REPORT OF THE PUBLIC BOARD OF INQUIRY ON DEPO - PROVERA

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REPORT OF THE PUBLIC BOARD OF INQUIRY ON DEPO-PROVERA

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I. THE PUBLIC BOARD OF INQUIRY: EVENTS LEADING TO ITS ESTABLISHMENT, ITS MANDATE, AND PROCEDURES

On July 20, 1979, at the request of the Upjohn Company, the Commissioner of the Food and Drug Administration (FDA) announced that a hearing before a Public Board of Inquiry (PBI) would be held

> to determine whether Upjohn's supplemental new drug application (NDA) for Depo-Provera (DMPA) sterile aqueous suspension for intramuscular injection as a contraceptive agent in humans contains reports of investigation adequate to show that the drug is safe for use under the conditions prescribed, recommended or suggested in the labeling as required by § 505(d)(1), (2) and (4) of the Federal Food, Drug, and Cosmetic Act (the Act), and whether that information combined with other information about the drug, provides a sufficient basis from which FDA can determine that DMPA is safe for general marketing in the United States [1].

The FDA had considered a supplemental NDA for the use of DMPA as a contraceptive on two previous occasions, in 1974 and 1978 [2, 3]. In 1978 the request was denied. It is to re-evaluate this decision that the PBI was appointed at the request of Upjohn. [For chronology of events, see Table 1, pp. 11-15.]

This was only the second time that the FDA had ordered a public hearing before a PBI under 21 CFR Part 13 in lieu of a formal evidentiary public hearing before an Administrative Law Judge under 21 CFR Part 12. The previous PBI had been established to consider the use of Aspartame as a sweetener and flavor enhancer in dry foods [4]. Upjohn

stated its reason for requesting a Public Board of Inquiry to be that the issues under consideration are "technically complex, require an understanding of sophisticated scientific concepts, and necessitate the comprehension and evaluation of a large body of scientific literature and other data" [5].

The PBI was established in September 1981 and mandated to consider and render an opinion on the following issues [6]:

1) Whether, in comparison with other drugs approved for contraception, the benefits of Depo-Provera in the United States outweigh its risks under conditions of general marketing.

2) Whether data from beagle dog and monkey studies submitted by Upjohn indicate a potential risk of breast or endometrial cancer in humans from Depo-Provera.

3) Whether the human data submitted by Upjohn can, as Upjohn claims, successfully refute the risk of human cancer suggested by the animal data.

4) Whether an approval of Depo-Provera for contraception under general marketing conditions is likely to increase use of the drug as a contraceptive under conditions not stipulated in the approved labeling or is it likely to increase use of the drug for unrelated indications for which safety and effectiveness have not been established (e.g., for hygienic purposes in mental retardees).

5) Whether, in the event of contraceptive failure, use of Depo-Provera may increase the risk of teratogenic effects to a greater extent than would other systemic contraceptives.

6) Whether, in view of Depo-Provera's adverse side effects or pharmacologic effect, estrogen therapy is likely to be prescribed in addition to Depo-Provera in a significant number of patients.

7) Whether there are conditions of labeling and distribution controls which would permit marketing of

> Depo-Provera as a safe and effective drug on a limited basis (i.e., Whether there may be certain patients in the U.S. for whom benefits of Depo-Provera for contraception outweigh potential risks). (Emphasis added)

All of these issues were raised by the FDA in 1978 in course of its review of the supplemental NDA for the use of DMPA as a contraceptive [3]. On September 10, 1981, we were appointed by FDA Commissioner Arthur Hull Hayes, Jr., to serve as members of the PBI [6]. We were acceptable to both the Upjohn Company and the FDA because none of us had taken any position on DMPA as a contraceptive in the past. In addition, among us, we covered the range of expertise relevant for evaluating the issues.1/

The process by which we have carried out our tasks involved:

1) A review of the documents in the administrative record in this matter as well as published literature on Depo-Provera. As new questions arose we asked one or the other of the parties to provide additional information for the record including an initial statement of position [8, 9]. All of the literature and documents we reviewed and on which we have based our decision were either already in or have

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1/ At the request of the Upjohn Company Dr. Stolley did not participate either in the review of the material concerning the potential teratogenicity of DMPA or in making the decision on this issue [7].

been placed in the administrative record and are accessible to the public.[2/]

2) A five-day public hearing held from January 10-14, 1983, where party and nonparty participants presented testimony and responded to our questions. Among those represented at the hearing, in addition to the two parties, the Upjohn Company and the FDA's National Center for Drugs and Biologics (now the Center for Drugs and Biologics) (Center), were the World Health Organization (WHO), the International Planned Parenthood Federation, the U.S. Agency for International Development, the Women's National Health Network, the Health Research Group, the Institute for the Study of Medical Ethics, the American College of Obstetricians and Gynecologists, and certain individuals representing themselves [10].

In addition, on August 12, 1983, a second hearing was held to receive the report of a panel of six pathologists who had been designated by us as consultants to review the histological slides of monkeys that developed uterine tumors following exposure to DMPA [11].

2/ In September, 1983, when we began, the documents in the administrative record in this matter occupied approximately 45 linear feet of shelf space. At the time of the submission of our report, the documents occupy approximately 54 linear feet.

3) Periodically, meetings were held to discuss the evidence, arrive at decisions, and outline our report.[3/]

4) Writing our report.[4/]

In all of these phases we were ably assisted by Ms. Rita Schinnar, research assistant to the PBI who, like us, was appointed a special Government employee.

Our report and conclusions about DMPA have evolved from these numerous encounters and discussions. Throughout this process, we have considered our primary task to be to evaluate the scientific validity of the information available. We attempted to determine how much of this information qualified as facts on which definitive conclusions could be based. We have attempted to identify and record the facts and to differentiate them clearly from assumptions and hypotheses. Assumptions are an inevitable

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3/ The entire Board met in Washington, D.C. on September 22, 1982; in Washington, D.C. on January 9, 1983; in San Francisco, CA. on March 6-7, 1983; in Hershey, PA. on August 13-14, 1983; and in Washington, D.C. on August 10-11, 1984. Dr. Weisz and Dr. Stolley met in Philadelphia, PA. on August 31, 1982; Dr. Weisz and Dr. Ross in Washington, D.C., on August 10, 1983, and in Houston, TX. on November 25-27, 1983; and Dr. Stolley and Dr. Ross in Houston on June 13, 1984.

4/ Because of illness, Dr. Ross was unable to participate in this fourth phase. He was a full participant in the earlier phases. (See his letter to Dr. Weisz, p. 181.)

and necessary part of science. But, no matter how widely accepted, they are subject to change as knowledge expands. Hypotheses, however plausible, can not serve as evidence until tested and proven correct. To qualify as a fact, information and data have to pass the test of having been generated and analyzed by adequate scientific methods. We recognize that the significance of facts is subject to interpretation and that this may vary among individuals and also change with time as knowledge expands. In making the recommendation on Depo-Provera, we strove to identify and record the basis for each of the conclusions. The report includes, in addition to an extensive list of references, a series of appendices (Appendix 1-5). In these appendices are detailed the data and the methods used to generate the data, as distinct from their interpretation, for certain key publications and documents on which our conclusions are based. This should permit the reader to judge the factual basis on which our evaluation of the data and our conclusions rest.

Our findings and conclusions will have the legal status of an initial decision under 21 CFR 13.40(a)(4) and 12.120. The initial decision becomes the final decision of the Commissioner by operation of law unless a participant files exceptions or the Commissioner files a notice of review. 21 CFR 12.120(e). The Commissioner's final decision is reviewable by the courts. 21 CFR 12.140.

The structure of our report is as follows: after a brief historical overview of the chronology of events relating to Depo-Provera, we address each of the questions presented to us by the Commissioner. We have, however, reordered the sequence in which the questions are addressed, so that the scientific evidence available for assessing the risks associated with the use of the drug, required to arrive at a regulatory decision, is presented and evaluated before considering the regulatory decision itself. Thus, answers relating to the carcinogenic and teratogenic potential of the drug (Questions #2, #3 and #5) are presented first. These are followed by a discussion of the issue of the possible increased use of estrogens that introduction of DMPA as a contraceptive may cause (Question #6) and by a separate brief section in which we address the question of the influence of MPA on bone and on plasma lipoproteins. The latter two issues, though not specifically addressed in the questions by the Commissioner, are ones that have been raised in the hearing process and that need to be considered in relation to the use of DMPA as a contraceptive. Recommendations concerning marketing of DMPA and the consequences of making the drug available as a contraceptive under conditions of general marketing are presented last (combining answers to Questions #1, #4 and #7). After this detailed statement of the reasoning on which our conclusions are based, we conclude with specific findings and references supporting and

explaining our conclusions, as required by 21 CFR 13.30(j).

II. HISTORICAL BACKGROUND ON DEPO-PROVERA

1. EXPERIENCE IN THE U.S.A. (SEE TABLE 1, pp. 11-15)

Depo-Provera (or Depot Medroxyprogesterone Acetate or DMPA) was developed by the Upjohn Company in 1954. It was initially intended for use in the treatment of endometriosis and for habitual or threatened abortions. When the FDA had approved Depo-Provera for use for these two indications in 1960, it did so in the absence of randomized controlled studies of efficacy. By 1973, the FDA rescinded the earlier approval of the drug for use in endometriosis and threatened abortion due to lack of evidence of efficacy and concerns about potential teratogenicity and delayed return of fertility [12].

In 1967, the Upjohn Company submitted a supplemental new drug application for Depo-Provera (NDA 12-541/S004) for intramuscular injection as a contraceptive agent in humans. In the late 1960's and early 70's a large number of studies were carried out to establish the efficacy of Depo-Provera and to identify an appropriate dose level. These early studies were also designed to provide data on physiological consequences and side-effects following short-term use of the drug, e.g., weight change, prolonged amenorrhea or bleeding,

return of ovulation, and psychological effects [13-20]. In these studies, observations on pregnancy outcome in women who discontinued use of Depo-Provera, or on the pathology of breast, cervical or endometrial biopsies in exposed women, were made only incidentally.

Concurrent with these clinical studies, the two long-term toxicity studies in animals (a 7-year study in Beagle dogs and a 10-year study in Rhesus monkeys) were initiated in 1968. A second 7-year study in dogs was started in 1972.

During March, April and May 1974, in the course of a Congressional investigation of the use of advisory committees by the FDA, new concerns were raised about the drug's safety; specifically, the possible increased risk of cervical cancer in women using the drug for contraception [2]. This led to the FDA's first announcement on October 30, 1974, of its intention to deny approval of the supplemental NDA for Depo-Provera [2].

Results from the two long-term studies in beagle dogs became available in 1975 and 1979, respectively. Both studies showed an increased incidence of malignant mammary tumors in dogs treated with DMPA at low and high dose levels [22-24]. These findings and the lack of human data to refute them led the FDA to propose to refuse approval of the supplemental NDA for DMPA in 1978 [3]. By 1979, the results from the long-term study in Rhesus monkeys became available.

These showed endometrial carcinomas in two of the treated monkeys [24]. Numerous reviews of the findings in the test animals and of the published literature on Depo-Provera were undertaken by various organizations in the U.S.A. and other countries to try to assess the relevance of these findings to humans [25-29]. As previously discussed, in March 1978 FDA proposed to refuse to approve Upjohn's supplemental NDA for the use of DMPA as a contraceptive, and Upjohn requested a hearing before a Public Board of Inquiry.

It should be added that since 1972, use of Depo-Provera has been approved by the FDA as adjunctive therapy and palliative treatment of inoperable, recurrent and metastatic endometrial carcinoma.

TABLE 1: CHRONOLOGY

1954:	Depo-Provera developed by the Upjohn Company
1956:	Clinical trials begun testing its use for habitual or threatened abortions and endometriosis.
1960:	FDA approved the use of Depo-Provera for the above indications.
April 1966:	FDA withdrew from the market the drug Promone (DMPA formulated for veterinary use) because of an increased incidence of cystic endometrial hyperplasia in treated dogs.
Feb. 27, 1967:	Upjohn Co. submitted a supplemental new drug application for Depo-Provera for intramuscular injection as a contraceptive agent in humans. This supplement was submitted to allow general marketing of this drug for contraceptive purposes.
May 1968:	Two long-term animal studies initiated: a 7-year study of Depo-Provera in beagle dogs and a 10-year study in rhesus monkeys. At the same time, clinical studies were initiated in several medical settings in this and other countries to test its efficacy and side effects when used as a contraceptive.
1971:	Results of the two-year toxicity studies of Depo-Provera in mice and rats were submitted to FDA. They were accepted by FDA although the results on the mice were uninterpretable because of the high mortality of animals in both the control and experimental groups, and inadequate pathological examination of such animals and in spite of the small number of rats studied [30].
1972-1978:	Depo-Provera used at the Grady Clinic under a formal IND status.
1972:	FDA approved the use of Depo-Provera as adjunctive therapy in treatment of endometrial carcinoma.

1972: A second 7-year study in beagle dogs started because of high mortality among dogs in first study attributed primarily to pyometra.

Oct. 10, 1973: FDA issued a proposal to provide patient labeling for Depo-Provera for contraceptive use. Having considered the potential complications of benign and malignant tumors of the breast (as already demonstrated at that time by the first studies of beagle dogs given Depo-Provera) and of infertility, the FDA was still of the opinion that the benefits from use of the drug outweighed its risks.

Oct. 10, 1973: FDA's Obstetrics and Gynecology Committee (meeting on Feb. 22, 1973) recommended approval for a limited and well-defined population; and the FDA proposed, as a cautionary measure, to restrict the distribution of the drug by the manufacturer to private practitioners, family planning clinics, hospitals and retail pharmacies. This was intended to maintain a registry of physicians who utilized the drug for contraception. The objective of this restriction of the distribution was that "in the event evidence appears in the future that the tumorigenic effect of Depo-Provera poses an increased risk of breast tumors in the human, direct notification of these physicians can be made and appropriate patient follow-up instituted [12]."

Oct. 10, 1973: Concurrently with the above, the FDA rescinded the earlier approval for use in endometriosis and threatened abortion due to lack of evidence of efficacy for these indications and concerns about potential teratogenicity, specifically, congenital heart defects.

March, April, May, 1974: During Congressional Hearings on the use of advisory committees by the FDA, the issue of cervical cancer in users of Depo-Provera was raised [21].

Sept. 12, 1974: FDA issued a final order providing for patient labeling for DMPA. This order was published in anticipation of the agency's approval of the pending supplemental NDA for use of Depo-Provera as a contraceptive.

Oct. 2, 1974: Letter sent by the Chairman of the Subcommittee on Intergovernmental Relations, Rep. L.H. Fountain, of the House Committee of Government Operations to the Secretary of HEW requesting that the FDA revoke approval of Depo-Provera because of unresolved questions concerning the drug's safety and its role in causing carcinoma of cervix [31].

Oct. 30, 1974: FDA stayed the provisions of the regulation until further notice as a question was raised about the incidence of cervical cancer among women who participated in studies sponsored by Upjohn under an IND.

May 1975: Results from the first beagle study became available and showed development of mammary tumors, including carcinomas, in treated dogs [22].

March 7, 1978: FDA advised Upjohn that the supplemental NDA was not approvable because of insufficient information to determine whether Depo-Provera was safe for general marketing in the United States as a contraceptive. Specific reasons given for this decision included the increased incidence of mammary carcinoma in beagle dogs; the lack of a significant patient population in the United States in need of this drug; and the belief that the manufacturer would not be able to implement a proposed post-marketing study in the United States to assess potential serious risks of the drug. At this time, presumably, FDA had been informally advised of the results of the second beagle study, but the final report was not submitted until 1982.

