creased risk of birth defects. But the uniform use of LSD by patients in the study, they argue, combined with observations of teratogenicity of LSD in animals, supports the suspicion that ingestion of illicit LSD is hazardous to human reproduction. And at the very least, they conclude, it is clear that multiple drug use and the counterculture environment present a very severe hazard to birth.

The increased incidence of infectious disease in the women enrolled in the George Washington University study is apparently typical among drug abusers. Other new evidence suggests that this increased susceptibility to disease may result, at least in part, from LSD use. Edward W. Voss, Jr., and his associates at the University of Illinois, Urbana, last month reported that LSD inhibits the production of antibodies by cultured rabbit lymphoid cells.

Voss removed the spleen and lymph nodes from rabbits that had been hyperimmunized to various antigens, and then cultured cells from these organs. He was able to show by appropriate methods that the cultured cells continued to produce antibodies under normal conditions. When the cells are incubated in the presence of small quantities (less than 10 micrograms per milliliter) of LSD or lysergic acid, however, the production of immunoglobulins is almost totally inhibited. The cells remain viable and protein synthesis, which was measured by incorporation of tritiated leucine, continues. But the proteins secreted by the cells show no measurable antibody activity, and are of much lower molecular weight than the expected immunoglobulin (whose molecular weight is about 150,000).

Examination of the secreted proteins shows that the ratio of incorporation of tritiated leucine to incorporation of ^{14}C-labeled tryptophan is much higher than in control cells. Voss thus suggests that the indole alkaloid LSD and its analogs can substitute for the indole amino acid tryptophan in protein synthesis in much the same fashion that the antimicrobial agent puromycin substitutes for tyrosine in many microorganisms. Because LSD does not have the carboxylic acid moiety necessary for formation of a peptide bond, its incorporation leads to premature termination of the growing peptide chain, and thus prevents formation of the whole immunoglobulins. Support for this thesis is provided by the observation that addition to the reaction medium of a large excess of tryptophan—and only of tryptophan—reverses the effect of LSD.

Voss's results are preliminary, however, and their full significance is not yet clear. The only supportive evidence that such an effect might occur in vivo, he says, are limited observations that animals under the influence of LSD show a reduced responsiveness to antigens. Nonetheless, his findings suggest that biochemical damage might be manifested in symptoms other than chromosome damage, or that such damage might occur by a more devious route than was previously suspected.

—THOMAS H. MAUGH II

Additional Reading

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Birth Control: Current Technology, Future Prospects

The news about birth control is that there is no news—at least, no news of the imminent availability of methods that differ radically from existing techniques for controlling human fertility. New variations on old themes, however, may offer better efficacy, more convenience, greater freedom from hazardous or uncomfortable side effects, or all of these. Advances in basic research on reproductive physiology also suggest that new techniques may be developed in the future—but a minimum of 10 to 15 years could be required before they are available for routine use.

The "pill," introduced in the early 1960's, did revolutionize birth control technology. Because the oral contraceptives produce virtually 100 percent inhibition of female fertility, their superior efficacy has not been questioned. Nevertheless, reports of side effects that range from the merely uncomfortable —nausea, excess water rentention—to the potentially dangerous—a higher incidence of abnormal blood clots in users —have sparked efforts to formulate oral contraceptives without these disadvantages. One such effort is the "mini-pill," now being marketed by Ortho Pharmaceutical Corporation, Raritan, New Jersey, and by Syntex Corporation, Palo Alto, California.

Oral contraceptives depend on synthetic steroids for their effectiveness. (Synthetic steroids must be used because they are not destroyed by the body's enzymes before they reach their target organs.) The older "pills," which contain both an estrogen and a progestogen, act primarily by inhibiting the monthly release of the egg from the ovary. The "mini-pill," on the other hand, contains only a progestogen in a daily dosage roughly one-third or less that of the other "pills"; the low concentration of progestogen apparently prevents the sperm from reaching the oviducts, where fertilization occurs, by maintaining the mucus at the opening to the uterus in a condition that hinders sperm migration.

