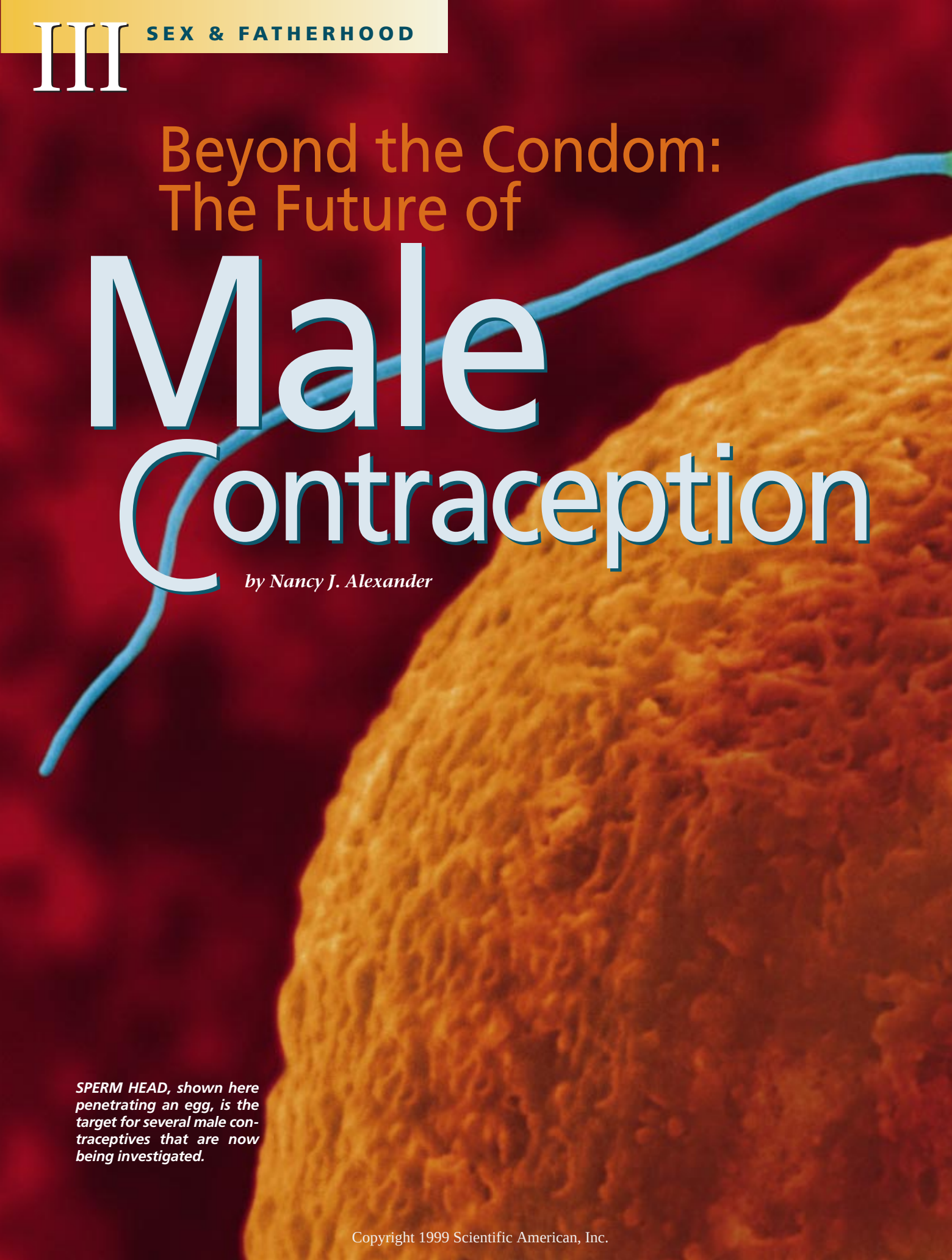
Beyond the Condom: The Future of Male Contraception

by Nancy J. Alexander



SPERM HEAD, shown here penetrating an egg, is the target for several male contraceptives that are now being investigated.