March 28, 1978: Upjohn challenged the FDA's decision to refuse approval of the supplemental NDA for Depo-Provera and requested an opportunity for a hearing. Upjohn waived its right to a formal evidentiary public hearing before an administrative law judge, and requested instead that a Public Board of Inquiry be established.

Oct. 24, 1978: FDA Commissioner accepted Upjohn's request for a hearing before a Public Board of Inquiry.

Dec. 1978: FDA audit of the conduct of the IND study of Depo-Provera at the Grady Clinic [32]. This terminated the use of the drug as a contraceptive by the single largest known population of subjects at a single center in the USA.

May 1, 1979: Findings from the 10 year study of the effects of Depo-Provera on Rhesus monkeys became available. It showed endometrial cancer in two of the monkeys in the high dose group. This was followed by reviews by several national and international organizations of the relevance to the human of the findings in the long term studies of monkeys and dogs [25-29].

July 27, 1979: FDA announced a hearing before a Public Board of Inquiry to determine whether the supplemental NDA for Depo-Provera contained reports of investigations adequate to show that the drug was safe for use as a contraceptive, and whether that information provided a sufficient basis from which FDA could determine that Depo-Provera was safe for general marketing in the United States for contraception.

Sept. 10, 1981: FDA formally established a Public Board of Inquiry, consisting of a three-member panel, assisted by a legal counselor and a research assistant.

Sept. 23, 1982: A prehearing conference was held to establish procedures for the public hearing.

Jan. 10-14, 1983: The Public Board of Inquiry held a 5-day public hearing on Depo-Provera, receiving testimony and responses to questions from Upjohn and the FDA (the parties), and from non-party participants.

Aug. 12, 1983: The Public Board of Inquiry held an additional one-day public hearing on Depo-Provera, to receive the report of an especially-appointed panel of 6 consulting pathologists who reviewed the histopathology slides from the monkey study to determine the nature and origin of the malignant tumors in 2 of 12 survivor monkeys in the high-dose Depo-Provera group.

The appointment of the special panel of pathologists was delayed until information could be obtained from Upjohn about what tissue blocks or sections from the monkey study were available for this independent review. In addition, slides were obtained for review from a control monkey in the IUD study of the Population Council that had been diagnosed to have endometrial cancer.

Presently: Depo-Provera is approved as adjunct therapy for patients with metastatic endometrial cancer.

Oct. 26, 1984: P.B.I. decision submitted to the Commissioner, FDA, and placed on file in the Dockets Management Branch. The findings and conclusions of the Board, based on the public hearing, will have the legal status of, and be handled as, an initial decision.

2. EXPERIENCE WORLDWIDE

Depo-Provera has been used extensively as a contraceptive in over seventy countries. According to the manufacturer's statistics [33], an estimated 11 million women have "ever used" DMPA; 2 million women are "current users"; 100,000 women used it for 10 years or longer, and 1.5 million women received their first injection over 10 years ago.

We have been cognizant of the great interest by and impact on countries overseas in a decision on this drug for women in the United States. At the same time, we are required by law and have the obligation to evaluate the benefit/risk ratio that is applicable to this country only.

REFERENCES

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DMB Vol. No. 20 - Tab #1 Announcement of Hearing on Depo-Provera.

2. 39 Fed. Reg. 38226 (October 30, 1974)
DMB Vol. No. 188 - Tab #93, pp. 446-447

3. 43 Fed. Reg. 28555 (June 30, 1978)
DMB Vol. No. 188 - Tab #93, pp. 193-194

4. 44 Fed. Reg. 31716 (June 1, 1979) Announcement of Hearing on Aspartame.
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5. The Upjohn Company, Letters of August 25, 1978 and October 17, 1978
DMB Vol. 1 Sup; HER # 4

6. DMB Vol. No. 189

7. Correspondence with the Upjohn Company over Dr. Paul Stolley's appointment. Confidential.
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8. PBI letter to the Upjohn Company, May 5, 1982.
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9. PBI letters to the National Center for Drugs and Biologics, September 9, 1982, and March 18, 1983.
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10. Official Transcript of Proceedings, Depo-Provera Public Board of Inquiry, January 10-14, 1983, Volumes I, II, III, IV, V. (hereinafter, TR-I, II, III, IV, or V).

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21. House of Representatives, Hearings before a Subcommittee of the Committee on Government Operations on the Use of Advisory Committees by the FDA, March, April, May, 1974, pp. 323-341, 353-390.
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22. IRDC, Long-Term Depo-Provera Study in Dogs, Final Report, 1976.
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23. Dawson Corporation, Long-Term Depo-Provera Study in Dogs, Final Report, 1982.
DMB Vol. No. 246 - Tab #252

24. IRDC, Long-Term Depo-Provera Study in Monkeys, Final Report 1979
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25. The Upjohn Company, Report of the Workshop to review the monkey endometrial findings and their relevance to the contraceptive use of Depo-Provera, Feb. 12, 1981. (See 3/8/82 PBI Update, Sec. U-13)
DMB Vol. No. 211 - Tab #192

26. World Health Organization, Special Programme of Research, Development and Research Training in Human Reproduction: Statement on Safety of the Long-Acting Injectable Contraceptive Depo-Provera, October 1978.
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27. International Planned Parenthood Federation: Statement of the International Medical Advisory Panel on Depo-Provera, November, 1980.
DMB Vol. No. 295 - Tab #321 Section III

28. United States Agency for International Development: Report of Ad-Hoc Consultative Panel on Depot Medroxyprogesterone Acetate. July, 1980.
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DMB Vol. No. 337 - Tab #461

31. Letter from LH Fountain, Chairman, Subcommittee on Intergovernmental Relations of the House Committee on Government Operations, to HEW Secretary Casper W. Weinberger, October 2, 1974.
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32. FDA audit of Grady Clinic, Dec. 18-22, 1978.
DMB Vol. No. 305 G-625 (summary), and DMB Vol. No. 305A (synopsis)

33. The Upjohn Company, Information for PBI on Depo-Provera: Responses to the Board's Questions. June 25, 1982, p. 1.
DMB Vol. No. 244 - Tab #219

III. THE SEVEN MANDATED QUESTIONS

The sequence of the answers to the seven questions that we were mandated to consider has been reordered as follows: Questions #2, #3, #5, and #6 are addressed first, and Questions #1, #4 and #7 were combined and reformulated and are addressed last. Thus, the evidence on the potential risks on the use of DMPA, relevant to the regulatory decision on the approval of the drug as a contraceptive under conditions of general marketing, is presented before our response to the more general questions concerning the regulatory decision itself and its potential consequences. A brief section on the evidence available on the influence of MPA on bone and on circulating lipids has also been included because of specific questions raised during the course of the present inquiry. The section has been inserted between the response to Question #6 and that to Questions #1, #4 and #7.

THE COMMISSIONER'S QUESTION #2:

WHETHER DATA FROM BEAGLE DOG AND MONKEY STUDIES INDICATE A POTENTIAL RISK OF BREAST OR ENDOMETRIAL CANCER IN HUMANS FROM DMPA.

Malignant neoplasias developed in the mammary glands and uteri of dogs and monkeys, respectively, the two species used for testing the consequences of long term administration of DMPA. To determine whether these findings are relevant to the human, the following three questions need to be addressed.

1) Is there evidence to support the assumption that the malignancies that developed in secondary sex structures of dogs and monkeys are due to factors other than DMPA? In the absence of such evidence the malignancies would have to be considered drug-related until proven otherwise.

2) If the malignancies in the secondary sex structures are to be considered drug-related, is there evidence of a dose-response relationship? Dose-response relationship is an important parameter in all toxicological tests. It is of special importance when testing steroid hormones since it has been suggested that the actions of very large doses of steroids may differ not only quantitatively but also qualitatively from those of smaller, more physiological amount (see testimony of Dr. C. Wayne Bardin [1]).

Quantitative differences refer to the usual dose-response relationship, i.e., a systematic change in the incidence or magnitude of an effect across the whole dose range. In contrast, if differences are qualitative, certain effects would be restricted to a certain dose range, implying a different mechanism of action at different doses. Within the context of dose response relationship, it is also necessary to consider comparative data available for the dog, the monkey and the human pertaining to factors that influence the effective dose, i.e., the activity and the amount of the drug reaching target organs (e.g., metabolism of the drug, metabolic clearance rate and steroid receptor function).

3) Have fundamental differences been identified between the human and the monkey, or the human and the dog in their responses to progestogen that would warrant a conclusion that the carcinogenic effects of DMPA seen in either of the species of test animals are unlikely to occur in the human?

At a more general level a fourth question raised relates to the guidelines set by the FDA for testing of contraceptive steroidal hormonal agents in animals. Specifically, there is concern that the toxicological principles that have been used to set up these guidelines may not be valid for testing steroid hormonal agents. The complexity of the issues involved may be gauged from the transcripts of the proceedings of a three day conference convened recently by the National Institutes of Health on the subject [2].

2.1. EXPERIMENTAL DESIGN AND EVIDENCE: ANIMAL STUDIES

Two long-term toxicity studies in beagle dogs to test the safety of DMPA were initiated in 1968 [3] and 1972 [4], respectively. In both studies, DMPA caused a high incidence of mammary nodules and mammary carcinomas. In addition, these neoplasias tended to appear at ages younger than the age when mammary tumors occur spontaneously in dogs (see Table 2A and Table 2B for details). The association between DMPA and mammary pathology was evident in animals treated with low as well as with high doses of the drug.

In the first study, carried out by The International Research and Development Corporation (IRDC) [3], a large number of the DMPA treated animals died early in the course of the experiment. This was attributed primarily to pyometra, an expected complication of progestogen treatment in dogs. The major relevant finding from this study was that none of the 11 controls that survived until the end of the study developed malignant mammary tumors, whereas two of the dogs treated with 25 times the human dose of DMPA developed mammary adenocarcinomas, with metastases, after 40 to 42 months of treatment (Table 2A, p. 26) [3, 5-7]. Because of the premature death of a large number of animals, a second study was initiated.

In the second study on dogs, carried out by the Dawson Research Corporation [4], the bitches used were younger and

were hysterectomized at the beginning of the study to avoid the complication of pyometra. The number of animals in each group was also larger (20 per group), and the effects of DMPA were compared not only with vehicle injected controls but also with two groups of dogs receiving different doses of progesterone. As in the earlier study, high doses of progestogens proved lethal to many dogs even when hysterectomized.

With respect to mammary tumors, in this study also, none of the control animals had mammary cancer, whereas malignant mammary neoplasias (some with metatases) developed in 5 dogs in the group receiving DMPA at X1 human dose, in 8 dogs in the group receiving DMPA of X10 human dose, and in 8 dogs in the group receiving DMPA at X25 human dose. Mammary cancer developed also in 1 dog in the group receiving low dose progesterone and in 2 dogs receiving high dose progesterone. Onset of the mammary tumors in the high dose DMPA group was at 46.9 months from start of the study compared to onset at 65.6 months in the lowest dose DMPA group (Tables 2B and 2C, pp. 27, 28) [4-8].

Finally, a ten-year study of Depo Provera in Rhesus monkeys was initiated in 1968. It was carried out by the International Research Development Corporation (Table 3, p. 29) [5, 9]. The major finding was the occurrence of endometrial carcinomas in two among 12 surviving monkeys in the high-dose group. In addition, nonmalignant mammary

TABLE 2A: Summary of Animal Experiments in Dogs

	IRDC STUDY (1968 - 1975) [3]	DAWSON STUDY (1972 - 1979) [4]
Design:	-36 female beagle dogs divided into three experimental groups: 16 controls, 4 low dose DMPA (1 X HD), and 16 high dose DMPA (25 X HD). -Individual dosages were adjusted based upon changes in body weight prior to each injection. -the dogs were "mature" (age unspecified), and were not Hysterectomized at the start of the study.	-140 female beagle dogs divided into six experimental groups: 40 controls, 20 low dose DMPA (1 X HD), 20 mid dose DMPA (10 X HD), 20 high dose DMPA (25 X HD), 20 low dose progesterone, and 20 in high dose progesterone. -Individual dosages were adjusted in the mid and high DMPA groups (from 6X to 10X-HD and from 23X to 25X-HD) at the 5th year of the study. -The dogs were about six months of age, and were all hysterectomized prior to the start of the study.
lts:	-An increased incidence of mortality and of papable mammary nodules at both dose levels of DMPA, compared to controls. survival: -11 of 16 controls survived the 7-year study period. -2 of 4 in the low-dose DMPA group survived to the end of the study. -All 16 dogs in the high-dose DMPA group died by 3 1/2 years from onset of the study. pathology: -5 mammary gland adenocarcinomas, described as being widely metastasized, found in 2 dogs receiving high dose DMPA. These dogs developed malignant mammary tumors identified at 40 and 42 months from onset of the study. -See Table 2B for details	-High mortality in the mid and high dose DMPA groups and in the high dose progesterone group. survival: -30 of 40 controls survived the 7-year study period. -14 of 20 low-dose DMPA; -0 of 20 mid-dose DMPA; -1 of 20 high-dose DMPA; -17 of 20 low-dose progesterone; and -0 of 20 high-dose progesterone. pathology: -Mammary malignancies did not develop in any control animal. Mammary adenocarcinoma and solid cell carcinoma developed in 5 dogs in low-dose DMPA group, 8 dogs in the medium-dose DMPA group, 8 dogs in the high-dose DMPA group, 1 dog in the low-dose Progesterone group, and 2 dogs in the high-dose Progesterone group. -not all malignant tumors with metastases. -See Table 2B for details.

