Of Babies and the Barren Man

by Marc Goldstein

Infertility is a medical problem with a long and somewhat ignoble history. In biblical times, a barren marriage was always blamed on the woman, whose womb was said to have been "closed" by God. That chauvinistic attitude toward infertility persisted in the medical community as well as in popular culture until very recently. Only in the past 50 years has research on the male reproductive system revealed the host of troubles that can plague a man's baby-making machinery. Today we know that in about half of all infertile couples, a male factor is a contributing cause, if not the only one.

In fact, about 10 percent of American men who are trying to have a child—about three million men—are infertile, and many others who are not attempting to conceive would not be able to if they tried. These men may have genital abnormalities that were present at birth, or they may be suffering a progressive decline in fertility because of sluggish blood flow from the testes. They may have compromised their fertility by using certain controlled substances or by having a vasectomy. Or their condition may be a result of infection, disease or even medical treatment for other, unrelated conditions.

Whatever the cause, infertility can be a difficult condition for men to accept. It is often mistakenly associated with impotence, or the inability to have an erection. (Impotence does not necessarily impair fertility, nor do most infertile men complain of it.) For many men, being able to impregnate a woman is also an essential part of a macho self-image. Even when these perceptions do not come into play, the failure to father a child can be a profound disappointment. Fortunately, advances in our understanding of the male reproductive system have dramatically improved the ability to diagnose and treat male infertility. Now the vast majority of infertile men have the potential to conceive a genetically related child. All that is required is some time, effort, money—and, of course, a woman.

In the not so distant past, the contribution of the male partner to the act of reproduction was rather obscure. Whereas the mother's role seemed obvious, no one was sure what exactly was required of the would-be father: mere mechanical stimulation, some chemical catalyst or an actual biological donation. When Dutch scientist Antonie van Leeuwenhoek invented the modern microscope in the 17th century, one of the first things he looked at was semen, the fluid that is expelled from the penis during ejaculation. And among the first things he saw were sperm, the whip-tailed cells that carry a man's genes.

It is now clear that conception occurs when a single sperm cell penetrates a woman's egg. The union of these gametes is aided by powerful psychosexual incentives such as arousal and orgasm, and most of the time the system works. About 85 percent of couples regularly having unprotected sex will conceive a child within a year. If a couple still has not conceived after a year of trying, then one or both of the partners may have a fertility problem.

Both partners will need to undergo a fertility evaluation. For women, such evaluations may take a couple of months and require hormone profiles, ultrasound tests, mucus cultures and monitoring of ovulation. The process is usually faster and simpler for men. Although a physical exam and hormone workup will also be performed, the cornerstone of the male fertility evaluation is the semen analysis: an assessment of the shape, number and movement of the sperm cells in a man's ejaculate and of the volume and viscosity of his semen. Abnormalities in any of these factors can cause infertility.

Sperm quantity and quality can be affected by many different factors, including exposure to substances that interfere with the normal functioning of the male reproductive tract [*see box on page 77*]. The inhalation of cigarette smoke, for example, has been shown to impair sperm quality in humans and other animals. Alcohol damages testicular function, lowering sperm counts as well as the male hormone testosterone in heavy drinkers. The active ingredient in mar-

Male infertility can now be treated with advanced surgical and reproductive techniques. Most infertile men can become fathers

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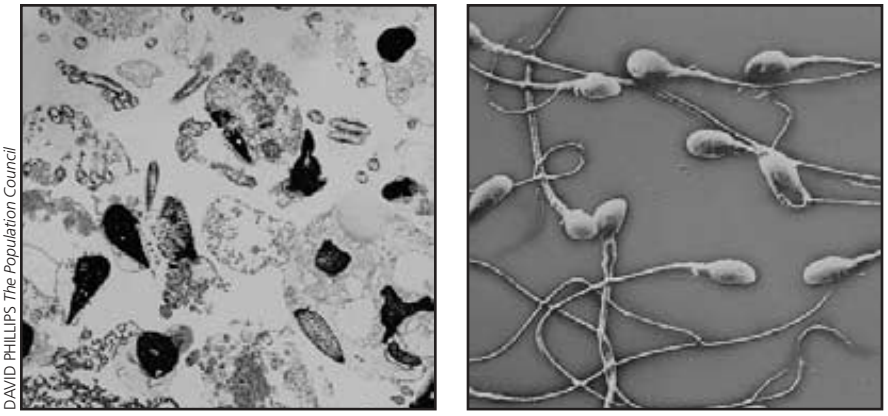
***SEMEN ANALYSIS** assesses the health of sperm placed in the center of the circular Makler chamber. A technician presses one of the buttons to register whether each sperm cell is normal or malformed or lacks mobility.*

