1. The benefits of Depo-Provera do not outweigh its risks under conditions of general marketing in the United States. Depo-Provera causes two types of cancer in two species of animal. An oral contraceptive containing the same ingredient as Depo-Provera was removed from the market in the early 1970's when it was found to cause breast tumors in dogs, and no oral contraceptives have been subsequently approved which caused a significant increase of tumors in long-term animal studies. Upjohn is asking the FDA to make an exception for Depo-Provera because of its uniqueness as a long-acting injectable contraceptive, but these features do not justify exposing healthy women to a dangerous drug. Depo-Provera also causes numerous other side effects, such as heavy bleeding, possible permanent sterility, serious ovarian changes and changes related to the development of cardiovascular disease and diabetes. As a long-acting drug, it presents the additional danger of remaining in the system for months — so that women who experience problems while on the drug cannot immediately discontinue drug exposure.

2. Beagle and monkey studies indicate that Depo-Provera causes cancer in animals. The endometrial cancer occurred in an animal close to humans on the evolutionary scale. Various arguments offered by Upjohn to refute the significance of these findings do not hold up to scrutiny. Moreover, studies in both animals and additional studies in rats and mice revealed other types of tumors from Depo-Provera. Animal studies are a reliable predictor of carcinogenicity for humans, and these findings in animals must be interpreted as evidence of Depo-Provera's potential carcinogenicity for humans.

3. Clinical studies conducted by Upjohn and others do not refute the risk of human cancer suggested by the animal studies. Upjohn's human studies, and human studies conducted by others, are inadequate to determine an increased risk, or the lack of an increased risk in cancer. Human cancer, particularly cancer which develops from hormone or other chemical exposure, has a latency period of ten, twenty or more years; but Upjohn and others did not follow up women for this length of time. Upjohn's studies, and many of the other human studies on Depo-Provera, did not use control groups, so the incidence of cancer or other adverse effects of the drug could not be compared with a similar population who did not use the drug. Upjohn's studies and other studies lost too many women to follow-up for accurate, representative analysis of the results. More recent human studies conducted on Depo-Provera do not provide evidence that Depo-Provera is safe, because they suffer from small numbers, inadequate length of follow-up, failure to match controls, and other problems.

5. Synthetic progestins, including Depo-Provera, have been found to cause masculinization of the fetus in animal and human studies. Progestogens or estrogen and progestogen compounds have been associated with numerous other defects in humans, such as limb reduction defects, hypospadias and an increase in total malformations. In 1973, the FDA...
withdrew approval of all pregnancy related uses of progestogens, because of the evidence of teratogenicity. Fetal exposure to Depo-Provera poses a greater risk to the child than exposure to oral contraceptives, because Depo-Provera is long-acting and stays in the system for at least 3 months. Urine pregnancy tests are not an accurate means of detecting an early pregnancy, and blood tests for pregnancy are not likely to be used on a routine basis, especially in a clinic population.

7. There is no identifiable human population for whom the benefits of Depo-Provera outweigh the risks. The increased risk of cancer and other serious side effects results in an unfavorable risk-benefit ratio for the general population and subjecting poor or mentally retarded women to these risks would create a double standard of safety which is morally offensive and unacceptable. Moreover, these groups of women are the least likely to be able to weigh the benefits and the risks of the drug and give true informed consent. They may also be more susceptible to pressure from physicians anxious to prescribe the drug, and may be less likely to identify early warning signs of serious side effects and take the steps necessary to discontinue drug use. If Depo-Provera were approved for a limited population, there would be no way to prevent it from being used in other women for whom it was not approved. The chances that it would be used for other women, and the risks associated with this widespread use, must be taken into account when weighing the benefits and the risks and deciding whether to approve the drug.
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SUMMARY

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STATEMENT BY DR. SIDNEY M. WOLFE, DIRECTOR
PUBLIC CITIZEN HEALTH RESEARCH GROUP
PUBLIC BOARD OF INQUIRY
DEPO-PROVERA
JANUARY 13, 1983

BACKGROUND

In both 1973 and 1976, FDA announced its intention to approve Depo-Provera (medroxyprogesterone acetate) for use as a long-acting injectable contraceptive in the U.S. On both occasions, Public Citizen Health Research Group strongly opposed the approval of this drug as a contraceptive, because it causes cancer in animals and therefore poses an increased risk of cancer for women. FDA intended the drug for use by the poor and mentally retarded, thus endorsing a two class system of drug safety. In 1978, FDA reversed its earlier intention and denied approval of Depo-Provera as a contraceptive, citing the animal cancer studies and the availability of safer alternatives. Since that time, results of a long-term monkey study reveal that the drug causes cancer in a second species.

Now, the manufacturer (Upjohn) will state its case before a Public Board of Inquiry held by the FDA, and will ask once again that FDA bend the drug safety rules and approve the drug. We strongly support the FDA's decision not to approve this dangerous drug as an injectable contraceptive.

ISSUE I. IN COMPARISON WITH OTHER DRUGS APPROVED FOR CONTRACEPTION, DO THE BENEFITS OF DEPO-PROVERA IN THE UNITED STATES OUTWEIGHT ITS RISKS UNDER CONDITIONS OF GENERAL MARKETING?

The benefits of Depo-Provera do not outweigh its risks under conditions of general marketing in the U.S. Depo-Provera causes cancer in two species of animal (discussed under Issue 2) and causes numerous other serious and frequently irreversible side effects. These risks are unacceptable for a contraceptive which is given to healthy women.