Table 2B: Details from DMPA Studies in Beagle Dogs, (based on Testimony by Gross p. 26) [7]

Dawson Study (1972-1979)

	Controls	DMPA			Progesterone	
		1x-HD (Low)	10x-HD (Medium)	25x-HD (High)	Low	High
No. dogs/group	40	20	20	20	20	20
No. dead in 7 yrs.	10/40	6/20	20/20	19/20	3/20	20/20
Mean no. months to death	54.9	67.3	67.3	59.1	75.7	44.9
No. with mammary malignancy	0	5	8	8	1	2
Mean no. months to onset of mammary malignancy	0	65.6	50.1	46.9	75.8	44.6
Incidence of benign mammary tumors	10%	85%	95%	85%	85%	40%
Mean no. of all mammary and tumors per dog	0.10	6.3	7.3	5.3	3.3	2.6

IRDC Study (1968-1975) [3]

	Controls	DMPA		
		1x-HD (Low)	10x-DH (Medium)	25x-HD (High)
No. dogs/groups	16	4	-	16
No. dead in 3.5 yrs.	5/16	2/4	-	16/16
No. with mammary malignancy	0	0	-	2
Mean no. months to onset	0	0		40-42

TABLE ___ 2C

Long-Term Depo-Provera Study In Dogs

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MALIGNANT MAMMARY NEOPLASMS - SUMMARY

Dose Group	Type of Tumor	Animal Number	Time of Onset	Month of Death	Nature of Malignant Neoplasm	Type of Death
Low Dose Depo-Provera	Solid cell carcinoma	X-41-72 ♀	+2212	85	Incidental Finding	T
		X-43-72 ♀	+2130	84	Incidental Finding	T
		X-44-72 ♀	+2157	85	Incidental Finding	T
		X-47-72 ♀	+2403	79	Metastatic Disease	E (Metastatic Disease)
		X-59-72 ♀	+2338	85	Incidental Finding	T
	Adenocarcinoma	X-47-72 ♀	+1940	79	Incidental Finding	E*
	Malignant mixed tumor	X-47-72 ♀	+1151	79	Incidental Finding	E*
Medium Dose Depo-Provera	Solid cell carcinoma	X-61-72 ♀	+1701	72	Incidental Finding	D (Intercurrent Disease)
		X-62-72 ♀	+1757	60	Incidental Finding	D (Intercurrent Disease)
		X-68-72 ♀	+1276	53	Metastatic Disease	E (Metastatic Disease)
		X-69-72 ♀	+1429	71	Metastatic Disease	D (Metastatic Disease)
		X-72-72 ♀	+1458	56	Metastatic Disease	E (Metastatic Disease)
		X-76-72 ♀	+1578	72	Incidental Finding	D (Intercurrent Disease)
		X-78-72 ♀	+1821	61	Incidental Finding	D (Intercurrent Disease)
		X-79-72 ♀	+1241	70	Metastatic Disease	D (Metastatic Disease)
	Adenocarcinoma	X-69-72 ♀	+1366	71	Incidental Finding	D*
		X-79-72 ♀	+1522	70	Incidental Finding	D*
High Dose Depo-Provera	Solid cell carcinoma	X-85-72 ♀	+1394	54	Incidental Finding	S
		X-88-72 ♀	+1187	49	Incidental Finding	E (Intercurrent Disease)
		X-89-72 ♀	+1911	67	Metastatic Disease	E (Metastatic Disease)
		X-90-72 ♀	+1487	71	Metastatic Disease	D (Metastatic Disease)
		X-94-72 ♀	+1577	71	Incidental Finding	E (Intercurrent Disease)
		X-99-72 ♀	+1369	52	Metastatic Disease	E (Metastatic Disease)
	Adenocarcinoma	X-81-72 ♀	+1212	66	Metastatic Disease	D (Metastatic Disease)
		X-94-72 ♀	+1306	71	Incidental Finding	E (Intercurrent Disease)
	Spindle cell adeno-carcinoma	X-92-72 ♀	+1549	60	Incidental Finding	D (Intercurrent Disease)
Low Dose Progesterone	Solid cell carcinoma	X-114-72 ♀	+2307	82	Metastatic Disease	E (Metastatic Disease)
High Dose Progesterone	Spindle cell adeno-carcinoma	X-122-72 ♀	+1184	60	Incidental Finding	E (Intercurrent Disease)
	Adenocarcinoma	X-133-72 ♀	+1528	51	Incidental Finding	E (Intercurrent Disease)

KEY: D = Died; E = Euthanized in Moribund Condition; S = Interim Sacrifice; T = Terminal Sacrifice

* See previous listing for this animal.

Note: This is a listing according to histological type of mammary neoplasm

TABLE 3: Summary of Animal Experiment in Rhesus Monkeys (1968-1978) [9]

Experimental Group	Original Group		+ Replacement Monkeys	Total Number Surviving at End	With Endometrial Cancer
	Number at Start	Number at End			
Controls	16	5	2	7	0
Low dose DMPA (1x-HD)	4	2	0	2	0
Mid-dose DMPA (10x-HD)	16	7	0	7	0
High-dose DMPA (50x-HD)	16	7	5	12	2

nodules were observed in 3 of 7 surviving monkeys in the mid-dose Depo- Provera group. In this study, at autopsy, hyperplasia of the ductal epithelium of the breast was also noted in monkeys receiving X10 the human dose of DMPA [5, 9].

2.2. CRITIQUE OF THE FINDINGS IN ANIMALS

2.2.1 CAN THE MALIGNANT NEOPLASMS IDENTIFIED IN THE MAMMARY GLANDS OF DOGS AND IN THE UTERI OF THE TWO MONKEYS BE ATTRIBUTED TO MPA AND IF SO, IS THERE EVIDENCE OF A DOSE-RESPONSE RELATIONSHIP?

The data from the study by the Dawson Research Corporation provides evidence that the mammary carcinomas in the dogs were drug-related. Moreover, in this well designed and executed study there was good indication of a dose-response relationship: malignancies developed both more frequently and earlier with increasing doses of DMPA (Table 2B, p. 27) [4]. The study also provides evidence that the findings in the mammary gland were due to the progestational actions of MPA and not to some structural peculiarity of the compound, since the effects of DMPA and progesterone were similar [4, 8]. The findings were not unexpected. They confirmed the association in the dog between progestational agents and breast pathology identified in previous published studies [3, 10-15]. However, the association between malignant neoplasms and progestational agents is more clearly

evident in the Dawson study than in previous studies in which treatment was often of shorter duration and the focus was on mammary nodules in general with less consideration being given to their histological characteristics.

The distinction in the progestogen treated dogs between malignant and benign tumors, and between nodules palpated and those characterized histologically is important. The nodules represent a variety of pathologies that are often reversible and include consequences of hyperstimulation of lobulo-alveolar growth as well as benign mixed or complex adenomas [8, 13]. It is, however, the histologically characterized malignant tumors, associated with the administration of progestogens, that are of major concern. The relationship between these malignancies and the more frequent benign hyperplastic lesions elicited by progestogens in dogs has not yet been the subject of any systematic investigation.

While the finding of neoplasias in the mammary glands of DMPA-treated dogs could be anticipated, the development of uterine carcinomas in the Rhesus monkeys was unexpected. Endometrial carcinomas are not known to occur spontaneously in Rhesus monkeys (see testimony of Dr. S. M. Sieber [16] and that of Dr. Norval W. King [17]). Consequently, there is reason to assume that the neoplasias identified in the genital tract of the two monkeys receiving the highest doses of DMPA were drug-related. Whether there could be any dose-response

relationship, and whether neoplasias might be elicited by lower doses of DMPA, can not be deduced from this study, because the study was so poorly designed and executed: the number of controls and animals receiving lower doses of DMPA was much too small (Table 3, p. 29), and the pathological examinations inadequate. Several animals died during the course of the study and were allowed to autolyze before undergoing pathological examination [9].

Whether uterine carcinomas occur spontaneously in Rhesus monkeys is of obvious importance in evaluating the significance of the findings in this small and inadequate IRDC study in which controls were few and animals from different sources were used. Consequently, we requested and were granted access to the histological slides from a control Rhesus monkey from a study of IUD carried out by the Population Council. This so-called "Tatum monkey," referred to several times at the public hearing (by Drs. Wayne Bardin [18] and by Roy Hertz [19]), was stated to have developed a spontaneous endometrial cancer. It was described in the initial pathology report as having "A superficial, 110 micron wide, circumferential ring of endometrium" showing "atypical hyperplasia, questionable neoplasia," interpreted as "microfoci of non-invasive adenocarcinoma" [20].

The histological slides were examined by the consulting pathologists to the PBI who concluded, unanimously, that the lesion was an epithelial plaque [21]. Epithelial plaque is a

benign, transient structure characteristically seen in the Rhesus in relationship to implantation and, occasionally, in the absence of pregnancy, as a response of a progestogen-primed uterus to trauma (see Section 2.2.2b). The original description of the gross appearance of the lesion (see above), as well as the fact that it was found in a uterus, "showing thick secretary endometrium," i.e., a progesterone-stimulated endometrium, is consistent with the pathologists' conclusion. To date, therefore, to the best of our knowledge, there has been no documented case in the Rhesus monkey of spontaneous, invasive, malignant uterine carcinomas, such as were identified in the DMPA treated monkeys. The latter, therefore, must be attributed to the progestogen treatment.

The conclusion that progestogens can elicit malignant transformation in the uterus of monkeys is reinforced by a recent report of a uterine carcinoma in a Rhesus monkey treated for 4 3/4 years with norethisterone enanthate (200 mg/kg, corresponding to 50 times the human dose, every 8 weeks) [22-24]. The consulting pathologists to WHO and to the German Ministry of Health who had the opportunity to compare histological slides from this animal with those from the DMPA-treated monkeys, described it to be of a similar, undifferentiated, invasive type [22, 23]. As stated in the report by WHO:

> All three tumors arose in animals with atrophic endometrium and mainly affected the corpus of the uterus. All three

> tumors were histologically similar, poorly differentiated carcinomas....In all three animals the tumors invaded the endocervix. Furthermore, this was the first time that WHO had been able to examine original slides from all three tumors together, and in contrast to the conclusions of the 1981 review, the three tumors appeared identical in type [23].

The undifferentiated, invasive nature of the neoplasias in the uteri of the two DMPA treated monkeys was also confirmed by the consulting pathologists [21]. These neoplasias had no unique histological features that would permit distinguishing them from highly undifferentiated endometrial carcinomas in other species, including the human.

There is only one report in the literature of a carcinoma in situ of the endometrium in a subhuman primate [25]. This was in a 22-23 year old chimpanzee. The endometrium was described as being hyperplastic, a change ascribed to hyperestrogenism due to ovarian pathology resembling that in patients with Stein - Leventhal syndrome. The authors state that the lesion might not have qualified as a carcinoma in situ, but only as a adenomatous hyperplasia, according to the criteria of other experienced pathologists, e.g., Gusberg, one of the pioneers in defining the association between hyperestrogenism and endometrial cancer. In any event, whether the pathology be considered neoplastic or only potentially neoplastic, it is clearly distinct from that found in the Rhesus monkeys treated with the progestogens, DMPA or norethisterone enanthate.

It has been suggested that carcinoma of the uterus was diagnosed also in two Rhesus monkeys receiving oral contraceptives. According to the description of these lesions by the pathologist only one of the two cases cited was considered to be possibly a carcinoma in situ in a somewhat hyperplastic endometrium, again a pathology distinct from that found in the progestogen treated monkeys [26]. We are, therefore, left with the conclusion that endometrial cancer, in particular of a highly anaplastic type, has to date been observed in monkeys only in association with progestogen treatment, i.e., treatment with DMPA or norethisterone enanthate. Consequently, the endometrial cancers found in the IRDC monkeys treated with DMPA have to be considered drug related.

It has been implied that the two monkeys receiving DMPA that developed the uterine pathologies were not representative of monkeys in general, because they were replacement monkeys [27]. We note that no neoplasias were identified in the uteri of two of the replacement monkeys in the control group that were, presumably, obtained from the same source. Under these circumstances, we must reject Upjohn's conclusion that "The cause of the endometrial carcinomas in the two monkeys is not established" [28], and until proven otherwise, must conclude that they were related to DMPA.

2.2.2 WHAT BASIC DIFFERENCES HAVE BEEN IDENTIFIED BETWEEN THE HUMAN AND EACH OF THE TWO ANIMAL SPECIES IN THEIR RESPONSE TO PROGESTOGEN?

2.2.2a THE RESPONSE OF DOGS TO PROGESTOGENS - EVIDENCE FOR SPECIES DIFFERENCES

It has been argued by Upjohn and others that the dog is an inappropriate model for studies of the potential adverse effects of the long term use of progestogens on the breast of the human female [29-33]. A summary of this position is presented in Upjohn's final brief: "Recent information about the mechanisms underlying the mammary response of dogs to C-21 progestogens like Depo-Provera supports the decision of several panels of experts that the dog is an inappropriate model for carcinogenicity testing of progestogens" [33]. On reviewing the several arguments that have been offered to support this proposition, we conclude that none has been adequately substantiated. Consequently the findings in dogs must be considered as having potential relevance to the human. While there are certain obvious differences at the descriptive level between the canine and human female in the overall regulation of reproductive function, differences in underlying mechanisms have not been defined to any extent. Specifically, the mechanisms by which progesterone and progestogens cause malignant neoplasias in the canine mammary gland have hardly been investigated. Consequently, it is

premature to attribute this response of dogs to the progestogens to some mechanism unique to the species.

The major arguments that have been presented in support of the thesis that the dog's response to progesterone is uniquely different from that of the human are evaluated below.

2.2.2a.1 SUSCEPTIBILITY OF THE BEAGLE TO MAMMARY TUMORS

Beagles, like other dogs, have a high incidence of mammary tumors, both benign and malignant [34-43].[5/] Of particular importance to the question at hand are the malignant neoplasias. The most frequently noted malignant neoplasias, as discussed below, appear to resemble histologically those found in the human [34, 36-38]. A number of similarities have been identified between the dog and the human in the epidemiological and biological characteristics of malignant mammary neoplasias. These include age-specific incidence and relationship to ovarian hormones [39-42]. Such similarities argue for, rather than against, the use of the

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5/ There are no data to support the notion that beagles are more susceptible to neoplasias of the breast than other strains of dogs [35]. Certain other pure bred strains of dogs have, in fact, been reported to have a higher incidence of such neoplasias than dogs in general, including beagles [35, 43]. However, beagles have been studied most extensively in an experimental setting because of their availability and convenience of use.

dog as one of the species in testing for potential promoters of mammary neoplasias.[6/] It is, however, obvious that evidence available on many other biological as well as epidemiological criteria need to be considered when trying to evaluate the relevance of the findings in the dog to the human. However, the fear expressed by Harold L. Upjohn, in a letter to the FDA Commissioner, that because "dogs develop a variable high incidence of spontaneous mammary tumors" this would make "proper control observations almost impossible" [44] has not been borne out, at least in the Dawson study. Differences between controls and progestogen treated animals in malignant breast cancer are readily identifiable and quantifiable in this well designed and executed study.

2.2.2a.2 DIFFERENCES BETWEEN THE HUMAN AND THE DOG IN THE TYPE OF MAMMARY NEOPLASIAS DEVELOPED

With respect to spontaneous neoplasias, the major difference between the two species relates to the high

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6/ We have not been able to find any comparative data on the incidence of cancer of the breast in different geographic locations in the world. One of the striking characteristics of cancer of the breast in the human female is the much higher incidence of the disease in the developed countries in the West. These regional differences are attributed in part to environmental factors, including diet. It would be of considerable interest to know if cancer of the breast in dogs is also subject to risk factors similar to those implicated in the human.

incidence in the dog of mixed mammary tumors, a type rarely found in the human. In dogs, the majority of these tumors are benign; the malignant mixed mammary tumors constitute only a small percentage of the malignancies in the mammary gland in this species [34]. The incidence of this type of malignancy was not increased by prolonged treatment with DMPA.

The majority of malignant breast tumors that arise spontaneously in the dog, as in the human, are described as adenocarcinomas. In the Dawson study, there were no malignant breast tumors in the control animals. In the progestogen treated groups, the two most frequent types of malignant tumors were solid cell carcinomas and adenocarcinomas (Table 2C, p. 28) [4]. The question of the cells of origin of these malignant neoplasias has not been studied systematically, although this would be of considerable interest and importance in attempting to understand their histogenesis and pathophysiology. The difficult problem of classification of mammary neoplasias in dogs has been approached by several groups of experienced veterinary pathologists [34, 36, 38]. They all rely on morphological criteria. The question of cells of origin was raised by Moulton [34]. However, there are no data at this time to suggest that the cells of origin of these malignant neoplasias in the progestogen treated beagles differ from those arising spontaneously, either in dogs or in the human female. In the human, adenocarcinomas of the breast are considered to have

their origin in ductal epithelium, and there is no evidence to suggest that this is different in dogs [45, 46]. Consequently, if the histological characteristics of the malignant neoplasias are taken into account, overall species differences in types of neoplasias can not constitute, at this time, a reason for dismissing as irrelevant to the human the finding of increased incidence of adeno- and solid cell carcinomas in the progestogen treated dogs.

