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The Near Miracle of Male Infertility Treatment

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The breakthroughs in fertility medicine since the birth in 1978 of the first "test-tube baby" have mostly been confined to new treatments for female infertility. But in the last decade, there has been a revolution in the treatment of male infertility—a revolution that has raised novel and important questions about the ethics of assisted reproduction.

Male infertility is relatively rare: less than 2 percent of the sexually-active men under the age of 45 in a recent survey from the Centers for Disease Control and Prevention (CDC) reported having been diagnosed with infertility. While many women seeking fertility treatments are healthy and simply experiencing a normal diminution of fertility with age, a man's infertility is always a symptom of something seriously amiss. Some men become infertile because of sexually transmitted disease, a bout of mumps, cancer treatments, or the development of varicocele (an enlargement of veins in the scrotum that results in the testes being too warm for optimal sperm development). Other men never developed fertility with puberty in the first place. The specific causes are still poorly understood, but it seems that perhaps half the cases of severe male infertility have genetic causes.

Until recently there have been few options for ameliorating male infertility. Even conventional in vitro fertilization (IVF) is not effective in cases of severe male infertility, and so couples with this diagnosis had to resort to adoption or to the use of donor sperm. These old approaches to dealing with male infertility denied couples the possibility of a full genetic connection to their children, and their children were inevitably left with questions about the identity of their genetic parents. For many prospective parents, the use of donor sperm is particularly difficult to contemplate because of the asymmetrical genetic relationship they would have to their children. Couples' discomfort with this one-sidedness—and perhaps a vague sense that the husband was being cuckolded—led many doctors to mix the prospective father's and the donor's sperm to maintain the appearance that the child could possibly be the true biological offspring of the father.

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In the last decade, an enhanced IVF technique called intracytoplasmic sperm injection, or ICSI (pronounced "ICK-see"), has so successfully transformed treatment of male infertility that there are now almost no men who cannot father their own children. ICSI allows couples suffering from male infertility to avoid the discomfort of not being their children's natural parents. But this is not without cost in many cases—a cost arising from the genetic origin of much of male infertility.

Prior to the advent of ICSI, the various causes of male infertility were a matter of only theoretical rather than therapeutic interest. But knowing the cause of a man's infertility becomes quite important when the possibility of treating it—and thus creating genetic offspring—arises. In cases in which a man's infertility is connected with genetic disorders, it is now mostly possible to produce a child, but not equally possible to evade the medical issues that may accompany the infertility, nor to ensure that the created child will not inherit the disorder. You may drive nature out with a pitchfork, as the Roman poet Horace said, but she will keep coming back.

When prospective parents choose ICSI over donor sperm or adoption even when there is a likelihood of passing on genes that increase the risk of disease or infertility in their descendants, they testify to the depth of their desire to have a child who is flesh of their flesh. For all the talk of assisted reproduction leading to "designer babies" with genes for brains and beauty, it turns out that what many prospective parents most want is a child that is "theirs," even if this means passing on problematic genes. This is not mere selfishness on their part but expresses their wish to give their child a natural ground to his or her place in both their families.

Prospective parents who do choose to pursue ICSI in instances where they risk passing along problematic genes are often invited to use preimplantation genetic diagnosis (PGD) to eliminate embryos with heritable conditions or chromosomal defects. Thus, couples who face a diagnosis of severe male infertility and yet want to have a child genetically related to them will face not just the profoundly difficult problem that all IVF parents face relating to the disposition of "extra" embryos but also additional moral questions about the kinds of genetic control that one generation should knowingly exert over the next—questions that require reflection on the ultimate meaning and purpose of parenthood.

Raising these questions about using assisted reproduction to treat male infertility arising from incurable natural causes does not imply a prejudgment that these men should refrain from fathering their own biological children—only that the choice to do so is complicated. Men with these conditions may even be confronted with new information about their health and

genetics for the first time when they are diagnosed with infertility. Because the possibility of overcoming such infertility by ICSI is so new, because discussion of male infertility is still taboo in many circles, and because of the new information men may learn about their own health and genetics, many patients faced with these questions find themselves on unfamiliar terrain.

How ICSI Compares to Conventional IVF

To understand the ways in which ICSI has changed fertility treatment and the increased risks that accompany its use, it is helpful to consider how ICSI differs from conventional IVF. In conventional IVF, the fertilization of the eggs in vitro (literally "in glass") takes place in a way roughly analogous to natural conception in vivo (in a woman's body): an egg is mixed with sperm—usually separated from the seminal fluid—and the sperm swarm the egg until one penetrates it and the egg excludes the erstwhile rival sperm. Like natural conception, success with conventional IVF requires a ratio of sperm to egg of millions to one. Therefore, when a couple's infertility is due to very poor sperm quality or quantity, conventional IVF cannot remedy infertility.