DENNIS KUNKEL *Phototake*

The physiology of sperm production complicates development of new forms of men's birth control, but contraceptive researchers continue to explore new leads

Men have long had a limited choice of contraceptive methods: abstinence, withdrawal, condoms and vasectomy. With about three million unplanned or unwanted pregnancies a year in the U.S. alone, however, there is clearly room for more effective methods.

Male contraceptive research today pursues the ideal of birth control that is safe, long-acting but readily reversible, virtually free of side effects and applied sometime other than just before sex. Such a method would also reduce the spread of sexually transmitted diseases and be inexpensive. No product under investigation can meet all these criteria, but several methods could potentially meet many of them.

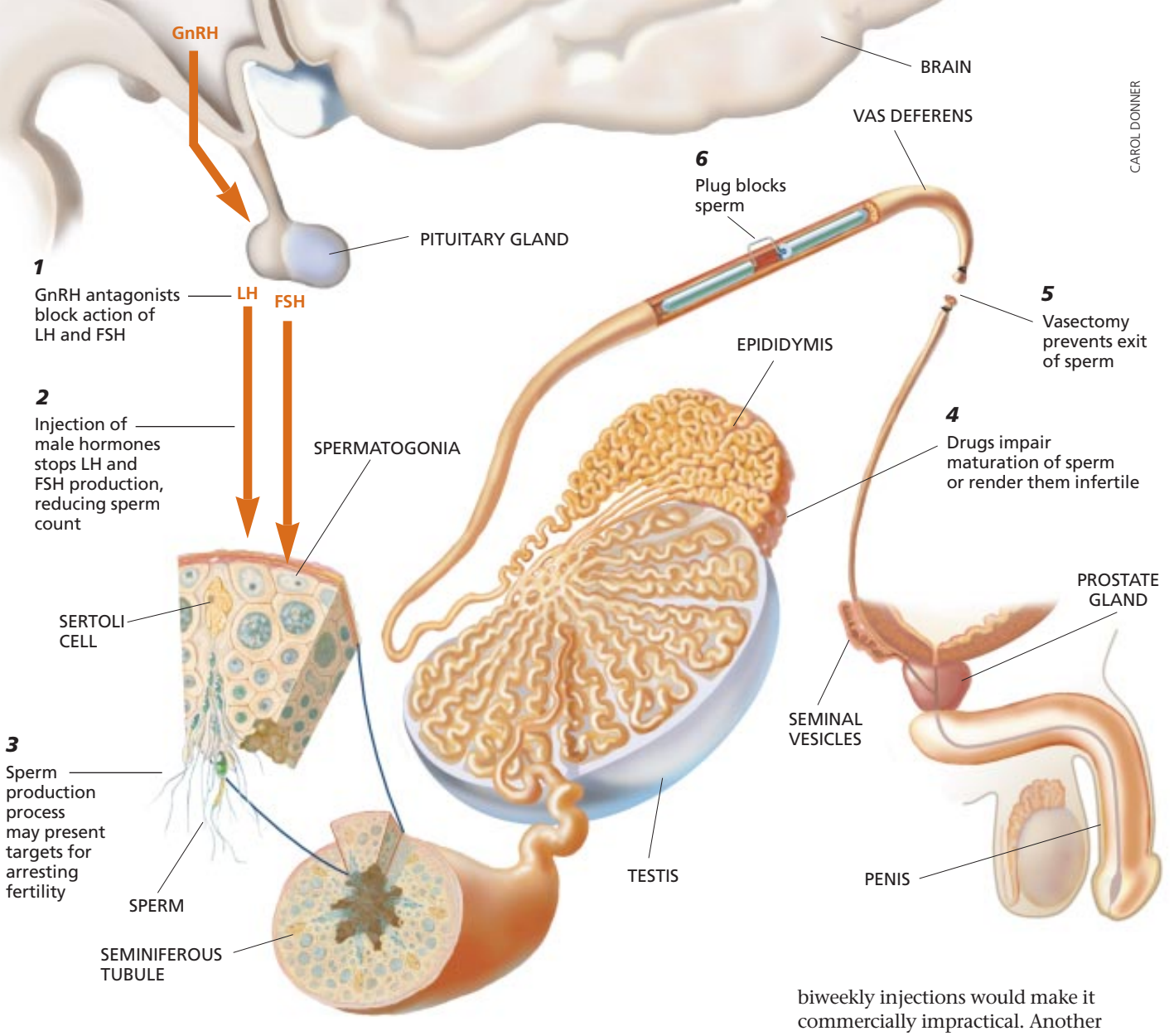
Although research has progressed, male physiology conspires against an easy solution. Every day a man produces tens of millions of sperm, making their elimination or inactivation a daunting task. A woman, in contrast, usually releases only one egg per ovulation cycle. What is more, production of sperm in the testes and their later maturation in the adjoining ducts of the epididymis, where they become capable of fertilizing an egg, take about 75 days. Thus, no intervention in the testes, even if it immediately suppresses the making of sperm, will be contraceptive for almost two and a half months. Conversely, it takes an equal amount of time to return to fertility after stopping use of the contraceptive.

