohen and his colleagues have demonstrated. Indeed, there has been more debate over---and far more research into---the implications of bioengineered corn than of bioengineered humans.

Now, many bioethicists believe that Cohen's experiment with cytoplasmic transfer was just one more small step towards a world in which eugenics is another name for making babies. Today, any couple with several thousand dollars to spare can choose the sex of their offspring, while parents who are carriers for certain genetic disorders can undergo IVF and have the resulting embryos genetically tested to ensure their children are free of disease. Tomorrow, parents may be able to enhance their offspring with designer genes. One day, the fertility industry's efforts to help couples conceive could bring society to the brink of altering the genetic heritage of the species.

All that currently stands in the way of parents bent on practicing homegrown eugenics are the ethics of individual fertility specialists and the technical hurdles. Most fertility doctors have the best of intentions, to help patients get pregnant, and to avoid transmitting debilitating disease. And it is by no means certain that science will ever be able to offer parents the option of bioengineering their offspring.

All the same, the pace of the technology is dizzying. A year ago, scientists at the Oregon Regional Primate Research Center announced the birth of the first genetically engineered primate, named ANDi (for "inserted DNA" spelled backwards), a rhesus monkey whose cells contained the gene that makes jellyfish glow in the dark. The experiment was something of a flop; ANDi does not glow. (Rodents implanted with the gene do.) But imagine that one day science does acquire the skills to make "designer babies," that the connections between genes and complex traits such as intelligence or musical ability are finally known. While only the weirdest of parents would to want to genetically engineer offspring with jellyfish genes, others would undoubtedly jump at the chance to "customize" their children with a sparkling personality, brains, and beauty.

One need not be deeply religious or oppose abortion to be troubled by the prospect of a society in which, as bioethicist Alexander Capron puts it, "the wanted child becomes the made-to-order child."

One near-term possibility that many parents, if given the opportunity, will want to weed out embryos carrying genetic traits for a host of non-lethal conditions, like baldness, shyness, short stature, or homosexuality. Fertility specialists are already getting requests from prospective parents who want to know if they can be assured their embryos won't turn out to be hyperactive or gay. Today, Tom Sawyer and Huck Finn would have been diagnosed with attention-deficit disorder and medicated. Tomorrow, they might not be allowed out of the petri dish.

Yet thanks largely to abortion politics and our collective squeamishness about intruding on the individual's right to become a parent, the nation has few mechanisms in place for controlling the pace of this new technology, ensuring the safety of patients, or even talking about the ethics of such experiments.

Since 1998, the Food and Drug Administration (FDA) has argued that genetically manipulated embryos are a "biological product," and therefore subject to regulation, just like medical devices and drugs. But because of a quirk in federal law, the FDA's authority in this sphere is far from certain.

Last summer, FDA sent warning letters to six fertility centers threatening "enforcement action," and asserting its regulatory power over "therapy involving the transfer of genetic material by means other than the union of [sperm and egg.]" Cohen's clinic at St. Barnabas chose to stop performing cytoplasmic transfer. But at least two other recipients scoffed at the agency's threat: Panos Zavos, an embryologist at a Kentucky fertility clinic, and Brigitte Boisselier, the scientific director of Clonaid, the clinic set up by a group known as the Raelians, who believes human beings were genetically engineered by aliens. Both have announced their intentions to clone a human being.

Both also disputed the FDA's authority, and several bioethicists and legal scholars had to agree that the FDA could not prevent them from tinkering with human bioengineering. "It's a stretch for the FDA," says R. Alta Charo, a legal scholar and bioethicist at the University of Wisconsin, and former member of President Bill Clinton's Bioethics Advisory Committee.

A Fertile Market

When the state of Virginia approved the opening of the nation's first IVF clinic in Norfolk, Va., in 1980, anti-abortionists protested by the hundreds. Abortion opponents were concerned that fertility doctors would be playing God with babies' lives, and that they would discard or experiment on imperfect embryos before implantation. They also feared that couples would be inclined to abort abnormal fetuses.