Beginning in the 1980s, there were various efforts to overcome the high sperm-to-egg ratio required by conventional IVF. Of these efforts, ICSI was by far the most successful. It requires a sperm-to-egg ratio of only one to one, thus reducing to an absolute limit the need for mature sperm. An ICSI treatment begins like a conventional IVF treatment, when the embryologist collects eggs from a woman whose ovaries have been hyperstimulated and a sperm sample from a man. (Most men considered infertile have some sperm in their ejaculate. For those few who do not, it is still usually possible to retrieve some through a surgical procedure called testicular sperm extraction, or TESE.) However, rather than simply mixing the eggs and sperm, the embryologist selects a single sperm under a microscope, draws that sperm into a thin pipette, pushes the pipette through the egg's outer membranes, and expels the sperm into the center of the egg—where, it is hoped, the sperm will fertilize the egg and the fertilized egg will grow into a healthy embryo.

YouTube and fertility-clinic websites show videos of eggs being fertilized by this technique. As one watches these videos, it is awesome to think that the embryologist's chance selection determines which sperm is joined with each egg, and so which person will potentially result from this therapy. Before ICSI, the unseen matching of the egg to one among many sperm was one of the few aspects of assisted reproduction still removed from human

control and shrouded in some mystery. It still is, insofar as the embryologist has no knowledge of what differentiates the selected sperm from all the others. But the weightiness of the act of selection is worth contemplating.

The first use of ICSI to create human embryos (the technique was used earlier to create rabbit and cow embryos) was announced in 1992 after a Belgian clinic employed it to produce four healthy children born to three couples. ICSI quickly became available at clinics in Europe and the United States, although initially at an extremely high price. It now costs only a couple thousand dollars more per cycle than conventional IVF and, in fact, ICSI is rapidly displacing conventional IVF as the method of choice for assisted reproduction. A recent CDC report noted that 37 percent of IVF cycles in the year 2007 were initiated to treat infertility that was wholly or partly attributed to male infertility, but ICSI was used in 63 percent of all IVF cycles that year, since it is thought (but not proven) to boost overall IVF success rates even in cases where male infertility is not considered a contributing factor. (And again, as noted above, the experience of the procedure for the woman is as physically demanding regardless of whose infertility is being treated.)

ICSI is already a widely accepted practice in cases of male infertility linked to conditions that will not affect the future health of the prospective father or his offspring, such as past sexually transmitted disease, successfully treated cancers, or a surgical vasectomy (ICSI in combination with TESE is increasingly replacing vasectomy reversal procedures). However, the power of ICSI to overcome infertility with a persistent natural cause has led to serious debate about its use in these cases. Indeed, shortly after the technique's first successful human use was announced, some doctors argued against letting ICSI enter the clinical mainstream because of their concern for the consequences of getting around genetically-caused infertility. Writing in the journal *Human Reproduction* in 1995, a pair of professors from the University of Nebraska Medical Center also raised questions about the potential safety hazards of fertilizing the egg in such a structurally different and invasive way and noted that little was known about the long-term effects of this technique even in animals: "given these two significant issues, perhaps ICSI should still be considered an experimental clinical procedure."

Male Infertility and Genetic Illness

There are at least thirty genetic illnesses that cause infertility in men, including cystic fibrosis, sickle cell anemia, myotonic dystrophy (the most frequent form of adult-onset muscular dystrophy), and Klinefelter's

syndrome (also known as XXY syndrome, which occurs when a man has two X chromosomes plus a Y chromosome rather than the normal pair of a single X and single Y chromosome). Previously, while infertile men might have been disappointed or even grief-stricken at their inability to have children genetically their own, their infertility also imposed a barrier to the transmission of certain illnesses and prevented the birth of children who would experience the illness or premature death of a father. Now many of these men can father children through ICSI, and they must contemplate the risks of transmitting disease to future generations as well as how their own illness bears on their prospective role as a father.

