

Substitute for the pill

New approaches in basic research are leading to better contraceptives

by Barbara J. Culliton

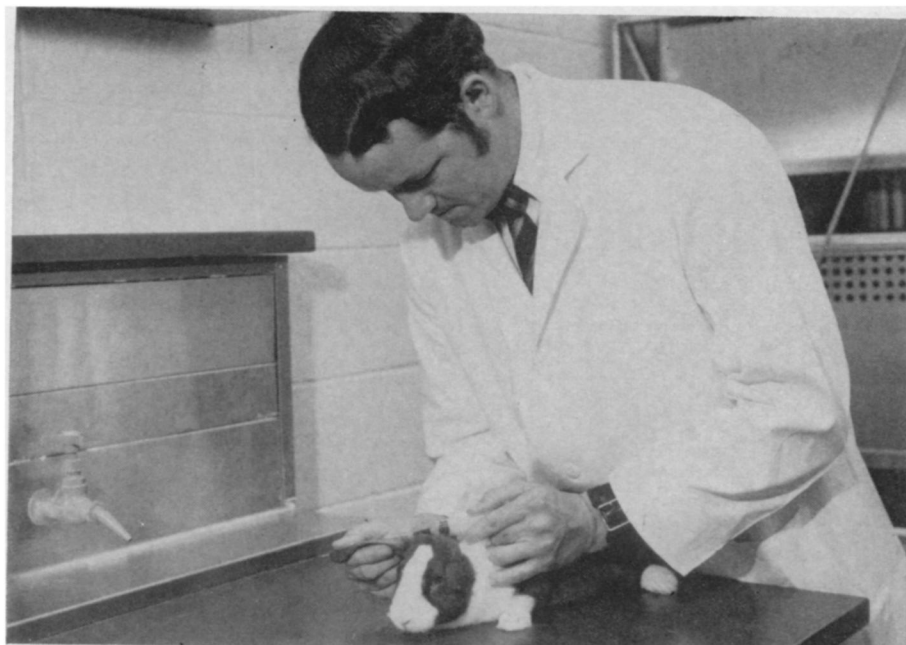
Birth control pills are not yet a decade old but already scientists eagerly await the day second, and even third, generation oral contraceptives emerge from the shelter of the laboratory.

"The pill that is available today is not an ideal contraceptive," says Dr. Philip Corfman, director of the Government's new Center for Population Research. "I think the nation's doctors are changing their attitude toward it."

According to the Food and Drug Administration, American women are also changing their attitude. Last year, only 500,000 women began the pill-taking regimen. In 1966 and 1967, FDA figures show, 750,000 women adopted the birth control pills for contraception. The peak of new users was in 1964 when 1.7 million women received initial prescriptions.

Dr. Louis M. Hellman, an obstetrician at Downstate Medical Center in Brooklyn and an adviser to the FDA, reports that official estimates are that 30 percent of new users drop the pill after the first year. He believes the percentage is even higher. Side effects such as nausea, weight gain and nervousness, he finds, account for some of the dropouts. Evidence that oral contraceptives have even more serious side effects—they have been linked to blood clotting, diabetes and cancer—explains why others stop taking them. The FDA has tied the pill to 223 fatalities since 1959 and 838 cases of serious complications since 1966.

Although a direct cause-and-effect relationship between hazards and birth control pills containing two potent hormones, estrogen and progestin, is still tenuous, mounting evidence is making most members of the scientific profes-



The Upjohn Company
Dr. Pharriss injects prostaglandin into the ear of an experimental rabbit.



Planned Parenthood

Dr. Spellacy: Diabetes a question.

sion cautious, if not fearful (SN: 5/3, p. 422).

"In every species of animal we have tested, including mice, rats and dogs, we find that estrogen induces cancer," declares Dr. Hellman. Whether or not large and continuous doses of the hormone will have the same effect in human beings is, at this point, impossible to tell. Even known carcinogenic agents may take 10 years to cause cancer. The human experiment with birth control pills is too young to yield information one way or the other.

Likewise, the connection between the pill and deaths from clotting is a murky area, although FDA chief Dr. Herbert L.



NIH

Dr. Corfman: Seeking new answers.