Comparative risk-benefit assessments of Depo-Provera and oral contraceptives are difficult to make, because the magnitude of many of the adverse effects are currently unknown for both drugs. But it is clear that if Depo-Provera were an oral contraceptive, it would never be approved. Since the FDA first required long-term studies in dogs and monkeys for steroid contraceptives, no contraceptives have been approved if they caused a statistically significant increase in tumors in these animal tests. In fact, in 1970, the FDA removed Provest, an oral contraceptive containing the same ingredient as Depo-Provera from the market because it caused a statistically significant increase in mammary tumors in beagles and other oral contraceptives were available which did not cause these tumors. There is no good reason for the FDA to make an exception in the case of Depo-Provera and go back on its own rigidly enforced requirements. Depo-Provera's main advantage is its convenience, which hardly outweighs the increased risk of cancer, heavy bleeding, permanent sterility and other serious and irreversible side effects.
Depo-Provera is as likely to cause some side effects as other methods of contraception, including oral contraceptives, and other side effects are more likely to occur with Depo-Provera than with oral contraceptives. Some of these adverse effects will be discussed below.

**BLEEDING**

Heavy or prolonged menstrual bleeding is a common adverse side effect of Depo-Provera. A review article of Upjohn's human studies reports that in the first 3 months after the initial injection of Depo-Provera, 35 percent of the women using the drug bled for 11 to 30 days each month, and one quarter of the women bled more than 11 days each month after the second injection. Bleeding has been serious enough in some cases to require hospitalization. Studies have also looked at the average amount of time that women bleed during each injection period and found that women bleed an average of 24 to 29 percent of the time after the first injection period (about 9 days a month) and 21 to 22 percent of the time after the second injection (6.3 days each month). This method of analysis is misleading, because it obscures the fact that some women bleed for a much longer period of time. For example, in one of these studies, one woman bled continuously for 50 days.

Bleeding is particularly severe in women given Depo-Provera postpartum (immediately after childbirth). In one study of 52 women, 33 (63%) bled continuously for 90 days, but this occurred in only 2 of 52 postpartum controls. In another study of 100 postpartum women, almost all of the women bled for more than 21 days during the first month, and 75% of the women bled for 8-30 days during the second month.

Upjohn claims that bleeding is heavy only after the first few injections but tapers off considerably, so that by one year of treatment, many of the women experience amenorrhea. But there are no reliable studies which demonstrate that the incidence of bleeding tapers off as quickly and completely as Upjohn maintains. Many women discontinue Depo-Provera, and bleeding disorders are one of the most commonly cited medical reasons for discontinuing use of the drug. Therefore, all studies to date on bleeding suffer from self-selection bias: women who experience the heaviest or most prolonged bleeding are probably more likely to discontinue use of the drug, and will not be included in the analysis of bleeding in the months that follow.

Upjohn claims that heavy bleeding occurs in only 1 to 2 percent of Depo-Provera users. In fact, it is difficult to know how often heavy bleeding occurs, because the term "heavy bleeding" is defined differently by different authors, and some do not define it at all. But if bleeding more than 11 days a month is considered heavy, and Upjohn's own data is to be believed, 35% of the women and not 1 or 2% bleed heavily during the first 3 months of treatment. Study results reporting the incidence of bleeding may not be accurate because they fail to account for the routine administration of estrogen, which would decrease the incidence and severity of bleeding. But even with estrogen use, heavy bleeding is higher than Upjohn maintains. One study of the bleeding patterns of 682 women using 6 month injections showed that 5.3% had heavy bleeding.
Bleeding in women using Depo-Provera is not only prolonged, it is also erratic, resulting in many short bleeding episodes, or combinations of short and long episodes, with varied lengths of time between them.4,6,7,8,13 One study described the situation as "menstrual chaos,"6 and another abandoned the concept of regular menstrual cycles completely and examined "intervals" between the start of one bleeding episode and the beginning of the next.7 This irregularity, in addition to being dangerous in cases of heavy bleeding, is also extremely inconvenient for women using the drug.

RETURN TO FERTILITY

Many studies have found that Depo-Provera causes a delayed return to fertility after women discontinue its use. Most studies on this problem are poorly conducted and analyzed, but show that at least 20 to 25 percent of women who stop using the drug are unable to become pregnant after one year.14,15,16,17 These results do not compare favorably with other methods of contraception. Studies have found that 88 percent of women who have IUDs removed,18 and 94 percent of women discontinuing the pill19 have become pregnant within one year. Depo-Provera's adverse effect on fertility is so severe that many of those who studied Depo-Provera,5,11,20,21 including Upjohn's own scientists,9 have acknowledged that Depo-Provera should not be used in women who wish to have additional children, and the FDA has stated that the drug should only be used in women who know that it may cause permanent sterility.22 Others have gone further. One study conclusively states that Depo-Provera "has an application in family planning practice for women who do not plan to have more children."7

