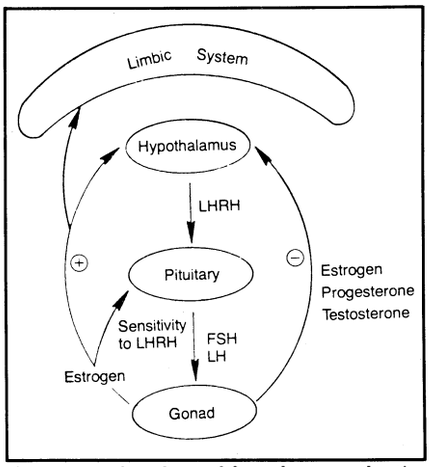
Unisex Birth Control Chemical

A hormone implicated in both male and female reproduction is a major — although slow to develop — prospect for contraception

BY JULIE ANN MILLER

The new generation of contraceptives so optimistically promised in the early 1970s has been frustratingly slow to mature. The optimism was based on what proved to be Nobel-Prize-winning work done separately by Andrew Schally and Roger Guillemin. In 1971, Schally (and soon after Guillemin) isolated, analyzed and synthesized luteinizing hormone-releasing hormone (LHRH), the brain peptide that controls numerous aspects of male and female reproduction, sexual development and sexual behavior. Schally immediately pointed to an array of potential uses for the synthetic hormone and related compounds, including prevention of pregnancy (SN: 2/10/73, p. 93). Chemicals, called analogs, were modeled after the hormone in the hope of discovering compounds that would be long-lasting and have very specific actions. Now, after synthesis of more than 1,000 compounds and with clinical trials of one of the compounds just underway (see box), the new generation of contraceptives appears to have reached adolescence.



A variety of male and female reproductive processes depend on the hormone LHRH.

Scientists anticipate that the compounds in question, peptide hormones, will be safer than the currently used birth control pills. Peptides have less of a general impact on the body than do steroids and would not be expected to have any effect on nonreproductive organs, such as the liver. Alan Corbin of Wyeth Laboratories, speaking at the recent meeting in Houston of the American Chemical Society, said, "We are very comfortable with these compounds in terms of safety."

Chemically synthesized LHRH already has been used clinically in a variety of special cases. One use, described by David Rabin of Vanderbilt University School of Medicine, is to diagnose and treat a syndrome in which secondary sexual characteristics fail to develop. In several cases, administration of LHRH has allowed infertile women to conceive and infertile men to produce sufficient sperm to father children, said Schally of Tulane University School of Medicine at the recent ACS meeting. LHRH has an advantage over current fertility drugs in that it doesn't induce multiple births, but it is fairly impractical, in that it is administered as a daily injection.

Because the compounds have had only limited use at this point and because there have been no clear and widespread clinical successes, strategy arguments flourish. Some researchers feel that agonists, chemical analogs that mimic the natural hormone but are more powerful, are the best candidates for contraceptives. Others argue that antagonists, compounds that block the natural action of the hormone, are the most likely antifertility agents. "Different groups sway one way or the other without overwhelming evidence," Gabriel Bialy, chief of the contraceptive development branch at the National Institute of Child Health and Human Development, told SCIENCE NEWS. For now, he holds to the middle ground with regard to the agonist-antagonist dispute, saying, "Conceptually, I think both of them will work."

The long wait for clinical triumph has made some researchers surprisingly insistent on claiming credit they regard due. Schally, who has done his clinical work in

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Clinical Trials Underway, At Last

Men and women, in separate clinical trials, are testing use of a "superagonist," a powerful variant of the brain hormone called LHRH. Sixty-four men are being recruited from a group who have requested vasectomies. In the first phase of the test, some will receive the superagonist by injection daily for 84 days; others will receive the same treatment together with testosterone and still others will receive placebo injections. David Rabin of Vanderbilt University School of Medicine and collaborators plan to measure sperm production and hormone levels and perform a variety of clinical chemistry tests. In the second phase of the test, Rabin plans to administer the superagonist intermittently — ten days on treatment, ten days off — for eighty days.