Charles Dean Jr., president of the Norfolk chapter of the anti-abortion Virginia Society for Human Life, told The Washington Post, perhaps somewhat presciently, "There was no proper study of the medical, moral, legal and scientific merits [of IVF]. Meanwhile, we're charging off into the darkness, and I feel it's a tragedy and a disgrace."

In fact, there had been two decades of research in animals on IVF, and the protesters failed to block the Norfolk clinic from producing its first test-tube baby a year later. But abortion foes did manage to take their case to the federal government. After Louise Brown, the first test-tube baby, was born in England in 1978, and the potential for the new technology became apparent, researchers at the Norfolk clinic, along with several other American scientists, applied for federal funds for embryo research.

The anti-abortion movement, however, intervened and successfully lobbied the government to ban federal funding in the field. The ban did little to address the protesters' core concerns about the implications and use of new reproductive technology. In fact, one could argue that it only made the situation worse.

As it turned out, fertility doctors didn't need federal money. With millions of American couples unable to conceive, doctors and embryologists found a lucrative market for the end products of their work, which could legally continue so long as it involved no federal funds.

Financed entirely with private money, the burgeoning fertility industry emerged without a framework for deliberating the ethics of the technology. It also was not bound by any of the requirements that would have come with federally regulated research funds to adequately test new techniques for safety and efficacy before putting them into widespread use.

Not surprisingly, the industry boomed. In 1985, there were 30 fertility clinics in the U.S. A decade later, there were

more than 300. More than one million couples seek fertility treatment each year, and spend more than $3 billion in pursuit of babies. Fees for IVF, the simplest procedure offered, vary between $5,000 and $15,000, with another $2,000 to $3,000 for fertility drugs. A new technology, called pre-implantation genetic diagnosis, or PGD, allows parents who are carriers for certain recessive genetic disorders, like cystic fibrosis and hemophilia, to screen embryos before they are transferred to the mother's womb. PGD can add several thousand dollars to the bill.

With so much money at stake, the market for fertility services is highly competitive, but without government regulation or oversight, the infertility business has become a bit like the dietary supplement industry. There are lots of miraculous claims but not much data to back them up---and tremendous financial incentive to push the envelope with radical new products.

For instance, not all clinics are equally adept at producing babies. Clinic success rates have improved steadily over the last few years, from an average of 17 percent in 1992 for women under 40, to nearly 30 percent in 1999, the most recent year for which figures are available. But these rates vary wildly, from as low as 14 percent to as high as 60 percent.

And babies, of course, are what patients are paying for---usually out of their own pockets, because most insurers do not cover IVF treatment. Clinics have strong financial incentives to inflate their pregnancy rates, or at least to persuade prospective patients that their chances of getting pregnant are high. The largest clinics have substantial advertising budgets, and they market heavily to primary care physicians, who refer patients to clinics, with lavish dinners and seminars in exotic locales.

Assisted Hatching

The fertility industry's self-promotion has gone largely unchallenged, either by the media or the scientific community. While the press has hailed each new development as a godsend for desperate would-be parents, with headlines such as "Amazing Medical Breakthrough" and "New Hope for Infertile Couples," medical researchers who may doubt the validity of these claims have for the most part remained mute. That's because the ban on federal funding for embryo research has made objective analysis of new techniques nearly impossible, and have left infertile couples the unwitting participants in a vast experiment of largely untested technology.

Scientific development in the field has fallen not to high-caliber, federally funded embryologists, but instead to the clinics themselves, which use profits from patients to conduct research. The technology has proceeded with minimal government oversight and peer review, and in the opinion of many biologists, has suffered in quality as a result. "There is no real hard-core scientific background on the part of many of the individuals who are doing this work," says Jonathan Van Blerkom, a leading embryologist at the University of Colorado. Clinics focus their efforts almost exclusively on increasing pregnancy rates, often with little regard for the basic biology and potential consequences to patients and babies.

In the early 1990s, for example, clinics were trumpeting an alphabet soup of new techniques, with names like GIFT, for gamete intra-fallopian transfer, and ZIFT, for zygote intra-fallopian transfer. Both involved surgery, and were used on hundreds of patients, only to be abandoned when clinicians figured out they did not improve pregnancy rates and other techniques proved more helpful.

