Depo-Provera Under Scrutiny

An FDA-appointed board hears evidence on the safety and effectiveness of a controversial injectable contraceptive

By ALLAN CHEN

"The Shot. Depo-Provera. Now that you've decided to use the Shot (the medical name is Depo-Provera), please read this pamphlet carefully. It will help you use the Shot safely and effectively."

So reads the cover of a pamphlet given to participants in a clinical trial of the injectable contraceptive at Grady Memorial Hospital in Atlanta that ran from 1967 to 1979. The trial revealed no significant health risks to women using Depo-Provera as a contraceptive. More than 15 years later, with these and other studies called into question, the Upjohn Co., Depo-Provera's manufacturer, is still trying to convince the Food and Drug Administration to approve the drug. Proponents say Depo-Provera is more effective and convenient than anything now available on the market, including "the pill"; opponents argue it causes cancer in animals and unacceptable side effects in humans. Depo-Provera is already in use as a contraceptive in more than 80 countries, and is manufactured for worldwide use by a Belgian subsidiary of Upjohn.

Depo-Provera, or DMPA (Depot-Medroxyprogesterone acetate), is chemically related to progesterone, a female sex hormone. Like the estrogen-progesterone combination in the pill, Depo-Provera suppresses the hormones that cause the release of the egg cell but lacks some of the estrogen-related side effects of the pill such as hypertension. Injected intramuscularly, tiny crystals of DMPA suspended in solution lodge in the muscle tissue, and the drug enters the bloodstream gradually as the crystals dissolve. A 150-milligram dose can prevent conception for at least three months.

First introduced in 1959, Depo-Provera was approved to treat amenorrhea (no menstrual flow), irregular uterine bleeding and threatened miscarriage. It was later approved to treat cancer of the endometrium (uterine lining). In 1974, FDA withdrew approval for anti-miscarriage treatment when the drug was found to have no real effect in preventing miscarriage and was further linked to increased incidence of birth defects such as malformation of limbs and heart defects. Testing of the drug's contraceptive effects began as long ago as 1963, but FDA twice denied approval for its use as a contraceptive, once in 1974 and again in 1978.

In January, at Upjohn's request, FDA convened a public board of inquiry composed of three independent medical experts to hear evidence of Depo-Provera's medical effects. The board will make a non-binding recommendation to Arthur Hull Hayes Jr., FDA Commissioner, who will decide whether or not to approve the drug as a contraceptive.

