Enovid: Contraceptive Pill Is Cleared by FDA, But Not All The Questions Have Been Answered

Last week's decision by the Food and Drug Administration to permit continued prescription sale of the oral contraceptive Enovid raises two questions: Is "the pill," in its present state, the undisguised blessing some have thought it to be? And what is the role of medical evidence in FDA's decisions about drugs?

"The pill" was developed in the 1950's for menstrual disorders and fertility promotion, and it has been marketed by the G. D. Searle Company as an oral contraceptive since the summer of 1960, first in 10-milligram doses, later in 5.

Although Enovid dominates the field at present, another company, Ortho Pharmaceutical, came on the market last February with a 10-mg pill called Ortho-Novum, and several other applications are pending both for new pills and modified versions of the present offerings. The pills vary a bit, but all are combinations of two synthetic female hormones, progesterone and estrogen. The pills in effect simulate the action of pregnancy: they act by suppressing ovulation and making conception impossible.

The response to the pill has been spectacular. It is impossible to say exactly how many women are using it, a fact of considerable importance in evaluating its safety, but estimates run as high as 2 million—which is remarkable not only because the drug has been available for so short a time, but because until December 1962 a month's supply cost $10, and because not all gynecologists regularly recommend them. (Prices have been reduced in the past few months: the 10-mg tablets now cost between $6 and $7, the smaller dosages about $3.50. Manufacturers are aiming for further reductions as their own costs diminish and as smaller dosages are approved for sale.) Approximately one out of four women experiences a variety of side effects and discontinues using the pill, but whatever the liabilities of physical discomfort or cost, the fact remains that somewhere between 1.3 and 2 million women have found the pill to be the most pleasant and satisfactory method of contraception yet developed. It is astonishingly effective: the number of reported failures where the drug has been used properly (a pill must be taken on each of 20 successive days of the menstrual cycle, preferably at the same time each day) can probably be counted on two hands.

In addition to the women at large who have "voted with their feet" by trekking to clinics and private physicians in search of prescriptions, the drug may acquire certain specialized clients that would add to its near-revolutionary impact. For one thing, there is a slim chance that the drug may constitute the first breach in the Catholic Church's disapproval of birth control since it sanctioned the rhythm method in 1853. John Rock, the Boston gynecologist whose interest in the drug grew out of his research into means of promoting fertility, in a recent book, *The Time Has Come: A Catholic Doctor's Proposals to End the Battle over Birth Control*, has taken on the theologians, arguing that the pill works by an essentially "natural" process that the Church could sanction. Boston's Cardinal Cushing and other churchmen disagree, and even non-Catholic physicians have described Rock's thesis as "medical fantasy," but Rock has not been silenced and will no doubt keep arguing the point. In the meantime, Catholic researchers are devoting themselves to perfecting the knowledge of human fertility on which effective use of the rhythm method must rest.

Clients of "The Pill"

Another large group of potential beneficiaries of oral contraceptives is the poor—not only in this country but in underdeveloped areas around the world. The early clinical trials of Enovid, sponsored by Searle in Puerto Rico and Haiti, made it clear that the drug could be taken effectively by poor, uneducated women in the areas most seriously blighted by the "population explosion." And a pilot project with welfare recipients in Mecklenburg County, North Carolina, who were given Enovid got results that would warm the heart of the most crusading family-planner—as well as the most budget-pruning welfare director. There were 264 women admitted to the Mecklenburg project, many of whom had had bad records with other attempts at contraception. As among many welfare recipients, the rate of previous pregnancy was very high, running from 1 to 19 apiece; the 264 women had a total of 1420 previous pregnancies among them. The project began in November 1960; 2 years later, 41 patients had left the study, for a variety of reasons, and not a single pregnancy had occurred among the 223 women who remained, leaving no doubt that the pill was both appreciated and understood by the impoverished and uneducated patients. The cost of the project is 1/25 the cost of public support of the unwanted children, and the Mecklenburg Welfare Department has reported intangible savings as well, in a tendency toward stabilization of family life and a growing confidence among the volunteers in their ability to manage their own destinies—characteristics that are traditionally absent from recipients of public welfare.

With all these rave notices behind it, it is not surprising that Enovid became big business very rapidly. *Business Week* called oral contraceptives "the hottest new product to come out of the drug industry's research labs in many years," and it is not hard to see why, if—as the article reports—Enovid has been responsible for boosting annual sales of medical contraceptives from, roughly, $20 million to $40 million. The stage was clearly set for a great American success story, with producer, consumer, and the doctors and druggists who serve as middlemen happily joining hands while the final curtain rang down on another triumph of the intellect over nature. But the small pill that was to be the hero of the drama did not prove quite equal to the task.

The pill has run into trouble in a variety of ways. That it produced certain undesirable side effects was always known. These ranged from the minor complaints frequently associated with pregnancy—weight gain, nausea, breast tenderness—to more disturbing and less explicable phenomena—loss or growth of body hair, sporadic bleeding, instances of jaundice. It was also discovered that attacks of migraine, asthma, epilepsy, and premenstrual tension might be aggravated by Enovid, and that diabetes might become more difficult to control.