ijuana binds to estrogen receptors in the testes and causes abnormally shaped sperm. Studies of cocaine in rats provide incontrovertible evidence that this substance, too, interferes with sperm production.

Some medicines prescribed by doctors for illness can affect fertility as well. A class of medicines for high blood pressure called calcium channel blockers, for example, can inhibit the enzymatic reaction that allows a sperm cell to penetrate the outer membrane of the egg. (Calcium channel blockers have even been contemplated as contraceptives [see "Beyond the Condom: The Future of Male Birth Control," on page 80].) Radiation or chemotherapy treatments for cancer often result in permanent or at least temporary sterility.

Folk wisdom has long acknowledged the vulnerability of sperm cells to a more ubiquitous threat: temperature. More than 2,000 years ago the Japanese used long, hot baths as a contraceptive method. Saunas, whirlpools or steam baths can also temporarily decrease fertility. Even the practice of crossing one's legs may have a detrimental effect: studies by my colleague Michael Bedford of Weill Medical College of Cornell University have shown that sitting with crossed legs elevates testicular temperature enough to influence sperm production. As for jockey shorts versus boxers, the evidence is conflicting. The only thing experts can say for certain is that one should not wear the tight leather pants, favored by some rock singers, that plaster the testes up against the body.

The placement of the testicles outside the body is thus no accident of evolution. The enzymes that regulate production of both sperm and testosterone operate most efficiently at several degrees below body temperature, and the external placement of the testes keeps them cooler than the rest of the body. English author Aldous Huxley made note of this sensitivity in his 1932 novel *Brave New World:* "… male gametes, they have to be kept at 35 instead of 37 degrees centigrade. Full blood heat sterilizes." In fact, if the normal operating temperature of the testicles is elevated by only one to



DAVID PHILLIPS *The Population Council*

***DAMAGED SPERM* (left) *have abnormal shapes and lack well-developed tails compared with their healthy, whip-tailed counterparts* (right).**

But I have introduced a microsurgical technique that circumvents the problems the earlier repair methods encountered. I developed the technique in the 1980s, while studying the reproductive system of rats at the Population Council's Center for Biomedical Research at the Rockefeller University. My studies required that I transplant testicles from normal rats to previously castrated ones. Rat testicles are quite large in proportion to their bodies; built to the same scale, human testes would weigh about a pound each. Even so, I needed the help of a microscope to sever and carefully reconnect the blood vessels and ducts of my subjects.

two degrees Celsius (two to four degrees Fahrenheit), sperm and testosterone production is adversely affected.

The exquisite temperature sensitivity of the sperm production process probably accounts for the single most common identifiable cause of infertility in men. That cause is varicoceles, a painless condition in which the veins in the scrotum become enlarged just like varicose veins in the legs [*see illustration on page 78*]. The enlarged veins do not drain blood as efficiently as healthy veins, and so the blood pools in the testes, thereby raising the temperature. Studies that I performed more than a decade ago corroborated the findings of the late urologist Adrian Zorgniotti of New York University Medical Center; we found that the temperature inside the testicles of infertile men with varicoceles was 2.5 degrees C higher than the normal testicular temperatures of fertile men without varicoceles—easily warm enough to have a major negative impact on sperm production and quality.

An Insidious Decline

Up to 40 percent of infertile men have varicoceles, and about 15 percent of all men have them. Although the condition may not always result in infertility, there is evidence that it causes a progressive decline in fertility as a man ages. For example, 80 percent of men who were fertile when they were younger and have become infertile later in life—a condition called secondary infertility—suffer from varicoceles. Thus, a fertile man with varicoceles has no guarantee that he will remain fertile as he gets older. This insidious decline in fertility is troubling to specialists as more men and women elect to postpone childbearing until they reach middle age.