2.2.2a.3 MAJOR DIFFERENCES IN THE COMPARATIVE ENDOCRINOLOGY OF REPRODUCTION BETWEEN DOGS AND HUMANS

The dog has a bi-annual heat period (interestrous period approximately 200 days) followed by a prolonged luteal phase. This luteal phase, or period of pseudopregnancy, lasts up to 60 days, and resembles, both in length and in hormonal profile, pregnancy in the dog. The luteal phase in the dog, like pregnancy, is characterized by high levels of progesterone. However, except for a brief period before ovulation, estradiol levels in the dog are relatively low [14, 47]. Thus, in the dog, during relatively long periods of time (60 days out of 260), circulating progesterone levels are relatively high at a time when levels of estrogen (or at least of estradiol, since other estrogens have not been measured) are relatively low. Whether and how these

differences between the bitch and the human female might be linked to differences in their response to progesterone and progestogens is not known. Certain, not very precise, hypotheses have been advanced, e.g., "The dog has probably not developed a control system which counteracts harmful effects of excessive progesterone levels" [48]. Studies have not been carried out to define what such control mechanisms might be. For example, there have been no systematic studies of how progesterone receptors are regulated in the various target organs in the dog. "State of the art" thinking and methods have not been applied to the question. The limited information available on this subject is discussed in the next section.

2.2.2a.4 DIFFERENCES IN THE RESPONSE OF DOG AND HUMAN MAMMARY GLAND TO PROGESTERONE IN TERMS OF STIMULATION OF GROWTH AND DIFFERENTIATION

The theme of species differences in growth and differentiation of the mammary gland in response to progesterone has been stated in a variety of ways. For example, "The dog is the only species besides the ferret in which progesterone alone can produce a considerable lobulo-alveolar growth of the mammary gland" [49], or "The dog differs from other laboratory species in that mammary hyperplasia can be induced with progesterone alone and does not require estrogen priming" [50]. These statements refer

to the fact that, in the dog, mammary development required for lactation starts promptly after ovulation under the influence of ovarian hormones and is sustained by them throughout pregnancy or pseudopregnancy. In the dog, the predominant steroid secreted by the ovaries during pregnancy (or pseudopregnancy) appears to be progesterone accompanied by relatively little estrogen. Therefore, not surprisingly, progesterone alone can elicit in this species good, albeit not optimal, lobulo-alveolar development even in the absence of estrogen. (A very similar reproductive strategy appears to have been evolved by the ferret. It exhibits a prolonged luteal phase comparable in length to pregnancy, and during such periods the breast achieves full lactational capacity [51]). In contrast, in the human female, mammary development in preparation for lactation occurs during pregnancy under the influence of the high levels of both progesterone and estrogens as well as other hormones secreted by the placenta [51].

This particular species difference, however remarkable, can not serve as a basis for deciding on the relevance of the findings in the dogs to the human without more information on the cells of origin of the progestogen related neoplasias in the dogs. The known differences between the species in hormonal response of the breast relate to lobul-alveolar development. In the human female, as discussed above, adenocarcinomas of the breast are considered to have their

origin in cells of the ductal epithelium; there are no data to support the notion that dogs differ in this respect. The type of longitudinal studies needed to establish the cells of origin of progestogen induced neoplasias in dogs have not yet been carried out.

The important considerations, then, are how ductal epithelial cells, that presumably give rise to the adenocarcinomas, respond to progesterone alone or, more importantly, to progesterone or progestogens in the presence of low levels of estrogen?

The focus in recent years has been primarily on the role of estrogens in the development and promotion of growth of neoplasias in secondary sex structures, including the breast. Progesterone, in contrast, is thought of as a neutralizer of estrogen and estrogenic action. The notion expressed in various ways is that estrogens act as promoters of neoplasias because they stimulate cell division (Dr. M. Lipsett in [2]). In so far as progesterone acts, as in the uterus, to arrest estrogen-induced cell division and to further cell differentiation, it can be viewed as an antidote to the neoplasia promoting actions of estrogens. There is, however, evidence that progestogens can also act on certain cell types within target tissues, including the mammary gland, to promote cell division and that it can do so in species other than the dog. First, in explanted mammary tissues from human females, not only estradiol but also progesterone has been

shown to stimulate the incorporation of labelled thymidine into ductal epithelial cells [52, 53]. The epithelial cells of the interlobular ducts appeared to be particularly responsive to progesterone. A second perhaps more direct line of evidence implicating progestogens with a potential to promote neoplastic transformation of breast cells comes from studies of mammary carcinomas induced in rats by the carcinogen dimethyl-benzanthracene (DMBA). Progesterone, like estradiol, administered during the latent period following the administration of DMBA, both reduced the time required for the development of malignant breast tumors and increased their size and number [54-57]. Once the tumors were established, some of them could be shown to be hormone dependent, requiring estrogen for their maintenance in the castrated rats. In contrast, progesterone was ineffective in maintaining hormone dependent carcinomas in castrated rats [56, 57]. Thus, while progesterone could in these experiments promote the development of malignancy during the latent period, it was not able to sustain malignant cells once established. In more general terms an absence of demonstrable dependence of a tumor on a particular hormone does not exclude the possibility that that hormone played a role in the development of that tumor.

In the human female and in test animals receiving contraceptive doses of DMPA, the progestogen, however, is not acting alone but in the presence of at least low levels of

estrogen, and these two classes of steroids are known to act synergistically on breast development in all mammalian species studied to date. Under these hormonal conditions some of the monkeys treated with DMPA showed hyperplasia of the intra-ductal epithelium [9, 58, 59]. Dr. Henry Norris, a witness at the public hearing experienced in both human and subhuman primate breast pathology, judged the ductal epithelial hyperplasia to be atypical, first, because of a resemblance to the micropapillary pattern of intraductal carcinoma of the breast in humans and, second, because of nuclear hyperchromatism, prominent nucleoli, and mitotic activity [59]. Irrespective of whether these changes have the same long term significance in monkeys as they are thought to have in the human, the findings attest to the possibility of ductal epithelial hyperplasia developing in a primate under conditions of prolonged, relatively unopposed progestogen action, the hormonal state characteristic of subjects receiving contraceptive doses of DMPA. The development in DMPA treated monkeys of changes that resemble a precancerous lesion in the human may be significant in light of the apparent resistance of this species to agents that induce malignancies in breast tissue of other species.

Finally, the uniqueness of the response of the lobulo-alveolar component of the breast of dogs (and ferrets) may be overstated. The difference between these and other species may be more quantitative than qualitative, as pointed

out by Trentin et al [60]. According to these investigators, in castrated dogs, lobulo-alveolar growth was not elicited by estrogen treatment alone but did occur following treatment with estrogen + progesterone and, to a lesser degree, following treatment with progesterone alone. The investigators state, "The rather good development of the mammary glands induced by progesterone alone is not without precedent. Mammary growth responses to progesterone in the absence of estrogen has been reported in the mouse, the rat and the monkey. The dose of progesterone required to produce a complete alveolar type of mammary development in dogs is relatively much less than in rats where 15 mg/day was required" [60].

2.2.2a.5 EVIDENCE FOR DIFFERENCES BETWEEN THE BEAGLE AND THE HUMAN IN THE SPECIFICITY AND REGULATION OF PROGESTERONE RECEPTORS

The statement repeated in various reviews of DMPA that progesterone receptors in the dog differ from those in the human, is based on a single study [61]. It represents the sole attempt to examine the concentrations and regulation of progesterone receptor in the canine. It is a study that would be important to follow up but which was too limited and incomplete to permit any conclusions. There are major problems with the experimental design and with the methods used in this study. For example: (a) the number of

animals studied was too small and the number of measurements made too few to establish a range of values within any single experimental group. Consequently, significant differences among experimental groups can not be established; (b) the tissues sampled for comparison of concentration of receptor in the dog with those of the human and for examining the effect of progesterone on the receptor were limited and appear arbitrary (e.g., myometrium, canine breast tissue before and after administration of a single dose of progesterone, and only at one time point, a single specimen of mixed mammary adenoma); (c) the comparison of specificities of the receptor in the human and the dog was made from a study of a single sample from each. Data on replicate determinations are not given; (d) The sensitivity of the assay is unusually and unaccountably low, several fold less than reported by others; and (e) data on the characteristics of the canine progesterone receptor under the conditions selected for the assay and the basis for selecting the conditions used in the assay are not reported (e.g., the reason for using a crude cytosol preparation, results of tests to determine the stability of the receptor under the conditions used, etc.). Considerably more detailed studies, both of the normal and neoplastic canine mammary tissues, are needed before it would be possible to make any statements about species differences in the regulation of the progesterone receptor by progesterone or in its affinities for different progestogens. Moreover,

information on more dynamic aspects of receptor function are needed to provide some meaningful basis for interspecies comparison of the role the progesterone in tissue response (see testimony of Dr. C. Wayne Bardin [62]).

Our conclusion from the above analysis is that there is too little comparative data on fundamental aspects of the action of progestogens in the two species to decide which, if either, is unique in its response, much less in what way it may be unique. Moreover, there are clues to suggest some common principles underlying the actions of progesterone in different species, including the dog.

2.2.2a.6 EVIDENCE FOR THE PRESENCE OF LATENT NEOPLASTIC FOCI IN THE CANINE MAMMARY GLAND NOT PRESENT IN THE HUMAN MAMMARY GLAND

Numerous references have been made various reviews on DMPA to the presence of latent progesterone responsive neoplastic foci in the dog [29-33, 63]. For example, "The evidence suggests the existence within normal beagle breast tissues of a large pool of microscopic neoplasms, the majority of which are benign and stationary, perhaps checked by immunological mechanism. As progesterone, but not estrogen, is a potent stimulant to growth of breast tissues in ovariectomized dogs, it is hardly surprising that administration of large doses of progesterone-like substances for long periods induces growth of these microscopic

neoplasms" [63]; "The Canine mammary gland contains latent neoplastic foci which do not exist in the human" [33]; or "Careful examination...of untreated, intact, mature bitches has revealed multiple microscopic neoplasias. These contain specific progesterone receptors, so that their growth is stimulated by progestogens. These effects are antagonised by estrogens, in that combinations of a progestogen with an estrogen give less tumors than the progesterone alone" [63].

These statements in various reviews, like those on the uniqueness of the canine progesterone receptor, are based on a single publication [64]. The data presented in this one brief publication by Cameron and Faulkin is, moreover, too scant and incomplete to serve as the basis for such statements. Cameron and Faulkin present data on the numbers and histological characteristics of areas of increased tissue density they identified when transilluminating whole-mounts of 32 mammary glands from eight beagle dogs. The dogs' ages were 7.6 - 8.5 years, i.e. an age when they become highly prone to neoplasias [39, 40]. Any unusual structural change, as compared to the normal lobularity of the surrounding mammary gland, was considered by the investigators to be an atypical nodule. A total of 509 of these were judged to be due to lobular hyperplasias, because they were found on sectioning to be larger than adjacent lobules. Proliferative changes identified in these nodules involved either both myoepithelial and epithelial elements or predominantly the

epithelial elements. Compression of surrounding tissues was absent and mitotic figures were rare, i.e. there was no evidence of neoplastic changes in these nodules. The authors state that they also identified a total of 94 nodules that they judged to be neoplastic, 80 of them in two of the animals. These, presumably, are the foci referred to in various reports and reviews in which this study is cited. However, the histological characteristics of the lesions judged to be neoplastic are not described in the original publication, the criteria for considering them to be neoplastic are not stated, nor do they appear to have been reported elsewhere. The authors' own conclusion, appropriately, is only that the method could be useful to study the development of breast tumors in dogs, a suggestion that has not been followed.

The data presented in this study can be interpreted as evidence that, during anestrous in the dog, complete regression of the lobulo-alveolar growth that had occurred during the preceding pseudopregnancy does not take place. However, whether these residual areas of persistence of epithelial and myoepithelial cell nests represent the substrate for subsequent development of neoplasias, either benign or malignant, is unknown. Since no description whatsoever is given of the nodules that the authors judged to be neoplastic, it is also not possible to deduce, or even to speculate, how these might be related to what were termed by

the same investigators atypical hyperplasias on the one hand, or to the neoplasias found in the progestogen treated dogs on the other hand. No measurements of progesterone receptors were carried out on tissue samples from this study or from comparable samples of canine breast tissue. Therefore, statements that these presumed neoplasias contain progesterone receptors are only speculations. On the other hand, the statements that no such atypical areas of hyperplasias are to be found in the human ignores the voluminous literature published over many decades concerning comparable findings in the human and the discussions of their implications for malignant breast disease in the human [65-73].

Comparative studies are badly needed of early changes that may be considered precancerous in the human and canine breast and how these relate to the subsequent development of frank malignant lesions in the two species. We have only been able to find one report of a study in which investigators experienced in human and canine breast pathology have joined forces to examine this question [38]. Relating the histological features of noninvasive lesions in mastectomy specimens from 232 dogs to the clinical course of their disease led these investigators to conclude that there are close similarities between the two species. This conclusion is clearly diametrically opposite to that reached

by various readers of the report by Cameron and Faulkin [64].

2.2.2a.7 COULD GROWTH HORMONE, RELEASED BY BEAGLES IN RESPONSE TO HIGH DOSES OF PROGESTERONE, BE RESPONSIBLE FOR THE INCREASED INCIDENCE OF MALIGNANCIES IN THE MAMMARY GLANDS OF DMPA TREATED DOGS?

Beagles, unlike humans, secrete excess amounts of growth hormone and become acromegalic when treated with high doses of MPA [4, 8, 74]. The hypothesis that growth hormone mediates or potentiates the actions of progestogens on the mammary gland of dogs is interesting and plausible. Growth hormone is required for mammary growth and resembles prolactin, which in some species, notably the rat, is implicated in the development of neoplasias of the breast. However, the hypothesis that growth hormone, acting alone or synergistically with progesterone, is responsible for the increased incidence of breast cancer in progestogen treated dogs remains to be tested. The correlation noted between growth hormone levels and incidence of breast nodules in no way constitutes proof of causality. Without direct experimental evidence, it remains a postulate and can not be used to explain the findings in the mammary glands of the MPA treated dogs.

2.2.2a.8 IS THE FACT THAT PROGESTOGENS CAN CAUSE REGRESSION IN SOME CASES OF HUMAN BREAST CANCER A REASON TO ASSUME THAT THEY ARE UNLIKELY TO PROMOTE THE DISEASE?

The ability of a sex steroid to promote the development or sustain the growth of a tumor in a target organ and to cause regression of the tumor once it is established are not mutually exclusive. This has been demonstrated in relation to estrogens. While estrogens at physiological doses may stimulate mammary cancer growth, when given in massive, pharmacological amounts they can cause the cancer to regress. This apparent paradox has been known for over three decades and has been applied to the treatment of mammary cancer in women [75-79]. By analogy, the fact that progestogens in pharmacological doses can cause regression of some mammary tumors does not exclude the possibility that at lower doses they could promote the development of such tumors.

2.2.2a.9 SUMMARY OF EVIDENCE ON POTENTIAL RELEVANCE OF THE FINDINGS IN THE DOG TO THE HUMAN

The canine, like the human female in the U.S.A., has a high incidence of malignant neoplasias of the breast and, in both, the incidence increases markedly in late adulthood. Though dogs are subject to a type of benign tumor of the breast rarely seen in the human, the most common types of malignant tumors in the two species appear to be similar.