Although most of the side effects of the "pill" are associated with the estrogenic component, the Food and Drug Administration (FDA) has warned that not enough data are available at present to determine whether the risks of bloodclotting are indeed lower with the "mini-pill." The FDA points out that a small percentage of the progestogen in the "mini-pill" is actually converted to an estrogen in the body. Moreover, the risk of pregnancy—almost 3 percent—is higher for "mini-pill" users. (A failure rate of 3 percent means that if 100 women use a contraceptive technique for 1 year, 3 of them will become pregnant.)

Other research on steroidal control of female fertility is directed at the design of more convenient methods of drug administration, especially those applicable in areas or countries where conventional medical care is not readily available. Some of these delivery methods use a plastic material impregnated with the contraceptive steroid, usually a progestogen. The plastic can be implanted under the skin or it can be fashioned into a ring that is inserted into the vagina. Depending on the amount of hormone released per day, steroids thus administered act either as ovulation inhibitors or by the same mechanism as the "mini-pills." The vaginal rings are worn

for approximately 1 month and are then removed so that menstruation can occur. Subcutaneous implants, which are easy to remove if pregnancy is desired, can provide protection for a year or longer. The Upjohn Company, Kalamazoo, Michigan, has also been testing a long-active injectable progestogen called Depo-Provera in Europe; a single intramuscular injection can provide contraceptive action for 3 months. The steroid has not been approved for use as a contraceptive in this country because it produced breast cancer in dogs.

The intrauterine device or IUD was another major contributor to the birth control revolution of the 1960's. The original devices suffered from several liabilities—including a high failure rate of approximately 20 percent—and side effects such as cramping, and excessive or irregular bleeding. They were not well tolerated by women who had never had a baby. Recent modifications have conquered or at least minimized these problems. Intrauterine devices with chemical adjuncts have proved particularly effective. One such device consists of a plastic "T" with a copper wire wound about it. The copper, leached from the wire by uterine secretions, probably acts by preventing implantation of the fertilized egg.

An IUD with Progesterone

The IUD may also be used to deliver natural—not synthetic—progesterone directly to the target organ, the uterus. Alza Corporation, Palo Alto, California, has been testing such a device in more than 2000 women for 2 years with only one recorded pregnancy. According to Bruce Pharriss of Alza, the polymeric film that coats the T-shaped IUD can be formulated to allow the escape of a known quantity—usually the minute dose of 100 micrograms—of progesterone per day. Pharriss states that the uterine lining rapidly destroys natural progesterone so that essentially none of the steroid should migrate to other areas of the body. This should eliminate the side effects associated with other routes of administration. The mechanism of action of the device is unknown, but Pharriss thinks that it either prevents fertilization by preventing sperm capacitation (a maturation process required before the sperm are capable of fertilization) in the female reproductive tract or that it alters the uterine lining so that implantation cannot occur. The device that Alza is testing in this country is designed to protect against pregnancy for 1 year, but protection for 2 or 3 years is a feasible goal.

The "morning-after pill" has engendered widespread interest, especially since the revelation that the controversial synthetic estrogen, diethyl stilbestrol (DES), has been used rather routinely for this purpose. Although DES has been linked to the occurrence of a rare type of vaginal cancer in the daughters of women who took the drug during pregnancy to prevent miscarriages, the FDA recently approved the use of DES as a postcoital contraceptive in "emergencies"—after rape and incest—but has not approved it for routine use.

The development of a reliable, safe "morning-after pill" would be a major breakthrough in birth control technology. It would eliminate the need for long-term exposure to steroids and other potent drugs, particularly for women who have intercourse infrequently. The Contraceptive Development Branch of the National Institute of Child Health and Human Development (NICHD), Bethesda, Maryland, issued a Request for Proposals (RFP) for the study of estrogenic "morning-after pills." The RFP specifically excluded DES from consideration. The response to the RFP was low and it does not appear that enough women for satisfactory drug evaluation will be included in the funded proposals.

Estrogens are effective as postcoital contraceptives presumably because they speed the passage of the egg through the oviduct so that it arrives in the uterus before the lining is prepared for implantation of a fertilized egg. Several investigators pointed out that the relatively large doses of estrogens required to produce this effect may also produce nausea and other unpleasant symptoms and may thus make them unsuitable for routine use.

