Special Communication

The Food and Drug Administration and Medroxyprogesterone Acetate

What Are the Issues?

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• **In 1978, the Food and Drug Administration denied approval of the three-month injectable contraceptive depot medroxyprogesterone acetate for use in the United States. This decision goes against the advice of the FDA's own scientific advisory panels, as well as the rulings of the World Health Organization and the drug regulation institutions of more than 70 developed and developing countries. In response to protest from the manufacturer of depot medroxyprogesterone acetate and from many health professionals, the FDA took the unusual step of scheduling a public board of inquiry to review its decision in January 1983. Reviewing the scientific literature on the risks and benefits of depot medroxyprogesterone acetate, we find no reason to deny depot medroxyprogesterone acetate approval, provided that studies of its possible side effects are continued and that women use it only after having made an informed choice between this and other methods of contraception.**

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INJECTABLE depot medroxyprogesterone acetate, popularly known as Depo-Provera (the Upjohn Company), is probably the most controversial contraceptive in use today. There are many reasons for this. One of these is the growing awareness of the complexity of chemical effects on human beings. Medical science has produced great and relatively safe advances in contraceptive technology but is still far from developing the "perfect" contraceptive. Furthermore, we have become aware of the limits and dangers of new drug development. The most effective contraceptives available all pose health risks of one sort or another, some of them serious risks that were not and could not have been foreseen. As a result, progress in contraceptive technology has been slower than expected.

See also p 2909.

In 1978, the Food and Drug Administration denied depot medroxyprogesterone acetate approval for use as a contraceptive (Marion J. Finkel, MD, written communication to the Upjohn Company, March 7, 1978). In January 1983, a special public board of inquiry on Depo-Provera was held to review once again the issues from the perspectives of the Upjohn Company, the FDA, and a number of international consumer groups and persons. (Reference will not be made to testimony given at the hearing, since it took place too close to the final review of this article to be included.) The decision of the board is forthcoming.

We will examine the reasons given for this action and the scientific data on which they rest. Such an assessment is essential before any country or individual can make a reasoned decision about the suitability of depot medroxyprogesterone acetate use. We will limit our discussion primarily to the issues raised by the FDA and others raised since 1978. We will not attempt comprehensive review of all aspects of this drug, since several good reviews have been published recently.[1-4] (To limit our extensive bibliography, when a specific issue is adequately covered in one of the review articles, we will cite the review rather than the original publication.)

Before we examine the complex issue of the safety of depot medroxyprogesterone acetate, it is worth reviewing its benefits, the attributes that make it worth the effort of continued controversy and evaluation. It has the highest use effectiveness of any reversible method and is the only available injectable contraceptive that is effective for three months. Furthermore, its effectiveness continues even if the user is a few weeks late in obtaining another injection. It is an especially desirable method for women who prefer injections over other forms of contraception. Depot medroxyprogesterone acetate is not used in relation to coitus, requires infrequent administration, is provided outside the home, and requires no supplies to be kept around the home, thus giving the user a high degree of privacy. Furthermore, it can be administered by any person who normally gives injections in a health care system and does not necessarily require a clinic setting for administration. Because it is administered periodically by injection and has few potentially harmful metabolic side effects, depot medroxyprogesterone acetate may be the preferred method of women who desire effective contraception but who have special medical or psychosocial needs that contraindicate the use of other methods and for whom sterilization is not legal, available, or desired.

Depot medroxyprogesterone acetate, in most studies, appears not to suppress lactation and may even increase milk volume, in contrast to combined oral contraceptives.[1] It has,

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therefore, been considered by some as advantageous for postpartum women. This could be a major benefit in developing countries, where successful and prolonged breast-feeding is important for child health. However, since there is inadequate information available on possible effects of the depot medroxyprogesterone acetate in breast milk on the nursing infant, additional studies in this area are essential, and some are already under way.

In populations where iron deficiency anemia is common, the development of oligomenorrhea and secondary amenorrhea during use of depot medroxyprogesterone acetate may help alleviate anemia, although this benefit has not yet been documented.