Upjohn argues that no one has proved that Depo-Provera actually causes this delayed return to fertility. More importantly, however, is the fact that Upjohn has failed to prove that this delayed return to fertility is not a problem. Upjohn's own studies of this problem are poorly designed and analyzed. For example, Schwallie and Assenza's summary of Upjohn's human studies17 reports that of 188 women who discontinued Depo-Provera to become pregnant, 114 were able to conceive. But 17 women in this group resumed contraception, and should not be included in the analysis, and 32 percent of the remaining women were lost to follow-up. The study then reports that 68 percent of these women became pregnant within 12 months, but only women who became pregnant are included in the analysis, which, needless to say, plays down the adverse effects of Depo-Provera on return to fertility and artificially inflates the results in favor of the drug. Other Upjohn studies on this problem23,24 merely report that infertility was found in several cases of women who discontinued drug use, but fail to identify how many women discontinued Depo-Provera to become pregnant or how many were successfully followed up.
Upjohn has also looked at the length of time that it takes for women discontinuing Depo-Provera to have normal menstrual periods, since normal periods may indicate that a woman is able to conceive. For example, one study analyzed the return of menstrual periods in 245 women, but since this was only 11% of the population who discontinued Depo-Provera, study results were probably not representative for the whole population of women and are of little value.\textsuperscript{25} A study by Scutchfield et al.\textsuperscript{12} found that women receiving more injections of Depo-Provera were less likely to return to normal periods after one year, so there may be a dose-dependent delay of return to fertility. Only 53 percent of the women who received 4 injections of Depo-Provera had normal periods 1 year after discontinuing the drug.

Upjohn claims that women return to normal fertility after Depo-Provera stops circulating in their systems,\textsuperscript{12} but this has not been established. They base their statement on the assumption that the average return to fertility after Depo-Provera is 8 months, an assumption which may be inaccurate given the quality of their studies—and the fact that a study has shown that Depo-Provera circulates in the system for a similar length of time—7 to 9 months.\textsuperscript{26} But Upjohn studies have not adequately examined the occurrence of pituitary, hypothalamic and ovarian changes during and after long-term of Depo-Provera use, nor have they examined the relationship between such changes and the delayed return to fertility. Until this is done, the relevance of these changes to post-Depo-Provera fertility problems cannot be dismissed.

Studies conducted by others have also looked at the effect of the drug on return to fertility, but, like Upjohn studies, many are of poor quality. In some studies, a large percentage of women are lost to follow-up\textsuperscript{5,13,14,27} and it is not known whether these women had similar problems in conceiving after discontinuing Depo-Provera use. Most studies observed only a small number of women\textsuperscript{5,13,15,16,27} and in some studies, women who have received only 1 or 2 injections were included, which may disguise the impact of the drug on delaying fertility in those who use it for an extended period of time. In some studies, women received estrogen routinely, and this may alter the results.\textsuperscript{14,15,16} No studies have followed women up for more than two years to see whether some of the women who were initially unable to become pregnant were still unable to conceive. Since this has not been done in Upjohn studies or other studies, a significant amount of permanent sterility cannot be ruled out. This problem is even acknowledged by Upjohn scientists who had said Depo-Provera is not suitable for "women planning on having additional children."\textsuperscript{9}
Since permanent sterility may be an effect of Depo-Provera, and even Upjohn's scientists have stated that women who want more children should not use the drug, why should women use Depo-Provera at all? Why shouldn't they be surgically sterilized in such cases, since sterilization has low complication rates, few side effects and avoids the risks of long-term hormone exposure? Overall surgical complication rates for the newer sterilization procedures are between .7 and 2.7%. Studies show that the major complication rate is .018% and post-operative complication rates are between 1.4 and 6%.

OVARIAN CHANGES

Depo-Provera has serious adverse effects on the ovaries. In one study, ovaries in women using Depo-Provera for 3 months to 3 years have been found to be smaller than normal, probably as a result of inactivity, and ovarian fibrosis, a condition in which the connective tissue in the ovary increases and the glandular, egg producing tissues decrease, was present in almost all Depo-Provera users. Fibrosis was much more common than in controls, and women using oral contraceptives. Monkeys given Depo-Provera showed similar effects: a significant, dose-dependent increase of ovarian fibrosis and ovarian atrophy. Ovarian changes in monkeys and women are probably a result of Depo-Provera's suppression of FSH and LH, which suppress estrogen release by the ovaries. These changes may not be temporary, and they may be related to the inability of some women to become pregnant after discontinuing use of the drug.

Seeing the relevance of such ovarian changes to permanent infertility and other problems, Upjohn would like us to believe that ovarian fibrosis does not occur. An industry-sponsored study reported an absence of fibrosis in women using the drug, but the authors of the study admitted that they did not use a staining method which was designed to detect this problem. The study had one further deficiency --women with amenorrhea from Depo-Provera were given estrogen to induce bleeding before surgical exploration. Since the ovarian changes are related to a lack of sufficient estrogen, estrogen stimulation may have counteracted some of the adverse effects that the authors were trying to evaluate. Even with these limitations, some ovarian changes were noted in Depo-Provera users: 9 of 13 women who had discontinued treatment for 2 to 6 months and all 14 women who had discontinued treatment for 7 to 14 months had cystic follicles, suggesting ovarian changes do not go away, even when women discontinue treatment. The authors claimed that these changes were similar to those observed in untreated women, but the study did not use a control group.
CARDIOVASCULAR DISEASE

Several studies have found an increased incidence in cardiovascular disease in women using oral contraceptives. Originally, this was believed to be related to the estrogen component of the pill, but evidence is beginning to accumulate that the progestogen content of the pill is also associated with the increased risk of certain cardiovascular diseases.34,35,36

Progestogens differ in their cardiovascular effects, and progestogens such as NEA and levonorgestrel do not necessarily have the same effects as Depo-Provera on the cardiovascular system, especially since these progestogens may interact with the estrogen component of oral contraceptives in ways that are not well understood.