Perhaps the larger concern for these men is the risk of passing on disease to their offspring. To counteract this risk, some turn to genetic screening of their already-formed embryos, using the previously-mentioned PGD technique to select embryos who do not share their fathers' problematic genes. The CDC reports that 5 percent of all IVF procedures performed in 2007 used preimplantation genetic diagnosis, which is not available at every clinic. Doctors and patients using PGD to favor some embryos and destroy others may feel that they are in some sense reinstating nature's "intent" to protect future generations from illness. The possibility of using PGD in this way depends on the genetic character of the particular disease. For diseases caused by a single dominant gene, such as myotonic dystrophy, the chance that any embryo will have the defective gene is 50 percent. In such cases, on average, half the embryos will be discarded; the remainder will be free of the father's illness.

For diseases such as cystic fibrosis and sickle cell anemia that are caused by a pair of recessive genes, afflicted fathers who have children by ICSI unavoidably pass along one of these genes to their children. When the children are ready to have children of their own, they will have to be concerned about whether their partners are also carriers and what that means for their children's health.

For diseases caused by an abnormal number of chromosomes, such as Klinefelter's syndrome, it is possible to use PGD to select for normal XX and XY embryos. On average, few embryos will be discarded, because most of the few sperm that men with Klinefelter's do have will be normal. However, PGD cannot guarantee that an embryo will not have Klinefelter's, because about one-sixth of Klinefelter's patients have so-called mosaic genetic compositions, with both XXY *and* XY genes; it is possible for only normal XY cells from an embryo to have been tested and abnormal XXY cells missed during PGD, in which case an embryo with mosaic Klinefelter's could be selected for transfer.

The technological possibility of using PGD to avoid transmission of certain genes raises moral problems, beginning with the strangeness of deciding not to allow the transfer of an embryo who could grow into a person very much like his or her father. This strangeness may be especially pronounced in cases where the illness does not lead to premature death or severe symptoms—as is the case with Klinefelter's syndrome. While this syndrome can be associated with behavioral and learning problems, many men with Klinefelter's are highly able individuals; in fact, some have appeared so normal that they were not diagnosed prior to seeking fertility treatment. More profoundly, since the syndrome is thought to influence behavior and personality, a man who is aware of his diagnosis may believe that it has contributed to making him who he is. Indeed, a man with Klinefelter's who arrives at a fertility clinic for treatment has presumably attracted a loving partner who wishes to have a baby with him—that is, someone who loves him not in spite of but partly because of the way his genes have shaped his personality. In such a case, deciding against the transfer of XXY embryos may seem like a partial rejection of oneself or one's spouse.

One case history of a man with Klinefelter's syndrome, published in *Human Reproduction* in 2000, illustrates the vexed issues and conflicted feelings facing many couples in this situation. In this case, the man did not know that he had Klinefelter's until he and his wife sought help to have children. They declined to have their embryos screened, even knowing that there was a greater than usual chance of having a child who would share his father's diagnosis. Three embryos were transferred into the wife's uterus following ICSI in hope that she would become pregnant with one or two of them. However, when it became clear that she was pregnant with triplets, the couple had the fetuses tested and soon found one was a male with Klinefelter's syndrome; the couple subsequently aborted that fetus. We cannot know what considerations led this couple first to decline screening their embryos in spite of significant risk of a Klinefelter's diagnosis and then to agree to an abortion of their fetus with Klinefelter's, but it seems that they had mixed feelings about having a child who shared this trait with his father.

The Responsibilities of Fatherhood

Transmission of disordered genes is not the only concern of prospective parents considering ICSI. Men with such diseases as cystic fibrosis (CF) and myotonic dystrophy must weigh the impact of their decline and

early death on their prospective children and on their own experience of parenthood. These questions have been raised most often for men with CF because it is such a common disease, especially among Caucasians, whom it affects at a rate of about 1 in 2,500. Men with CF have a natural vasectomy: a congenital absence of the vas deferens (CAVD), the ducts that carry the sperm from the testes. Thus, 90 percent of men with cystic fibrosis produce sperm, but, like men who have had surgical vasectomies, it cannot enter their ejaculate. Indeed, some men who have CAVD but lack other CF symptoms are now recognized as having a genital form of cystic fibrosis; 1-2 percent of men with zero sperm counts are thought to have this condition—men who would never have received a CF diagnosis apart from having sought treatment for infertility. Men with CF are now able to father children through the combination of TESE and ICSI, and many are choosing to do so.