At the present time, there appear to be no absolute contraindications to depot medroxyprogesterone acetate use other than pregnancy. There have been no reports of deaths attributable to this drug, despite its extensive use for gynecologic and contraceptive purposes in the United States and other countries. This lack of reports of fatal complications does not eliminate the need for careful epidemiologic studies of its safety. However, before the life-threatening side effects of the pill and intrauterine device (IUD) were well documented, there were case reports that pointed out the hazards of these methods.

The benefits of depot medroxyprogesterone acetate have made it a popular method of contraception in many settings in both developed and developing countries. The manufacturer of the drug, the Upjohn Company, reports that about half of all depot medroxyprogesterone acetate is used in developed countries (the Upjohn Company, oral communication, December 1980 and August 1981). In developing countries, where effective means of contraception are often difficult to obtain, the drug has proved to be in great demand. Some of the reasons for this are an aversion to the IUD in some areas, the convenience of the method (compared with the pill), and its effectiveness.

Offering women in developing countries a convenient, reliable method of contraception has important public health implications. Recent surveys in many developing countries have shown that a large proportion of women desire no more children and yet are not protected against unwanted pregnancies.[5] To control their fertility, millions of women in such countries resort to illegal and dangerous induced abortions every year, and tens of thousands of these probably die of abortion-related complications.

Clearly, the benefits of depot medroxyprogesterone acetate would make it a valuable addition to many types of family planning programs. However, over the years there have been reports commenting on its risks as well as its benefits. These reports are of two general types: medical reports with responsible discussions of its potential risks and benefits, and reports that use selected evidence and biased interpretation to make a particular point.[6] Some of the latter type (usually aimed at the general public and designed to play on good intentions and lack of information) have had a great deal of influence on the history of depot medroxyprogesterone acetate and may well have been a factor in the FDA's 1978 decision regarding its use. We will concentrate on the scientific evidence.

Several evaluations of the scientific data on the safety of depot medroxyprogesterone acetate have taken place in the past few years. In 1978, the FDA completed a decade of deliberations by announcing that it would not approve the drug for use as a contraceptive in the United States (Marion J. Finkel, MD, March 7, 1978). Subsequently, the World Health Organization's Toxicology Review Panel conducted its own review and found no reason to recommend that it be withdrawn from use.[3] Finally, in 1980, the Ad Hoc Consultative Panel, after an 18-month period of review, finalized its findings and recommendations made on behalf of the US Agency for International Development (USAID), which had asked for advice on the safety of depot medroxyprogesterone acetate for use in international family planning programs.[7] (The USAID's policy has been not to provide programs with any drugs not approved for use in the United States. However, after the FDA's denial of approval of depot medroxyprogesterone acetate, the USAID decided to review this policy, in light of the growing number of requests from the governments of developing countries for the agency to provide the drug at reduced cost, as it does other contraceptives.) The Ad Hoc Panel recommended that the USAID make the drug available to national family planning programs, on request, in the same way that it does other methods of contraception, after ascertaining that the requesting government has had access to all the current information on the drug. This recommendation was based on careful consideration of the medical and ethical issues involved by panel members with expertise in the fields of obstetrics and gynecology, animal physiology and toxicology, epidemiology, pathology, law, and health policy.

Depot medroxyprogesterone acetate is at present marketed as a contraceptive in more than 70 developed and developing countries (the Upjohn Company, oral communication, January 1983) (Table 1). However, the decision by the FDA to deny approval for this use in the United States, together with materials released by US consumer groups, has caused great concern among health authorities around the world. We will examine the history of and reasons for the FDA's decision, together with the evaluation that led to the recommendations of the Ad Hoc Panel, which was chaired by the lead author of this article. In so doing, we hope to put into perspective the various risks of this drug as they are known today, as compared with the benefits.