However, the preliminary evidence for Depo-Provera is not reassuring. Upjohn's human studies reported a number of cases of thrombosis,25 but since there were no comparison groups, these results could not be interpreted. Other studies have measured lipid blood levels in women using Depo-Provera, because increased cholesterol, and increased LDL, a lipoprotein which transports cholesterol to the blood and tissues, have been associated with an increased risk of heart disease and atherosclerosis, and there is reasonably good evidence that decreased levels of HDL, another lipoprotein, is associated with an increased risk of atherosclerosis and heart attack. In one controlled retrospective study, women using Depo-Provera for at least one year were found to have significantly lower levels of HDL in their blood.37

Similar results were found in another study, but the study used a small number of women and did not give sufficient information on the length of drug treatment or the matching of controls.38 Decreased HDL levels were found in a study by Silverstolpe et al.,39 but the decrease was not significant. Subjects used oral doses of Provera for only 3 weeks, so the results might not be indicative of the effect of long-term injectable Depo-Provera on lipid levels. One human study found a significant increase in cholesterol from pretreatment values at 20 days after the first injection, but not at other times throughout the year.40 However, all of the later tests were conducted three months after an injection, when Depo-Provera levels may have been lower and its effect on lipids reduced. Upjohn reported no change in cholesterol values in women using Depo-Provera,9 but it is not clear whether women had been using Depo-Provera for an extended period of time, so its negative results are not reassuring.

Real concern about Depo-Provera's effect on the cardiovascular system is raised by Upjohn's dog studies. In the study conducted by the International Research and Development Corporation41 in which all of the highest dose dogs were dead at 3 1/2 years, pulmonary thrombosis (blood clots) occurred in three dogs given the highest dose of Depo-Provera. In the Dawson study, which lasted for seven years,42 there was an extremely high incidence of thrombosis, particularly pulmonary thrombosis, and infarction, in dogs given medium and high doses of Depo-Provera.
Increased platelet counts, one of the risk factors for thrombosis, was present in medium and high dose Depo-Provera dogs from the first year of treatment, and occurred in the fifth year of the study in low dose Depo-Provera dogs, indicating a dose-dependent response.

The authors of the Dawson study try very hard to dismiss the significance of these results for humans. They claim that special studies of platelets and fibrin (both of which form thrombi and obstruct blood vessels) did not reveal anything to explain the high incidence of thrombosis.\textsuperscript{42} They don't mention that they had already noted an increase in platelet counts, one of the risk factors contributing to thrombi formation, in dogs exposed to the drug. Then, the authors delve into a discussion of atherosclerosis, another cardiovascular disease which was not present in the dogs, and because the symptoms of atherosclerosis were not present, they state that "thrombosis in progesterone and Depo-Provera treated dogs appeared to have significant dissimilarities from that found in man." Based on their arguments, they have proved only that thrombosis is not the same as atherosclerosis. They have offered no evidence that thrombosis is different in dogs and man, nor have they proved that the results of this study are not relevant for humans.

The Dawson study found increases in risk factors for other types of cardiovascular disease. After 64 months of treatment, all groups of Depo-Provera dogs had significantly higher LDL (lipoprotein) values than controls. Medium and high dose Depo-Provera dogs had significant increases in total cholesterol, LDL, VLDL and HDL compared to controls. Average total cholesterol, which shows the strongest evidence of increasing the risk of cardiovascular disease, was increased in a dose-responsive manner and appear earlier in higher dose than lower dose dogs. Hypercholesterolemia was frequent in the high dose dogs.

Combining the results from human and animal studies, there is evidence to suggest that Depo-Provera may increase the risk of cardiovascular disease. In this respect, Depo-Provera can not be said to offer an advantage over oral contraceptives.

**GLUCOSE AND INSULIN**

Studies have shown that Depo-Provera increases average blood glucose levels\textsuperscript{43,44} in those using the drug. In one study of 49 women given only 2 injections of Depo-Provera,\textsuperscript{43} 86 percent of the women had fasting glucose values which were significantly higher than pretreatment values. While some of the women in the study had family histories of diabetes or other predisposing factors for diabetes, their values after Depo-Provera treatment were not significantly different from the values of other women. One woman in the study who had borderline results at her pretreatment test developed overt diabetes during this short term treatment. One study of 10 oophorectomized women given oral doses of Provera for cervical carcinoma found that after 3 weeks of treatment, fasting and summarized glucose values than were significantly higher than before treatment. In a study of
12 potential and actual diabetics receiving 2 to 12 monthly injections of Depo-Provera, blood glucose levels were significantly increased from pretreatment levels in potential diabetics. Another study found no significant difference between the average blood glucose levels of Depo-Provera treated women and a group of controls, but one half of the controls were judged to be potential diabetics, so their average glucose levels would be expected to be high, and thus there would not be a large difference between their glucose values and the high values of Depo-Provera users.