"Co-culture," the practice of mixing reproductive tissue taken from animals with the culture medium was widely used to incubate embryos, with little regard for the possibility that animal tissue might contain contaminants, such as the infectious agent that causes mad cow disease. Without quantitative results to guide the field, such untested techniques as co-culture are often adopted on faith.

In most cases, patients and potential offspring were unharmed, but not always. Take, for example, "assisted hatching" a technique that involves creating a tiny hole in the outer covering of an embryo just before transferring it to the mother's womb. Many fertility specialists believe that assisted hatching helps embryos implant properly in the womb and boosts pregnancy rates, although they have little hard evidence for this. Assisted hatching also may increase the risk of conjoined, or Siamese, twins. But there are no statistics available to pin down the risk, because most families choose to abort, and clinics are reluctant to publish such results.

Then there's intra-cytoplasmic sperm injection (ICSI), a procedure that was hailed in the mid-90s as a breakthrough in male infertility. ICSI does indeed allow men with few or feeble sperm to become fathers. An embryologist draws a single sperm into a micro-needle and then injects it directly into the mother's egg, rather than simply mixing sperm and eggs in a petri dish, as in normal IVF.

To date, several thousand American babies have been born thanks to the steady hands of embryologists. Yet the technology's long-term safety is still unclear. "ICSI is almost certainly going to increase the likelihood of male infertility in the offspring," says Murdoch University's Jim Cummins. Since ICSI is only ten years old, there's no way to settle the question until ICSI boys grow up.

In the meantime, ICSI children may be vulnerable to birth defects. In November 1997, The British Medical Journal published a controversial study that found that ICSI babies were 200 percent more likely to have a major birth defect than babies conceived naturally, and 50 percent more likely to have a minor defect. Some critics argue that this study suffers from statistical flaws, but a variation on the technology, known as second-day ICSI, heightens the risk of such chromosomal abnormalities as Down's syndrome, and clinics have stopped using it.

Multiplicity

Even when techniques pose a clear danger to offspring, clinics are loath to abandon them as long as they boost pregnancy rates. The most glaring example is the practice of transferring multiple embryos to a woman's womb. Since 1980, according to the National Center for Health Statistics, the number of twins born per year has risen 67 percent. The rate of triplets and higher-order birth multiples has soared from 37 per 100,000 live births in 1980 to 184 per 100,000 in 1999. The increase is due almost entirely, according to federal statisticians, to fertility treatments. Only 20 percent of triplets and higher-order multiples are conceived naturally. (Most extremely high-order multiples, like the McCaughey septuplets, occur when the woman is given fertility drugs and her doctor fails to recognize how many eggs she has produced.)

The risks to multiples and their mother are substantial, and so is the cost. Women pregnant with multiples are more likely than those with singletons to suffer premature delivery, toxemia (a potentially fatal form of high blood pressure), and hemorrhage. Their infants are vulnerable to cerebral palsy, learning disabilities, blindness, developmental delays, and mental retardation, largely because they are often born prematurely. While there are no national statistics on the cost of multiples, a recent study, published in The Journal of Maternal and Fetal Medicine, found that the average charge per triplet pregnancy at one New York City hospital was nearly $190,000. Other studies have shown that triplets can cost as much as 400 times a standard singleton pregnancy and delivery.

"Data on higher-order gestations have been known for years," says Van Blerkom. But fertility clinics have been unwilling to do anything about it he says, for fear they would cut their pregnancy rates. "Have you ever seen a fertility specialist stand next to a couple with their premature quads and say, ŒThis is a disaster for these patients. I think we blew it?'" says Van Blerkom. "Most people in the field were content to let selective terminations at week 13 or 14 clean up the problem."

Under pressure from insurance companies, who often refuse to pay for IVF but wind up footing the bill for multiple births, the American Society for Reproductive Medicine finally issued guidelines last year aimed at reducing the chances of multiples. From the outside, the guidelines seem self-evident: For younger patients, ASRM recommended transferring at most two embryos to the mother's womb; older women, whose embryos are less likely to implant in the uterus and begin developing, can receive as many as five.