Ley concludes that the evidence is so strong that proof is simply a matter of time and more research. Again, the estrogen in the combination oral contraceptives is the suspicious agent in the double hormone drugs.

Dr. William Spellacy of the University of Miami School of Medicine says, after a study of 1,000 women, "We cannot definitely link estrogen to diabetes, but it appears to raise blood levels of sugar and insulin." As with cancer, if oral contraceptives induce diabetes, it would be a slow, steady process, requiring 10 years or more.

Instead of waiting to find out, scientists are working on the second- and

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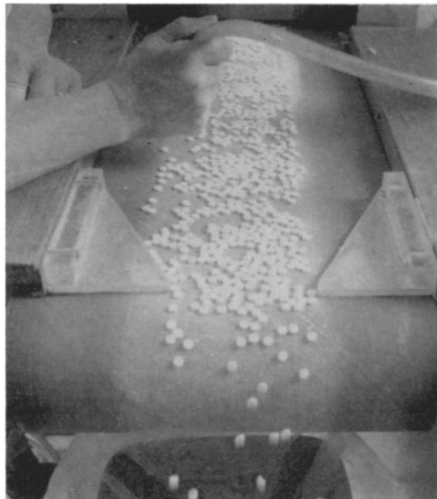
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third-generation drugs that may eliminate some of the hazards before too many fears are confirmed.

Closest to the marketplace are contraceptives containing low doses of a single hormone, progestin. Researchers, including Drs. Corfman and Spellacy, generally agree that a low-dose progestin will be safer than estrogen-progestin combination pills. But, Dr. Hellman cautions, "Even they may have side effects that we do not yet know anything about. After all, 10 years ago, we didn't suspect the combination pills to have the effects they do."

Among the newest progestin devices is a vaginal ring, developed by scientists at the Upjohn Company in Kalamazoo, Mich., and now in clinical testing in California and elsewhere. The ring is a rubber or Silastic doughnut-shaped device the size of a diaphragm. According to Dr. Bruce B. Pharriss of Upjohn, the Silastic ring is inserted by the woman herself at the end of her menstrual cycle. It is left in place for three weeks, after which it is removed and thrown away. Progestin within the ring slowly migrates through the Silastic and is absorbed by the body. "During the 21 days the ring is in place," Dr. Pharriss says, "it releases less than the amount of progestin a woman gets from orals in three days. One of its great advantages, in addition to low drug doses, is that a steady level of drug is maintained in the blood. You do not get a daily peak of drug concentration as you do with orals." Within three years the ring could be generally available, with FDA approval.

In tests with 39 women, Dr. Daniel Mishell of the University of California at Los Angeles School of Medicine reports no discomfort or apparent side effects. "Both women and their husbands seem to like the ring," he declares.

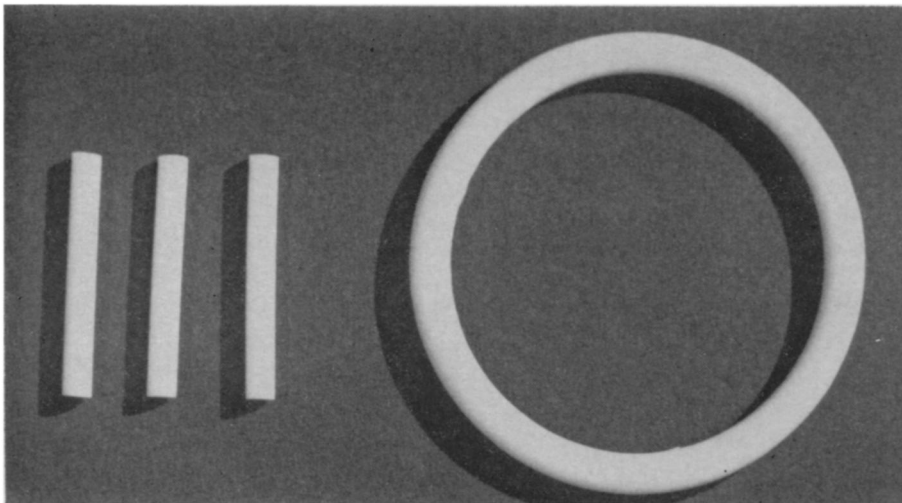
And preliminary studies indicate that, once a woman removes the ring, she menstruates within a day or two and resumes a normal cycle of ovulation and menstruation the next month if she does not insert a new one.