One French study followed twenty-five men with CF who wished to have a child: twenty-three initially chose ICSI, while only two chose donor sperm and none chose adoption. During the course of the study, which lasted from 1994 to 2004, nine patients succeeded in fathering children by ICSI—with all of those children becoming carriers of a CF gene. The doctors noted that these men and their wives had to contemplate how fatherhood would affect their decision about whether or not to have a lung transplant as their condition worsened, as well as the prospect of dying while their children were still young. One patient died during the study, leaving behind his wife and a five-year-old daughter. Since most CF patients do not live past their thirties or forties, and the median age of the French patients when they first sought reproductive assistance was twenty-nine, most of the other children fathered by the men in this study will be young children or adolescents when their fathers die. (However, the fathers' families might be more likely to maintain relationships with those children, because of the genetic link to the father, than if the children had been conceived with sperm from an unrelated donor.)

Of the clinics that assist men with CF in having children whom they are unlikely to see to adulthood, many decline to treat postmenopausal women who wish to have children. Are these practices contradictory? Despite the occasional headlines about ever-older mothers who conceived with the help of maverick doctors, most fertility clinics acknowledge the legitimacy of societal concerns about the ability of prospective parents to raise children conceived through assisted reproduction through to adulthood, and so they maintain age limits for female patients that typically stretch the *likely* but not the *possible* age at which a woman may conceive naturally. Part

of the justification for these age limits concerns the diminished prospect for achieving a healthy pregnancy so late in a woman's life, but they are also motivated by concern about an older mother's prospects for enjoying enough years of good health to raise her children. But a healthy fifty-year-old woman has a much greater chance of seeing her child grow to adulthood than does a thirty-year-old man with cystic fibrosis. Older women who wish to have children through IVF might point to the treatment of men with CF to insist on fertility treatments for themselves.

To explain away the apparent contradiction, fertility doctors may reason that an older woman may no longer be in that season of life best suited for rearing young children. By contrast, a young man, even one with CF who has a sobering knowledge of his imminent mortality, may have the adaptability to new experiences and challenges required by parenthood. Moreover, his wife will usually be there to raise their children after he is gone. Clearly, many men with CF—as well as women with CF, who are usually fertile—are deciding that they will welcome biological children in spite of the fact that these children will be carriers of the gene and will probably lose a parent at a young age.

The Infertility Gene

In addition to the men whose infertility is connected with genetic disease, there are genetic defects that seem to carry no ill consequences for general health but do cause severe and heritable infertility in men. Chief among these are the azoospermia factor (AZF) microdeletions in three spots on the Y chromosome, termed the AZFa, AZFb, and AZFc regions, which are found in up to 15 percent of men with very few sperm. In the stark language of geneticists, these mutations are "genetically lethal"—that is, these are mutations that would naturally preclude fathering offspring. ICSI has changed the prospects for most of these men, as men with microdeletions in the AZFc region, the most common of the three, harbor enough sperm that it is possible for them to father children. (Microdeletions in the AZFa and AZFb regions, which are comparatively rare, result in such complete infertility that TESE cannot yield enough sperm to allow ICSI.) Genetic testing on the ICSI-produced sons of men with AZFc microdeletions shows that the mutation is invariably passed down. A new generation of boys who will inherit their fathers' infertility is being born.

Because AZF microdeletions are a fairly common cause of severe infertility, and because they lead to infertility in male offspring, clinics now routinely screen severely infertile male patients for them using genetic testing.

Patients with infertility due to an AZF microdeletion are thus required to make a choice to proceed with ICSI knowing the consequences for their male children. Many parents are not dissuaded from proceeding with ICSI by the knowledge that any sons will inherit their fathers' infertility: one study conducted in Belgium and the Netherlands found that four-fifths of prospective parents went ahead with ICSI after the man received a diagnosis of a microdeletion in the AZFc region. Most parents who choose ICSI in spite of a father's AZFc microdeletion likely reason that a son could use ICSI to father children just as they have done. The one-fifth of prospective parents who received a diagnosis of AZFc microdeletion and then abandoned their efforts to have a child genetically related to the father perhaps believed that there is something wrong with counting on ICSI to begin a line of sterile male descendants. Of the prospective parents who did not choose ICSI, more discontinued their fertility treatment than opted for donor sperm—suggesting that they would rather adopt a child or remain childless than have a child genetically related only to the mother.

The same study noted that it is possible to avoid the birth of infertile males by employing PGD to select for female embryos, although none of the clinics that participated in the study offered sex selection in the case of AZFc microdeletions. In the past, sex selection through PGD was used only for couples who risked passing along the genes for serious diseases, such as hemophilia, thalassemia, Duchenne/Becker muscular dystrophy, and fragile X syndrome. Since men with AZFc microdeletions typically enjoy good health apart from their infertility, the possibility of using PGD to select against male embryos who would carry this mutation reopens troubling questions about what kind of criteria society will accept as reason enough to eliminate a nascent life.