Originally, depot medroxyprogesterone acetate was used for treatment of two conditions—one benign (endometriosis) and one malignant (endometrial carcinoma). In both instances, high dosages of the drug were used, often starting at 1,000 mg/wk, with lower maintenance dosages, as compared with the contraceptive dosage, 150 mg once every three months. Treatment at these high dosages was maintained in some instances for one to two years with no short-term toxic effects reported.[8] However, we know of no published systematic studies that specifically reported on long-term follow-up of women receiving this treatment.

The review of this drug by the FDA took place over a long period and was unusual in many ways. In 1967, a new drug application for approval of depot medroxyprogesterone acetate as a contraceptive was filed by the Upjohn

Company.[9] In 1973, after a favorable recommendation by its Advisory Committee on Obstetrics and Gynecology, the FDA announced its intention to give qualified approval for contraceptive use by women who had difficulty with other forms of contraception. In September 1974, the FDA announced its proposed final form of approval, which was to take effect on Oct 15, 1974. Letters to this effect were sent to physicians throughout the country. At approximately the same time, however, a subcommittee on intergovernmental relations of the US House of Representatives held hearings that resulted in a letter of protest from the chairman of that committee to the secretary of the Department of Health, Education, and Welfare, who then stayed the approval of the drug.

In 1975, the FDA convened a joint meeting of its Advisory Committees on Obstetrics and Gynecology and on Biometric and Epidemiological Methodology.[9] These committees appointed a subcommittee task force that, after open hearings, recommended that the FDA approve depot medroxyprogesterone acetate with the earlier limitations. After continued review, however, the FDA announced its decision in March 1978 to deny approval of the Upjohn application for the following five reasons: (1) safety questions raised by studies in which beagles showed an increased incidence of mammary tumors associated with the drug, (2) the availability of a number of safer alternative methods of contraception in the United States and the lack of clear evidence that a substantial patient population in need of the drug exists in the United States, (3) the possibility that bleeding disturbances caused by the drug may necessitate administration of estrogen, imposing an added risk factor and decreasing the benefits of a progestogen-only contraceptive, (4) the possibility that exposure of fetuses to depot medroxyprogesterone acetate, if the drug fails and pregnancy occurs, poses a risk of congenital malformation, a risk potentially increased by the prolonged action of the drug, and (5) serious reservations about the ability of the postmarketing study for breast and cervical carcinoma, proposed by the Upjohn Company, to yield meaningful data.

This decision was appealed by the Upjohn Company, and the FDA announced, after a delay of two years, that it had appointed a public board of inquiry to review the matter.

Table 1.—Countries in Which Depot Medroxyprogesterone Acetate Is Marketed as a Contraceptive

Africa	Asia and the Pacific	Europe	Latin America	Middle East
Cameroon	Bangladesh	Belgium	Antigua	Bahrain
Ethiopia	Burma	Denmark	Barbados	Cyprus
Ghana	Hong Kong	England and Wales	Bermuda	Iraq
Guyana	Indonesia	France	Colombia	Kuwait
Kenya	Malaysia	West Germany	Costa Rica	Lebanon
Liberia	New Zealand	Iceland	Curacao	Muscat and Oman
Libya	Pakistan	Ireland	Dominican Republic	Qatar
Madagascar	Philippines	Luxembourg	Ecuador	Saudi Arabia
Malawi	Singapore	The Netherlands	El Salvador	Syria
Morocco	Sri Lanka	Norway	Guatemala	United Arab Emirates
Nigeria	Thailand	Portugal	Haiti	
Reunion		Spain	Honduras	
Rwanda		Sweden	Jamaica	
Sierra Leone		Switzerland	Mexico	
South Africa		Yugoslavia	Nicaragua	
Sudan			Panama	
Tanzania			Peru	
Uganda			Surinam	
Zaire			Trinidad and Tobago	
Zambia				
Zimbabwe				

The Breast Cancer Issue

The Ad Hoc Panel reviewed the literature on depot medroxyprogesterone acetate studies involving beagles. The evidence strongly suggests that the beagle reacts differently to progestogens[1-4,7] (including progesterone) than do women, as Table 2 shows. Depot medroxyprogesterone acetate stimulates the endometrium of beagles to such an extent that mucometra, pyometra, or both develop in a large proportion of them, often resulting in death. Mammary nodules developed in almost all dogs given the drug that survived the first few years of the experiment, and some of these nodules became malignant.