Progesterone, secreted by a structure called the corpus luteum, is required to prepare the uterus for implantation and also to maintain pregnancy during the first few months. (After the ovarian follicle releases the egg, the follicle is converted to the corpus luteum.) Therefore, luteolytic agents—materials that destroy the corpus luteum—will prevent or terminate pregnancy. Several unrelated chemicals including oxymetholone (a steroid), aminoglutathimide, and prostaglandins are being examined for their luteolytic capacities.

Prostaglandins have frequently been characterized as "miracle drugs"—and perhaps they are—but at present they are something less than miraculous as contraceptives. Several investigators have indicated varying degrees of disillusionment; Alza Corporation, for example, is scaling down, although not eliminating, its research program on the contraceptive action of prostaglandins. Nevertheless, Pharriss has found that some prostaglandins have luteolytic activity in subhuman species. Thus they have a potential use as postcoital contraceptives if similar activity occurs in the human.

According to Earl S. Gerard of the Upjohn Company, a luteolytic agent could be employed either to induce menstruation on schedule, whether or not conception had occurred, or to induce a delayed menstrual period. Prostaglandins do induce bleeding but the dose required also produces considerable discomfort, including nausea, vomiting, diarrhea, and cramps. Moreover, the bleeding may be the result of uterine contractions rather than luteolysis. Prostaglandins stimulate the contractions of the smooth muscle of the gastrointestinal tract (and thus produce the side effects) and of the uterus. For this reason they can be used to induce labor at term and as abortifacients.

Prostaglandins and Abortion

Prostaglandins are being used in Europe to induce abortions. Pharriss thinks that prostaglandins, probably $PGF_{2\alpha}$ and PGE_2, may eventually replace saline infusion as the method of choice for induction of abortion during the second trimester of pregnancy. In order to induce abortion, the prostaglandin may either be administered intravenously or it may be injected through the vagina into the uterus between the fetal membrane and the uterine lining. The second method produces fewer unpleasant side effects.

Most of the natural prostaglandins display a wide spectrum of systemic effects. The synthesis of prostaglandin analogs that possess only specific effects is the goal of investigators in several laboratories. Josef Fried of the University of Chicago has synthesized two such compounds; they have luteolytic activity, at least in animals, but only negligible activity in stimulating the smooth muscles of the intestinal tract. They are also resistant to the enzymes that normally deactivate natural prostaglandins. Although these results are encouraging, the effectiveness of the analogs in the human remains to be demonstrated.

Sterilization is, of course, a very ef-

fective means of preventing conception. Current sterilization procedures suffer from two major disadvantages: They are essentially irreversible, and they require surgery—relatively minor in the male and somewhat more serious in the female. Investigators at the Illinois Institute of Technology Research Institute (IITRI), Chicago, are developing improved techniques for the sterilization of both men and women. Erich Brueschke and his colleague, Marvin Burns, are using dogs to test a valve that would allow reversible sterilization. The valve is inserted into the sperm duct; when closed the valve would block sperm passage, but it could be opened later if desired.

Procedures for female sterilization that do not require abdominal surgery and that can be performed with local anesthesia and without hospitalization are also in the offing. Both Brueschke and Ralph Richart and Robert Neuwirth at the International Institute of Human Reproduction, Columbia University, New York, are developing instruments called hysteroscopes. These instruments, which are inserted through the vagina into the uterus, enable the physician to see the oviducts and to occlude them by an appropriate method. The investigators at Columbia have already used their hysteroscope to sterilize about 90 women, usually by electric cautery. The IITRI group is investigating both chemical and mechanical (use of plastic plugs) methods of occluding the tubes. They are testing the device and the sterilization techniques on baboons but are not yet ready to use them in the human.