The evidence for the adverse effect of varicoceles on testicular function in male infertility is overwhelming. The success of surgeons' attempts to repair varicoceles, however, has been disputed. The idea behind the varicocelectomy is simply to tie off the damaged veins in the scrotum so that blood gets shunted through healthier vessels. Over the past 50 years, studies on the efficacy of a variety of surgical techniques to reverse varicoceles have found conflicting results. Testicular function was not always restored by the repair procedure. The inadvertent cutting off of the main blood supply to the testes that may occur during some types of operations is unlikely to enhance fertility—and serious complications can result from stopping blood flow or tying off the surrounding lymph ducts. For that reason, varicocelectomies were regarded with suspicion by some fertility specialists.

When I began my infertility practice years later, I found that it was likewise almost impossible to find the tiny arteries and lymph ducts in human testicles without the aid of a microscope. But by magnifying the area from six to 30 times, I could almost always identify and spare both the testicular arteries and the lymph ducts while ensuring that all the enlarged veins were closed off [*see illustration on page 78*]. Interestingly enough, my friend and colleague Joel L. Marmar of the Robert Wood Johnson Medical School at Camden in New Jersey independently developed the same procedure at nearly the same time I did. Our results have been encouraging: after employing this technique in several thousand patients, Marmar, our colleagues and I have found that the number of healthy, swimming sperm in men with large varicoceles more than doubles and that impregnation rates after one year of trying are 43 percent.

In contrast, men with varicoceles who decline operations achieve successful impregnation only 17 percent of the time. These findings were supported by a 1995 study showing that the impregnation rate for men with varicoceles who underwent varicocele repair was six times higher than the rate for men who did not. The results were especially meaningful because the study, which was sponsored by the World Health Organization, was the first of its kind to compare outcomes between subjects who did and who did not get varicocelectomies. (Previous reports had used before-and-after comparisons of subjects who were operated on.)

Despite these encouraging statistics, varicocelectomy is not appropriate for all men. Those with small varicoceles will have only a 25 percent improvement in the number of healthy, swimming sperm as a result of the operation. The men who will benefit most have varicoceles that are large enough to be felt on physical examination—especially the largest veins that a man can see himself, which look rather like a bag of worms inside the scrotum when he is standing. There are compelling reasons to repair these varicoceles. Because they cause progressive damage to the testicles, they not only decrease sperm count but also lower levels of testosterone, which affects sexual function, the amount of facial hair and muscle strength. We have shown that varicocele surgery raises testosterone levels in infertile men who have low levels to begin with. Thus, men with large varicoceles should consider having them repaired to prevent future impotence resulting from hormone deficiency as well as to prevent further damage to sperm production.

There are alternatives to microsurgery for men with low

sperm counts or poor sperm quality. With in vitro fertilization (IVF)—the technology that gave us the "test-tube baby"—the healthiest sperm can be culled from a man's ejaculate and used to orchestrate conception in the laboratory. With a new technique called intracytoplasmic sperm injection (ICSI), which was pioneered in Belgium by Gianpiero Palermo before he joined our group at New York Hospital–Cornell Medical Center, we can even physically insert a single sperm into an egg cell with a very fine needle. But most couples prefer to do things naturally, and varicocele repair allows conception by way of ordinary sex. It is also much cheaper than IVF. According to calculations published by my urologist partner Peter N. Schlegel, the "per baby" rate—that is, the rate per successful delivery—is less than a third of the per baby rate for IVF, which is about $89,000. The per baby rate includes, in addition to the surgical or fertilization procedures, the costs for the child's delivery, hospital stays and other expenses. For varicocele repair, the surgical fees are $5,000; each in vitro procedure costs about $10,000, and several attempts are usually needed to conceive.