Benign breast adenoma commonly develops in beagles without any treatment, and there is also evidence that they have multiple microscopic foci of neoplasia. These foci can be stimulated by synthetic progestogens and by progesterone itself. Progestogens of the same type as depot medroxyprogesterone acetate (17-acetoxy progestogens) bind much more strongly to progesterone receptors in the beagle breast than in the human. Thus, the effect in the beagle may be a function of potency and dosage; given the potency of these compounds in the beagle, the dosage can be considered massive for the species.

There are other differences in the effect of depot medroxyprogesterone acetate on beagles and on women. While it stimulates the endometrium of beagles excessively, it produces an initial stimulatory effect in women, followed by continuous suppression of endometrial growth. Furthermore, beagles demonstrated an increased release of growth hormone, resulting in acromegalic changes. This complication is not seen in women.

Studies using varying research designs have shown no increase in breast disease incidence among women who have taken depot medroxyprogesterone acetate, although more data are necessary before we can say that there is no effect.[1-4,7] In the only published US study (a retrospective case-control study), there was no increased risk of breast cancer developing among users of the drug.[2,7] The authors note that the small number of women and the short average exposure to depot medroxyprogesterone acetate mean that this result should be interpreted cautiously. However, several other reports released in the last few years support these studies. Data from 11 years of prospective study of women using oral contraceptives in Britain were analyzed to see if women using pills containing a progestogen closely related to depot medroxyprogesterone acetate (and that had also been implicated in beagle studies) caused any increase in the incidence of breast cancer.[10] No increase was found. A ten-year study of postmenopausal women using es-

Table 2.—Similarities and Dissimilarities in the Response of Beagles and Humans to Depot Medroxyprogesterone Acetate

Similarities
Prevents ovulation
Decreases plasma cortisol levels
Mild disturbance in carbohydrate metabolism
Dissimilarities
Endometrium
Beagle endometrium stimulated, causing mucometra, pyometra, or both
Growth
Acromegalylike condition in beagles
No such changes in women
Death
High doses often cause death in many beagles because of pyometra or vascular changes
No deaths reported among women receiving high dosages of depot medroxyprogesterone
Breast
Benign and malignant breast tumors developed in beagles.
No evidence of depot medroxyprogesterone-induced breast pathologic conditions in women

trogens and depot medroxyprogesterone acetate in pill form showed that these women had a substantially *lower* rate of breast cancer than did women using estrogen alone.[11]

As a result of species differences in reactions to this drug, both the WHO Toxicology Review Panel and the Ad Hoc Panel stated that it was not possible to conclude from the beagle studies that depot medroxyprogesterone acetate poses any increased risk of breast cancer to women. The Committee on Safety of Medicine of the United Kingdom concluded that "because of differences between the beagle bitch and the human female in the sensitivity to and the metabolism of progestogens, positive carcinogenicity studies in the beagle bitch can no longer be considered as indicative of significant hazard to women" and stopped requiring beagle studies of contraceptive steroids.[12]

Teratogenic Potential

The Ad Hoc Panel reviewed the available data on teratogenic effects of steroid sex hormones in general and found that several studies suggested that prenatal exposure may pose some increased risk, probably about twofold, although other data are equivocal.[4,7] However, there is little information on the effects of progestogens alone, since most of the studies have been done on women who have taken combined oral contraceptives. The panel concluded that the data do not suggest that depot medroxyprogesterone acetate poses more of a threat of fetal malformation than do other hormonal contraceptives. Furthermore, the panel pointed out the following:

> Since effective contraception prevents both normal and abnormal pregnancies, it can be shown that even if a two-fold increase in congenital defects were associated with prenatal exposure to DMPA [depot medroxyprogesterone acetate], widespread use of the drug would result in a significant net decrease in the number of anomalies. Because of this, only a very small number of fetuses would be exposed to the two-fold increased risk associated with maternal use of the drug.