The women participating in the other clinical trial are volunteers who have been fitted with IUD's or who have had tubal ligations or whose husbands have had vasectomies. Samuel Yen of the University of California San Diego School of Medicine will administer two injections of the superagonist on consecutive days at specified times in the menstrual cycle. Such treatment is expected to induce premature menstruation, which would prevent pregnancies.

Yen plans to compare the effectiveness of giving the peptide subcutaneously, intranasally, intravaginally or under the tongue. Hormone levels in the blood will be monitored and the superagonist will be followed by a radioimmunoassay to determine how long it remains in the body.

Clinical trials of two other agonists are also being planned, says Gabriel Bialy of the Contraceptive Development Branch of the National Institute of Child Health and Human Development. "Within the next few weeks we hope to initiate a much larger study in Canada to look at ovulation suppression," Bialy says. Fernand Labrie of Laval University Hospital in Quebec will administer a peptide synthesized by Hoechst-Roussel Pharmaceuticals, Inc.

Discussion is underway also with researchers at another drug company to test a peptide that they have developed, Bialy says. That agonist differs from the two others chosen for NICHHD clinical tests in that it does not have an ethylamide as the final amino acid. Bialy says there is a possibility it could be safer than the other two.

These first "expensive" clinical studies are intended to make sure that the superagonists are safe and act as the scientists expect, says Bialy. If those expectations are fulfilled, much larger studies — perhaps in three years — will be undertaken to evaluate the drug's effectiveness as a contraceptive. In addition, Bialy expects that in the next year peptides that inhibit LHRH, instead of mimicking it, will be ready also for clinical testing.

. . . LHRH

Central and South America, was not at a recent meeting announcing NICHHD contracts with other researchers for the new U.S. clinical trials. After reading accounts of that meeting he wrote letters objecting that his laboratory's work had been slighted. He charged that other researchers "... almost rewrote the history of the discovery of LHRH, its clinical use, and the development and clinical use of LHRH agonists and antagonists from their own very selfish viewpoint. The facts were badly distorted and the impression created was that they alone were responsible for both the chemistry and clinical use of these compounds despite the fact that several other major groups, especially ours, were pioneers in the area."

Yet this somewhat quarrelsome field appears finally to be on the verge of making major advances in both pro-fertility and anti-fertility medication.

The peptide LHRH is a chain of 10 amino acids. "That's about as small as peptides go," says Wylie Vale, a chemist from the Salk Institute in San Diego. At the recent NICHHD conference Vale explained that analogs are made by subtle modifications of the native LHRH structure, for example changing one or a few of the 10 amino acids. Among the analogs, the first three amino acids seem to play a role in the molecule's activity, its signal to a pituitary or gonadal cell. The amino acids in the fifth and sixth position seem to influence the peptide's ability to bind to the LHRH receptor, Vale says.

Although logically the antagonist analogs seem more fertile ground for contraceptive drugs, it is an agonist that has been chosen for the first U.S. clinical trials. That peptide, in which the sixth and the final amino acids have been replaced, binds to LHRH receptors 140 times more strongly than does LHRH and stays in the body longer.

At first scientists had predicted that the peptide, which they call a "superagonist," would be powerful in treating infertility. Surprisingly, however, in early experiments the superagonist prevented ovulation and terminated pregnancies in rats. Likewise in male animals it had antireproductive effects. It decreased testosterone production and reduced the size of the testes, seminal vesicles and ventral prostate. It also markedly decreased production of sperm.

One hope has been that analogs of LHRH might distinguish between the role of the natural hormone in sperm production and its role in maintaining secondary sex characteristics and sex drive. For contraception the scientists want to be able to block the former but not the latter. Results with the superagonist have bolstered that plan. After an animal receives the superagonist, its testosterone production recovers well before sperm production begins, Vale finds. Similarly, injections of testosterone during treatment with superagonists can maintain the sex characteristics and libido without restoring sperm production.

In a preliminary test, ovulation in women was inhibited by a daily injection of superagonist, says Robert Casper who works with Samuel Yen at the University of California San Diego School of Medicine. In a separate study in Sweden (SN: 8/25/79, p. 133) a different superagonist was administered intranasally. It inhibited ovulation, but there was occasional "breakthrough" ovulation and some unpredictable vaginal bleeding.