While these visible reactions were not considered hazardous, the FDA required information about them to be included in Searle's literature to physicians concerning the drug, together with a warning that caution should be used in treating patients with histories of breast or cervical cancer and thromboembolic conditions. Since knowledge about the long-term effects of the therapy was limited, FDA originally rec-

ommended its use for only 2 years. But the warning seems to get lost in the shuffle of patients' enthusiasm and is probably not widely observed. Some researchers and gynecologists have wondered whether 11 years of clinical testing is adequate for a drug whose implications are for the full 25 years of a woman's child-bearing span. Questions have been raised about Enovid's possible long-term effect on the body's hormonal balance and on the pituitary gland as well as its relation to thrombophlebitis and certain female cancers.

These questions might have remained academic had it not been for the increase in public skepticism about new drugs that the furor over thalidomide seems to have engendered. As early as December 1961, Searle and the Food and Drug Administration were receiving reports of deaths from thrombophlebitis (blood clots), but these received little attention outside of professional circles until the thalidomide story broke, in the summer of 1962. Senator Humphrey, in his investigation of FDA's handling of thalidomide, raised certain questions about Enovid, and appeared satisfied by the answers. Public agitation continued to increase nonetheless, and in January 1963 the FDA took what was for it an unusual step—it appointed an expert committee, headed by Irving S. Wright of New York, to investigate the possible relationship between Enovid and thromboembolic conditions. At that time, 350 cases of blood clots, and 35 deaths, had been reported.

More Questions than Answers

The narrow task of the committee—to investigate one possible effect of Enovid—was narrowed still further by its discovery that data on the occurrence of thromboembolism were not available, and that it could neither exclude nor establish the possibility that Enovid increased the clotting tendency. Statistics on mortality from thromboembolic complications in users and nonusers of Enovid could, however, be assembled, and the committee focused its attention on the deaths. Only 12 or 14 of the 35 reported deaths could be conclusively attributed to thromboembolism, and after figures supplied by the company had been pared down to match the sample from the general population, 1 million was taken as the number of women using Enovid. With this base, the committee found that through age 34 there was no significant difference in the rates of death from thromboembolism for users and nonusers of Enovid, but that for women in the 35–39 age group the rate among Enovid users was 2.4 times that for nonusers, and that for women in the 40–44 group the rate was 3.8 times as high for users as for nonusers.

In the closing paragraph of its report, submitted to the Food and Drug Administration 2 weeks ago, the committee warned that "any firm reliance on the risks as calculated is tempered by the assumptions made." One of the assumptions that troubled it most was that concerning the number of users of Enovid.

Accurate distribution figures are impossible to obtain—the number of prescriptions refilled or lapsed cannot be determined, and company sales records are apparently not kept in a manner conducive to precision. But if only 10 percent fewer patients took Enovid than the committee calculated, it reported, the death rate from the drug would come very close to statistical significance for all ages; and if 50 percent fewer people took it, the rates would be very significantly greater. If 50 percent more people are presumed to have taken the drug, the danger declines for the 35–39 year group but remains significant in the 40–44 year range.

The committee's report, in sum, is by no means a clean bill for Enovid. The committee set out to answer the question of the possible relation between Enovid and thromboembolism, which was only one of the several questions that have been raised about the safety of Enovid. Its answer was that there were not enough data to give an answer. On the single question of deaths from blood clots, the committee's report can hardly be called reassuring.

This being the case, FDA's reaction to the report is more than a bit puzzling. In announcing the continued availability of Enovid for prescription sale, FDA took note of the "apparent hazard" for women over 35 but recommended that this be weighed against the demonstrated hazards of pregnancy—and not against the hazards of other methods of contraception. In addition, the FDA chose this occasion to extend its sanction of the drug—which is now recommended for a 2- to 4-year instead of a 2-year period—at the same time it announced that further studies need to be undertaken.

Although there is no hard evidence against the drug, there are clearly some uncertainties, and FDA's action is more positive than it might be. Part of the explanation is that science can tolerate more uncertainty than can bureaucracy, and that, unlike the committee report, which could say "maybe," the FDA had no noncommittal alternative. When the FDA said "yes," drug law, drug promotion, and Enovid's popularity being what they are, the decision opened the possibility that millions more women may be exposed to a drug whose effects are not yet unimpeachably established. Had it said "no" and insisted that Enovid be withdrawn from the market for a further period of experimentation, the FDA would not only have antagonized the present and future manufacturers (and reversed a past decision of its own physicians) but would have disappointed the growing number of women who have become converts to oral contraception as well. The FDA may have its private reasons for supporting Enovid, but its public reasons—in terms of the medical evidence alone—do not seem above dispute.—ELINOR LANGER

Announcements

Rice University has established a **satellite research laboratory** as a basis for the experimental program of the school's space science department. The laboratory includes facilities for design, construction, checkout, and testing of instruments and payloads; a telemetry and command station; and facilities for data reduction and analysis. Curtis D. Laughlin, former research physicist at the State University of Iowa, is chief of the laboratory.

A center for research on **enzymes** has been established at Tufts University, Boston, under a grant from the U.S. Public Health Service. The major purpose of the new center is to expand the production of enzymes for use in research at hospital and university laboratories. Enzymes commercially available will not be produced at the Tufts center. Stanley E. Charm, associate professor of biomedical engineering at the university, has been named technical director of the facility.