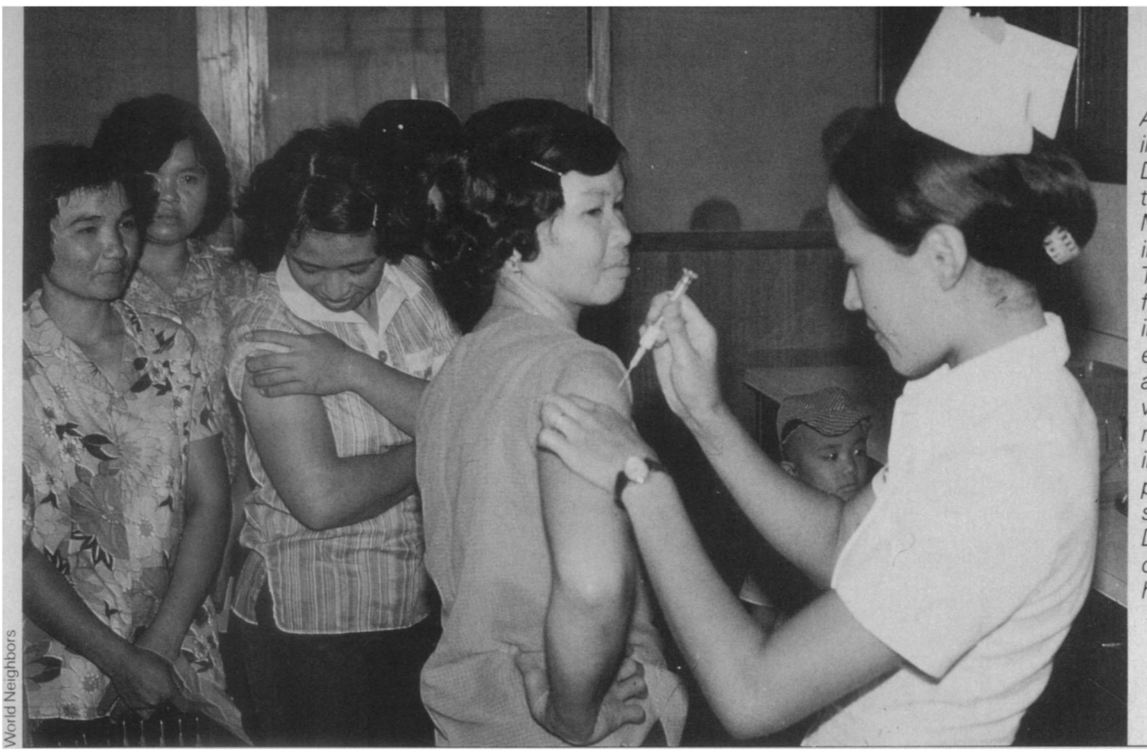
Such hearings have only been called once before in FDA's history, when the manufacturer of Aspartame, an artificial sweetener, sought and won reversal from Hayes of FDA's ban on that product. This came in spite of that panel's recommendation against approval (SN: 7/25/81, p.54). The Depo-Provera panel heard evidence for five days from Upjohn and FDA scientists and consultants, and from independent participants including the World Health Organization, the International Planned Parenthood Federation, Ralph Nader's Health Research Group and the National Women's Health Network.

The medical controversy centers on studies by Upjohn scientists of beagle dogs and rhesus monkeys, and on human trials of the drug both in the United States and abroad. In one study, two of 16 beagles given varying doses of Depo-Provera developed malignant breast cancers, and in a second, several dogs in medium- and high-dose groups developed breast cancer. Upjohn contends that these findings do not imply an increased risk of breast cancer in humans because beagles react differently to progestins (a class of hormones that regulate pregnancy, including both progesterone and Depo-Provera) than humans do. Gordon R. Duncan, a research manager at Upjohn, told SCIENCE NEWS, "the whole physiology of the mammary gland in the beagle dog is different than in the human."

Upjohn cites the findings of several panels, including the Committee on Safety of Medicine of the United Kingdom, that the beagle is not a good model for the carcinogenicity testing of contraceptives. Upjohn used beagles and monkeys in its tests because FDA requires trials on these animals as part of its contraceptive-approval procedure.

Critics respond that the difference in physiology between the human and another species is irrelevant. In a written statement, Ruth W. Shearer, a consultant to the National Women's Health Network, echoes the view of many epidemiologists: "it is widely accepted that a chemical which is carcinogenic in one species will be carcinogenic in others, but not necessarily in all others and often not in the same organ in different species."

In a study of rhesus monkeys, two monkeys in a high-dose group of 16 developed what was thought to be cancer of the endometrium. Upjohn scientists concluded that the lesions were not spontaneous, but were related to treatment by Depo-Provera. At the hearings, however, the company argued that these results were inconclusive. Of the 52 monkeys from all dose levels that started the 10-year trial, only 28 survived at the end of the study. Most of the other 24 monkeys died of old age. The two that developed cancer were added to the study. "There is no consensus on what the monkey studies do represent. [The monkeys that got cancer] were part



World Neighbors

A woman being injected with Depo-Provera during a trial of the drug at the McCormick Hospital in Chiang Mai, Thailand. The study found no abnormal incidence of endometrial cancer among those who were followed after receiving the injections, but its procedures were severely criticized by Depo-Provera's opponents at the FDA hearings.

of a replacement set, so there were some irregularities," Duncan said. Because no one knows what might have happened to those monkeys before they joined the study, he said, "we may never know just why they got cancer."