The discovery of hormones secreted by the brain that regulate reproductive processes has opened a new and highly promising approach to the control of human fertility. This avenue of investigation is being explored in the laboratories of Roger Guillemin at the Salk Institute, La Jolla, California, and of Andrew Schally at the Veterans Administration Hospital, New Orleans, Louisiana. The hormone of interest—luteinizing hormone releasing hormone (LH-RH)—is secreted by a part of the brain called the hypothalamus and stimulates the release of luteinizing hormone by the pituitary gland. Luteinizing hormone in turn is the trigger for ovulation.

The releasing hormone is a relatively simple molecule—a peptide consisting of ten amino acids. Consequently, not only has the synthesis of LH-RH been accomplished, but also the synthesis of closely related chemical analogs. Both Schally and Guillemin would like to synthesize analogs that block the activity of the natural hormone on the pituitary gland and thus prevent ovulation. Although Guillemin has reported synthesis of analogs with limited inhibitory powers, none have yet been found that are suitable for clinical trials as birth control agents. Both investigators are optimistic that such compounds will be synthesized in the future.

Use of LH-RH may also greatly increase the reliability of the rhythm method of birth control. Rhythm, the only method sanctioned by the hierarchy of the Catholic Church, frequently fails—about 25 percent of the time—partly because of inadequate knowledge of the time of ovulation. Administration of a suitable preparation of LH-RH may enable a woman to control precisely the time of her ovulation. According to Guillemin, an oral preparation is feasible, even though the peptide is susceptible to digestion in the gastrointestinal tract. The releasing factor is so extremely potent that if the oral dose is large enough, a quantity of LH-RH sufficient to cause ovulation should enter the blood stream. Finally, because it can induce ovulation, LH-RH may be employed in the treatment of some forms of infertility.

Immunological Birth Control

The application of the immune system to reduce fertility is not an immediate prospect, but several investigators think that this approach may be possible in the future. Antigens specific to sperm have been identified, isolated, and used to immunize both males and females against the sperm that carry the antigen. For example, Erwin Goldberg at Northwestern University, Chicago, Illinois, found that serum containing antibodies to the sperm-specific form of the enzyme lactate dehydrogenase (LDH-X) suppressed the pregnancies of up to 60 percent of mice injected with the antiserum after copulation. The amount of suppression declined as the time between copulation and administration of the antiserum increased. Goldberg detected no pathological changes in the animals that had received antiserum. Moreover, the effect was reversible; when a group of the treated mice were later mated, all delivered normal litters.

The results of preliminary experiments—and Goldberg stresses the word "preliminary"—have encouraged him to think that the immune system can serve as the foundation of one type of male contraception. When Goldberg injected mouse LDH-X into male rabbits, the fertility of the rabbits decreased in proportion to the concentration of LDH-X antibody in their blood. The effect was reversible, but a booster shot of the enzyme restored the infertility. Also encouraging was the observation that the rabbits did not suffer from diminished libido.

Oral contraceptives for males, although long predicted, remain elusive. Male fertility can be chemically depressed by preventing sperm formation entirely or by inhibiting sperm maturation. Several laboratories have programs to test various drugs for these activities in experimental animals, but few promising chemicals have been found as yet. Most investigators expressed the opinion that women would continue to bear the responsibility for contraception—as well as the consequences of its failure—for the foreseeable future. However, Alvin Paulsen and his colleagues at the University of Washington Medical School, Seattle, have been testing a potential male oral contraceptive in approximately 50 human volunteers. In early trials with Danazol, a synthetic analog of a male hormone, they did not observe consistent reductions in sperm counts; moreover, the concentrations of male sex hormones declined, as did libido in volunteers—a common problem when male hormone production is disrupted. In more recent experiments, Paulsen combined Danazol with a synthetic androgen and achieved more satisfactory results. Sperm counts were reduced without apparent side effects. Paulsen, citing FDA regulations for new drug development as his reason, did not care to estimate when full clinical trials of the drug would begin.

The declining birth rate in the United States has indicated the acceptance—at least for the present—of fertility control, as well as the methods available for achieving such control. Nevertheless no method is perfect for all situations. The goal of current research is to improve older technologies and to develop new ones so that the demands of diverse social, economic, cultural, and religious conditions can be met.

—JEAN L. MARX