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THE MANLY ART OF CONTRACEPTION

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Population growth in developing countries continues to exert pressure on resources, slowing economic and social development. Yet although surveys indicate that more than half the women of reproductive age want no more children, typically two-thirds do not use any method of fertility control.

Coupled with the need to contain population growth rates is a growing demand for males to share the responsibility and the risks of birth control. Women assume all the health risks of childbearing as well as almost all the risks of adequate contraception, and are becoming increasingly dissatisfied with that role.

Still, more than 70 percent of research funds are paid out in seeking new contraceptive methods for women, and only six percent are earmarked for new male methods. The remainder is applied to finding technologies applicable to both male and female reproductive systems, such as hormonal releasing factors.

One of the constraints to developing new male methods lies in the lack of understanding of the male reproductive system. Relative to research into female systems, the state of knowledge about the male system has advanced little since the discovery that sperm were more than parasites.

Halting male fertility is biologically difficult. Up to a billion sperm are produced daily, and controlling or stopping this proliferation is more difficult than intervening in the female system to regulate a once-a-month ovulation involving only one egg. The genetic material in sperm is also more susceptible to damage, particularly since any method of control must be powerful enough to totally prevent or impair function — sperm reductions of 80-90 percent are not sufficient to guarantee infertility.

The three approaches presently taken in male contraception entail stopping sperm production, blocking sperm transport at the time of intercourse, or altering the quality or capacity of sperm to fertilize. All the methods now actually in use are based on physically blocking sperm from entering the female reproductive system — vasectomy, condoms, or withdrawal before ejaculation.

The goal of new male contraceptive research is to develop an effective, reversible, easily used method that neither interferes with libido nor the act of intercourse, and is free of any dangerous side effects. For developing countries, two additional characteristics are essential — the method must be inexpensive and easily distributed.

THE PAST

Withdrawal before ejaculation of sperm is probably the most ancient of male contraceptive methods. However, it is also the least reliable.

The condom evolved from the failures of withdrawal to adequately reduce unplanned pregnancies or provide protection against venereal disease. But although it effectively raises a barrier against fertilization, its effectiveness depends on timing and correct technique in putting on the condom. Concern over the health risk of the pill and iuds coupled with the renewed epidemic levels of sexually transmitted diseases (see Reports 10(3), October 1981) has nevertheless resulted in increased use of condoms.

Vasectomy — male sterilization involving severing or blocking the vas deferens tubes that carry semen from the testes to the penis — has become an important part of contraceptive programs in many countries. In a sense, sterilization is the choice of last resort, since the procedure is not easily reversible and there are indications that men (and women) would prefer to exercise choice over when they have children rather than whether.

IRC is currently supporting an investigation into a possible link between vasectomy and arterial disease. Sperm production is not halted by vasectomy, but since their normal outlet is blocked, new mechanisms for disposal of the sperm are brought into play. Sperm can cross the blood-testis barrier to enter the bloodstream, where they trigger production of antibodies. Animal studies suggest that the build-up of antibody complexes damages artery walls and promotes the sort of harden-
ing and thickening usually associated with age and coronary artery disease. Research funded by IDRC will attempt to determine whether the same effects are produced in human males who have undergone vasectomies.

New research seeks the "male pill," a simple, self-administered, reversible contraceptive. As with egg production in women, sperm production in men is regulated by hormones, and most interest is focused on regulating hormone levels to induce infertility by halting sperm production.

In both men and women, a hormone produced in the hypothalamus region in the back of the brain appears to be the master control of reproductive functions. The luteinizing hormone-releasing factor (LHRF) gets its name from its function: it regulates the production and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), pituitary hormones known as gonadotropins. The gonadotropins' most important effects in men are on the testes: LH stimulates the Leydig cells to produce testosterone and the other steroids that maintain libido and secondary male sexual characteristics, such as deeper voices, musculature, etc.; FSH stimulates the Sertoli cells in the bundled seminiferous tubules to start producing sperm.

One approach to male contraception attempts to duplicate the action of female oral contraceptive pills containing steroids. Administering male hormones or synthetic hormone analogues acts on the brain and pituitary to decrease gonadotropic hormone levels and inhibit sperm production. In effect, a false signal is given that the testes are over-producing sperm and hormones, and the natural controls are turned down to levels that cause sperm production to stop.

Direct administration of testosterone, the male sex hormone, has been shown to sharply reduce sperm production as a result of this feedback mechanism to the pituitary. But side effects such as weight gain, acne, breast development, and lowered libido weigh against its use.

As testosterone is inactivated when taken by mouth, dosages must be injected regularly, making the regime valuable only for "an exceedingly dedicated subject," as Dr Keith Smith of the University of Texas Medical School notes. Smith, reporting on the first major clinical trials of testosterone, adds, "I do not feel that I could follow this schedule myself of administering a shot in the buttock every 10 days."

Using other steroids to suppress sperm production, with smaller doses of testosterone to maintain libido and secondary male physical characteristics, has so far produced mixed results. The approach has not consistently produced low enough sperm counts.

There are serious concerns about possible genetic damage by these chemicals. Sperm continuously develop from cells in the testes. If any of the genetic complements of the cells are damaged, the resulting sperm could also be affected. Should conception occur, the genetic message of damaged sperm could be translated into deformed fetuses and carried on to other generations.

The search for non-steroid contraceptives has taken researchers back to the brain. The master control LHRF, although it is hormonally active, has a different chemical structure than the steroids. It is a chain of linked amino acids with the same basic molecular structure as a protein—a polypeptide. Peptides are known to have more specialized and specific sites of action in the body, and are shorter-lived than steroids.