According to Robert N. Hoover, chief of the environmental epidemiology branch at the National Cancer Institute, the primate is closest to the human on the evolutionary ladder, and therefore the monkey studies should be taken seriously. "By most criteria, Depo-Provera sums up as a worrisome drug. It causes cancer in animals, not just neoplasia [an abnormal growth of tissue not necessarily malignant], it causes cancer in more than one site in animals, and it causes cancer in more than one species of animals ... and yet now it is being proposed for use in the general population," he said.

In written testimony to the board concerning the monkey studies, Sidney Wolfe of the Health Research Group charged, "Upjohn has been unable to identify any differences between the replacement monkeys and other monkeys that would account for their differences in tumor growth."

But Upjohn has also argued that the cause of endometrial lesions in the monkeys is suspect, since Depo-Provera is used to treat endometrial cancer in humans. Opponents of Depo-Provera cite the testimony of Gisela Dallenbach-Hellweg, an M.D. at the University of Heidelberg's Frauenklinik. She related evidence that the monkeys' tumors were actually cancers of the cervix and endocervix, a common cancer of the female reproductive system. Adds Hoover, "the fact that a particular drug may be given to treat a tumor doesn't mean that it may not have some function in causing the tumor."

Human clinical trials of Depo-Provera both at home and abroad are many, but their value is disputed by the experts. The trials include those at Grady Memorial Hospital, the McCormick Hospital in Chiang-Mai, Thailand, and the Los Angeles County-USC Medical Center. Upjohn spokesmen say that these trials are a strong testimonial to the safety and effectiveness of DMPA. "We have some 23 years worth of experience now in humans with 100,000 women," Duncan says, "and the clinical evidence shows no abnormal incidence of cancer risk." In the Thailand study, for example, thousands of women were given Depo-Provera for 15 years. Among those who were followed, investigators reported no increase in the incidence of endometrial cancer.

However, those studies' detractors have criticized the poor follow-up rate of those given DMPA, the small sample size of some studies, the lack of a comparable control population, the short time some women were followed and, in some cases, incomplete record-keeping. Says Wolfe, "the human epidemiological studies are essentially worthless in predicting cancer risk in humans."

Hoover is more sanguine: "We have to see whether the human evidence ameliorates the animal studies or not, and there are no relevant human studies on which to evaluate that.... In the absence of knowledge about what the specific mechanisms [of cancer development] in humans are, it would be foolish to ignore [animal] trials that suggest it may cause cancer."

In response to one criticism, the possibility that cancer will turn up after a study is completed, Duncan argues, "We assume a latency period of about 20 years, but we have a distribution — some cancers should start to show up at three, four or five years after use. We don't necessarily feel that the latency concept is applicable, but even if it is, we think that [a higher incidence of cancer] should have started to show up by now."

Critics also cite Depo-Provera's side effects as evidence of the drug's inappropriateness for human use. In certain women, these effects include heavy bleeding, disrupted menstrual cycles, long lag time between discontinuation of DMPA and return to fertility, a possibility in a small number of women of permanent sterility, increased glucose levels, water retention and mental depression.

Whatever the FDA commissioner ultimately decides, a lot more is at stake than sales of DMPA in the United States. A spokesman for Upjohn said that between 5 and 9 percent of women practicing contraception in the United States might switch to Depo-Provera if it were approved. This is about 1.5 million to 4 million women. However, some observers feel that Upjohn's sales to developing nations would greatly surpass domestic sales. If FDA approves U.S. use, the health ministries of several countries, which often wait for an FDA decision before making their own, may approve it as well.

A factor that might prove significant in the final decision is the support of Upjohn by several international organizations, including WHO, the International Planned Parenthood Federation and the Agency for International Development. Many developing countries with population problems may choose an easily administered, inexpensive contraceptive without the disadvantages of mechanical methods or side effects of the pill, in spite of its possible risks.

While the board deliberates, opponents of DMPA are already moving on other fronts. Belita Cowan of the National Women's Health Network has announced that her organization will sue Upjohn for compensation on behalf of women who have been injured by DMPA. They will also ask for more adequate information in the drug's packaging to warn patients and doctors of the possible hazards of DMPA use. □