These "paradoxical" effects of agonists have shifted much of the interest from fertility to antifertility uses. Corbin says that he expects the compounds to be of little use in helping infertile couples to conceive. Schally, however, says the agonists show promise for fertility aid, and he is more skeptical of their potential use as contraceptives. He says that the paradoxical effects are all a matter of dosage; the agonists have simply been oversupplied.

"The peptide will not induce paradoxical effects if the smallest active dose is used," Schally claims. He cites cases in which agonists restored normal cycles to nonmenstruating women and sufficiently increased sperm production in infertile men to allow them to impregnate their wives.

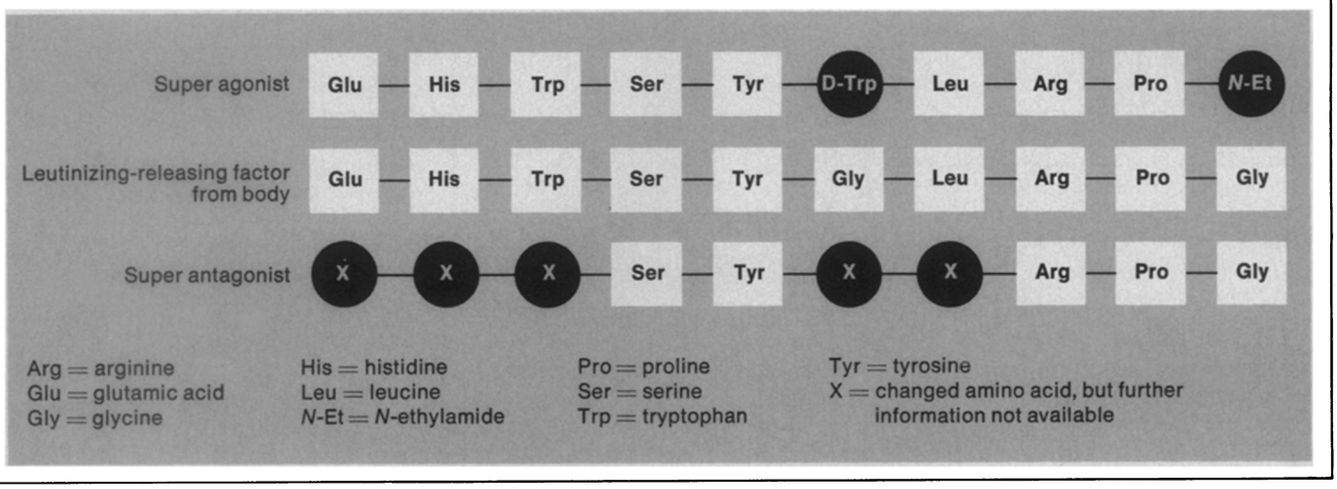
Antagonists, the peptides that block rather than mimic LHRH action, are a better approach to contraception, Schally believes. The problem with using them has been that they have not bound tightly enough to LHRH receptors to be an effective block at reasonable doses.

Within the last six months, however, antagonists have been developed that bind better. Vale says his laboratory has synthesized an antagonist that is 25 times as powerful as LHRH. Because in the modeling of new compounds a progression of changes is made from the original LHRH, Vale attributes his group's successful synthesis to "numerous laboratories that have collaborated inadvertently, mainly through the literature."

In animal experiments the new "superantagonist" inhibits ovulation and blocks sperm production. It dramatically reduces testicular weight — even more so, and more consistently, than do the superagonists. "We are encouraged that antagonists will be applicable to contraception in man," Vale says.

Some other antagonists have been tested with promising results on a small number of persons in Mexico City, Schally says. He concludes: "The synthetic approach based on inhibitory analogs of LHRH has been proven to be feasible for development of a new class of drugs which may be useful in birth control." Results of ongoing and projected experiments may soon tell whether or not the new generation of contraceptives can grow to a useful maturity. □

Analogs of peptide hormone may act as contraceptives



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Changes in first three amino acids interfere with LHRH *(center) activity; changes in position 5 and 6 increase binding strength.*