Whether the histogenesis of the common malignant neoplasias is similar in the two species is not known. There are some obvious and marked differences in the hormonal pattern of women and of bitches during both the fertile and infertile cycles as well as in the relative importance of estrogen and progesterone in breast development. Whether and how these differences may be reflected in species differences in fundamental aspects of the actions of progestogens on their different target organs remain to be established. The evidence cited is inadequate to support the assertion that there are fundamental differences between the dog and the human in the mechanism of action of progestogens. There is, therefore, at this time no valid scientific basis for dismissing as irrelevant to the human the observations made on the carcinogenic potential of progestogen in the dog.

Whether the canine is, or is not, an appropriate species for evaluating the potential consequences of prolonged, relatively unopposed progestogen action has been debated since the late 1960's. The same arguments, based on the same limited, inconclusive evidence, have been repeated over and over. It is disappointing that there has been virtually no systematic effort to expand the data base needed to resolve this important issue.

2.2.2b THE RESPONSE OF THE RHESUS MONKEY (MACACCA MULATTA) TO PROGESTOGENS - EVIDENCE FOR SPECIES DIFFERENCES

The following are the major reasons given to support the contention that the endometrial neoplasias identified in the Rhesus monkeys recieving DMPA are unlikely to be relevant to the human [80]:

1) The neoplasias arose from a cell type present in the uterine epithelium of the Rhesus monkeys but not in the human, a cell type that responds to progesterone with proliferation;

2) The neoplasias in the Rhesus arose in an atrophic endometerium while in women endometrial neoplasias are associated with hyperplastic endometrium;

3) In the human, progestogens act to counter the development of hyperplasia and associated neoplasias of the endometrium. Moreover, when administered in pharmacological doses, progestogens can cause regression of such neoplasias. Therefore, progestogens are unlikely to promote neoplastic transformation in the human endometrium;

4) The neoplasias occurred only in the monkeys receiving the highest dose of DMPA. At these doses, actions of the progestogen may differ not only quantitatively but also qualitatively from those obtained with the lower doses.

The first three reasons given are closely interrelated. They are based on current understanding and beliefs of the

relative roles of estrogens and progestogens in the development of endometrial carcinomas in the human. They were articulated in relation to the problem of the etiology of the endometrial cancers in the DMPA treated monkeys first in 1979 by the expert pathologists appointed by the Upjohn Company to review the histological slides from the monkeys in the IRDC study [58] and subsequently restated in various reviews and documents [28, 80, 81].

The unexpected finding of malignant neoplasias, of presumed endometrial origin, in the uteri of two of the DMPA treated monkeys led the Upjohn Company to request a panel of highly experienced pathologists to review the histological slides from the uteri and breast tissue from these monkeys [58]. These pathologists did not question the diagnosis of endometrial carcinoma. However, they puzzled over the cells of origin of the malignancy. The pathologists looked for, but failed to find, any evidence of hyperplastic changes in the epithelial elements that they could interpret as precursor lesions. They noted decidualisation of the stroma in the DMPA treated monkeys, but none in the glandular epithelium, the main expected site of decidualisation in response to progesterone in this species (letter by Dr. Arthur A. Hertig, Dec. 21 1979 [58]). Neoplasias arising from the chronically stimulated, decidualised stroma would have been expected to be sarcomas rather than carcinomas. But both at the light and electron microscopic level the lesions had the

characteristics of carcinomas and not of sarcomas. Absence of epithelial hyperplasia, commonly seen in women with endometrial carcinomas, was commented on. To resolve the apparent paradox, Dr. Valerio, one of the pathologists consulted, offered a hypothesis linking the neoplasias to the epithelial plaques that develop in Rhesus monkeys in relation to implantation. She postulated these carcinomas as "possibly arising from the epithelial cells in the surface epithelium and the mouths or necks of the uterine glands. These epithelial cells respond differently in the female Rhesus monkey than in women to implantation or experimentally to a lesion or trauma of the superficial endometrium in a hormonally (progesterone) prepared uterus. If this is the case in these two tumors, then histogenetically they would not be the counterpart of endometrial carcinoma in women which is generally believed to be associated with growth stimulation by estrogen" (letter by Dr. Marion Valerio, April 9, 1979, p. 101 of Reports [58]).

An alternative resolution of the apparent paradox was proposed by Dr. Gisela Dallenberg-Hellwig, a Center witness, and presented at the public hearing [82]. She considered the neoplasias to have originated not from endometrial but from endocervical cells. Since the action of progestogens on the latter cell type is, presumably, to promote cell division rather than differentiation, the findings could be accommodated into current ideas of how sex steroids may act

as promoters of neoplasias [2]. However, the consulting pathologists we appointed to re-examine the histological slides from uteri of the IRDC monkeys did not find evidence for endocervical origin of the malignancies [21, 83]. They, like the majority of the pathologists appointed by the German Ministry of Health and WHO, did not find any reason to question the endometrial origin of the tumors [22, 23].

The hypothesis that the neoplasias arising in the progestogen treated monkeys originate in epithelial cells that respond differently from those in the human is a reasonable one. It deserves and needs to be tested, as Dr. Valerio suggested when she proposed the hypothesis in 1979 [58]. Epithelial plaques were studied by pioneers in the field of reproductive endocrinology several decades ago [84-86], but not since. Specifically, there has been no study since 1979 to test the hypothesis proposed by Dr. Marion Valerio. Consequently, like the hypothesis on the role of growth hormone in the progestogen induced breast cancer in dogs, it is only a hypothesis.

It is worth considering what prompted the pathologists to advance such a hypothesis in the first place. There were apparently two reasons: the absence of any obvious precursor lesions in the uteri of the DMPA treated monkeys, and a preoccupation with the role of estrogens in endometrial cancer. In the monkeys, the endometrium was obviously atrophic, and there was no evidence of hyperplasia.

Consequently, the lesions did not resemble those most commonly encountered in women in this country. Endometrial cancers in the human are most often found in association with hyperplastic endometrium, and these are frequently relatively well differentiated. They are often hormone dependent and tend to regress when estrogen is withdrawn or when patients are given high doses of progestogens. In many cases, development of neoplasias with these characteristics can be related to prolonged estrogenic stimulation inadequately balanced by progesterone. However, this is not the only type of endometrial carcinoma to be found in the human, and the view that estrogen is the only predisposing hormonal factor for endometrial cancer may be too limited and limiting.

The consequences of hyperestrogenism in women, in particular on the uterus, are well established. Hyperestrogenism occurs relatively frequently in developed countries either in association with certain diseases or as a result of hormone treatment. In contrast, there are no common disease states associated with chronic unopposed, or relatively unopposed, progestogen action. Consequently, there is no body of clinical observation on what the long term consequences of such a state might be. The use of synthetic progestogen in treatment of certain neoplasias and, more importantly, when used as a contraceptive, is providing the first opportunity to observe what these consequences might be. This opportunity has, to date, been largely neglected.

The majority of cases of endometrial carcinomas seen in this country are, indeed, associated with a hyperplastic endometrium [87]. However, there are cases with little or no evidence of hyperestrogenism or of endometrial hyperplasia. There are even some instances, albeit rare, in which the endometrium is atrophic [87-89]. These carcinomas tend to be less well differentiated and not hormone dependent. In some populations they could represent a higher proportion of the cases. This is suggested by a recent report from Russia in which in 25% of the subjects the neoplasias were found in association with an atrophic endometrium and in patients without apparently any evidence of hyperestrogenism [90]. Therefore, neither the histological characteristics of the malignant uterine neoplasias in the monkeys, nor of the uteri in which the neoplasias were identified, constitute an adequate reason for considering the findings in the monkeys unique to that species and irrelevant to the human. Until adequate experimental evidence becomes available on the cells of origin and natural history of the uterine malignancies in progestogen treated monkeys, the proposition that these malignancies are in a cell type unique to the Rhesus and that it has therefore no counterpart in the human must be considered only a hypothesis. The etiology of this type of neoplasia in the human is not known. Furthermore, the histological appearance of the uterus as well as of the neoplasias in the monkeys may have been influenced by the

continued administration of DMPA in pharmacological doses [89]. To gain insight into the cells of origin of these neoplasias in the Rhesus, which is what the consulting pathologists attempted to do, would require serial observations. In the IRDC study, regrettably, monkeys that died in the interim and that might have provided some information on the subject were allowed to undergo autolysis and were unsuitable for pathological examination [9].

The proposition that progestogens are unlikely to act as promoters of neoplasias because they can cause regression of endometrial cancer has also been raised in relation to breast cancer. The therapeutic value of progestogens rests on their potential to act as anti-estrogens. In this capacity, progestogens can, when given in physiological amounts, reduce the incidence of the type of endometrial neoplasias associated with relatively unopposed action of estrogens [87, 91, 92]. Progestogens, in pharmacological amounts, can also cause regression in hormone-dependent neoplasias of the endometrium [87]. Some of the biochemical phenomena underlying these effects have been identified (e.g., decrease in estrogen receptor concentrations and, in the case of the endometrium, also induction of 17B-hydroxysteroid dehydrogenase causing increased conversion of estradiol to the less potent metabolite estrone [87, 92] and testimony of Dr. S.B. Gusberg [91]). However, progestogens cannot be exonerated from contributing to the development of endometrial

neoplasias on this basis. As mentioned earlier, estrogen cannot be implicated as an etiological factor in all cases of endometrial carcinomas. Moreover, as discussed in relation to breast cancer, there is no basis for excluding the possibility of progestogens having paradoxical effects on the neoplastic process, such as has been identified in relation to estrogens and breast cancer (see p. 53). Briefly, while estrogens are implicated in promoting the development and growth of cancer of the breast, they can, when administered in pharmacological amounts, cause the regression of a significant proportion of such cancers in the human. Evidence for a similar paradoxical effect of estrogens on the uterus is only available with respect to the non-malignant endometrium. It has been reported that involution of endometrial tissue can be accomplished in the primate by prolonged administration not only of a progestogen or of progesterone, but also of an estrogen [87 (p. 156)].

The relevance of the endometrial cancers identified in the monkeys to the human has been questioned also on the grounds that the cancers occurred only in animals receiving the highest doses of DMPA. The implication is that the pathology would not occur at the lower, contraceptive doses used in humans and that, at the high doses, new and different mechanisms of action come into play. This argument could have been examined critically only if sufficient numbers of animals had been included in the different experimental groups and

followed adequately to determine the nature of the dose-response relationship; however, this was not the case in the IRDC study of the monkeys (Table 3, p. 29).

The doses administered to test animals are defined operationally and represent multiples of the human dose, adjusted for differences in body weight. In the absence of adequate data on the many factors that may modify effectiveness of the drug after its administration, this remains a practical basis for comparison of drug effects across species. There is no evidence that DMPA's potency in the Rhesus would be greater than in the human. On the contrary, there are some data to suggest that progestogens may be cleared faster in monkeys than in the human and that, therefore, more of the drug would have to be given to achieve the same effect [93-95]. In the frequently cited study by Mora and Johannson monkeys were given the same dose of DMPA as humans (150 mg total dose to each), although their body weights were only a tenth that of the human [95]. Nevertheless, as far as can be deduced from the minimal data presented, after an initial, brief period during which blood levels of immunoreactive DMPA measured in monkeys were somewhat higher than in the human female, the levels in the two species were stated to be comparable, and evidence of return of ovulation occurred, in both species, at about the same time [95]. The histology of the endometrium of DMPA treated Rhesus monkeys also suggests that the potency of

a given amount of DMPA may be less in the Rhesus than in the human. Specifically, only at ten times, but not at one times the human dose, did the changes in the endometrium of the monkeys resemble those in the human receiving contraceptive doses of the drug.

2.2.2b.1 SUMMARY OF EVIDENCE ON POTENTIAL RELEVANCE OF THE FINDINGS IN THE MONKEY TO THE HUMAN

None of the major reasons proposed for dismissing the relevance of the findings in the Rhesus to the human can be substantiated by the evidence presently available. The poor design and execution of the IRDC study preclude the conclusion that the endometrial cancers were a consequence of the extreme dose of the drug used or that the two monkeys were in some way unique and not representative of monkeys in general. The hypothesis that the cancers originated from an endometrial cell type present in the monkeys but not in the human remains to be tested. Finally, whether the endometrial cancers that developed in the two monkeys in the IRDC study were the consequence only of circumstances unique to the particular experimental conditions of the IRDC study, as claimed by Upjohn, can not be determined without repeating the experiment in an adequate manner.

2.3 ANIMAL TESTING FOR CARCINOGENESIS: APPROPRIATENESS OF GUIDELINES FOR TESTING AND INTERPRETING RESULTS WITH STERIOD HORMONES TO BE USED AS CONTRACEPTIVES

The reliance on animal testing has been conventionally applied to drugs as a prelude to their widespread administration to humans. Such tests are aimed at screening for major adverse effects of the drug, its toxicity following short term use, and its carcinogenic potential following long term use. The principles underlying animal tests of drugs, in general, have been incorporated into the guidelines established for testing of contraceptive steroidal agents [96]. The pitfalls and the limitations of such animal tests have been recognized and debated since these guidelines have been established. The complexity of the issues involved may be gauged from the discussions held during a three day workshop held by NIH in 1983 [2].

The debate among proponents and opponents of a drug that fails the animal test screen, as in the case of DMPA, tends to center around two theoretical problems: the doses of the drug used and the appropriateness of the species selected for study.

The traditional approach in studies of drug safety has been to administer a wide range of doses of the drug, including doses much larger than those proposed for use in the human. This convention can be rationalized on several grounds. It is assumed that use of high doses will permit

the observations of events that otherwise may take a very long time to develop or require a very large number of animals to detect. Use of a wide dose range helps delineate a safe dose range and if a dose-response relationship exists, it provides evidence for causal relationship between the drug and a specific adverse effect.

In relation to hormonal steroids, the use of very high doses has been challenged on the grounds that their effects may differ not only quantitatively, but also qualitatively, from those of lower, more physiological amounts. It should be noted that similar questions have been raised in relation to chemical carcinogens in general [97]. One way to compensate for this problem is to design the tests so that the nature of dose-response relationships can be defined rather than to abandon the use of multiples of the human dose. This was accomplished in the study of dogs by the Dawson Research Corporation, but not in the IRDC study of monkeys.

The problem of uncertainties about the suitability of any particular species has been addressed by the requirement that the drug be tested in several different animal species. Thus, according to FDA quidelines, all contraceptive drugs must be tested in rodents, dogs and monkeys. If a carcinogenic effect is demonstrated in any one species, in particular, in a site that is expected to be affected by the particular drug or hormonal agent (i.e., a known target

organ), this is considered to constitute evidence of lack of safety. If a drug is found to produce cancer in more than one species, the strength of the evidence is increased. It is recognized that a single carcinogenic agent may cause cancer in different organs in different species and that cancers may be induced in unexpected sites, not previously identified as target organs. Only if relevant biological responses in the species affected are known to differ in a major way from those of the human would it seem prudent or justified to dismiss major findings [97 (pp. 21599-21600)].

Tests on DMPA were conducted on all three species mandated. Neoplasms were identified in known target organs of progestogens in two of the species, the dog and the monkey. It would require compelling evidence that the human is uniquely different from each of these two species to disregard these findings. Such compelling evidence, in our opinion, is not now available. Whether DMPA treatment of mice, the third test species, was associated with any increase in neoplasias is not known. The results of the tests on mice presented by Upjohn to FDA are uninterpretable, because of the very high mortality in both the controls and the experimental groups [98-100]. This problem is compounded by inadequate information on the pathology of the large number of mice that had died and were either canibalized or autolysed [98, 99]. Unfortunately, FDA apparently did not request that these

early, relatively short term experiments on the rodents be repeated.