Progestin in Silastic also appears to be promising for long-term contraception, lasting up to three years. Instead of putting progestin in a throwaway ring, it is placed in a device, about half the diameter of a pencil, to be implanted under the skin. Because migration through the rubber is slow, the device's supply of progestin is expected to last three years or more. In tests with about a dozen women who have had an implant for four months, "it appears to be effective," Dr. Pharriss reports. The device secretes about five milligrams of drug per month.

Progestational pills, rings and implants will usher in the second generation of birth control agents only to be replaced by third-generation compounds. More subtle and sophisticated than their predecessors, these will block conception without using the potent family of steroid hormones at all. The Center for Population Research, part of the National Institutes of Health in Bethesda, Md., has outlined some of the approaches to the third generation and has, this year, at least \$1.5 million to get started.

The NIH center stands as the Government's first concerted effort to sponsor research in reproduction in an organized way. Until 1965, it would not even fund scattered individual research projects in the field; now its official interest is so great that population research was one of the few areas to get an increase (\$5 million) in the President's budget (SN: 4/26, p. 399).

So far, says CPR director Corfman, 250 research groups have submitted re-



The Upjohn Company

Silastic implants and the vaginal ring secrete low doses of progesterin.

quests for support and more than 70 have been approved. At present, four target areas are under attack:

- The ways in which sperm mature and the conditions vital to their ability to fertilize an egg.

- The structure and function of the oviduct (tube through which an egg ovum travels to the uterus) and means by which the egg is picked up from the ovary and transported.

- The function of the corpus luteum, a progesterone-producing tissue which forms after ovulation and which, in animals at least, is essential to pregnancy.

- The biology of an egg before it implants itself in the wall of the uterus after fertilization.

"Many scientists," Dr. Corfman observes, "believe that the corpus luteum is the most promising target." He believes that if researchers can prove it is as vital to maintaining pregnancy in women as it is in animals, "a way could be open to develop a contraceptive taken by a woman once a month at the time of her period." Agents called luteolysins which destroy the corpus luteum even if an egg has been fertilized are being studied.

One such chemical is prostaglandin, a substance found in a variety of human tissues in various forms. One, known as PGF₂ alpha (SN: 1/18, p. 64), apparently affects the corpus luteum because it constricts the flow of blood, and thus hormones, from the ovaries, cutting off the luteal food supply.

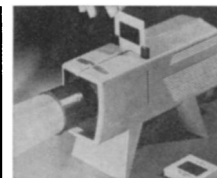
"We, as yet, have no idea how prostaglandin works in human beings or whether it has any side effects," says Dr. Pharriss, who is studying it at Upjohn, one of the world's major suppliers of the material for research. "One current handicap is that it does not work orally, but when we inject it into animals, it prevents pregnancy."

In all likelihood, prostaglandin itself will never become a drug for human use as a contraceptive but Dr. Pharriss explains, "scientifically it is unique and interesting." It may be one tool with which scientists can explore unknowns about corpus luteum function, leading to other effective agents which may be molecularly similar.

The search for third-generation contraceptives is predicated on the assumption that much more needs to be known about the basic mechanisms of fertility and reproduction. "In spite of the fact that millions of women (seven million in the U.S.) are using oral contraceptives which act by inhibiting ovulation," Dr. Corfman declares, "there is little known about the events which precede and accompany ovulation and about the exact role of hormones in this process." To this end he is seeking the support of scientists from fields other than biology to help find ways to observe and quantify the biology of reproduction. "To develop new methods of fertility control, we need biophysicists, bioengineers, systems analysts and mathematicians," he says.

For example, scientists using ultrasound beams have had some success in visualizing the movement of heart valves and the walls of major blood vessels. Similar techniques, Dr. Corfman proposes, could be used to visualize, from outside the body, the contractions of the oviducts and uterus. Fiber optics, which could deliver light to otherwise inaccessible areas, might also be used to get a visual image of what happens to egg and sperm in the female reproductive tract.

Such approaches ultimately will produce the third-generation contraceptives which, ideally at least, will be safe, effective, easy to use and inexpensive. But they are a decade away. ◇



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