Given these inherent challenges, wholly new types of male contraceptives may not arrive for at least five to 10 years. This lag may seem surprising, but development of any new contraceptive technology takes 10 to 20 years. In the interim, new approaches to conventional contraceptives, including better condoms, may help meet the demand for improvements in male birth control [*see box on page 84*].

The dream of the male Pill—or its semblance—has not faded, though. Longer-term research is targeted at male contraceptives that function by disrupting hormones, by altering the production and maturation of sperm or by rendering sperm infertile.

Suppressing Hormones

The first truly innovative approach to male contraception will manipulate hormones to stop sperm production. Sperm manufacture is controlled by the secretions of gonadotropin-releasing hormone



***INHIBITION OF MALE FERTILITY** can occur along pathways to sperm production and maturation. Synthetic compounds can impede hormones that eventually trigger sperm production in the testes: gonadotropin-releasing hormone (GnRH) from the hypothalamus and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary (1, 2). Spermatogonia—precursor cells of sperm—develop in the seminiferous tubules and are nurtured by Sertoli cells; both sites present targets for intervention (3). Drugs might also inhibit sperm maturation in the epididymis (4). Vasectomies cut the vas deferens, preventing the exit of sperm (5). Plugs in the vas deferens would block sperm passage; removal of the plugs would allow the sperm to flow again (6).*

(GnRH) from the brain's hypothalamus, which drives the pituitary to produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the testes to produce testosterone. This steroid, together with FSH, induces cells called spermatogonia in the testes to divide and ultimately give rise to sperm.

One avenue of hormonal attack would be intramuscular injection of an androgen (testosterone or related male hormones), leading to release of the hormone in the bloodstream. The strategy, which is being studied intensively by the World Health Organization, derives from the finding that circulating androgens instruct the brain to dampen secretion of GnRH and thus of LH and FSH. The reduced production of LH and FSH dramatically decreases sperm production.

This approach has proved highly successful in clinical trials, but the required biweekly injections would make it commercially impractical. Another drawback is that high levels of circulating androgens could produce troubling side effects—notably, increased irritability, acne and lowered levels of high-density lipoproteins (the "good" kind of cholesterol). Fortunately, adding a progestin (a synthetic form of the female steroid progesterone) seems to allow men to take a lower androgen dose, an innovation that should eliminate side effects and be safer than taking an androgen alone. A study in Indonesia that employed both Depo-Provera, a progestin used as a contraceptive in women, and one form of testosterone resulted in zero sperm count. Such a combination treatment will probably offer three months of protection—comparable to what women get from Depo-Provera—and might be marketed by the year 2010.

A similar strategy, adopted by William J. Bremner of the Veterans Administration Medical Center in Seattle, has

explored mixing an androgen with an antiandrogen, a synthetic steroid, which reduces the amount of androgen needed to arrest sperm production.

As an alternative to administering androgens, one could block the activity of GnRH with molecules that do not cause androgen-related side effects. Antagonists consisting of small proteins, or peptides, already exist, but they do not stay in the circulation long enough to be contraceptive unless injected daily. Investigators at Merck have designed a nonpeptide inhibitor, which could lead to a pill. Blockage of GnRH would suppress testosterone production, so that men would have to take replacement androgens to retain muscle mass, male sexual characteristics and libido. Biochemists may also tailor "designer" drugs that mimic the sperm-inhibiting effects of androgens, without accompanying side effects. The Population Council, in fact, has begun testing a testosterone analogue (7-α-methyl-19-nortestosterone). Unlike testosterone, the compound resists degradation into dehydrotestosterone, a metabolite that can trigger acne and swelling of the prostate.