Nevertheless, even this small risk (in terms of numbers of children affected) is of concern, since some women may begin use of depot medroxyprogesterone acetate with an unrecognized pregnancy or conceive before the drug has completely cleared from their systems.

Animal data indicate that exposure in utero might produce masculinization of female fetuses, but the studies of human infants to date do not confirm this risk. These questions cannot be studied unless large numbers of women use depot medroxyprogesterone acetate and their offspring and those of women not using it are evaluated in a standardized manner.

Use of Estrogen

The most common side effect associated with depot medroxyprogesterone acetate use is a change in menstrual pattern.[2,3] Most women note irregular spotting and staining, particularly during early use. Almost 50% of users eventually become amenorrheic. A very small proportion of users will have one or more episodes of heavy vaginal bleeding, although treatment is rarely necessary. When it is, the bleeding almost always responds to estrogen therapy; curettage is almost never needed. The topic of menstrual side effects of depot medroxyprogesterone acetate use was reviewed in a three-day WHO symposium.[3] These side effects are the major complaint leading to discontinuation of use of this method. It seems that the problem is viewed differently in different cultural settings. It is true that this drug disrupts the menstrual cycle, but there is general agreement that estrogen therapy generally is not indicated, except in the rare cases of acute heavy vaginal bleeding.

The FDA's allegation is probably based on the fact that, during the 1960s, estrogens in low doses were sometimes used to treat menstrual disturbances caused by depot medroxyprogesterone acetate, but the results of this practice were equivocal and it is no longer recommended.[2] Cyclic estrogen administration to induce monthly bleeding also is not recommended. Therefore, the drug is not suitable for women who will not tolerate spotting or amenorrhea. For other women, thorough and supportive patient counseling is the best method of dealing with concerns about irregular bleeding and amenorrhea.

In a US study analyzing the provision of exogenous estrogens to women receiving depot medroxyprogesterone acetate, 63% of all women had possible "indications" for exogenous estrogens (amenorrhea or irregular menses), but only 5% of these received even a single course of estrogen therapy.[13] Moreover, in only 0.2% of all cycles of depot medroxyprogesterone acetate use were exogenous estrogens provided to women receiving the drug. The investigators concluded that it can be provided employing exogenous estrogens infrequently.

Planned Studies

Several agencies, including the WHO, the Centers for Disease Control, and the International Fertility Research Program, have planned additional safety studies. These will use data from family planning programs wherein substantial numbers of women have used depot medroxyprogesterone acetate for many years. The most important study is a nine-country case-control study being undertaken by the WHO, which is assessing the relationship between use of this drug and cancer of the breast, cervix, endometrium, and ovary. Preliminary results are expected this year. The manufacturer of the drug has also begun new studies on such issues as the effect of the drug in the mother's milk on the nursing

Table 3.—Characteristics of Women Who Discontinued Use of Depot Medroxyprogesterone Acetate or Oral Contraceptives to Become Pregnant, Chiang Mai, Thailand*

	Former Depot Medroxyprogesterone Users	Former Oral Contraceptive Users
No.	756	437
Mean age, yr	24.5	22.3
Mean gravidity	1.5	0.7
Proved pregnancy, mo		
6†	53%	75%
12	75%	85%
24	92%	94%
Mean	5.5	2.5

*Data from Testimony of T. Pardthaisong.[14]

†Months after stopping contraception. Contraception was considered stopped after the last cycle of oral contraceptives was taken or three months after the last injection.

infant. The Ad Hoc Panel stressed the importance of careful studies of the drug's effects but concluded that, given the commitment of international health agencies to this task, this requirement does not pose a barrier to current use of this method. Unfortunately, one cannot foresee at the outset all the possible rare risks or problems that might arise after a long lag time. The panel believed that the available data were sufficiently reassuring to warrant continued use. Although the Ad Hoc Panel had not been asked by the USAID to evaluate the FDA's claim that there was no need for depot medroxyprogesterone acetate in the United States, the panel did not agree with this assertion.

Return of Fertility

In addition to the issues raised by the FDA in 1978, there were several others that the Ad Hoc Panel thought needed careful consideration. One of these is the apparent delay in the return of fertility after discontinuation of depot medroxyprogesterone acetate use. However, this seems to be a temporary effect, and there is no evidence of permanent impairment. Table 3 compares a series of 756 users of the drug with 437 oral contraceptive users in Thailand.[14] The women in both groups had discontinued use to become pregnant. The mean time for establishment of pregnancy after discontinuation was 5.5 months for depot medroxyprogesterone acetate users, as compared with 2.5 months for pill users. The Table shows that there is a delay in return of fertility, with substantial differences at six and 12 months. By 24 months, however, there was no substantial difference.

Further analysis of the data from this Thai population showed that the proportions of women who had become pregnant were almost identical at 12, 18, and 24 months among women who had discontinued use of depot medroxyprogesterone acetate and those who had an IUD removed to conceive.[15] Because of these data and other studies with similar findings, the panel concluded that, "while there is a delay in the return of fertility, the vast majority of women desiring a pregnancy were able to conceive within a two-year period of time. Thus, concerns about irreversibility, or chemical sterilization, do not appear to be substantiated."[7]

Endometrial Cancer

A second issue not addressed by the FDA in 1978 is that of endometrial cancer. In December 1978, after the FDA had announced it would not approve depot medroxyprogesterone acetate for contraceptive use in the United States, and after the Ad Hoc Panel had concluded its meetings, it was learned that the FDA-required ten-year studies of the drug in rhesus monkeys had been concluded. The autopsy findings contained the surprising information that endometrial cancer had developed in two of the ten monkeys receiving 50 times the human dose for the duration of the study, while none of the 20 monkeys receiving other doses of the drug and none of the seven control monkeys showed any signs of endometrial disease.[2,4,7]

The chairperson of the Ad Hoc Panel, after consultation with panel members, arranged for a special toxicology committee to consider this information and the reports of consultant toxicologists (to the Upjohn Company) who reviewed the microscopic specimens of all the test monkeys. A group of experts was recruited for this meeting from a variety of relevant fields, including obstetrics and gynecology, gynecologic pathology, veterinary pathology, and reproductive physiology. Committee members trained in these fields all had experience with endometrial disease in either primates or humans. In addition, other committee members had experience in cancer epidemiology and international public health programs, and one was a lawyer with experience in medical ethics.

In its deliberations, the committee stressed the difficulty of interpreting the information because so little is known about endometrial disease in monkeys. Few experimental institutions keep monkeys for prolonged periods (ten years in the Upjohn study), with the result that there is no information on the baseline incidence of endometrial cancer in monkeys. However, it does seem to be uncommon. For example, the San Diego Zoo performs autopsies on all animals. Of 46 female macaque monkeys examined, none had endometrial abnormalities. However, the zoo's Director of Research, Dr Kurt Benirschke, who gave the committee this information, cautioned that there is great variation among the many species of macaques; there were also less than a dozen rhesus monkeys (the species of macaque used in the depot medroxyprogesterone acetate test) in their sample. The Armed Forces Institute of Pathology did not have any case reports of uterine cancer in its collection of reports on primate neoplasia. On the other hand, committee members reported two cases of premalignant or early-malignant endometrial changes in monkeys, neither of which had received hormones. One case occurred in a control monkey in a Population Council study of the copper IUD, the other in a control monkey in a Wyeth Laboratory oral contraceptive study.[4]

It was suggested by the committee that the monkeys' endometrial cancer could have arisen from any of three

routes: through hormonal action of the depot medroxyprogesterone acetate, through some nonhormonal, toxic action of the drug, and independently of it, by chance. If the hormonal action of the drug caused the cancers, then they were unusual in several ways: (1) they were associated with the superficial layers of the endometrium, whereas in women, cancer usually arises from deeper layers of the endometrium, (2) similarly, endometrial cancer in women is associated with hyperplasia, such as that caused by estrogen, and there was no evidence of hyperplasia among the depot medroxyprogesterone acetate-treated monkeys, and (3) the endometria of the monkeys treated with the drug were atrophied, a condition that has been thought to decrease the risk of carcinoma, at least in premenopausal women. In short, even if the hormonal action of the drug caused the endometrial cancer in the test monkeys, the mechanism of action seems different from that of endometrial cancer in women.

Additional evidence against the hormonal action of depot medroxyprogesterone acetate having caused the endometrial cancer is found in a variety of clinical and epidemiologic studies. Excess estrogen is known to increase the risk of endometrial cancer developing in women. There is evidence that progestogens neutralize this effect. For example, while use of estrogens by postmenopausal women increases the incidence of endometrial cancer, use of a combination of estrogen and a progestogen does not increase the incidence of disease.[11] Similarly, while use of sequential oral contraceptives (which emphasize estrogenic action) appears to increase the risk of this disease among young women, use of oral contraceptives that contain estrogen and progestogen in each pill does not seem to have this effect. In fact, there is new evidence from case-control studies that suggests that women who use combined oral contraceptives may have less risk of endometrial cancer than women who do not take oral contraceptives.[2] In other words, these data suggest that progestogens provide protection against endometrial cancer.

One reason that the monkey findings were such a surprise is that depot medroxyprogesterone acetate and other progestogens have been used for years to treat women with endometrial hyperplasia and carcinoma in situ who wish to preserve their childbearing functions and also to treat advanced metastatic endometrial cancer.[1-4,7] In the latter case, remission is common, but progestogens do not effect a permanent cure. While none of these findings rule out the possibility that the drug may have caused the cancer found in the monkeys, they do call into question the meaning of that finding.

It is also possible that the massive doses of depot medroxyprogesterone acetate may have affected the monkeys in the group receiving 50 times the human dose through some nonhormonal action, ie, as a toxin. The committee members thought that this seemed unlikely, because there was no evidence of a dose response. There was not higher mortality among the monkeys receiving depot medroxyprogesterone acetate than among the control monkeys or any increase in mortality with increasing dosage. Cancer was not found in sites other than the uterus.

Finally, the possibility that the two cases of endometrial cancer arose by chance in the group receiving 50 times the human dose cannot be ruled out. Statistical analysis showed that the probability that the results of the monkey test could have occurred by chance was at least one chance in three. In addition, exploration with a variety of statistical techniques by panel members showed that these data lack both statistical significance and power, even if margins of error much larger than usual are allowed.[7]

In addition to trying to interpret the monkey data and assess their applicability to humans, the committee considered the experience of women who have used this method of contraception. In response to the endometrial cancer finding at the conclusion of the monkey trial, Drs McDaniel and Potts made an effort to determine whether there was an increase in the incidence of endometrial cancer among women in Chiang Mai and Lumpoon provinces in Thailand, where depot medroxyprogesterone acetate has been used by more than 86,000 women since it was introduced in 1965.[16] They reported that a search of the records of all seven hospitals operating in these areas produced evidence of 39 cases of proved or presumptive endometrial cancer during 1974 to 1978. During these years, they note that "there has been a steadily increasing patient load of diseases of all kinds." However, there was no clear increase in the number of cases of endometrial cancer seen each year.

Of the 27 women with proved endometrial cancer, 16 came from Chiang Mai or Lumpoon provinces, where they could have received depot medroxyprogesterone acetate. Of these 16, four were too old to have received the drug (63 to 84 years old at diagnosis), one had never been married, and two could not be located at the time of the report. Of the remaining nine women, none had ever used the drug. Because the numbers are so small, the time too short, and the conditions of the study far from satisfactory, these findings cannot be construed as proof that depot medroxyprogesterone acetate does not cause endometrial cancer. Nevertheless, as the authors note, the lack of a substantial increase in endometrial cancer in an area where hundreds of women are known to have used the drug continuously for ten to 13 years and many thousands for shorter periods "is a reassuring preliminary observation."[16]

The committee members emphasized the need for further and more intensive investigation of this issue. Several studies are already planned by the WHO and the International Fertility Research Program.