Microsurgery has also greatly aided the repair of blockages or obstructions in the male reproductive tract. Obstructions are suspected if a man with apparently normal testes has no sperm at all in his seminal fluid, a condition called azoospermia. Even though men with varicoceles experience a gradual decline in fertility, their sperm counts rarely drop all the way to zero. But fertility specialists will often see patients who have a zero sperm count—in fact, it is the second most common cause of infertility in men. Before we can treat a man with azoospermia, we need to ascertain whether the condition is caused by a blockage or whether the testes simply are not producing any sperm. To find out, we can measure the blood levels of a hormone called follicle-stimulating hormone, which governs the production of sperm. We also do a testicular biopsy, removing a tiny piece of the testicle and examining it under a microscope for evidence of sperm pro-

Lifestyles of the Infertile




SUBSTANCE OR BEHAVIOR	MECHANISM OF ACTION
ALCOHOL	Decreases sperm production, lowers testosterone levels
ANABOLIC STEROIDS	Disrupts normal hormone activity, lowers sperm count
CALCIUM CHANNEL BLOCKERS	Destroys sperm's ability to penetrate egg
COCAINE	Lowers testosterone levels, sperm production and libido
MARIJUANA	Deforms sperm, impairs sperm movement, decreases sperm production and lowers testosterone activity
NICOTINE	Lowers sperm production, alters sperm shape and impairs sperm movement
RADIATION, CHEMOTHERAPY	Kills sperm cells
WEARING TIGHT PANTS, TAKING SAUNAS, CROSSING LEGS	Raises temperature of testes and reduces sperm production

SOURCE: JON L. PRYOR *University of Minnesota, left to right:* NICK DOLDING *Tony Stone Images;* BERTRAND RIEGER *Tony Stone Images;* LYNN GOLDSMITH *Corbis;* PAUL CHERFILS *Tony Stone Images*

duction. About half the time, the tissue looks like it is functioning normally, and the problem lies elsewhere in the ducts in the scrotum that transport the sperm.

Swimming School for Sperm

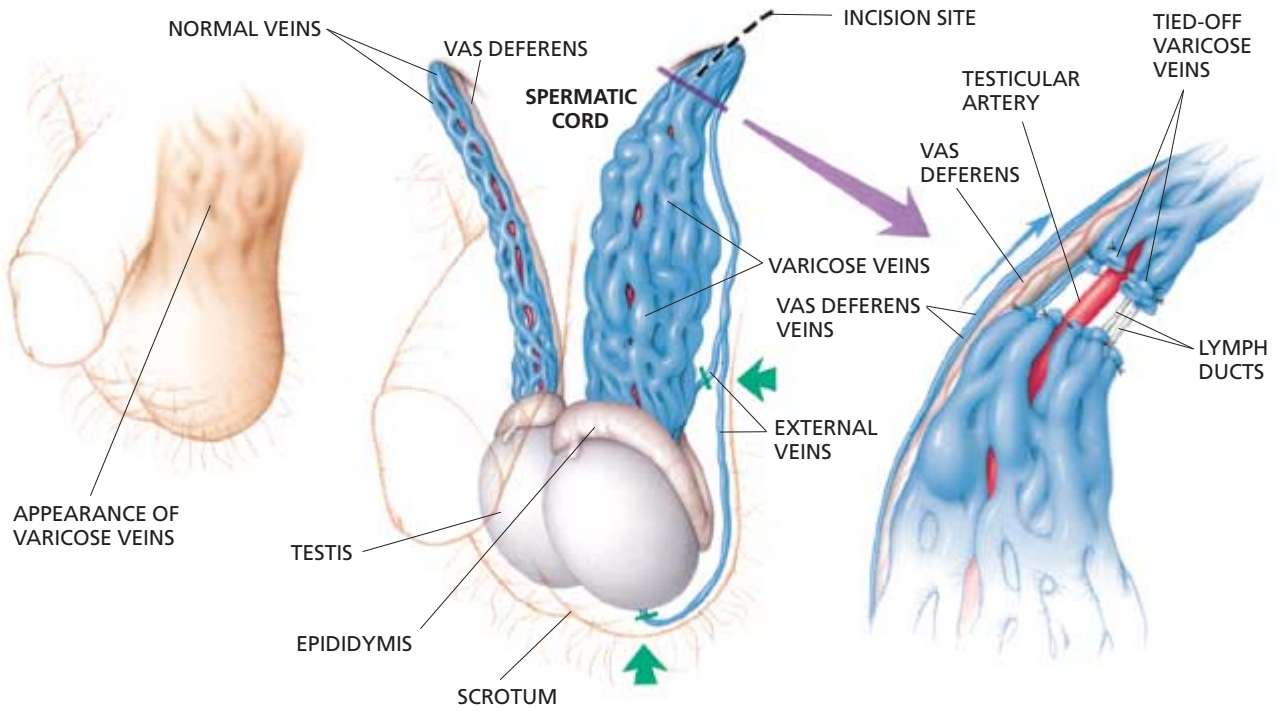
Blockages can result when a urinary tract infection spreads to the reproductive organs, or they can be caused by sexually transmitted diseases, in particular gonorrhea and chlamydia. These infections can scar the epididymis, a narrow, tightly coiled duct that links the testicles to the passages called the vas deferens and serves as a swimming school for sperm. Until the advent of microsurgery, such blockages could rarely be repaired because the epididymis is so small—the duct itself measures just one and a half times the diameter of a human hair. But with magnification and suture materials one seventh the diameter of a hair, the success rates of microsurgical blockage repair are now quite high: sperm return to the semen in more than 75 percent of cases. Much of this success is owed to the efforts of Earl Owen of the Microsearch Foundation of Australia in Surry Hills and his former student, Sherman Silber, a fertility specialist in St. Louis, who together introduced the microsurgical techniques for repairing blockages; the surgery costs about $10,000.

