Contraceptive Methods Go Back to the Basics

Contraceptive development has moved rather slowly over the past several decades—if it has moved at all. It has remained the province of a few traditional methods, almost all designed to be used by women. But researchers have long hoped to develop novel technologies, including hormonal methods that would level the playing field by being designed for men. That's been difficult to achieve, but recently researchers at the World Health Organization (WHO) obtained early signs of progress. In a study expected to be published early next year, WHO researchers gave men testosterone, which signals the body to slow the reaction cascade leading to sperm production. The findings: Among the female partners of more than 300 men whose sperm counts dropped from at least 20 million per cubic centimeter to under 3 million, there were only four pregnancies in 12 months.

Contraception is further explored in this special issue on Reproduction in News stories that begin on page 1484. Stories examine contraceptive vaccines and barriers to further contraceptive development. In addition, another News story looks at the search for early warning signs of premature birth. Articles on reproduction start on page 1494. They examine topics such as implantation in mammalian pregnancy, sex determination, estrogen receptors, and fertility trends in human populations. Reports appear on pages 1578 and 1581.

That is just one of the findings that are triggering optimism among some contraception researchers these days—and not just because of the hope of male contraceptives. In addition to sperm suppression, new efforts to understand and stop the molecular reactions involved in the fusion of sperm and egg tantalize people such as George Gerton, a reproductive biologist at the University of Pennsylvania School of Medicine, with the promise of novel technologies. "If we can find proteins unique to sperm and egg cells that orchestrate sperm-egg binding and fusion, we may be able to design specific reagents to interrupt the process," Gerton says. And while researchers have yet to turn up such specifically targeted drugs, says Gerton's colleague Greg Kopf, "it's getting very close."

But not—in the estimation of some people—close enough. Some researchers warn that weekly injections, as used in the WHO work, are no recipe for a widely used contraceptive. Others have a more general skepticism. "Not one of these methods will be used by people before the year 2010," predicts Stanford University chemist Carl Djerassi, inventor of the modern oral contraceptive pill. Djerassi says the same barriers that have been preventing new contraceptives from reaching the market for decades—high development costs, poor profit potential, and fears of litigation on the part of drug companies—are still firmly in place. "The current reality is that it's very difficult to commercialize any new contraceptive development," says Gabriel Bialy, acting director of the Center for Population Research at the National Institute of Child Health and Human Development (NICHD) in Bethesda, Maryland.

Nevertheless, researchers are pressing ahead, partly, says Kopf, out of pure scientific interest in the biology of reproduction and partly in hope that the discovery of new targets for contraceptive drugs might spark renewed interest among drug companies.

Both of these goals have motivated the work on sperm suppression. The WHO research, which is already in its second round of clinical trials, is based on the principle that high levels of testosterone in the blood slow the release of two pituitary hormones—follicle-stimulating hormone and luteinizing hormone—that trigger the production of sperm and, in a feedback loop, more testosterone. When these hormone levels drop, so does sperm production; hence administering testosterone, researchers reason, could provide a route to cutting sperm production.

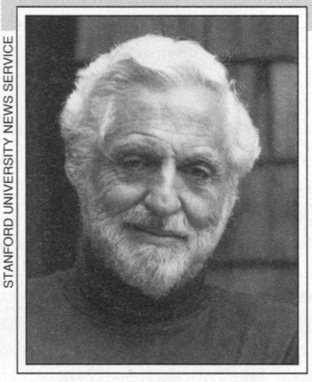
In WHO's first clinical test of this approach, completed in 1990, researchers gave members of a study population 52 weekly injections of 200 milligrams of testosterone as a contraceptive and found that it shut off sperm production completely in nearly 70% of the men. Over that period, the partners of the more than 300 men in the study had only one pregnancy. The second study also included men whose sperm production was lowered, but not stopped, and it demonstrated a similar contraceptive effect, says Christina Wang, a professor of medicine at the Harbor–UCLA Medical Center, who is also an adviser for the WHO program.

In spite of these encouraging data, researchers acknowledge that the sperm-suppression approach is not ready for the real world. The weekly injections "are definitely not going to catch on," says Nancy Alexander, who heads the Contraceptive Development Branch of the Center for Population Research at NICHD. The hormonal treatments also produced side effects such as increased acne and slight weight gain, says Wang. To get around the side effects and the need for weekly shots, other researchers are working on developing longer acting male sex hormones or novel delivery systems that will reduce the frequency of injections to once or twice yearly. For the same reason, still other researchers are working on long-lasting contraceptive vaccines (see story on p. 1484).