The World Health Organization, in its monograph on "Evaluation of the Carcinogenic Risk of Chemicals: Human Sex Hormones" [101], lists three responses in test animals that are to be used as indicators of carcinogenicity: 1) the occurrence of types of neoplasias not observed in the controls; 2) a significant increase in the incidence of the same types of neoplasms as found in the controls; or 3) a decreased latency period as compared with controls. All three types of responses were observed in animal studies with DMPA.

Similar and some additional criteria for evaluating the findings from toxicity testing in animals have been proposed by Squire: (1) positive results obtained in two or more animal species; (2) induction of two or more histologically distinct types of neoplasms in one or more species; (3) induction of tumors that are normally rare in the test animals; (4) induction of neoplasm after administration of low doses, or a shorter latency period required to induce a neoplastic response; (5) induction of malignant neoplasms, rather than benign tumors; and (6) positive results obtained from genotoxicity studies suggesting mutagenic potential [102]. All but the last of the phenomena have been observed in the animal tests of DMPA. According to the criteria set by FDA, by the World Health Organization, and those proposed by Squire, as well as by those suggested most recently in the

Office of Science and Technology Policy's Report on Chemical Carcinogens [96, 97, 101, 102], the findings must remain a source of concern.

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THE COMMISSIONER'S QUESTION #3:

CAN THE HUMAN DATA SUBMITTED BY UPJOHN SUCCESSFULLY REFUTE THE RISK OF HUMAN CANCER SUGGESTED BY THE ANIMAL DATA?

The data relating to the question whether in the human the use of DMPA as a contraceptive is associated with any change in the risk of neoplasias of genital organs are inadequate and inconclusive. Most of the data are derived from studies that were not designed as epidemiological studies and therefore do not provide the information needed. The few studies that specifically address the question of the effect of DMPA on the incidence of cancer in genital organs in the human suffer from major limitations in design and/or execution. Systematic investigation of the incidence of neoplasias in long term users of DMPA as a contraceptive have only been initiated recently. Consequently, the data available can not serve to resolve the questions that have been raised concerning the carcinogenic potential of DMPA, in particular, when used over an extended period of time or after a period of latency. The legitimacy of these as yet unanswered questions and the need to resolve them by observations on the human rests not only on the findings in the test animals. An increased incidence of neoplasias in

genital organs, the cervix and the breast, in DMPA users was suggested in a few studies [1-3].

Careful epidemiological observations of women using DMPA as a contraceptive are of particular importance since they represent the first large group of humans exposed for a prolonged period of time to a novel hormonal environment. This is a hormonal state characterized by relatively high levels of progestogens in the presence of low, early follicular phase levels or estrogens. There is no adequate body of knowledge that could serve as a basis for predicting with any degree of certainty what long term consequences, good or bad, such a hormonal state may have.

Opinion may differ on the value of animal studies and the interpretation that can be placed on findings derived from them. However, there is general agreement that with agents such as contraceptives that are likely to be used by large numbers of healthy women for long periods of time, it is imperative that their long term consequences, bad or good, be assessed by adequate human studies. Moreover, experience with oral contraceptives in the past has shown that there may be populations of subjects at special risk for certain adverse effects and the need to identify such subjects. There is also a general consensus on guidelines of design and execution of studies that need to be followed to provide acceptable epidemiological data [4, 5].

There is general agreement that the data available on the human are inadequate, as discussed at the public hearing by witnesses both for Upjohn (Drs. R. Hertz and R. Gray [6]) and FDA (Dr. R. Hoover [7]). Two arguments have been presented by those who, while in agreement with this conclusion, nevertheless feel that DMPA is unlikely to pose any significant cause for concern as a promoter of neoplasias in the human. The first is that even though the human studies individually may be inconclusive and questionable on scientific grounds, they are, in their totality, reassuring and sufficient to provide a basis for a regulatory decision. According to this view, quantity of data can substitute for quality. This viewpoint was most graphically formulated by the lawyer representing the Upjohn Company at the Hearing held by the U.K., Department of Health and Social Security, in London 1983:

> If you have 30 studies...in which each has a flaw but which flaw cannot be pointed to as being a biased flaw, a flaw which is likely to exclude the people who particularly have the cancer, with any one paper you can say that there is a flaw, and those cancer cases might have slipped through that hole. But if you have 30 papers, each with a theoretical flaw but no bias, then it is inconceivable that an increased incidence could slip through all 30. ...If you take 30 pieces of paper, each with a random hole in it, and you put them together, you have then got something solid with no gap in it because it is inconceivable that in a large number of varied studies, presumably each with no bias, the increased incidence could slip unnoticed through all of them [8].

The second argument is that if the drug had any significant effect on the incidence of neoplasias, this would have made itself evident and been recognized even without any specific studies. The assumption underlying this argument is that if DMPA caused an increase in the incidence of neoplasias, this would have been noted by the health care professionals and/or would have been brought to the attention of the Upjohn Company through the voluntary reporting system.

Neither of these arguments is acceptable. There are few circumstances under which an adverse reaction to a drug will make itself obvious in the absence of systematic study [9]. The quantitative information needed on the human to provide some rational basis for evaluating risk versus benefit can rarely be obtained either from casual observations or from poor, inconclusive studies, however numerous.

In connection with DMPA, there were early indications that there might be a special need to obtain human epidemiological data on the carcinogenic potential of the drug, and that concerns about its use might arise if such data were not forth-coming. The first suggestion that there might be an increased incidence of <u>cervical neoplasias</u> was made in 1971, by Seymour and Powell [1], and the subsequent analysis of the data obtained from subjects receiving DMPA under an IND between 1968-72 [2, 10]. These findings were a major factor why questions were raised concerning the

approval of DMPA as a contraceptive in 1974. The report of the first beagle study became available one year later. It suggested an association between DMPA and malignant neoplasias of the breast. Even earlier, at a meeting of the FDA's Obstetrics and Gynecology Advisory Committee held in 1972 to assess the safety of DMPA in the human when used as a contraceptive, concern was voiced about the risk of breast cancer that may be associated with the use of DMPA in the human [11].

According to the testimony given at the public hearing by Dr. Roy Hertz, a witness for Upjohn, members of the Obstetrics and Gynecology Advisory Committee objected when the dog and monkey studies were first proposed as a means to assess the potential risks of hormonal contraceptives on the grounds that:

> ...the pertinence of the pre-existing data on rats, mice, hamsters and guinea pigs could never be resolved by additional animal studies. On the contrary, some of us felt that only through a carefully designed epidemiological study could we determine the real significance and some of the untoward implications of earlier animal studies [12].

Large numbers of women in various countries including the U.S.A. were receiving DMPA as a contraceptive while the long term dog and monkey studies were being completed. Yet not until recently, and only after approval for general marketing of the drug in the United States was denied, were plans made or acted upon to collect data in any systematic

manner from humans on the consequences of long term use of DMPA on the incidence of neoplasias in the secondary sex structures. It will now require several years before information will begin to become available from systematic follow-up of users in different countries that are planned (New Zealand and Kenya) or are ongoing [WHO] [13]. It is likely to take many additional years of observation before the full picture can emerge. Until then, all we have are results from studies often designed for other purposes in which observations on neoplasias were made incidentally, and from a few attempts at epidemiological studies based on retrospective surveys, aptly termed as "epidemiological archeology" [14]. These studies have major problems which limit their value as a source of epidemiological data.

3.1 EXPERIMENTAL DESIGN AND EVIDENCE: HUMAN STUDIES

For details of the relevant studies, see Appendices 1-3.

3.2 CRITIQUE OF THE EVIDENCE ON THE HUMAN

The following are major, recurring deficiencies in the studies reported:

1) Too few subjects, especially long term users of DMPA, studied. Yet it is prolonged use of the drug that is thought to be required for the induction or promotion of neoplasias;

2) Too short a period of follow-up, thereby precluding recognition of neoplasias in secondary sex structures that may require a long period of latency to develop;

3) Inadequate or inappropriate controls for comparison of frequency of neoplasia in users versus nonusers;

4) Failure to control or adjust for the many known confounding risk factors for carcinomas of the cervix, endometrium, and breast;

5) Lack of documentation of the adequacy of data collection on subjects. There is, in fact, evidence both in the United States and abroad of poor recording of information on subjects that constitute the basis of some of the studies [15-17]. It is recognized that in many of the centers where DMPA has or is being used, and that have served as a source of published information, follow-up of patients is difficult because of local conditions and limited resources (e.g., migrant population in Africa [18] or rural population in Thailand [19]). This conclusion is supported by the testimony of witnesses at the public hearing and by documents on record [20, 21]; and

6) Lack of information on subjects in the United States or in populations that may be expected to respond similarly to those in the United States. There are well known, marked differences in the incidence of neoplasias of the breast, endometrium, and cervix in different regions of the world [22, 23]. They are based on, as yet, little understood

genetic and environmental factors. Therefore, it is particularly unfortunate that the opportunity was missed to collect meaningful information at the Grady Clinic, the only large center in this country where a significant number of subjects were receiving DMPA as a contraceptive under an IND over a relatively long period of time (11,500 or 15,600 subjects, depending on the source) [24-27]. This was a setting in which, at least theoretically, resources might be expected to have been available for adequate collection of data relevant to the population in the United States. That this was not the case is evident from the findings by the FDA audit in 1978 of the conduct of the IND at the Grady Clinic and the information contained in various documents submitted and published from that Clinic [15, 24-29]. It is also regrettable that studies were not initiated earlier in countries such as New Zealand, where the drug is apparently used widely as a contraceptive, where adequate data collection should be feasible and the incidence of neoplasias of the breast and endometrium are comparable to those in the United States [22].

The problem of lack of information on any significant numbers of long term users of DMPA and the lack of adequate long term follow-up of such subjects cannot be obscured or overcome by pooling of data from women who have used the drug for different periods of time and presenting these data in terms of "number of women-years or months" of DMPA use, i.e.

experience with the drug or surveillance following its use. The fallacy of this approach has been stated most aptly, by a witness for the Women's Health Network to the effect that while it takes nine months to produce a baby, nine women, each one contributing one month, can not produce a baby [Statement not recorded in transcript].

3.2.1 REVIEW OF HUMAN STUDIES OF BREAST CANCER

There are nine publications [3, 10, 18, 27, 28, 30-33] in which data are presented on breast pathology in subjects using DMPA as a contraceptive (Appendix 1).

Observations made on breast pathology on 11,631 women during studies conducted under an IND when DMPA was first being tested as a contraceptive are summarized in two related publications [10, 30]. Though the number of subjects is relatively large, the data are of limited value for the following reasons. The information was pooled from over 80 different centers, some outside the United States. Thus, the subjects represent different populations which have, however, not been identified or defined and for which there were no controls. It is, therefore, not possible to assess the significance of 5 cases of breast cancer in this mixed population of subjects. Nor are data given on how many of the subjects were long term users of DMPA. Instead, the data are pooled and presented only as number of women years of experience. The number given, 17,408 women years, though

seemingly large, represents an average of less than two years per subject. More importantly, data presented in this fashion are essentially useless for trying to assess cancer risk in relation to duration of drug use.

Neither the study reported from Chile [31] nor the one from South Africa [18] included control groups. There are, moreover, no published data available for comparison on the incidence of breast cancer in comparable populations in the same geographic locations from which the subjects were drawn. Both of these reports are examples of studies that were not designed to provide epidemiological data. They are descriptive clinical reports on patients receiving DMPA.

Specifically, in a prospective study in Chile, 2,418 women were followed for up to 7 years [31]. This is one study in which a reasonable proportion of the subjects had received DMPA for a relatively long period of time (52% of women had taken the drug longer than three years). Of ten women with breast nodules, two were found to have adenocarcinoma. No conclusions can be drawn from this report, not only because there were no controls, but also because the doses of DMPA given varied, and some of the subjects were receiving estrogens as well.

In the South African study [18], though the number of subjects observed was much larger (19,875 women), they included only few long term users: seventy percent had received DMPA for only one year or less and another 28.8% for

between one to three years. Moreover, since these subjects were from a migratory population, follow-up was difficult and incomplete, as acknowledged by the investigators. Not a single mammary carcinoma was identified in this large group of subjects either at initial examination or during follow-up [18]. The absence of breast pathology at first examination in this number of subjects suggests that the background incidence of breast cancer in this population is likely to be low. However, information on this important point is not provided or available. Consequently, the significance of the data can not be evaluated.

In an update of the "Mexican Experience", Pena-Delgado et al., describe the incidence of breast pathology in 1,025 randomly selected long-term users of DMPA, i.e., subjects who had used DMPA regularly for three to eight years [33]. In this group of women, 83% of whom were between the ages of 25-39, there were no cases of mammary carcinomas. Once again, there was no control group for comparison, and information is not available on the baseline incidence of breast cancer in the type of population studied. Therefore, the significance of the findings can not be evaluated.

McDaniel and Pardthaisong report in a cross-sectional study on the results of breast examination conducted at one time point on 1,270 Thai women receiving DMPA with monthly supplement of DES [32]. Controls comprised of 257 subjects presenting themselves at the clinic for contraceptive

services for the first time. No cases of malignant breast lesions were identified in either group. The number of subjects was small. Moreover, it included only very few long term users of DMPA (39.6% were using DMPA for one year or less, 32.8% for 1-2 yrs., and, only 27.5% for longer than 2 years). To determine what magnitude of change in the incidence of breast cancer could have been detected in so small a number of subjects would require information on base-line incidence of the disease in Thailand. This information is not available, but it is reasonable to assume that the incidence of breast cancer is likely to be lower in Thailand than in the United States [22, 23]. If so, a larger number of subjects would have had to be studied in order to be able to detect a rare (i.e., low incidence) event.

There have been two recent reports from the Grady Clinic, the one center in the USA where a large number of subjects (11,400 or 15,600 depending on document) have received DMPA as a contraceptive between the years 1968 and 1978 [27, 28]. Both were retrospective studies, based on information retrievable from files and records. Obviously, the quality of the initial collection and recording of the data is of crucial importance in determining the value of the information presented. There are reasons to question both the accuracy and the completeness of the records kept on the patients because of the findings by FDA in an audit of the records, in 1978, at the Grady Clinic [15]. Reports,

published and unpublished, from the Grady Clinic also acknowledge that in a number of cases essential information such as parity and dates of injection were not recorded, and that there were even uncertainties whether some of the subjects identified through the computer as having received DMPA had actually received the drug [24, 25, 26].

Liang et al [28] attempted to retrieve information on the incidence of cancer of the uterus, breast, and ovary in 5,000 black women receiving DMPA at the Grady Clinic over a 10 year period. In this retrospective survey, computerized information on subjects at the Grady Clinic was linked with composite files of hospitalization at the Grady Hospital. Besides the questionable accuracy and completeness of the data base, discussed above, this study is of limited value because of the short exposure of the majority of subjects to DMPA (58.7% had received DMPA for less than one year, and only 12.6% for longer than 3 years). In these subjects, no increased incidence of neoplasias was identified above that expected in this age-and-race-specific group. The authors' conclusions are appropriately guarded: "This study indicates that there is unlikely to be a strong association between DMPA use and cancer of the breast, uterine corpus, or ovary." To this should be added "at least not after a short period of use of the drug."