Microsurgery has also helped men who want to reverse a vasectomy, which can be thought of as an elective blockage of the vas deferens. With at least 500,000 men undergoing vasectomies every year and divorce rates topping 50 percent, there is actually quite a demand for such reversals. The procedure is simple in theory: cut out the quarter-inch section of the vas deferens that was closed off and then reattach the free ends. In practice, it is a bit trickier because the part of the vas deferens that was behind the blockage, lacking an outlet, becomes swollen by pressure; meanwhile the part that was on the far end of the obstruction (toward the penis) stays its normal size. Trying to make a leakproof seal between the two is like trying to stitch a garden hose to a fire hose. Again, using magnification, ultrafine sutures and a technique I developed that guides the placement of the sutures, we have had much success in reversing vasectomies. Sperm return in the semen of more than 90 percent of the men on whom we operate, and the average subsequent impregnation rate is 63 percent.

It is true that these blockage repair techniques are of no help to the 5 percent of infertile men who have zero sperm counts because their testes are not producing sperm. In the past, this "nonobstructive" azoospermia resisted treatment altogether. But ICSI, the single-sperm injection procedure, has now made it possible for many of these men to conceive, albeit in the laboratory. In about half of all men with zero sperm counts, a few, rare sperm cells can be found wedged among the other cells of the testes. The hard part is knowing where to look. By avoiding the blood vessels on the surface of the testicles and identifying the tubules that are more likely to contain sperm, New York–Cornell physicians Zev Rosenwaks, Palermo and Schlegel have facilitated impregnation in at least half of these patients. In other words, a quarter of all men with nonobstructive azoospermia, formerly hopeless cases, can now conceive genetically related children.

The recent success stories of infertility treatment are not without their cautionary footnotes. The treatment of nonobstructive azoospermia by way of ICSI is a good case in point.

BAG OF WORMS **(left)** ***is how the scrotum appears with swollen varicose veins that pool blood in the testes, raising their temperature. In a varicocelectomy, a surgeon makes a one-inch incision in the groin area*** **(center)** ***and clips veins*** **(green arrows)** ***external to the spermatic cord, which contains the arteries, vas deferens and other veins. The varicose veins are then tied off, with care taken to avoid the testicular artery and the lymph ducts*** **(right)***. The blood gets routed through healthier veins alongside the vas deferens* **(blue arrow)***.*



JOHN W. KARAPELOU

Genetic testing done by David C. Page and his colleagues at the Whitehead Institute for Biomedical Research and by Schlegel and his associates has revealed that 10 to 15 percent of men with the condition are missing a piece of the Y chromosome, the chromosome that determines the male gender in humans [see "The Key to Masculinity," on page 20]. The genes that control sperm production are also on the Y chromosome, and it is likely that male children born to men with the Y deletions will have the same infertility problem as their fathers. Thus, our treatment for nonobstructive azoospermia may help perpetuate the disease. Fortunately, the chromosomal abnormality does not appear to be associated with any other medical problems.