But LHRF is too weak naturally to be used as a contraceptive. Uncovering its structure made possible the synthesis of analogues—substances with similar characteristics, but in which desirable properties could be strengthened. A variety of analogues have been investigated: agonists, which imitate natural LHRF; antagonists, which block its action; and selective agonists, which duplicate only some functions of LHRF. Some 1000 analogues have been created.
The most extensive trials have involved one analogue, a super agonist which is about 144 times more powerful than LH-RH. However, instead of accelerating hormone production, the super agonist paradoxically inhibits reproductive functions by overstimulating the pituitary, thus exhausting its capacity to respond further and produce LH and FSH sufficient to maintain sperm production.

Dr David Rabin, who directed the super agonist LH-RH study at Vanderbilt University in Nashville, U.S.A., reported that sperm production dropped by 75-100 percent. All subjects recovered fertility within 10-14 weeks after administration of the super agonist was stopped. He noted, however, that in some subjects the regime of daily injections reduced testosterone levels and had side effects: impotency, reduced libido, and “hot flashes” — momentary increases of body temperature.

Effective, reversible, and safe, synthetic LH-RH shows promise as a male contraceptive. The annoying — but not dangerous — side effects must still be eliminated, and a more convenient mechanism than daily injections developed.

GOSSYPOL

The closest researchers have yet come to a male pill appears to be work under way in the People's Republic of China on gossypol — a compound found in the seed, stem, and roots of the cotton plant.

An investigation of high rates of infertility in a province of China eventually linked them to the local use of crude cotton seed oil for cooking. Gossypol was identified as the active agent.

Clinical trials of a gossypol pill began in 1972, and about 10000 men have been studied. Results are reported in the Chinese Medical Journal as 99.89 percent effective, and side effects are “mild and of low incidence.”

Gossypol is known to be toxic when eaten regularly, however, and also tends to accumulate in the body, leading to concern over long-term health effects. About three-quarters of one percent of its male users developed a paralysis caused by potassium deficiency.

Gossypol apparently works by inhibiting an enzyme that is vital to the metabolism of sperm and sperm-generating cells. As it does not act on sex hormone levels or impair libido, expectations are high that gossypol may be the first of the new male contraceptives to become widely accepted. But along with the sperm enzymes, gossypol also inhibits other enzymatic activity in the body — including some that function to detoxify organic compounds, a few of which are linked to cancer.

Sperm in the testes are immature, incapable of either fertilization or movement. They gain these capabilities as they develop in the epididymis, the set of long cordlike ducts that lies immediately behind the testes. Little is known about the biochemical changes that occur as sperm pass through the epididymis, except that certain chemicals — like gossypol — can interrupt or inhibit the maturing process.

Researchers in Thailand, with Ipcrc funding, are attempting to characterize the biochemical processes that take place as sperm mature. The work of Dr Montri Chulavatnol and colleagues in the biochemistry department of Mahidol University may open the way for sophisticated techniques of modifying the process as a means of contraception. Dr Chulavatnol is examining the mechanism that enables sperm to convert chemical energy stored in cells and transmit and use it as mechanical energy, powering the sperm's flagellum or tail as it swims towards the egg after ejaculation into the female. Preventing the formation of the particular compound that is the energy source, or preventing its use once formed, could be the key to a male contraceptive that poses little risk of genetic damage or of producing children using a larger scale within the body system.

A still more finely targeted approach, again supported by Ipcrc, aims at providing contraception precisely at the point where sperm and ovum meet.

It focuses on two enzymes that play a part in the penetration of sperm through the layers that surround the ovum. Hyaluronidase allows sperm transport through the cumulus, an outer layer, and acrosin facilitates penetration of the zona pellucida, the inner layer. Dr Horacio Croxatto, of Chile's Centro Nacional de la Familia in Santiago, and Dr John Elce at the Department of Biochemistry of Queen's University in Kingston, Canada, are carrying out work that could potentially lead to a male contraceptive vaccine. The presence of antibodies to sperm has been noted in men with vasectomies. There is also evidence that suggests some cases of infertility may be due to the immunological response of women to sperm.

Drs Croxatto and Elce speculate that if the two particular enzymes, hyaluronidase and acrosin, could be isolated and sufficiently purified, they could perhaps be used to provoke a specific immune response against them. Having achieved the response, the specific antibodies to hyaluronidase and acrosin could then be isolated, purified, and manufactured as a vaccine.

The vaccine approach is elegant and simple. It would have only one effect — sperm would be unable to penetrate the ovum. In this case, the side effect would be infertility. But one of the principal advantages of the vaccine may also be a drawback. As a vaccine, perhaps only one injection, or one and a series of boosters every few years, would be necessary to confer infertility. But, having turned on the body's defenses against sperm, how will the antibodies be suppressed again when a user wishes to have children?

There are many questions concerning male contraception that must be answered through research before the goal of an effective, reversible, safe, and inexpensive technology is realized. Males are unlikely to accept a contraceptive technology that is less than perfect. And without men assuming more responsibility for family planning, the greater goal of balancing world population with resources seems ever more remote.

Spermatozoa are attached to the outer layer of the ovum, but are unable to penetrate and fertilize it due to the inhibition of two important sperm enzymes. Some of the chemical components of sperm are identified as foreign infections and trigger an immune response in the body. Researchers are attempting to duplicate and enhance the action to create a vaccine that would give “immunity” to fertilization by increasing resistance to two sperm enzymes, acrosin and hyaluronidase.