Other Possible Risks

Other side effects include weight gain, headaches, abdominal bloating, and a variety of other complaints. These usually are of a minor nature and are rarely causes of discontinuation, with the possible exception of complaints of headache and weight gain.

The cardiovascular problems associated with oral contraceptive use have generally been thought to be associated with the estrogen component of the pill. Recently, however, data have been reported that suggest that the progestational component may also play a role.[17] We know of no

reports relating use of depot medroxyprogesterone acetate to an increased incidence of cardiovascular disease, but there may be insufficient use of the drug for such an effect to be noted in case-control studies. In general, its use has not been associated with a hypertensive effect, although there is some evidence to suggest that the progestin component of the pill may play a role in the hypertension noted among pill users.[18]

Fraser and Weisberg[1] have reviewed the metabolic effects of depot medroxyprogesterone acetate in detail. They state that "steroidal contraceptive agents in general have been shown to induce multiple changes in biochemical parameters, but in spite of the high and sustained blood levels of progestogen following a 150 mgm DMPA [depot medroxyprogesterone acetate] injection, remarkably few metabolic changes can be confirmed." In general, there have been minor or no changes reported in liver, renal, or thyroid function or in blood coagulation. Changes in carbohydrate metabolism have been noted in most but not all studies. These changes are similar to but milder than those seen with oral contraceptive use. The most common finding is an exaggerated insulin response to glucose tolerance tests. Despite the glucocorticoid activity of depot medroxyprogesterone acetate, there has been no evidence of clinical adrenal insufficiency.

Conclusion and Recommendations

Weighing the data on risks against the considerable benefits of the drug, the Toxicology Committee was unanimous in supporting the original recommendation of the Ad Hoc Panel that depot medroxyprogesterone acetate should be made available to family planning programs on request as a part of the USAID's assistance program, provided that careful study of its possible health effects continues. Thus, the committee was in agreement with the WHO's Toxicology Review Panel, which, after reviewing all the data, concluded that the adenocarcinomas in the two monkeys were the result of massive overdosage, that current and planned WHO studies of the health effects of depot medroxyprogesterone acetate should continue, and that there was no reason to recommend discontinuation of its use.[3]

The Ad Hoc Panel recommended that a variety of studies be conducted, including the institution of surveillance mechanisms (collection of case reports, periodic cross-sectional surveys, and registries) to monitor potential complications of the drug's use and special studies on such topics as effects on nursing infants, return of fertility, and cancer incidence.

Depot medroxyprogesterone acetate is the subject of popular as well as scientific controversy. It seems that the issue serves as a lightning rod for a variety of concerns, many of them legitimate. Unfortunately, some of the popular debate is distorted by misrepresentation and misinterpretation of the medical evidence. This has the effect of polarizing the advocates of different views to an unnecessary extent, thus precluding meaningful dialogue. An example of inflammatory anti-depot medroxyprogesterone acetate journalism appears in an article in the journal entitled *Women and Health*.[6] Unfortunately, we do not have the space herein to discuss this article thoroughly, but an excellent critique has been published by Benagiano and Fraser.[4]

The *Women and Health* article asserts that the USAID is "dumping" dangerous contraceptives (notably depot medroxyprogesterone acetate) on the Third World, with no concern for the health of the people. In fact, however, the USAID has not distributed this drug in developing countries. Furthermore, more than half of all depot medroxyprogesterone acetate distributed abroad has been distributed in developed countries. The article contains a number of frightening but unsubstantiated statements about its effects on women's health and uses inappropriately selected references and unauthenticated data. This article was circulated widely to ministries of health in developing countries. A covering letter, signed by a number of physicians, presents these hypotheses and allegations as facts, without any effort to present a balanced picture of risks *v* benefits. In the end, each country must do its own risk-benefit analysis.

Open discussion of these complex issues can lead to honest disagreement, but partial and distorted presentation of information can only lead to polarization and miscommunication. We hope that in the future a more meaningful dialogue can be established between consumer groups and those health professionals currently working in this field, both in the United States and in other countries.

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