Evidence from long-term dog studies supports the finding that Depo-Provera has an adverse effect on glucose tolerance. In the Dawson study there was a dose-dependent increase in glucose and glucose tolerance levels in Depo-Provera treated dogs. Glucose and glucose tolerance values were significantly higher than controls only occasionally in low dose dogs but were consistently increased in medium and high dose dogs, and these effects occurred earlier in the medium and high dose than in the lower dose dogs. At least 3 dogs, including one medium dose and two high dose Depo-Provera dogs developed diabetes.

With respect to carbohydrate tolerance, Depo-Provera cannot be considered to pose an advantage over oral contraceptives.

Clinical experience with Depo-Provera reveals that its side effects are experienced as undesirable—or intolerable—by many women, since many discontinue using the drug. Many studies show that at one year, only 50 to 60 percent of the women who have started Depo-Provera continue to use it, although in one study of postpartum women, only 24% of the women were still receiving injections after 12 months. A large percentage of women who discontinue Depo-Provera do so after a short period of time. One three year study found that 79 percent of the women who stopped using the drug did so by the third injection, and another study found that 30 percent of the women discontinuing use of the drug did so after one or two injections. Medical side effects such as bleeding are a frequent reason cited for discontinuing use of the drug, although the true magnitude of this reason cannot be determined because many studies had a large loss to follow-up or reported discontinuation for "personal reasons" and did not go to great lengths to collect accurate, unbiased data on the reasons for discontinuation.

If there is such a need for this drug, why have so many women found it intolerable after such a short period of time? Although women only need to receive an injection once every 90 days, and it is much more convenient than other methods of contraception, the continuation rates for Depo-Provera at one year are not that much higher than for other contraceptives.
THE RISKS OF A LONG-ACTING DRUG

Depo-Provera's main advantage is its convenience—because it is long-acting, women need to receive an injection once every 90 days. But even this long-acting property of the drug has its risks. Once a woman receives an injection, Depo-Provera circulates in the blood for many months. One study found that after one injection, Depo-Provera can be detected in the blood for 7 to 9 months. This means that when a woman experiences a side effect from the drug, the drug cannot be removed from her system, and she may have to wait for months before being free of the drug's effects. No other method of birth control places women in this vulnerable, dangerous position.

ISSUE 2: DO THE DATA FROM THE BEAGLE AND MONKEY STUDIES SUBMITTED BY UPJOHN SUCCESSFULLY REFUTE THE RISK OF HUMAN CANCER SUGGESTED BY THE ANIMAL DATA?

MAMMARY CANCER AND NODULES IN BEAGLE DOGS

Several studies, conducted by Upjohn and others, have shown that Depo-Provera induces mammary tumors in beagle dogs. Some of these tumors are malignant. Mammary cancer occurs in a dose-responsive manner, with more cancer occurring in dogs given higher doses of the drug. Even Upjohn admits that the mammary cancer in dogs is not spontaneous but is a result of drug treatment. Mammary cancer occurs at high and medium doses of the drug, but in the Dawson study conducted for Upjohn, there was a substantial incidence of mammary carcinoma (7/20 dogs) in dogs exposed to the equivalent human dose of Depo-Provera for an extended period of time (0/20 control dogs had mammary carcinoma).

Beagle studies have also found a dose-dependent increase in non-malignant mammary nodules in dogs exposed to Depo-Provera. Higher doses cause more nodules, larger nodules, and cause nodules to develop at an earlier age. Some of the mammary nodules disappear after treatment has been discontinued and others disappear during treatment—but some nodules do not disappear. It is not known whether mammary cancer originates from these benign nodules, or whether it develops from another source.

Upjohn and other advocates of Depo-Provera argue that dog studies do not indicate any danger of Depo-Provera for humans, because dogs have a high incidence of spontaneous mammary nodules and because beagles have an acute sensitivity to progestogens. These arguments do not hold up to scrutiny. Mammary cancer is rare in dogs which are not exposed to Depo-Provera, but occurs significantly more often in dogs exposed to Depo-Provera. Mammary nodules do occur in control dogs (those not exposed to Depo-Provera) but they do not occur at the frequency with which they occur in Depo-Provera-exposed dogs. Nor do beagles have a special sensitivity to progestins. Some of the Depo-Provera dog studies, including the Dawson study, administered progesterone (the natural hormone, to which synthetic versions like Depo-Provera are related) to groups of dogs. These dogs developed mammary nodules and in some cases mammary cancer, but not as frequently as Depo-Provera treated dogs. In the
Dawson study\textsuperscript{42} 45\% of the dogs treated with the high dose Depo-Provera had mammary carcinoma, while only 10\% of the dogs receiving the high dose of progesterone developed mammary carcinoma. In other words, beagles do not show an acute sensitivity to all progestational agents, and the high incidence of mammary cancer in Depo-Provera dogs cannot be dismissed on these grounds.

Upjohn and others argue that certain hormonal interactions related to mammary nodule growth in the dog are not present in humans. Specifically, they argue that mammary nodules in Depo-Provera treated dogs are associated with an increase in growth hormone, but increases in growth hormone have not been observed in women given Depo-Provera. But Upjohn has offered no evidence that differences in growth hormone actually accounts for the presence of nodules or cancer in the dogs, or that the absence of such an increase in women can assure the absence of mammary nodules or cancer in women using Depo-Provera. The observation concerning differences between growth hormone responses in dogs and humans is just that—an observation. Its significance is not known, and it does not prove that Depo-Provera is safe for women.