Greenspan et al. reported a retrospective case-control study of 30 subjects with breast cancer (29 black, 1 white)

and 179 matched controls [27]. Again, the duration of DMPA use was short (average number of injections: 2.8 for those with cancer and 3.2 for the 179 controls). No increased risk of breast cancer was identified in users of DMPA compared to nonusers in a study design that could have permitted identifying a three-fold increase in risk. Again, the conclusion of the authors is appropriately modest: "It seems reasonable to conclude that short-term use of DMPA in black women is not associated with any increased risk in breast cancer". To this should be added "at least not a 3-fold increased risk." It is important to remember that with respect to a neoplasia with an incidence as high as that of breast cancer in the USA (1 woman in 10 is estimated to be at risk of developing breast cancer in her lifetime), even a small increase in risk, one that the above study could not identify, cannot be considered insignificant. Such risk, if it exists, would constitute a serious individual as well as a major public health problem.

A positive association between the use of DMPA as a contraceptive and breast cancer was reported in one study [3]. Using a restrospective survey of nine centers for the mentally retarded in Canada, Zarfas reported 3 deaths from breast cancer among 533 females known to have received DMPA. He calculated that this number of deaths due to breast cancer in users of DMPA was much higher than the expected number of deaths in a comparable age-cohort in the general population

in Canada. But this study, too, is flawed in that these women had received, in addition to DMPA, anticonvulsive and psychoactive medication, and also may have had other risk factors for breast cancer, such as nulliparity.

The Zarfas study is the only one in which DMPA use was implicated in causing an increased incidence of breast cancer. Advocates of the use of DMPA tend to stress the deficiencies of this study and to discount it on scientific grounds. Conversely, those opposed to the use of DMPA point to the weaknesses of the studies in which no association between breast cancer and the drug were identified. But if the same standards are applied equally to all studies, we are left essentially without information on the effect that the use of DMPA as a contraceptive may have on the incidence of breast cancer. The application of appropriate standards to studies on which decisions are to be based is not simply an academic exercise. It is a fundamental requirement for arriving at conclusions that are not subjective and arbitrary, and conclusions that can provide an adequate basis for a regulatory decision. It is also required by the health care professionals and their clients for making an informed decision when chosing among therapeutic options.

3.2.2 REVIEW OF HUMAN STUDIES OF ENDOMETRIAL CANCER

Most of the evidence presented by the Upjohn Company in relation to the endometrium and the long term use of DMPA as a contraceptive consists of findings from endometrial biopsies [34]. Understandably, the number of subjects that could be studied by this invasive approach is too small to provide any definitive data on the incidence of endometrial cancer in subjects using DMPA as a contraceptive. All but the last three of the studies cited by Upjohn were carried out before the endometrial neoplasias were identified in the monkeys. The primary aim of these earlier studies appears to have been to define the morphological changes induced by the drug as these relate to its contraceptive effects and to some of its side effects, e.g., amenorrhoea, menorrhagia, and return of fertility [35-38]. Therefore, not only were the numbers of subjects studied small, but the duration of DMPA use, as well as the follow-up after termination of use of the drug were short. Finding no cases of cancer of the endometrium under these conditions can not constitute a basis for any conclusions on the issue. The design of these early studies was appropriate for achieving the stated objectives, but not for providing information on long term consequences of DMPA on the incidence of endometrial cancer.

Following the discovery of endometrial cancers in the two monkeys, five additional studies were initiated. Three

of these, again, were based on endometrial biopsies. The last two studies represent attempts to determine, retrospectively, whether there was any association between the use of DMPA and cases of endometrial cancer identified in hospital records (Thailand) [32] or death certificates (Mexico) [17]. None of these latter studies contributes to the resolution of the question, because in the biopsy studies the number of subjects was small and the epidemiological studies had major flaws [Appendix 2].

Pena-Delgado biopsied 92 subjects from a group of 1,025 women and found no neoplasias [34]. Cervantes and Azcona reported on 76 biopsy specimens, 40 from long term users of DMPA (4.5-13 years) and 36 from women who had stopped taking DMPA for 0.6-5.4 years following long term use of the drug. Our attempts to obtain additional information on these subjects pointed up serious questions about the quality of the data [16]. The deficiencies in the data base were identified under the following circumstances: since the biopsy material obtained by Cervantes appeared unique but the description of the pathological findings presented in the report by the Upjohn Company ambiguous [39], we wanted to have the histological slides examined by the pathologists appointed to review the slides from the uteri of the IRDC monkeys. In the course of trying to obtain additional information on the subjects, the following problems were identified:

1) According to the dates provided in the tables by the Upjohn Company, three of the subjects receiving DMPA were pregnant at the time when they were biopsied. Yet the pathologists did not report having seen any of the characteristic changes of pregnancy in the tissue examined.

2) The Upjohn Company confirmed that one of the subjects was, indeed, known to be pregnant. However, it was unable to clarify the status of the other two subjects at the time of the biopsy or the fate of the offspring if any were born, because "the original clinic records apparently have been destroyed" [16].

3) Upjohn was also unable to offer any explanation for the obvious discrepancy in at least the one case, Subject #27, between the pregnant state of the subject and the pathologist's finding.

4) Upjohn did not have and was unable to obtain information on the dates the biopsies were taken in a number of the subjects. The dates provided were stated to have been estimated from interview dates [16].

Since it was evident that accurate information could not be obtained on these subjects, we abandoned plans to have the histological slides examined by our panel of consulting pathologists.

There have been only two studies designed as epidemiological investigations of the effect of DMPA on endometrial cancer [17, 19]. In both there is serious

question of ascertainment. In the study from Thailand [19], subjects with endometrial cancer were identified from hospital records. It is not known what proportion of subjects who become sick in rural Thailand are actually hospitalized, but it is reasonable to assume that it is small (see quote from Gray's letter below). In this study, in only 9 out of 45 probable cases of endometrial cancer did the investigators attempt to determine whether they had been exposed to DMPA (for details see Appendix 2). Similarly, in the Mexican study, it is difficult to appraise the accuracy of the diagnoses obtained from death certificates, the basis on which the cases were identified [17]. Finally, in both of these retrospective studies, in an undefined number of cases, relatives rather than medical records were the source of the information on whether the subjects had received DMPA. Relations are unlikely to be an accurate source of information, especially if we accept the claim that one of the advantages of DMPA is the privacy it affords.

Some of the problems with the study from Thailand [32] are highlighted in the letter by Dr. R. H. Gray from the London School of Tropical Medicine and Hygene to Dr. Colin McCord:

> The review of endometrial cancer admissions to the Chiang Mai Hospital between 1974-78 was not intended as a case control study. It is merely a first look at available data. We are aware that case acertainment would be incomplete and that the data might be biased in several

> respects, but still it seemed to be a reasonable evaluation of the situation.... One can not interpret the findings that none of the 10 women in the limited review of cancer cases had used DMPA. The relative risk would have to be increased more than 20 fold if we were to detect any significant effects in such a small sample. Having said that, I think that your calculation that only 2.2% of the cases were reported may be a considerable underestimate. You used U.S. data to calculate expected deaths, but it is known that endometrial carcinoma is far more frequent among Americans than among Asian women. For example, U.S. rates are more than 12 times greater than in Japan and around 4.7 times greater than in the Malay population in Singapore... We do not know the figures for Thailand, so we can not estimate the degree of under reporting. Undoubtedly some cases were missed since hospital coverage is limited in northern Thailand. However, there is no indication of bias since we have no information to suggest that the use of DMPA might be different among non-hospitalized as compared to hospitalized cases [21].

Finally, the unpublished study by Greenspan, representing a further attempt to retrieve information from the "Grady Experience" information, this time on endometrial cancer, serves only to demonstrate the problems of trying to retrieve data when no appropriate record system was set up from the beginning [40]. It also highlights how misleading it may be to rely on information obtained from answers given by patients, in particular when the questionaires are inadequate (Appendix 2).

Thus, the issue of the risk of endometrial cancer in long-term users of DMPA appears not to have received much

consideration until after such cancers were identified in the monkeys in 1978.

In conclusion, there are no data available that could serve as a basis for deciding whether in the human the use of DMPA as a contraceptive has an effect on the incidence of endometrial cancer and whether in this respect the human female's response is similar to or differs from that of tne Rhesus monkey.

Since 1980, the Upjohn Company has been alerted to two instances in which endometrial carcinoma was diagnosed in subjects receiving contraceptive doses of DMPA [42, 43]. These cases are of interest primarily because they point to problems that may arise in the diagnosis of cancer of the endometrium in subjects receiving DMPA. The significance of irregular bleeding, which is the symptom of such cancers, may not be recognized because it is an expected side effect of DMPA use. Thus the use of DMPA might delay the diagnosis of endometrial carcinoma. Both subjects in whom endometrial cancers were diagnosed were older women. In one of the cases the carcinoma was undifferentiated (Class 3, Grade 1a) and was diagnosed 9 months after the last injection of DMPA. In the second case the carcinoma was, apparently, well differentiated.

3.2.3 REVIEW OF HUMAN STUDIES OF CERVICAL CANCER

Historically, the first question raised concerning DMPA's carcinogenic potential was in relation to carcinoma of the cervix. This occurred shortly after the introduction of DMPA for contraceptive use. When data on the efficacy and short-term side effects of DMPA were being collected under an IND, a higher incidence of abnormal cytology was observed at one of the centers in women receiving DMPA than expected in that hospital population [1]. Specifically, in a group of 1,123 women using DMPA, Powell and Seymour reported finding abnormal cervical cytology in 34 women and cervical cancer *in situ* in 11 women [1]. These findings were noted over a 66 month period; however, 60% of subjects discontinued using DMPA over this 5 1/2 year period and only 40% remained in the cohort at completion of the observation period. An attempt was made to obtain cervical smears on all continuing patients and a "majority" of the discontinued patients; apparently smears were obtained in 1,107 patients. The authors calculated a rate of about 10 cases of carcinoma *in situ* per 1,000 patients in the DMPA group--over a variable and unclear time period. They compared this to a figure of 5 per 1,000 "for the past 3 years" in an unexposed group of women seen in the same hospital. No information about age, race, etc. is listed for the comparison group.

Subsequently, B.D. Litt of the FDA attempted to provide a suitable comparison group for the 10 per 1,000 figure of Powell and Seymour, but concluded he was unable to do so because of the incomplete description of the study population and the inability to relate the observed rate to a defined time period [2]. Litt used for comparison the figures provided by the Third National Cancer Survey but pointed out that this could be questioned since the more careful screening of the participants in the DMPA study could inflate the rates.

A curious feature of the observations made on these subjects is that in many the cervical abnormalities were diagnosed only a short time after initiation of drug use. This raises the question whether the pathology can be attributed to the drug, since with chemical carcinogens a long lag time is to be expected between exposure to the carcinogen and the development of neoplastic changes. Under the influence of progestogens there are hyperplastic changes in cervical histology, in particular in the endocervix [44, 45]. However, it would seem unlikely that experienced pathologists would mistake these for cervical cancer.

In summary, the problems with the observations reported by Seymour and Powell are:

(1) No verification of cytological diagnoses;

(2) Rates of dysplasia and *in situ* cancer not related to duration of exposure or elapsed time since exposure;

(3) The dysplasia and *in situ* cancers are not analyzed in relation to concomitant estrogen supplementation; and

(4) No suitable comparison group included in the study design.

The issue of carcinoma of the cervix in DMPA users was brought out at a Congressional hearing [46], and was the basis for FDA's staying, in October 1974, the provisions of approving the NDA for use of the drug as a contraceptive (Table 1, p. 13).

As a consequence of the questions raised at the Congressional hearing, FDA obtained from Upjohn an update of information on subjects that were diagnosed to have carcinoma of the cervix while receiving the drug as a contraceptive under an IND [47], and then attempted to analyse all the data available. The FDA noted, in addition to the problems listed above in relation to the report by Seymour and Powell, that the data were collected from subjects at various centers, both in and outside the United States representing different populations with unknown background incidence of cervical cancer. Therefore, only for the women in the United States on whom such information was available, could some meaningful attempt be made to analyse the data. In both white and non

white subjects the age-specific and age-adjusted incidence was higher than the expected rate based on the Third National Cancer Survey [2]. This was evident irrespective of the dosage of DMPA used and whether supplemental estrogen was administered or not. As in the study by Seymour and Powell, the finding of an increased incidence in cervical cancer in the DMPA treated subjects could have been due to the closer surveillance of subjects being treated under an IND. Appropriately designed studies needed to test this assumption were not initiated, at least not until recently.

In their memorandum of May 17, 1974, officers of FDA who reviewed the issue of the effect of DMPA on the incidence of cervical cancer raised at the Congressional hearing, concluded: "FDA analysis of the data has been hampered by the poor quality of the submission and the inaccessibility of the required information" [47].

In the same memorandum the following recommendations were made:

1) The FDA should undertake a more thorough evaluation of the Depo-Provera NDA and all NDAs dealing with contraceptives, especially with regards to adverse reactions.

2) An orderly procedure should be developed for calculating event rates on person years of exposure and characterizing the population in each clinical trial of a contraceptive by relevant demographic characteristics.

3) Standardized and age specific rates should be computed for all important medical events observed during a contraceptive trial.

There is no indication in the interval between 1974 and the resubmission by Upjohn of a supplemental NDA in 1978 that these basic considerations were incorporated into the design of studies undertaken on the influence of DMPA on "important medical events" or whether FDA had been successful in implementing its own recommendations.

In the response to our questions, Upjohn cites, in addition to Powell and Seymour [1] and Schwallie [10], only one other set of observations. This report by Ide et al [48] is lacking in detail and the data presented cannot serve to support the authors' conclusion that "a possible carcinogenic effect of the hormone contraceptive on the cervix could be related to its estrogenic component" [48].

There is one additional report, not cited in either party's responses to us, that addresses the issue of DMPA and carcinoma of the cervix [52]. Though the study was too small to resolve the issue, it is of interest since it represents the single attempt in the past to carry out an appropriately designed, prospective epidemiological investigation of carcinoma of the cervix in DMPA users. In this study from Chile no statistically significant differences were found in the incidence of cervical cancer in a group of 2,239 women receiving DMPA for up to seven years and in 2,409 women using

an IUD as a contraceptive. The number of years of observation on which the incidence rate is calculated is not clear. According to the tables, it was four years, while the text implies seven years. In either case, as the authors acknowledge, the number of women studied and the duration of follow up were insufficient to provide conclusive evidence that DMPA has no influence on the incidence of cervical cancer.

It is evident that the questions raised in 1974 concerning the incidence of the cancer of the cervix in DMPA treated subjects could only be resolved by appropriately designed epidemiological studies, that is, studies that include a suitable control group for comparison. Yet, no such studies were initiated until very recently. The one started by WHO in October 1979, is not yet completed and only preliminary data are available.

The studies of the epidemiology of carcinoma of the cervix are known to present special difficulties. The problems relate not only to the numerous putative confounding factors that need to be controlled for, but also to the lack of agreement among pathologists on histological diagnosis [49]. It has even been suggested that these problems preclude studying the effect of DMPA on cervical cancer [50]. This pessimistic view seems not to be shared by WHO: carcinoma of the cervix is among the end points included in its multinational case control study and is also to be

investigated in the study sponsored by Upjohn in New Zealand [51].

Thus, until the reports from the above studies are published, the early suggestions that the drug may increase the incidence of cervical neoplasia can not be dismissed. We have examined the preliminary, confidential report by WHO of its initial findings, and found no basis for changing this conclusion.

