Male contraception: One door opens, another closes

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We have often heard that a new male contraceptive is "five to ten years" away. But are we getting any closer? The answer may finally be "yes." This week marked the announcement of one hot new lead and one dead end.

A door opens

Researchers in Italy and at the Population Council in New York have announced a breakthrough on a non-hormonal compound known as Adjudin (*Nature Medicine*, Oct. 29). By injecting the compound as an attachment to a modified hormone that seeks out the testes, researchers have found that a low dose is both safe and effective in rats. Without this targeting mechanism, only much higher doses are effective--but they are harmful to the body's organs.

Dr. Diana Blithe of the U.S. National Institutes of Health, a long-time funder of the Adjudin research, says that "This [new breakthrough] is what they were looking for and it looks like it's working."

The next step is to find a more appealing delivery system than shots; both a gel and a matchstick-sized implant have been discussed.

But will the contraceptive work as well in humans as in rats? Nothing is guaranteed. Elaine Lissner, director of the nonprofit Male Contraception Information Project, says the public gets frustrated because media

reports make it sound as if every advance means a new contraceptive lies right around the corner. "People really need to distinguish between research in animals--or even in a lab dish--and studies in men."

Adjudin study coauthor Dr. Yan Cheng agrees, and says dedication will be required. "Obviously we're quite excited--but we still have a lot of work to do and a lot of hurdles to overcome."

End of the road for miglustat

The latest promising contraceptive that didn't make the leap from mice to men is miglustat (trade name Zavesca) (*Human Reproduction*, Oct. 25). The drug is already FDA-approved and on the market in both Europe and the United States for treatment of a rare genetic disorder, Gaucher disease. So scientists were very excited when they realized that it was acting as a contraceptive in their male mice at a tenth of the disease-treatment dose. With safety testing already out of the way, they thought this male "Pill" could potentially be brought to market very quickly.

Because of the growing public interest in male contraceptives, researcher Dr. John Amory at the University of Washington, Seattle was able to obtain funding to test the drug's effect in seven healthy men. The result? Nothing--no effect on fertility, even at a dose high enough to cause diarrhea, stomach upset, and other unpleasant side effects.

"We knew it was going to be either a strike out or a home run," says Amory. "It was a big disappointment."

Unbeknownst to Amory, pharmaceutical giant Schering was simultaneously testing miglustat in rabbits and another strain of mice, and found the same results--contraception in the first strain of mice, but no effect in the other strain or other species.

The original studies used C57 Black/6 mice, the most common strain of laboratory mouse. Dr. Aarnoud van der Spoel, research associate in the department of pharmacology at the University of Oxford and an author of those early studies, confirms that the mouse strain is somehow different. He has now tested multiple strains of mice and found some effect, but not enough to produce infertility.

"Biology is full of surprises. Clearly in the case of miglustat, a man is not a mouse," he adds.

Next?

So with Adjudin showing positive results--but in rats--and miglustat no longer an option, will men see a new contraceptive in the near future?

"The trick is to make sure we follow up on the leads we have," says Lissner. "There's a tendency to support glamorous new research in the lab, but abandon it when it gets to the expensive part: actually testing it in men and getting it to market."

This problem of moving leads from the lab to human studies affects all types of contraceptive research. Michael Free, vice president and senior advisor for technologies at Seattle-based nonprofit PATH, points to the female condom as an example.

"We got funding to design a great female condom that men and women like much better than what's out there," he says. "But now we're ready to do the big clinical trials, and our funders just don't have the money."

But change may be in the air. Lissner cites the recently opened Intra Vas Device trial as proof. The long-term male contraceptive is being developed by a startup company, supported by a small U.S. National Institutes of Health grant. Due to popular demand, the trial has been

expanded to four U.S. cities and can accept 90 participants. Similar approaches have been shown to work in men in studies in China and India.

Stresses Lissner, "Only public pressure can get researchers the funding they need to see which of these leads is going to work out."

Studies Cited:

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