CANCER IN MONKEYS

Results from a 10 year monkey study conducted for Upjohn and completed in 1979\textsuperscript{50} casts further doubt on the safety of Depo-Provera. Two of twelve monkeys given 50 times the human dose of Depo-Provera developed cancer of the endometrium, and one of the monkeys had cancer of the cervix as well. The cancer in this monkey metastasized to other parts of the body. The incidence of spontaneous tumors of any kind in monkeys is low.\textsuperscript{51} The International Research and Development Corporation, which conducted the study, and most of Upjohn's consulting pathologists felt that because they appeared only in monkeys given the highest dose of Depo-Provera, the cancers were not spontaneous but were related to drug treatment. The association between progestins and endometrial cancer should come as no surprise, since according to one of the Upjohn consulting pathologists,\textsuperscript{52} progesterone and progestogens have been found to cause endometrial cancer in mice.

Of course, Upjohn has tried to deny that the evidence of cancer in the monkeys poses any risk for women. At a roundtable discussion on the matter held by Upjohn\textsuperscript{53}, it was concluded that the small numbers of animals in the study and the absence of information on the monkeys' age or prior history precluded drawing any conclusions about the study or the association between Depo-Provera and cancer. But if this is true, Upjohn has only itself to blame for the study design.
Upjohn has also pointed to so-called vast differences between monkeys and humans which supposedly indicate that Depo-Provera poses no similar risk of cancer in women. In fact, Depo-Provera causes very similar endometrial and ovarian responses in monkeys and women: in both, it causes initial proliferation of the endometrium, but endometrial atrophy and pseudodeciduous transformation of the endometrial stroma over time, and causes ovarian fibrosis and atrophy. Upjohn also claims that the cell from which the monkey cancers originated is a "cell type" not present in women. This argument was originally made by Dr. Valerio, one of Upjohn's consulting pathologists, who stated that the monkey endometrial cancer grew in a pattern similar to that of endometrial plaques which form in monkeys during pregnancy (when there is exposure to progesterone). Since the plaques don't form in women during pregnancy, Dr. Valerio concludes that endometrial cancer would not occur in women using Depo-Provera. This "logic" is extremely unscientific—and dangerous. There is no evidence that the epithelial plaque in monkeys forms from the same cells that developed cancer—it is merely a similarity between the two that has been noted. Furthermore, there is no evidence that because women don't form epithelial plaques, they are immune to the risk of endometrial cancer from Depo-Provera.

Upjohn has also pointed to the fact that the two monkeys with cancer were both 'replacement' monkeys—animals which were added to the study after it began, to replace monkeys that had died. But Upjohn has been unable to identify any differences between the replacement monkeys and other monkeys that would account for their difference in tumor growth. Furthermore, one of Upjohn's consulting pathologists noted that another monkey given the highest dose of Depo-Provera (not a replacement monkey) exhibited endometrial changes which could be a precursor to cancer.

It has been pointed out that endometrial cancer is a puzzling effect of a drug that causes endometrial atrophy, and not endometrial growth. There is now evidence which may clear up this mystery. Human pathologist Dr. Dallenbach-Hellweg has examined the tissues from the monkey cancers and determined that the cancers arose from the endometria but from the endocervical mucosa. In addition to this observation, there is a significant increase in hypersecretion of the mucous glands of the cervix in Depo-Provera treated monkeys. The finding that the cancer originated in the endocervix is extremely relevant for humans, because of all cancer of the reproductive organs, cancer of the cervix is the most common in women.

Of 16 monkeys given the medium dose of Depo-Provera, 3 of 7 monkeys alive at the end of the study were found to have mammary nodular hyperplasia. One of the pathologists who reviewed the tissues felt that in two of the monkeys, the nodules were cancerous. These findings provide additional evidence that the beagle is not unique in its response to the drug. Upjohn claims that such nodules often regress, and that mammary nodules in control low dose and other medium dose monkeys did regress during the
study, while all of the nodules that appeared in control and low dose animals did. FDA witness Dr. Henry Norris studied tissues from 188 monkey breasts of monkeys exposed to oral progestins or combined estrogen-progestin pills and found a high incidence of atypical breast lesions, which indicates that Depo-Provera is no different from other progestins in its effects. As a result of the findings from Dr. Norris' study, the steroid contraceptives in question were not approved.

Depo-Provera is tumorogenic not just in breasts and reproductive organs but in other parts of the body. Hansel and others found liver adenomas in dogs treated with Depo-Provera, and the Dawson study found a significant increase in hepatitis or liver granulomas and liver cysts in Depo-Provera treated dogs. Liver adenomas found in the study by Hansel were similar to those found in women using oral contraceptives. Thyroid adenomas were also significantly increased in Depo-Provera treated dogs. The monkey study showed a significant dose-related increase in the sum of all benign and malignant tumors in Depo-Provera treated animals. These findings prove that beagle breasts are not the only organ sensitive to Depo-Provera's tumorogenic effects and that the response in monkey reproductive organs is not bizarre.

MICE AND RAT STUDIES

Upjohn conducted 18 and 24 month studies in mice and rats which add to concerns about Depo-Provera's safety. The studies were poorly conducted (for example, one half of the control mice died before the end of the study) and in the available summary, poorly reported as well (results are only reported for the highest dose, and animals which died before the end of the study are not included in the analysis of the findings). But the study results which were reported indicate that Depo-Provera has adverse effects on rodents. There was a statistically significant increase of total neoplasms in the female mice given the highest dose of Depo-Provera. This high incidence of neoplasms was due principally to the increased incidence of hemangiomas and malignant lymphoma. Male rats given the highest dose of Depo-Provera had a significant increase in adrenocortical nodules, and female rats at this dose had a significant increase in pyelonephritis. While study limitations decreases the value of these findings, it is clear that these studies do not prove that Depo-Provera is safe in rodents.