But for clinics, the dual pressures of profitability and desperate patients have made such seemingly obvious precautions difficult to follow. "We're under pressure to have high pregnancy rates," complains one clinic doctor. "The problem is we've never had any way of knowing what was the right number of embryos to transfer."

European fertility specialists, who are often required by law to transfer no more than one or two embryos to a single patient, don't seem to have the same trouble. They use research conducted by Van Blerkom and others in the late 1990s showing how to select the most viable embryos and reduce the number that is transferred to the mother. But choosing embryos requires painstaking attention, often at odd hours of the night, and American fertility clinics have been reluctant to invest in technologists who can perform it.

Without federal funding for studies, or oversight from a government body like the FDA, reproductive medicine has had little outside incentive to make such changes as bringing down the rate of multiple births. "We've got the worst system you could possibly come up with," says Dr. Lawrence Udoff, a fertility specialist and director of the pre-implantation genetics program at the University of Maryland at Baltimore. "There are people in this business who are a lot better at marketing than they are at replicating their results. The patient ends up footing the bill for procedures that are untested."

The industry trade group, the American Society for Reproductive Medicine, argues that fertility doctors are doing nothing different from any other specialist. "Reproductive medicine starts from the same regulatory basis as every

other kind of medicine," says ASRM spokesman, Sean Tipton. If a heart surgeon thinks a new way of tying off an artery might work, she simply does it. If the patient lives, she tries it again. Eventually, she may take a retrospective look at her cases and compare the outcomes of those who received the new method versus the old.

It is also true, however, that the history of medicine is littered with examples of doctors unquestioningly adopting new treatments long before they have been evaluated, only to abandon them when they turn out to be ineffective---or worse. More than 30,000 women with breast cancer received high dose chemotherapy with bone-marrow transplants in the 1980s and 90s. At least 9,000 died from the treatment before researchers finally performed clinical trials, which ultimately demonstrated that high dosage is no better than standard chemotherapy regimens.

The deeper question, of course, is why we allow uncontrolled experimentation on human subjects in any branch of medicine. But the issue is particularly pressing for reproductive technologies, especially now that fertility centers are wading into the uncharted waters of the gene pool.

Embryologists have already experimented with transferring the nucleus of an older woman's egg into a young donor's egg from which the nucleus has been removed, a technique that is similar to the method used to create Dolly, the sheep. Another fertility team successfully split a human embryo into several identical copies, a trick that could one day help infertile women who produce very few eggs. But it could also make possible such Dorian Gray scenarios as multiple identical embryos being thawed and then born several years apart, or a woman giving birth to herself.

Baby Blues

In hindsight, perhaps the anti-abortion activists who feared the emergence of technology like IVF were right to step back and question the larger implications. While few Americans would begrudge infertile couples the babies that have been produced through IVF, the issues now being raised by genetic engineering are not ones to be taken lightly, and a national consensus can only be arrived at through vigorous public debate.

Some of that debate emerged in 2000, when Lisa and Jack Nash briefly made the news when their son Adam was born in Colorado. The Nashes already had one child, six-year-old Molly, who was born with a rare genetic bone marrow disease that would kill her unless she received a transplant from someone with the identical tissue type. Both Lisa and Jack were carriers for Fanconi anemia, a genetic disorder, leaving them with a one-in-four chance of having another affected child each time Lisa got pregnant.

The Nashes elected, instead, to conceive 15 embryos and subject them to PGD, or pre-implantation genetic diagnosis. A single cell was taken from each embryo and tested for the presence of the genetic mutation that causes Fanconi anemia. Then the Nashes went a step further, and had the embryos checked to see which one carried a tissue type that matched their daughter, Molly's. Adam was born in Denver in August. In September, doctors in Minnesota performed a stem cell transplant on Molly, using blood taken at birth from Adam's umbilical cord and his bone marrow. Today, the Nashes have two healthy children. Faced with the same situation, many American parents would undoubtedly choose the same course.