The desire for a more convenient method has also prompted efforts to develop postcoital contraceptives as an alternative to the daily hormonal pill for women. Much of the attention here has focused on anti-progestins, such as the controversial drug mifepristone, or RU 486, used in recent years as an abortion pill. Recently researchers at WHO have also been looking at combinations of anti-progestins and prostaglandins to gauge their usefulness as a once-a-month menses inducer, which would induce menstruation even if an egg implanted in the uterus. In a study expected to be published early next year in *Human Reproduction*, WHO researchers in six countries showed that a combination of RU 486 followed 2 days later by prostaglandin induced menstruation in 98% of women who were up to 10 days late in getting their periods, according to WHO's Helena von Hertzen. But even if such a strategy appears successful, "all people may not accept that approach," because many will view it as another chemical abortion pill, says von Hertzen.

"Not one of these methods will be used by people before the year 2010."

—Carl Djerassi



STANFORD UNIVERSITY NEWS SERVICE

While objections to abortion may slow efforts to market anti-progestins, they aren't likely to stop several new basic research efforts that attempt to halt fertilization by blocking the molecules responsible for sperm

and egg cells recognizing and binding to one another. Much of this research involves proteins associated with the "shell" surrounding the egg—the glycoprotein coat known as the zona pellucida.

In 1980, Jeffrey Bleil and Paul Wassarman, both then at Harvard Medical School in Boston, identified one such molecule, a glycoprotein in the zona pellucida called ZP3 that exhibited binding action with sperm. They later demonstrated that even minute quantities of purified ZP3 bind to sperm cells, blocking subsequent fertilization by keeping the sperm from attaching to the zona. Wassarman and Harvey Florman also discovered that a sugar group known as an O-linked oligosaccharide, which branches off the ZP3 protein chain, serves as the actual binding site.

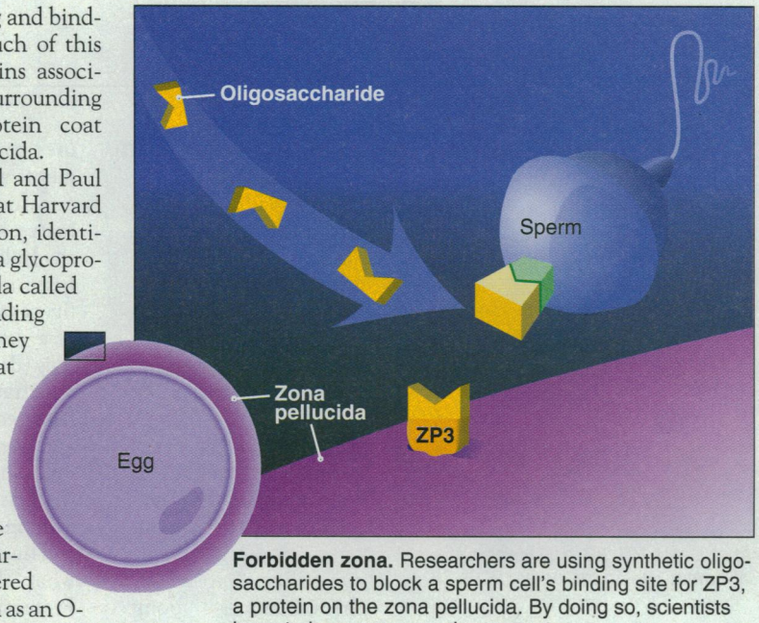


ILLUSTRATION: K.SUTLIFF

Forbidden zona. Researchers are using synthetic oligosaccharides to block a sperm cell's binding site for ZP3, a protein on the zona pellucida. By doing so, scientists hope to keep sperm and egg apart.

Over the last 3 years, a group of Finnish researchers has begun synthesizing synthetic oligosaccharides that mimic this receptor portion of ZP3. And in a paper recently submitted to the journal *Biochemistry*, Wassarman, now at the Roche Institute of Molecular Biology in Nutley, New Jersey, and his colleague Eveline Litscher report that in an in vitro study with gametes from mice, two types of these oligosaccharides—among 13 such molecules that were tested—also bound to the sperm cells and prevented fertilization.