ANIMAL STUDIES WHICH SHOW CANCER INDICATE A POTENTIAL RISK OF CANCER FOR HUMANS

Cancer scientists rely on animal tests to determine whether substances pose a risk of cancer for humans because: (1) human evidence of cancer is extremely difficult to obtain and is obtainable, if at all, only after years of exposure by many people; and (2) animal studies have proven to be reliable predictors of human susceptibility to cancer-causing chemicals. All substances known to cause cancer in humans have also caused cancer in laboratory animals (with the possible exception of inorganic arsenic, still under study).
In its report to the Surgeon General, the Ad Hoc Committee on Evaluation of Environmental Chemical Carcinogens stated that:

Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential cancer hazard for man. Exceptions should be considered only where the carcinogenic effect is clearly shown to result from physical rather than chemical induction, or where the route of administration is shown to be grossly inappropriate in terms of conceivable human exposure. No level of exposure to a chemical carcinogen should be considered toxicologically insignificant for man. For carcinogenic agents, a 'safe level for man' cannot be established by application of our present knowledge.

In the case of Depo-Provera, cancer has been found in not one but two species of animals. In the face of such evidence, the drug must be concluded to be unsafe for humans.

ISSUE 3: CAN THE HUMAN DATA SUBMITTED BY UPJOHN SUCCESSFULLY REFUTE THE RISK OF CANCER SUGGESTED BY THE ANIMAL STUDIES?

Upjohn conducted its human studies on Depo-Provera without a control group. Normally, when a drug is studied scientifically, it is given to one group of women, and another group of women who are similar to the first group do not get the drug. Both groups are carefully monitored. If unusual problems appear only in the women given the drug, or if they appear more often in the women given the drug, they are considered to be caused by the drug. Upjohn did not use control groups therefore it could report how many cases of cancer occurred, but it could not evaluate the significance of the results to determine whether the rate of certain adverse effects such as breast endometrial cancer was abnormally increased. Both groups of authors of these studies admitted that without control groups, statistical analysis and meaningful interpretation of the results was not possible. Several others who have studied the carcinogenicity of Depo-Provera in humans have also failed to use control groups.

Upjohn studies, and other human studies of Depo-Provera including controlled studies, failed to follow up women for a sufficient length of time after Depo-Provera exposure to adequately determine whether the drug resulted in an increased risk of cancer. Most of the studies merely screened women for breast or uterine cancer during drug treatment but did not even follow women up after drug use stopped. Since the human latency period for cancer is 10-20 or more years, none of these studies allowed a sufficient amount of time to go by before measuring the carcinogenicity of the drug. For this reason, human studies conducted on Depo-Provera to date are not useful for the purpose of determining the safety of the drug.
Depo-Provera studies conducted by Upjohn and others have numerous other limitations, for example, in many cases, estrogen was administered in addition to Depo-Provera for the control of abnormal bleeding. Estrogen use would certainly influence the risk of cancer, but this is never controlled in studies. In all of the studies women use Depo-Provera for varying lengths of time and because of high discontinuation rates, most use it for a short period of time. Most studies did not account for this fact. For example, in a recent study of over 5,000 women who used Depo­Provera, more than half of them used it for less than 1 year.68 Other major problems include high loss to follow-up64,68 in prospective studies, failure to control for important risk factors,67,69 lack of prescreening in prospective studies to ensure that tumors developed after drug exposure3,25 rather than being present before the study began, and selection bias.69 In sum, human studies have not proved that Depo-Provera is safe for women.

**ISSUE 5: IN THE EVENT OF CONTRACEPTIVE FAILURE, WILL DEPO­PROVERA INCREASE THE RISK OF BIRTH DEFECTS?**

Synthetic progestins,70,71 including Depo-Provera70,72 have been found to cause masculinization of the fetus in animal studies. In humans, exposure to Depo-Provera and other similar progestogens during pregnancy has also been associated with masculinization of the female fetus.73-78

Progestogens have also been associated with numerous other birth defects in humans. In 1973, the FDA withdrew approval of all pregnancy-related uses of progestogens, in part because of their association with birth defects.79

Studies have linked progestogen or combined progestogen and estrogen exposure during pregnancy to limb reduction defects,80 a syndrome of limb, heart and other defects,81 hypospadias,82 and an increase in total malformations,83,84, although a more recent study did not find an association between female sex hormones and cardiac defects85. Because of small numbers, human studies have not looked at exposure to individual progestogens such as Depo-Provera, but animal studies have found a dose-dependent statistically significant increase between Depo-Provera and cleft palate86,87 and an increase in the absence of pubic bones and thumbs, which did not occur in rabbits unexposed to the drug.86
Depo-Provera use might occur during pregnancy under 3 sets of circumstances: a woman may be pregnant when she receives her injection of Depo-Provera, she may wait more than twelve weeks before receiving the next injection and become pregnant in the interim (and because many women are amenorrheic on Depo-Provera, such a pregnancy would not be suspected), and she may become pregnant after discontinuing Depo-Provera when the drug is still present in her system. All of these types of exposure can occur with oral contraceptives as well, but when progestogen exposure occurs with Depo-Provera it poses a much greater risk to the child. Since the drug is long-acting, a child would be exposed to the drug for at least 3 months during pregnancy and this increases the likelihood that exposure would occur during a critical period of development.