On the other hand, the cumulative social consequences of conceiving infertile boys through ICSI will be challenging. Some studies have attempted to estimate how quickly this will cause a rise in the fraction of men who are infertile. One estimated that if 90 percent of men who are infertile due to a genetic defect used ICSI to father children, the rate of male infertility with a genetic basis would rise from 1.0 to 1.9 percent of all men in one generation, and to 6.7 percent of all men in ten generations. The authors note that for a variety of reasons, including the cost prohibition and the advent of other developments in biomedical progress, this particular scenario is unlikely. But as ICSI and related techniques become more effective and less expensive, it seems likely that the trend will at least be in this direction. In a society with a large proportion of infertile men, technologically assisted reproduction would need to be an increasingly common avenue for reproduction, perhaps

producing a dulled sense of what it means to be subject to natural processes of birth, growth, maturity, sexual reproduction, and decline.

Already, there are many boys with AZFc microdeletions, conceived through ICSI, who will experience their natural infertility not as an unhappy discovery in adulthood but as a long-known fact. When and how should parents tell their boy that he is infertile? This knowledge will shape his experience of his sexuality; the boy will be in the unusual position of understanding his virility as separate from the potency to impregnate a woman. As most girls and boys enter adolescence, their new sexual desires are restrained and educated, in part, by the possibility that sex could result in pregnancy. But what would it mean to be a teenage boy who knew he could not possibly get his girlfriend pregnant? These boys may suffer both from a sense of impotence and a total freedom from restraint.

The knowledge that these boys can grow up to father biological children through ICSI mitigates but does not abolish the consequences of infertility and their awareness of it. Even with the existence of modern assisted reproduction techniques, natural fertility is still strongly desired; fertility makes a difference to our experience of ourselves and our sexual relationships. Couples who learn that they must undergo fertility treatment in order to have a baby experience stress and sadness not only because of the physical and financial burdens of treatment and the anxiety about whether it will even work, but because the infertile person feels a loss of potency—and because the couple is denied the prospect of producing a baby through sex with each other. Similarly, adolescent boys undergoing cancer treatments, and the parents of those boys, still grieve over their loss of natural fertility, even though they can now be assured that it will be possible through ICSI to have a biological child.

To be sure, masculinity and femininity, as well as a loving sex life, do not require fertility. Men and women can and do incorporate the fact of infertility into their understanding of themselves and their marriage. But we should not ignore the way that natural infertility is a source of grief, sadness, and a sense of loss. For the first time, there will be large number of boys for whom this fact might shape their view of their own sexuality from childhood onward.

The Uncertainties of Undiagnosed Infertility

Men who are infertile because they suffer from a genetic illness, as well as men who come for fertility treatment and receive a diagnosis of an AZF microdeletion, make a choice to father children by ICSI with information

about the underlying cause of their infertility. These decisions can be difficult, but they are at least made with some sense of the likely consequences. Other infertile men must consider the choice to have ICSI with a dearth of information about the risks they or their potential offspring face.

Indeed, one of the most frustrating elements of an infertility diagnosis in an otherwise healthy man is that often doctors cannot identify a cause. Researchers suspect that many of these men, while healthy themselves, either produce sperm with high numbers of chromosomal abnormalities or carry genes that may increase the risk of disease in descendants. We are just beginning to learn about the kinds of genetic risks associated with infertility from an undiagnosed cause.

For example, one Canadian research team found that, as a group, men whose sperm have low motility produced a higher fraction of sperm containing two X chromosomes and sperm containing an extra copy of chromosome 13. An XX sperm that fertilized an egg would produce a girl with three X chromosomes; she would appear physiologically normal but be at risk for premature ovarian failure as well as learning disabilities. A fetus with an extra copy of chromosome 13 would likely miscarry or, if born, would have multiple severe birth defects and not survive infancy. (This disorder is called trisomy 13, or Patau syndrome.) And although these researchers did not find that the men whose sperm had low motility were unusually likely to have XY sperm, they did report that one of their male patients with a very low sperm count had a fourteenfold greater than normal fraction of XY sperm; following ICSI, his wife became pregnant with an XXY fetus that was not carried to term.