Mimicking the zona pellucida sperm cell receptors to interrupt fertilization is a strategy with "definite potential," says Bleil, now at the Scripps Research Institute in La Jolla, California, because if a duplicate of the ZP3's sugar receptor can be engineered, it should be able to block fertilization—even in minute concentrations, as ZP3 itself does.

But Wassarman acknowledges that he's not there yet. Even the best oligosaccharides his lab is using now have an affinity for sperm cells that is 50 times lower than that of ZP3. Not only that, he says, oligosaccharides are present in everything from nerve cells to immune cells, raising the possibility that injecting synthetic versions to prevent fertilization could have wide-ranging side effects. "One has to show there are specific oligosaccharides that will interfere with conception. But we have not been able to do that yet," he says.

Preventing sperm from locking onto ZP3 is not, however, the only way to knock fertilization off the rails. It's possible to interfere even after this point, during an event known as the "acrosome" reaction. The acrosomal membrane houses a series of enzymes in the head of the sperm cell. When this membrane fuses with the outer membrane of the sperm—which most researchers believe happens as a result of sperm binding to the zona—that releases the enzymes near the egg. Those enzymes then chew a small hole in the zona pellucida, allowing the sperm to wiggle through and fuse with the egg.

Recently, researchers have begun investigating ways to stop this fusion of the two sperm membranes after the sperm have bound to ZP3 but before the zona-digesting enzymes have been released—thereby stopping the sperm from hitting its final target.

To achieve that goal, they're zeroing in on changes that take place in the outer sperm membrane before the enzymes are released. One such change allows calcium ions to flow into the sperm. And this calcium in turn helps trigger the acrosome reaction. "But the mechanism by which this happens is not well understood," says Florman, now at the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts. But Florman has found that drugs that block calcium channels prevent fertilization between mouse sperm and egg cells in vitro. He is currently working to identify the genes that code for sperm calcium channel proteins. He then hopes to determine the amino acid sequence of these proteins, eventually tailoring drugs to block their actions.

The final stage in fertilization, when the sperm has penetrated the zona pellucida and is preparing to fuse its outer membrane with that of the egg, is also attracting the attention of interventionists. In 1987, Paul Primakoff of the University of Connecticut (UC) and his colleagues discovered a sperm membrane protein—originally called PH 30, later dubbed fertilin—that is at least partly responsible for fusion. And earlier this year, Primakoff, along with UC's Diana Myles and other colleagues, published a report in the *Proceedings of the National Academy of Sciences* focusing on small peptides that mimic a specific portion of fertilin. These peptides inhibited this final membrane pairing in guinea pigs and reduced sperm-egg fusion by 90%. But even if this strategy turns out to be a practical way to prevent human fertilization, Kopf cautions that it would be "a bit risky" to use such a strategy by itself as a contraceptive. "It's kind of waiting to the last moment to intervene," he says.

But in the end the best contraceptive strategy of all may be "a multipronged approach that stops several molecular reactions," says Florman. The possibility that such a strategy can be pulled off will likely grow as researchers continue to probe these and other strategies aimed at blocking fertilization, as well as other efforts aimed at preventing other critical molecular reactions required for conception, including maturation of the sperm and the implantation of the egg in the uterus.

But as Djerassi emphasizes, any successful new drug targets for contraceptives face a long and tortuous road in the development process—if any companies can be found that are even willing to pursue such leads (see story on p. 1489). Drug company executives, such as Bennett Shapiro, who heads basic research efforts at Merck Research Laboratories in Rahway, New Jersey, say they will eagerly follow up such new strategies as long as they have excellent targets for breakthrough drugs. Djerassi, however, calls such pledges "utter rubbish." He notes that while sperm-suppression research such as the WHO work has been going on for years, no drug company has taken it up. The reason, he argues, is that the companies fear lawsuits from men who might blame the hormones for causing problems such as impotence. While that may be, Shapiro says "I don't think there are any insurmountable barriers to working in contraception," and companies will take risks if the approach seems fresh enough. Researchers like Kopf also express greater optimism that drug companies would pursue solid leads that arise. "I don't think [the search for new drug targets] is a moot issue," he says, "because the new strategies have the potential to create specific contraceptive drugs without [widespread] side effects" such as with hormonal contraceptives. And if researchers continue to produce such targets, the willingness of Shapiro and other drug company officials to pursue them will eventually be put to the test.

–Robert F. Service