Another cautionary example is the case of men who are born without a vas deferens. This congenital deformity occurs in about 1 percent of all infertile men, and it can be circumvented by retrieving sperm from the epididymis and injecting them into eggs via ICSI. In fact, most men with the condition can now father children. In collaboration with Rosenwaks, Palermo and Schlegel, our group has attained pregnancy rates of more than 60 percent after just one attempt at sperm retrieval with ICSI.

But it is now known that most men who are missing their vas deferens are also carriers of the gene for cystic fibrosis. Boys with the disease have severe impairments of their respiratory and digestive systems and rarely live to adulthood. Men who carry the gene but do not have the disease risk passing on the gene through IVF techniques, and if the female partner is also a carrier, the test-tube child could end up with the disease itself. Happily, recent advances in IVF technology have allowed fertility specialists to screen embryos for genetic disease before they are returned to the mother's womb, so that they can decide which ones to implant.

Some experts have expressed concern that the techniques of artificial reproduction themselves may be harmful to the children being conceived. Whereas no increase in the incidence of birth defects has been observed with older IVF methods, a doubling in both major and minor defects was recently reported for ICSI births. The resulting rate is still quite low, affecting at most 3 percent of ICSI children. But this troubling statistic is part of a broader good news/bad news scenario that surrounds human reproduction at the close of the 20th century.

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***FROZEN SPERM** for in vitro fertilization are held in a vat cooled by liquid nitrogen at Weill Medical College of Cornell University.*

Mimicking Estrogen

Increasing albeit disputed evidence hints, for example, that chemicals introduced into the environment by industrial processes, by the metabolism of pharmaceutical compounds and by modern changes in diet may be undermining male fertility. These substances, called endocrine disrupters, resemble the female hormone estrogen and have been implicated in genital abnormalities such as undescended testes and hypospadias, an abnormal opening of the urethra (urinary tract) on the underside of the penis rather than at its end. Both these conditions are associated with male infertility, and rates of both abnormalities are escalating throughout the world. In addition, sperm counts in many countries seem to have decreased over the past 50 years, whereas the global incidence of testicular cancer has risen dramatically.

At the same time, our ability to combat male infertility has never been stronger. The same techniques that in the past few years have produced cloned mice and sheep also have tremendous potential for fertility treatments. It is entirely possible that within 10 to 20 years scientists will be able to take cells from any tissue in a man's body and induce the kinds of changes that would enable those cells to fertilize an egg in the laboratory using some future version of ICSI. The steps in such a process are very complex and not clearly understood at present. Once the process is mastered, however, male infertility will become a thing of the past. SA

The Author

MARC GOLDSTEIN pioneered the microsurgical approach to varicocele and blockage repair. Goldstein practices medicine at the New York Hospital–Cornell Medical Center, where he is professor of urology and has been director of the Center for Male Reproductive Medicine and Microsurgery since 1982. He received his medical training at S.U.N.Y.–Downstate Medical Center in Brooklyn and Columbia Presbyterian Medical Center in Manhattan before doing three years' service overseas as a flight surgeon in the U.S. Air Force. On returning, he studied reproductive physiology at the Population Council's Center for Biomedical Research at the Rockefeller University. Goldstein is also a long-distance runner who has finished 14 New York City marathons.

Further Reading

THE COUPLE'S GUIDE TO FERTILITY. Updated edition. Gary S. Berger, Marc Goldstein and Mark Fuerst. Main Street Books, 1995.

MALE INFERTILITY AND VASECTOMY REVERSAL. American Society for Reproductive Medicine, Birmingham, Ala., 1995. Available from the publisher at 205-978-5000, ext. 127.

TREATMENT OF MALE INFERTILITY. Stuart S. Howards in *New England Journal of Medicine,* Vol. 332, No. 5, pages 312–317; February 2, 1995.

The Center for Male Reproductive Medicine and Microsurgery at New York Hospital–Cornell Medical Center site is at www.maleinfertility.org on the World Wide Web.