The kind of testing done at this Canadian clinic is unusual, and most men with unexplained infertility will be treated by ICSI without knowing whether they have a higher than normal fraction of sperm with chromosomal defects. In almost all cases, a normal child will be conceived—even with the higher rate of abnormalities, their sperm is mostly normal. Nevertheless, there seems to be a greater risk of conceiving a child with a genetic defect by ICSI even when the father does not himself have one: a 2010 study estimates that the rate of *de novo* (not inherited) chromosomal abnormalities is six in one thousand ICSI births—three times the normal rate. For individual men, such as the Canadian patient above, the risk may be much greater. At present, it is very difficult to identify which infertile men have high fractions of genetically abnormal sperm. Nevertheless, as this technology improves, there is likely to be more interest in identifying such men among patients with unexplained infertility—and more pressure on them and their wives to use PGD on their embryos.

A related concern is the still poorly understood connection between infertility and a genetic phenomenon known as "anticipation." This phenomenon is found in conditions such as Kennedy disease, a rare disorder that afflicts men in early adulthood and results in progressive, debilitating loss of muscle strength and control. It is caused by an unusually high number of repetitions of genetic material on one stretch of the X chromosome that has some function in governing how the body responds to the male hormone androgen. Men with Kennedy disease are infertile or become so as their disease progresses. When the condition runs in families, as the X chromosome passes from one generation to the next, the abnormal section may expand, resulting in symptoms becoming more debilitating and beginning earlier in life in each subsequent generation. Geneticists refer to this as "anticipation," since disease in one generation anticipates more severe disease in later generations.

Suggestions for Further Reading:

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Paul J. Turek and Renee A. Reijo Pera, "Current and future genetic screening for male infertility," *The Urologic Clinics of North America*, vol. 29, no. 4 (November 2002): 767-792.

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Researchers have found that men with very low sperm counts typically have higher than usual numbers of repetitions of the genetic material that causes Kennedy disease. Such men may not have enough copies of the aberrant material to cause Kennedy disease, but still have enough to inhibit the production of sperm. An infertile man who employs ICSI may pass along an X chromosome with an expanded stretch of problematic genes to a daughter, who would be an asymptomatic carrier of this material but could pass along this X chromosome to her son. (If a son resulted from the ICSI treatment, he would have his father's Y chromosome and so would not inherit the problematic genetic material.) In such a case, the infertility patient's grandson could suffer from Kennedy disease. Although the disorder is rare, ICSI's power to overcome a natural barrier to the transmission of aberrant genetic material may bring about new cases of disease that would not have occurred without this technology.

In the coming years, researchers will learn much more about the genetic risks associated with infertility, and they will be better able to identify which men assume the most serious risks when fathering children by ICSI. Meanwhile, these preliminary studies show that "unexplained" infertility does not necessarily imply that the infertility is only a technical problem to overcome. For all of us, fertile and infertile alike, hoping for a child means taking a chance and preparing to care for him or her, come what may. And for the children who do come along, the blessing of the fact of their lives eclipses any health or genetic complications they may have. But a decision to proceed with ICSI in the face of unexplained infertility is occasion to hope even more fervently that what one does for one's children is truly for their good rather than to satisfy one's own desires.

Prospects for the Future

ICSI has helped many couples to become parents of children who are the biological offspring of both parents. Almost all of these children are healthy, and hopefully all of them fulfill their parents' ardent desire for children. However, this good news must not exclude consideration of the consequences of this powerful technique. In many cases, ICSI treats forms of infertility that do not raise concerns about the future health of the prospective father and his offspring; in other cases, overcoming the infertility brings with it new questions about the health of children, the ethics of genetic screening, and the experience of parenthood for seriously ill fathers. Raising these questions can help us think about the challenges and moral dilemmas these hopeful parents will face.

The concerns connected with ICSI are not necessarily that it will lead to the birth of many children who bear genetic disease—although there are certainly some individual families who will have the challenge of raising children with chromosomal defects and perhaps other illnesses related to the use of ICSI. It is likely that most of these families would say that the joy of sharing their lives with a child, regardless of the challenges involved, outweighs the sadness of being without children.

But it is worth considering the implications of the fact that ICSI is likely to deepen the medicalization of reproduction in the coming years. Many couples will face difficult questions about whether they should try to control some of the genetic characteristics of their embryos and about their willingness to accept a child who shares his father's malady. And if ICSI increases the number of naturally infertile men in coming generations, more and more couples will need to turn to assisted reproduction to bear children. We may find that we prefer to face these dilemmas through ever more frequent use of assisted reproduction rather than accept the infertility of so many couples. Nevertheless, there are costs to this technology—costs to be paid in funds for treatment, in anxiety and uncertainty, and sometimes in the experience of new illness—that are worth pondering as we look to the future.