Perhaps in 20 years men will have access to long-acting agents (protective for months) that instead of disturbing natural hormone balances directly interrupt spermatogenesis, the complex process of sperm production. Other agents might also impede subsequent maturation of newly made sperm in the epididymis, one of a pair of four- to six-meter (13- to 20-foot) coiled tubes leading from the testes. Or they may inhibit the fusion of sperm and egg. Contraceptives that act directly on these processes could theoretically overcome two disadvantages of male hormonal methods: their interference with testosterone production and the long delay in both onset of contraceptive action and restoration of fertility.

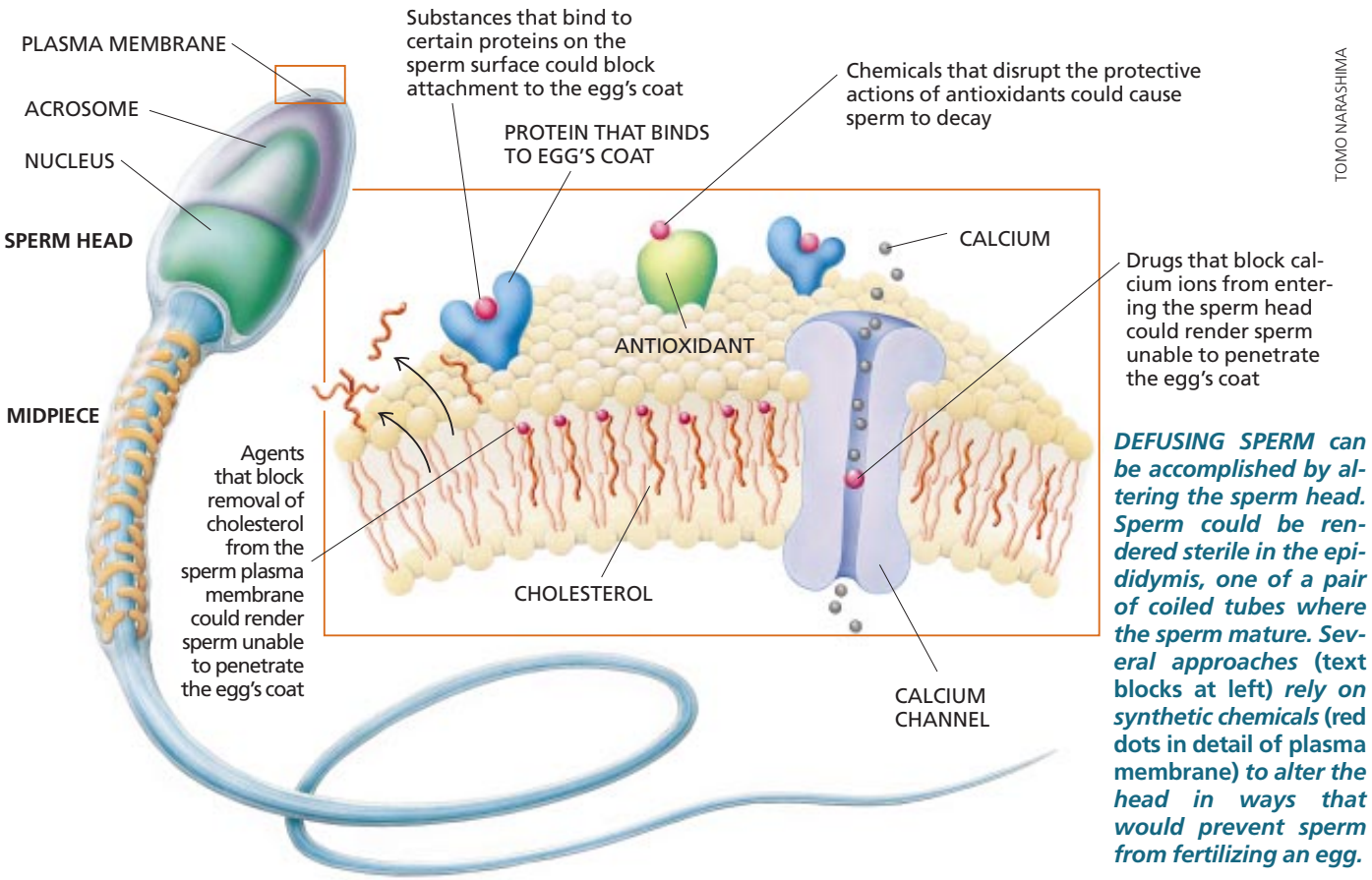
New Strategies

Basic research on sperm formation may lead to an array of new contraceptive strategies. In sperm development the spermatogonia, the cellular precursor of sperm, arise from undifferentiated stem cells found in thin, coiled structures in the testes, the seminiferous tubules. When the stem cells divide, some of their progeny develop into the spermatogonia, which eventually become sperm; the rest remain as stem cells, thereby replenishing the supply of these cells.

Once these events take place, the sperm-cells-to-be move slowly to a central part of the seminiferous tubules, while receiving sustenance from another type of cell, the Sertoli cell. The budding sex cells go through a type of division called meiosis—in which each divides twice, producing four new cells. After meiosis, each new cell contains 23 chromosomes, half the usual number, allowing it to combine with the 23 chromosomes found in the female's egg cell.

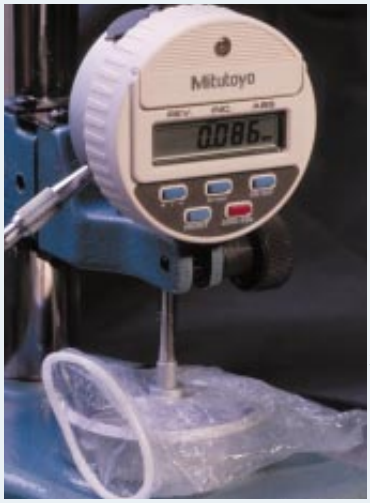
Before fertilization can happen, the sperm cells undergo a metamorphosis (spermiogenesis) in which they develop flattened, paddle-shaped heads connected to long tails. At this point, the sperm cells move to the epididymis, the coiled tube that connects a testis with the vas deferens. There maturation continues—sperm become motile, for instance. The young sperm cells remain in the epididymis until they are expelled from the body to become potential fertilizers of an egg.

A drug might interfere with almost any stage of this process. It could prevent the stem cells from differentiating into sperm cells, or it might also work



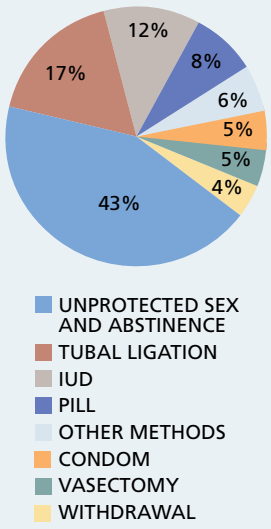
***DEFUSING SPERM** can be accomplished by altering the sperm head. Sperm could be rendered sterile in the epididymis, one of a pair of coiled tubes where the sperm mature. Several approaches* (text blocks at left) *rely on synthetic chemicals* (red dots in detail of plasma membrane) *to alter the head in ways that would prevent sperm from fertilizing an egg.*

Condoms and Abstinence: Current Options for Male Contraception



NATALIE FOBES *Corbis*

***TESTING MACHINE** evaluates the thickness of a condom, still one of the world's most widely used male contraceptive methods.*



LAURIE GRACE

***AVERAGE CONTRACEPTIVE USE** around the world shows that males take less responsibility than their partners do.*

Men who take the responsibility for avoiding their partners' pregnancy can put on a condom, get a vasectomy, practice withdrawal or just say no. The practices of abstinence and withdrawal have not changed much over the centuries, but a few improvements have been forthcoming for condoms and vasectomies.

Abstinence: All adults have periods of abstinence. The definition of abstinence varies, from no genital contact of any kind to not engaging in penetration. Efficacy is virtually 100 percent.

Withdrawal: Coitus interruptus, or withdrawal, has been a major contributor to the diminishing overall birth rate. It is 80 percent or better effective and depends on consistent withdrawal before ejaculation, which may prove difficult for some couples.

Condoms: Properly used, condoms are more than 95 percent effective and are used by an estimated 49 million men. Only latex condoms have been effective against infection by the human immunodeficiency virus (HIV) in clinical trials. Nonlatex condoms, which recently reached the market, have the advantages of longer shelf life and of not being affected by oils and creams that might be used as a lubricant. Some of the new condom designs purportedly provide greater sensitivity because they are of a different material—polyurethane or various copolymers—and may be thinner than latex. Barriers, both physical (condoms) and chemical (spermicides), remain the birth control of choice of 21 percent of women in the U.S.

Vasectomy: This procedure cuts the vas deferens, a muscular tube that connects the epididymis with the urethra. It is an effective method of sterilization used by 45 million men worldwide. Vasectomy prevents the exit of the millions of sperm in the semen and does not affect production of androgens, testosterone and dihydrotestosterone (DHT), which are essential for characteristic male traits, such as facial hair and musculature. In 1985 a new technique was introduced, called no-scalpel vasectomy, that involves teasing the skin apart through a tiny puncture rather than a conventional incision. It speeds healing and reduces fear of surgical mishap.

Although vasectomy can be surgically reversed, it is thought to be a permanent method not appropriate for couples who are considering having children at a later date. A surgical technique, vasovasostomy, can remove the scar tissue where the vas deferens was closed off during the vasectomy and then attach the free ends [see "Of Babies and the Barren Man," on page 74]. The procedure, however, does not always work. It is also expensive and so would be inappropriate for developing countries. Reversible vasectomy methods, which have relied on valves and plugs for the vas deferens, have so far not been sufficiently tested in humans. Ideally, a magnet or electrical impulse would turn off or on the flow of sperm. The strong musculature of the vas deferens, however, usually expels the device.

A newer model, developed by Lourens J. D. Zaneveld of Rush-Presbyterian–St. Luke's Medical Center in Chicago, has circumvented this problem by employing two cylinders of a polyurethane elastomer separated by a thread. Vas deferens contractions during ejaculation move the cylinders within the vas deferens but do not expel it. Studies in Brazil of the reversibility of the procedure have shown promise. But clinical studies have proved difficult to administer: men with successful vas deferens implants seldom want a reversal after only a short period in order to test a scientific concept.

New, nonsurgical methods to block the vas deferens would hold an advantage over a typical vasectomy. Injection of sclerosing agents into the vas deferens, for example, plug the cavity, stopping the advance of sperm. One compound, developed by Sujoy K. Guha of the All India Institute of Medical Sciences in New Delhi, is a liquid plastic that can act as a barrier while only partially blocking the sperm pathway. It generates a positive electrical charge that appears to disarm the acrosome, a bag of enzymes in the sperm head, which fosters sperm-egg binding. A second injection of sodium bicarbonate can reverse the induced infertility. Studies in rats show that fertility was restored 90 days after injection of sodium bicarbonate. Further studies are now ongoing to explore this technique.

In another effort, Chinese investigators have injected a combination of carbolic acid and *n*-butyl cyanoacrylate—the main ingredient in Krazy Glue—as an adhesive to close the tubular passage of the vas deferens. Undoubtedly, finding better ways to turn the vas deferens off and on will continue to preoccupy the research community in the years to come.

—N.J.A.

on the numerous enzymes and other proteins that regulate the function of Sertoli cells, meiosis and spermiogenesis.

In surveying the various stages for intervention, researchers have suggested that disrupting maturation in the epididymis—where the sperm become mobile and achieve the ability to fertilize an egg—might be the most feasible option. Why? Whether delivered by mouth, by injection or by implant, drugs aimed at altering sperm maturation would have to reach the testes or epididymis via the bloodstream; however, blood-borne drugs often cannot pass out of the circulation and into the part of the testes where sperm are manufactured. Further, many drugs that are capable of stalling sperm synthesis have proved toxic to spermatogonia in the testes and would thus lead to irreversible sterility.

The epididymis presents a number of targets for new drug research. Intervention at the level of the epididymis can both affect sperm count and hamper the ability of sperm to fertilize an egg. One set of investigators has found that triptolide, an isolate from a Chinese plant originally used for treatment of skin diseases and rheumatoid arthritis, affects fertility by hindering sperm motility in the epididymis.

Because triptolide disrupted sperm production, researchers worried that it might cause permanent infertility. More recent studies in rats by Amiya Sinha-Hikim and his colleagues at Harbor University of California at Los Angeles Medical Center have shown that at lower doses, triptolide appears to leave sperm production in the testes intact but reduces the number of active sperm in the epididymis by 70 percent.

During sperm maturation in the epididymis, changes in the sperm's outer lipid plasma membrane take place that allow a biochemical reaction that gives sperm the capability of fertilizing an egg. When it encounters an egg cell, a mature sperm's outer membrane merges with a bag of enzymes at its tip (the acrosome). The enzymes then eat through the egg's outer layer to permit fertilization.

Investigators have explored the potential of the antihypertensive drug nifedipine to inhibit fertility, perhaps by preventing the incorporation of a cell receptor into the plasma membrane while a sperm is in the epididymis. This receptor is needed for the plasma membrane–acrosome reaction to allow the sperm and egg to fuse. Susan Benoff and her colleagues at North Shore University Hospital in Manhasset, N.Y., discovered this contraceptive effect when they found that sperm from some men did not fertilize their mates' eggs during in vitro fertilization. Subsequent sleuthing revealed that the men were taking nifedipine, a calcium channel blocker. Stopping the medication reversed the effect.

Benoff suggests that the drug interferes with the discharge of enzymes from the head of the sperm that are essential for fertilization of the egg. Current studies are attempting to determine whether a calcium channel blocker similar to nifedipine can be designed so that it would affect sperm function but would not decrease blood pressure and heart rate, as nifedipine does.

Study of the epididymis may also suggest other ways to inhibit fertility. During the 10 to 14 days that they develop in the epididymis, sperm acquire cholesterol that prevents them from undergoing prematurely the biochemical reaction between the plasma membrane and the acrosome. Chemicals that disrupt the uptake of cholesterol by sperm in the epididymis—either by starving or by overloading them with the substance—might yield contraceptives that would either block the plasma membrane–acrosome reaction or cause it to take place in the epididymis before it can occur between the sperm and egg. Another strategy for a new contraceptive would hinder the action of antioxidants in the epididymis that protect the plasma membrane from free radical chemicals that could damage it.

Selling the Male Pill

In the near term, the challenges may lie as much in the marketing as in the science. Some companies hesitate to develop male contraceptives because of the difficulty of marketing to men. Unlike women, who typically see a gynecologist once a year, men often do not have any relationship with a family physician or urologist, who would alert them to the availability of new drugs.

As with any drug, moreover, potential side effects could lead to a liability quagmire for manufacturers. But perhaps the biggest worry is that a male contraceptive may introduce a new set of tensions between sexual partners. Women must trust the partner—who does not risk pregnancy—to ingest a pill faithfully or to self-administer an injection. To gain acceptance for a male contraceptive, drug companies may have to market accompanying test kits that a woman could use to ascertain a man's sperm levels, an assurance that the man meant what he said.

Regardless of which approach clears the science, marketing, legal and social hurdles, researchers will press on in their pursuit of new male contraceptives to address the important issues of population growth and unintended births. World population currently stands at 5.8 billion and is still increasing rapidly. In the U.S., of the nearly three million unwanted or unintended pregnancies, according to the most recent (1994) statistics, about half ended by elective abortion. Male contraceptives that are more convenient, reliable and accessible can play a role in controlling a burgeoning population and in making more births those of choice. SA

The Author

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Further Reading

ANTIHYPERTENSION DRUG MAY DOUBLE AS MALE CONTRACEPTIVE. Rachel Nowak in *Journal of NIH Research*, Vol. 6, No. 1, pages 27–30; January 1994.

MALE CONTRACEPTION: IDEAS FOR THE FUTURE. David E. Cummings and William J. Bremner in *Current Therapy in Endocrinology and Metabolism*, Vol. 6, pages 300–304; 1997.

Information on male contraceptives is available at the Population Council site at http://www.popcouncil.org on the World Wide Web.