At the same time, the Nash case raises the unsettling possibility of parents bearing children not to love and cherish them, but for the purpose of harvesting their tissue. And what about parents who simply want their kids to be like them, genetic warts and all? Consider the deaf lesbian couple in Washington, D.C., who recently sought a sperm donor who was also congenitally deaf, so they could be assured of a deaf child. Such desires might seem reasonable if not for the fact that any parent who deafened a hearing baby would be charged with child abuse.

Under the current political landscape, the nation has little control over what it deems acceptable. Americans may one day decide that it is perfectly all right to genetically engineer children with blue skin or webbed feet or any other trait that parents see fit. In the meantime, current practices in the fertility industry could use some oversight. Thus far, however, the only legislative response to worrisome reproductive technologies has been to ban them and accuse their practitioners of "playing God," an argument that appeals to conservative constituents but will in the short term, at least, prove futile. Says former bioethics committee member Charo, "As soon as you have absolute prohibitions you run into constitutional challenges."

Over the long term, banning certain technologies, such as reproductive cloning, may well be advisable, but reining in the pace of reprogenetics now is going to take a network of regulatory solutions. First on the list: Update the FDA's decades-old charter. In recent years, Congress has generally sided with business against the agency, beating back its efforts to rein in the herbal medicine industry, for example. But legislators have already signaled their distaste for reproductive cloning, and the balance of power is likely to shift when it comes to giving the FDA

regulatory control over reprogenetics.

The FDA, along with the U.S. Department of Health and Human Services (HHS), jointly oversee the protection of human subjects in clinical trials, which are required to demonstrate safety and efficacy before new drugs or medical devices can be licensed for market. Most of the time, companies put their products through rigorous testing in animals long before proceeding to human experimentation. Applying the same standards to human embryo experiments would compel fertility clinics to perform similar tests before subjecting patients to new reprogenetic technologies. It would also entail the creation of specialized review boards with the expertise to evaluate human reproductive experiments.

Tweaking tort law would also impose greater discipline on fertility doctors and would-be human genetic engineers. Current malpractice law rests on the idea of negligence, which means that plaintiffs must demonstrate that a doctor failed to provide care in accordance with accepted standards. In fast-moving, innovative arenas of medicine, such as fertility, there is no established or accepted "standard of care." Not surprisingly, fertility patients almost never sue, in part because they can't find lawyers to take their cases.

One solution, says Charo, is to stop using negligence as the standard for reproductive medicine, and impose strict liability instead. If the patient or child suffers a bad outcome, the clinic is liable, and patients could, in effect, sue for wrongful life.

England also offers a model for creating boundaries for thornier issues bordering on eugenics. A decade after the birth of the first test-tube baby, Parliament created a licensing board, the Human Fertilization and Embryology Authority (HFEA), which has kept a tight lid on burgeoning genetic technologies since 1991---to the dismay of some would-be patients and clinic directors.

In a recent case before the HFEA, for example, a family with four boys that had lost their young daughter in a fire asked to be allowed to choose female embryos for IVF. HFEA refused, fearing that sex selection for purposes other than to prevent a sex-linked disease, such as hemophilia, would push British society toward eugenics, or at least widespread sex-selection. A national licensing board like the HFEA would probably prove unworkable in this country, but the U.S. would do well to create an advisory panel for reproductive technologies that would provide a public forum for what are now individual decisions with huge social consequences.

Finally, anti-abortion activists need to recognize that federal involvement in embryo research is critical for limiting the risks posed by genetic engineering of the future and improving the current outcomes for families desperately seeking to have a child. Tens of thousands of embryos are discarded by fertility clinics each year because embryologists are not allowed to work on them using federal dollars. If conservatives wish to ban the creation of embryos for the purpose of research, they should focus their formidable political power on allowing research on embryos created in the hopes of producing a child.

Funding such science would certainly bring a higher level of rigor to the field and increased oversight of human experimentation. The nation is already sliding down a slippery slope toward the age of reprogenetics. Our only hope of slowing the pace is to apply the brakes of regulation.

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