Urine pregnancy tests are not an accurate means of detecting early pregnancy, so even if such a test were given systematically to women before the first injection of Depo-Provera, they may miss a very early pregnancy. Blood tests, which are more accurate for detecting early pregnancies, are not currently used on a routine basis. It is extremely unlikely that blood tests for pregnancy would be used on a routine basis for women receiving Depo-Provera, particularly if the drug is used mainly in poor and mentally retarded women.

ISSUE 7: IS THERE AN APPROPRIATE PATIENT POPULATION IN THE U.S. FOR WHOM THE BENEFITS OF DEPO-PROVERA OUTWEIGH THE RISKS--AND IF SO--COULD THE DRUG'S USE BE SUCCESSFULLY CONFINED TO THIS LIMITED POPULATION?

There is no group of women in the U.S. for whom the benefits of Depo-Provera outweigh the risks. Depo-Provera causes cancer in two species of animals and thus poses a potential risk of cancer to humans. It has numerous other serious and often irreversible side effects. These risks, when combined, are not justified in a contraceptive which is given for long periods of time to healthy women.

When the FDA first intended to approve Depo-Provera as a contraceptive, it was to be approved for use by a limited population: women who were incapable of accepting the responsibility for other methods of contraception, and women in whom other methods of contraception had repeatedly failed. Amongst those groups for whom Depo-Provera was intended were the poor and the mentally retarded. Subjecting these groups of women to an increased risk of cancer and other serious side effects which are judged to be unacceptable for other women creates a double standard of safety which is morally offensive and unacceptable.

Mentally incompetent women and women who are unable to accept the responsibility for other methods of contraception are the least appropriate candidates for a contraceptive such as Depo-Provera. These women are the least likely to be able to weigh the benefits and the risks of the drug (even if such risks are detailed in a patient information sheet) and give true informed consent. The FDA, which in
its original proposed labeling suggested that a guardian may need to consent for such women, recognized that for many of the women in this subgroup, informed consent was impossible. Women not capable of handling other methods of contraception are ill suited for Depo-Provera for other reasons. They may be more vulnerable to pressure from physicians who are anxious to prescribe the drug, and they may be less likely to connect side effects to the drug and take the steps necessary to discontinue its use when problems arise.

Even if a double standard of safety were acceptable, and informed consent was possible, it would be extremely difficult, if not impossible, for the FDA to define the subgroup of women who are unable to use other methods of contraception. Approving the drug for such a subgroup would place a high degree of responsibility on physicians to accurately identify women in this subgroup, and it would encourage physicians to make certain subjective judgments and assumptions about who is and is not able to cope with other methods of contraception. Moreover, it could easily lead to a self-fulfilling prophesy whereby women are assumed to be unable to cope with other methods of contraception, do not receive adequate contraceptive instruction for other methods, and therefore become ill equipped to use other methods effectively.

If Depo-Provera were approved as a contraceptive for use by a limited population, there would be no way to prevent physicians from prescribing it for other women for whom its use was not approved. In this case, the approved population would be only a small fraction of the unapproved population. Given Depo-Provera's convenience, and its simplicity of administration (two features which are beneficial to physicians as well as women), it is extremely likely that it would be used outside of the limited subgroup for whom it was approved, especially if physicians glorify the benefits of the drug without placing equal emphasis on its risks. The likelihood that this would occur, and the risks associated with the drug use in this larger population must be taken into account when deciding whether to approve this drug. Former FDA Commissioner Donald Kennedy made this point when defending the FDA's decision not to approve the drug as a contraceptive for a limited subgroup:

You cannot guarantee that a drug intended for a limited population is going to be confined, in actual use in the U.S. health care system, to that patient population. So when you talk about the size of a patient population, you are really talking about the issue of whether it can be successfully confined, and obviously that affects safety considerations.
FOOTNOTES


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42. Dawson Research Corporation. Long-term Depo-Provera study in Dogs DRC 6205 June 11, 1982


50. International Research and Development Corporation. Summary of long-term monkey study with Depo-Provera

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52. Letter from Dr. Ralph Heywood to Dr. E.S. Feenstra, The Upjohn Company, April 15, 1979, contained in Upjohn's summary of the IRDC monkey study.

53. ISM and PBI Committees, The Upjohn Company. Roundtable Depo-Provera discussions. February 27, 1982


55. Letter from Dr. Marion Valerio to Dr. E.S. Gerard, The Upjohn Company, July 14, 1982, contained in Upjohn's summary of the IRDC monkey study

56. Letter from Dr. Kurt Benirschke to Dr. E.S. Gerard, The Upjohn Company, July 14, 1982, contained in Upjohn's summary of the IRDC monkey study

57. Testimony of Dr. Gisela Dallenbach-Hellweg, Food and Drug Administration, Depo-Provera Public Board of Inquiry, December 23, 1982

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88. Statement of Donald Kennedy, Commissioner of the Food and Drug Administration, before Select Committee on Population, U.S. House of Representatives August 8, 1978 p. 35