An examination of the documents and events relating to the question of cervical cancer and DMPA provide an insight into the basis of the problems with the evidence submitted on the safety of DMPA. The initial collection of data under an IND was not adequate to provide a basis for evaluating whether the drug had any influence on "important medical events" whether carcinoma of the cervix, breast or endometrium. This is perhaps not surprising, since at the early phases of research into the use of the drug as a contraceptive, the major objective was, understandably, to establish efficacy, decide on dosage and identify immediate, short term side effects. Hence the different sources of subjects, the range of doses given with or without estrogen supplementation, and the relatively short and variable period of observation. The attempts to derive epidemiological data from such observations, as in the case of carcinoma of the cervix, only demonstrate the difficulties inherent in trying to derive such data from studies not designed to provide

them. Even when these early studies did point to the possibility that DMPA might increase the incidence of a major medical event, such as carcinoma of the cervix in the human (not in a test animal), no attempt was made to initiate appropriately designed studies to resolve the issue. Consequently, the NDA submitted in 1978 did not contain any new, substantial evidence on this or any other of the major outstanding issues.

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THE COMMISSIONER'S QUESTION #5:

WHETHER, IN THE EVENT OF CONTRACEPTIVE FAILURE, USE OF DMPA MIGHT INCREASE THE RISK OF TERATOGENIC EFFECTS MORE THAN OTHER CONTRACEPTIVES?

There is no evidence to suggest that MPA, intrinsically, would be more teratogenic for humans than other progestogens incorporated into oral contraceptives. Like other progestogens, MPA may influence sexual differentiation, most obviously that of the external genitalia and, possibly also affect the incidence of some rare but serious malformations of other organ systems. However, there are two reasons why, in practice, MPA used as a depot preparation might increase the risk of any adverse effect the compound may have on the developing organism. First, the action of DMPA, once injected, can not be terminated even if pregnancy is diagnosed. Second, since the use of DMPA is associated with amenorrhea or irregular bleeding, one of the best and earliest indicators of pregnancy is lost. Consequently, pregnancy may go undiagnosed and the mother may receive additional injections of the drug. (This potentially important problem is not mentioned in the literature and it is not clear how and when such patients get alerted to the fact that they are pregnant.) These two features of DMPA will tend to increase the duration of exposure of the fetus

to the drug and, thereby, the number and range of critical events that might be affected by it.

On the other hand, provided that the injections are administered correctly and the schedule is adhered to, contraceptive failure with DMPA should occur only rarely. In so far as use failure can be reduced or eliminated, overall failure rate should be lower than that achieved in the general population with oral contraceptives. Similarly, if guidelines for avoiding injecting patients who may be pregnant are strictly followed, and, in case of doubt, pregnancy tests applied, the incidence of inadvertent exposure of the fetus to DMPA should be reducible still further. Finally, judging from the experience gained when progestogens were used during pregnancy for therapeutic purposes, the frequency with which the teratogenicity of the drug is likely to express itself can be estimated to be small. Therefore, the chance of an individual using DMPA as a contraceptive giving birth to an abnormal offspring is very small and, within reasonable limits, quantifiable. Consequently, the teratogenic potential of DMPA should, in itself, not constitute a reason against using DMPA as a contraceptive, when otherwise indicated.

The above conclusion should, however, not be equated with the view that progestogens such as DMPA, whether administered alone or in combination with estrogens, have little or no potential to harm the developing fetus [1,2].

There is, in our opinion, inadequate basis for rejecting the possibility that progestogens may be teratogenic, although this potential action of this class of steroids may be relevant to only a few, susceptible individuals. The difference in viewpoint and interpretation of the data are not simply of academic interest. It is likely to influence the degree of care taken to avoid injecting women with DMPA who may be pregnant and, therefore, the number of fetuses exposed to the drug unnecessarily.

The fact that the increased risk indicated in some studies is not confirmed by others can not be explained simply on the basis of differences in quality of positive versus negative studies.7/ Rather, it could reflect the fact that when an agent poses only a small added risk, as is the case in the positive studies implicating progestogens as teratogens, and the base line incidence of the abnormality is low, one is operating close to the limit of sensitivity of the epidemiological methods used. It would take very large studies of many subjects and accurate collection of data to detect consistently any changes in incidence [6]. Small risks identified in epidemiological studies could be

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7/ Details of the design and the findings in the various studies have been tabulated in the testimony submitted by Dr. Grey, witness for Upjohn [3] and will not be restated. A similar analysis of the substantive portions of the studies is found in the submission of Dr. Done, witness for The Women's National Health Network [4].

artifacts and there may, indeed, be no causal relationship. However, the small size of the risk attributable to progestogens in the positive studies could be due to the presence of a small number of susceptible individuals in the large, heterogeneous population of subjects studied in the epidemiological surveys. Factors, including some that are clearly genetically determined, are being identified that can account for marked differences in individual susceptibility to specific xenobiotics, environmental agents as well as drugs [7]. Under these circumstances, while the risk may appear negligible, at least for the population at large, for the few that are susceptible, it is not small. Therefore, we think it is unwarranted to deny the possibility that exogenous progestogens can cause significant harm to any fetus on the grounds that epidemiological findings are contradictory. We also reject the argument that the progestogens are unlikely to cause extragenital abnormalities because no mechanisms have been identified by which they might do so. This argument assumes a completeness of knowledge about the mechanisms of action of steroid hormones in differentiation and on their target cells that is unwarranted. Accepting either of these premises is likely to encourage a decrease in precautions taken to avoid injecting DMPA to pregnant women. That this may, in fact, have happened is suggested by Upjohn's estimate that approximately one woman in 200-250 receives her first injection of DMPA

when already pregnant [1]. It is reinforced by such finding, as those in the report by Cervantes, in which certainly one, and possibly three out of 40 long term users of DMPA were apparently pregnant, presumably unbeknown to themselves or their physicians, when biopsied for endometrial specimens (see Question 3).

Proponents of the use of DMPA as a contraceptive have stressed the very low incidence of any malformations that might be attributed to DMPA have tended to focus on the genital abnormalities, specifically in females, and to minimize their severity. Opponents of the use of DMPA, on the other hand, have concentrated on the range and severity of the congenital malformations that DMPA might cause, with little regard for the frequency with which such effects may be expected to occur. However, both of these factors, the nature of the abnormalities and the frequency with which they may be expected to occur following use of DMPA as a contraceptive need to be evaluated to arrive at an estimate of risk.

In summary, the two primary concerns in this evaluation have been to try to determine whether sufficient data are available to arrive at a conclusion on the nature of the abnormalities that may be caused by MPA, and to make a reasonable estimate of the magnitude of risk to the individual, that is, the chance of her bearing a child with a congenital abnormality when using DMPA as a contraceptive. A

detailed comparison with the risk posed by other contraceptive agents was not attempted.

5.1 EVIDENCE ON THE TERATOGENICITY OF DMPA: SOURCES OF INFORMATION

The rate of inadvertent exposure of fetuses to contraceptive doses of DMPA can be deduced from data available on contraceptive failure. However, there have been no systematic studies to define the circumstances under which inadvertent exposure tends to occur and, most importantly, the fate of such exposed infants. That there must be several thousand such offspring can be deduced from the estimates of the number of women years of experience with DMPA as a contraceptive (stated by Upjohn to be to be over 11 million) and the rates of contraceptive failure reported in the various studies (generally below 1 but up to 1.5/100 women years of use in some series) [1]. Yet specific reference to the fate of fewer than 50 such infants can be found in the literature. (See Appendix for summary of some representive publications in which these cases are mentioned.) For the most part, even the sex of the baby is not stated. Yet altered sexual differentiation of the external genitalia is the best documented and understood congential malformation associated with the use of progestational agents during early pregnancy. There is also no evidence that the infants exposed inadvertently to DMPA in

utero were reexamined at any time after the immediate post partum period, though it is recognized that many birth defects, including severe abnormalities, go undetected if the babies are not followed after birth. For example, in the prospective study of 20,000 deliveries by women who were members of the Kaiser Foundation Health Plan, the incidence of serious congenital malformates diagnosed at birth was 1.1%, rose to 2.5% at year 1 and to 3.7% at five years [8]. The corresponding figures for non-severe abnormalities in the same study were 1.8%, 6.2% and 11.3%. Serious anomalies were considered ones that, if not corrected, would interfere with the child's development and/or well being, e.g., congenital heart defect, limb reduction, cleft lip [8]. Consequently, neither the scant information contained in the few reports in which mention is made of a few infants born to mothers who had received DMPA inadvertantly while pregnant nor the fact that only a single case of mild virilization was reported to the Upjohn Company under a voluntary reporting system [1], can provide the data base needed to try to quantify the risk of teratogenicity of DMPA when used as a contraceptive or to identify the nature of the abnormalities that might be attributed to the drug under these conditions.

In responding to our questions Upjohn stated that "After 15 years of postmarketing experience with Depo-Provera, sample sizes are just becoming adequate to allow systematic epidemiological studies of children exposed in utero to

contraceptive doses, particularly those that have reached at least five years of age" [1]. This statement implies that information on such children might be retrievable. Documentation has, however, not been provided that adequate records have been kept on a sufficient number of cases to make such retrospective survey meaningful. In addition, Upjohn refers to plans for one retrospective and one prospective study in Thailand and New Zealand, respectively. Until these studies are completed and the data published, they clearly can not serve as a source of information on the effects of exposure of fetuses in utero to contraceptive doses of DMPA.

Since contraceptive failure rate with DMPA is low, a substantial number of subjects would have had to be followed in order to accumulate information on an adequate number of infants born to mothers receiving the drug as a contraceptive. Theoretically, such information would have been simpler to accumulate than that on the incidence of neoplasias in individuals using DMPA as a contraceptive. The risk of exposing an infant to DMPA inadvertently and the effect the drug might have on the fetus may be assumed not to be effected by the duration of use of the drug. Consequently, information can be pooled from subjects irrespective of duration of treatment and the terms "women years of experience" can be used legitimately and meaningfully. This is in contrast to the use of the term in

relation to the development of neoplasias, in which case the length of exposure of each individual has to be taken into consideration if the data are to be meaningful (see p. 88).

In the absence of adequate information on the incidence of birth defects in infants born to DMPA users as a result of contraceptive failure, one has to fall back on data available on the teratogenic effects of MPA and other progestogens when used in the human for purposes other than contraception. There is an extensive literature on the effect on fetuses of progestogens used therapeutically, or to diagnose pregnancy and of progestogens combined with an estrogen used as a contraceptive or to diagnose pregnancy [2, 5]. The problems associated with these studies and with extrapolating from these data are well recognized. They include the following:

(1) The estimates of risk are based on pooled data on the outcome of pregnancy in women who have received different progestogens, frequently in combination with estrogens and other drugs. Though synthetic progestogens share many actions in common, there are important differences among them. These are reflected in differences in relative potency with respect to various biological end points that progestogens may effect and, hence, in the spectrum of salient actions characteristic for each. Progestogens are known to differ markedly in their androgenic potency, the aspect of their action through which they cause

masculinization of female fetuses. Their antiandrogenic potency, the basis for their ability to interfere with masculinization of male fetuses, is also likely to vary. But this aspect of their action has been less well characterized. Thus there is inadequate basis for comparing the relative antiandrogenic potency of the different progestogens that have been administered over the years to pregnant women.

(2) There has been a wide variation in the nature and doses of progestogens given and the time in pregnancy when they were administered.

(3) The progestogens were given therapeutically to women suspected of being at risk for spontaneous abortion and therefore, possibly, already at increased risk for giving birth to offspring with deformities.

(4) Lack of adequate controls constitutes a major problem in a number of studies.

(5) A key problem referred to previously is the small size of the increase in risk attributable to progestogen even in the positive studies. Consequently, any effect is likely to be close to the limit of sensitivity of the epidemiologic methodology used.

5.2 INFLUENCE OF PROGESTOGENS ON SEXUAL DIFFERENTIATION: GENITAL STRUCTURES

In experimental animals progestogens can masculinize the external genitalia of females by acting as an androgen.

However, because of their antiadrogenic potential, progestogens can also interfere with the normal masculinization of these structures in males [6,9]. A number of characteristics of progestogens' actions on its target organs have been identified that help explain this apparent paradox (see below).

There is general agreement that in the human, as in experimental animals, progestogens may masculinize the external genitalia of females. There is, however, disagreement whether in the human the converse, defective masculinization of the external genitalia, manifested as hypospadias, can be attributed to progestogens.

A causal relationship between exogenous sex steroid administration and masculinization of external genitalia of the human female could be established relatively easily. This abnormality occurs only rarely and, when it does, it can be related in most instances to congenital adrenal hyperplasis or adrenogenital syndrome, an enzyme defect causing abnormal androgen secretion by the adrenal cortex. When masculinization of the female fetus occurs in the absence of any such abnormal endogenous source of androgen secretion, there is little difficulty in assigning the cause to the exposure of the fetus during the critical early stages of its development to an exogenous agent of known androgenic potential, such as a progestogen [10].

The ability of progestogens to cause permanent masculinization of the external genitalia of the human female was recognized when these agents were widely used therapeutically for recurrent or threatened abortions [5, 10]. However, as was also noted during this period, masculinization occured only in a small proportion of the fetuses of mothers given the progestogen. Moreover, only in a few of these was the masculinization severe enough to result in labioscrotal fusion. In mild cases, clitoral enlargement, the most frequent abnormality, was noted to become less obvious with time, leading to the impression that the defect is reversible. However, true reversibility of the abnormality, as suggested by Upjohn [1], would be most surprising if masculinization occurred during the period of organogenesis, before the 12th week of life. Only if the androgen or androgenic progestogen acted during the later stages of pregnancy could the clitoral enlargement be expected to regress.

Fusion of the labioscrotal fold requires corrective surgery. Whether the abnormality is considered slight and the requirement for surgery a relatively trivial matter, as claimed by Upjohn [1], would depend on the context in which it develops. Such abnormalities were initially considered trivial, because the investigators believed in the efficacy of the progestogen treatment and that its benefits far outweighed this risk or side effect. As stated by Wilkins et

al in their first publication on the subject, "It is most probable that most of the patients we have studied would never have been born without their use" i.e., without the progestogen [10]. Under those circumstances, not surprisingly, they considered even surgical correction to be a simple and relatively trivial matter. However, underplaying this side effect, in relation to the use of progestogens as a contraceptive, may mislead physicians and result in less care being taken to avoid injecting women who may be pregnant.

We have only been able to identify four studies that provide information on the actual incidence of masculinization of female offspring of mothers receiving progestogens therapeutically during pregnancy. According to a retrospective survey by Bongiovanni and McPadden [11], from a total of 650 female offspring of mothers receiving 17 ethinyltestosterone or its nor derivative starting before the 7th week of pregnancy, only 2 females were noted by their attending physician to exhibit signs of virilization of the urogenital sinus at birth and on follow up. In a prospective study, Burstein and Wasserman also reported a low incidence of masculinization, 2 cases in 172 mothers receiving Provera, an incidence of 0.6% [12]. In contrast, Jacobson identified signs of virilization in 18% of female offspring of mothers receiving norethindrone [13]. One reason for the much higher incidence in this study could be a more focused examination

of the offspring for signs of masculinization by a single physician. Finally, in a Japanese study an incidence of 2.25% virilization was recorded in 888 female offspring of mothers treated with progestogens [14]. It should be noted that in none of these publications is there a definition provided of the criteria used to consider the clitoris to be pathological in size.

Since DMPA is relatively less androgenic than many of the progestogens used therapeutically, the frequency and the magnitude of the clitoral enlargement is likely to be less in susceptible fetuses exposed to contraceptive doses of DMPA than recorded in these surveys. The reason(s) why only a few fetuses are susceptible to maculinization, while others are not, is not known. Hypotheses have been offered but none tested. