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REPRODUCTIVE PHYSIOLOGY

Turning off sperm

Million-dollar search for a contraceptive pill for men instead of women; problems with the male psyche

by Barbara J. Culliton

Scientists foresee the time when men as well as women will be taking birth control pills.

Fearful of the long-term effects present oral contraceptives may have on the 11 million women who use them, and confident that the male is a much easier target for a safe birth control pill, more and more researchers are switching their attention to male reproductive physiology. While the hunt continues for a female contraceptive that would work without disrupting a woman's normal reproductive cycle, scientists at a number of medical centers and at least four major drug houses are devoting their time—and upwards of \$1 million—to finding a male birth control drug.

But when they find it, will it sell? **To the delicate male psyche**, fertility and virility are practically synonymous. Exactly how responsive men will be to a drug that makes them sterile, even if only temporarily, remains to be seen. Even though a male pill would have absolutely no physiological effect on sex drive, the majority of workers in the field believe it will take an extensive educational campaign—and time—for men to get used to the idea.

Meanwhile, the challenge of developing a drug that will interfere with spermatogenesis without causing lasting damage is foremost. From studies of rats and humans, Drs. Emil and Anna Steinberger of Albert Einstein Medical College, Philadelphia, have identified several specific stages of cell formation that take place during the eight to nine weeks an infant sperm grows to maturity. "This means there are a number of places we can hit spermatogenesis and makes the male a less complicated target than the female," Dr. Emil Steinberger explains.

In order to interfere with conception in women, who are born with one supply of eggs that are released singly every month, a pill has to upset normal hormone secretion—a complex, finely balanced and cyclic system. But because men are constantly replenishing their supply of sperm cells, sperm production can be attacked directly without blocking hormonal activity at all. And, because the mechanism of sperm production is essentially separate from

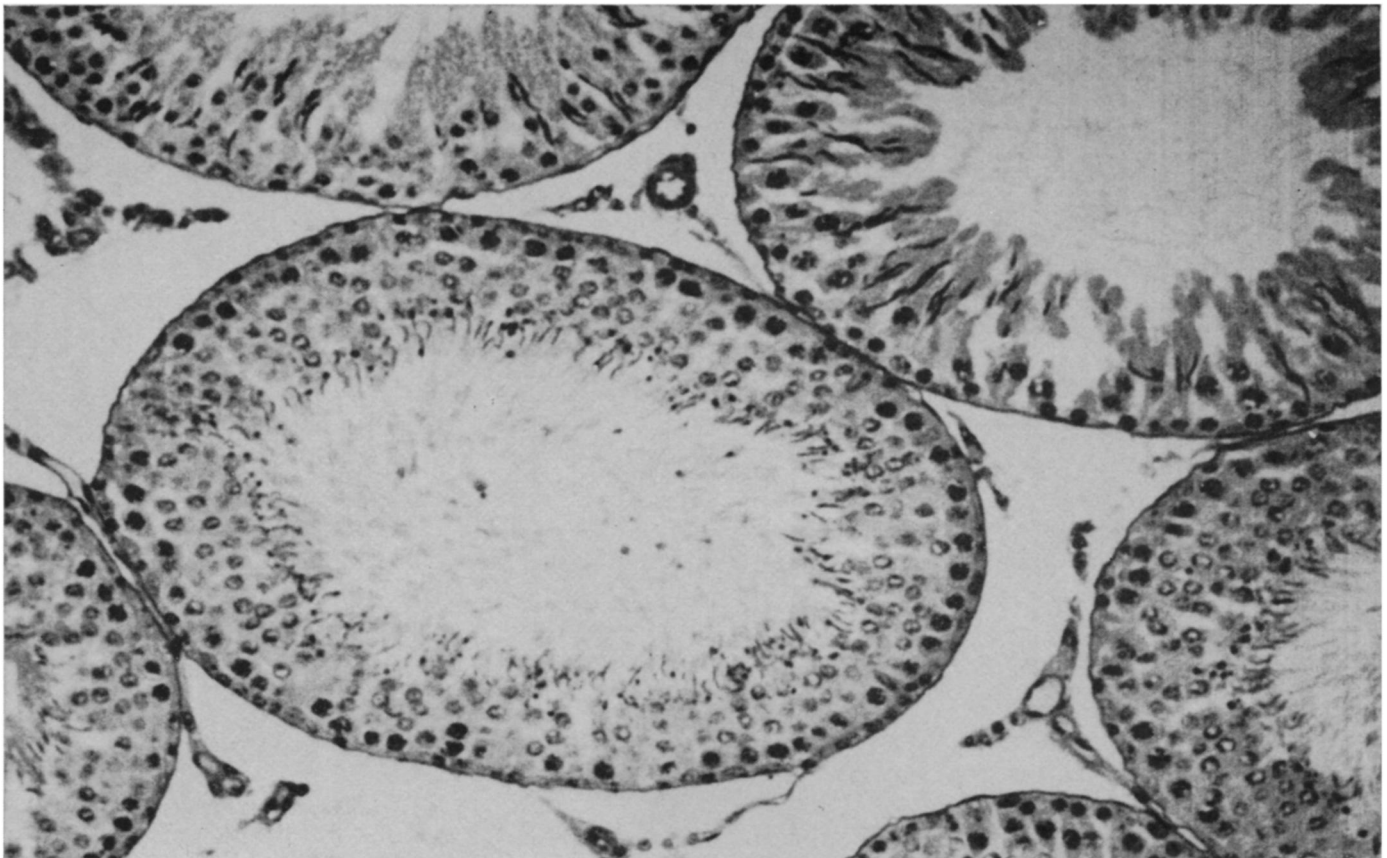
that involved in male hormone output, a chemical that turns off spermatogenesis need not necessarily affect libido which is influenced by male hormones. Sperm cells form in the testes in tiny tubules resembling garden hoses. Androgens, male sex hormones, are produced outside these tubules.

The Steinbergers and others have found a number of compounds capable of interfering with spermatogenesis at various specific stages, but all have unacceptable side effects—ranging all the way up to irreversibility. Among the most promising recent preparations is a diamine compound that scientists at Winthrop Laboratories came up with about two years ago. Experiments with prisoners showed the diamines have no lasting side effects, so physicians tried them on patients. Then they discovered, much to their dismay, that if a man who took the pill also took a drink—which prisoners normally don't—his eyes turned bright red. Further research hasn't resolved the problem.

At Merck Sharpe and Dohme, Rahway, N.J., Dr. Dolores Patanelli is working with several sperm-inhibiting compounds—all in experimental stages. One of them effectively cuts off sperm production in rats and is reversible. Animals that stop taking the drug regain fertility and have normal offspring. At least, no genetic abnormalities have shown up in first generation rats studied so far. In spite of the problem of the delicate male psyche, and the association of infertility with loss of virility, Dr. Patanelli believes men are becoming more sophisticated and responsible in matters of birth control—especially the well-educated. In her opinion, a once-a-month male pill will be well received, but anything that would last longer—up to a year for instance—might be less popular.

Merck's market researchers report interest in a male contraceptive among men in Taiwan and India. Upjohn, another company where male reproduction is being studied, sees a male pill as a complement but not a substitute for oral contraceptives for women.

Dr. Carl Heller of the Pacific Northwest Research Foundation, Seattle, has been testing a variety of anti-spermatogenesis drugs on prisoners—usually about 50 men in each test—for several



Dr. Emil Steinberger

Sperm cells grow from black dots at tubule wall to free-swimming adults at center.

years. In spite of limited success so far, he says, "orally active male hormones will one day prove to be the best for blocking spermatogenesis without lowering libido. And," he predicts, "this will be perfectly acceptable to men."

On the other hand, Dr. John MacLeod of Cornell University Medical College, New York, says the outlook for a male contraceptive is "very discouraging." He has been experimenting with a compound called depoprovera. In 60 prisoners in Alabama, he reports from studies concluded last month, sperm production was halted, but after as many as 140 days, there are no signs it is going to resume. "I am forced to the conclusion that it will be extremely difficult to produce reversible sterility in the male."

But opinion varies with almost every researcher. Implicitly stating its view of the future of male contraceptives, Ortho Pharmaceuticals, Raritan, N.J., has just initiated a program to explore male contraception by immunological means. The idea is to make men immune to their own sperm. Experiments with guinea pigs show that if a bit of testicular tissue is removed from the animal, homogenized and then injected back into him, the injected material sets off an antigen-antibody reaction in the testes that results in sterilization. Be-

cause of the reaction, the animal's body thinks its sperm cells are really foreign bodies and so it sends out antibodies to destroy them. It may be possible to induce a similar reaction in men by injecting homogenized animal testes, but this hasn't been tried yet.

What Ortho plans to do in its study is unknown, however. "We are just getting started in this area of investigation and would not be able to reveal anything of value," a spokesman says.

From a somewhat different approach to the study of male reproductive physiology, scientists at Upjohn in Kalamazoo, Mich., are on the track of a new type of contraceptive that would be taken by the woman, would not interfere with her biochemical processes, but would act against sperm. Dr. Ronald Ericsson has been studying a phenomenon called capacitation which is known to operate in rats, rabbits, guinea pigs, dogs and possibly in higher primates, including man. Sperm cells from these animals are unable to fertilize an egg until they have resided inside the female's body for a matter of hours during which they capacitate or gain the capacity to penetrate the egg. Although there is no conclusive proof of how this works, Dr. Ericsson postulates that an enzyme in the uterus works on the sperm cells to remove a protective outer coat. If he is right, a drug that

interferes with the enzyme would prevent conception without affecting either ovulation in the woman or spermatogenesis in the man.

At Yale University, a team of scientists lead by Dr. John McLean Morris plans to use Dr. Ericsson's method to try to detect sperm capacitation in primates. "It's still in the monkey business stage, though," Dr. Morris says of his future work which will involve Yale's extensive primate colony. Low-dose progestin pills that contain no estrogen—the female hormone used in the combination oral contraceptives for women—may inhibit sperm capacitation, some scientists speculate, but there is no substantial evidence to back this hypothesis yet. It is merely one of many suggested to explain why these progestin pills work.

Whatever the future of male contraceptives, research on reproductive physiology in man will undoubtedly fill large gaps in existing knowledge. From studies of sperm-blocking agents scientists are learning more and more about how reproduction works. Even if they never find an ideal male pill, they are confident they will be better able to cope with the reverse problem—making infertile men fertile. Every step that brings them closer to knowing how to turn sperm production off brings them closer to knowing how to turn it on.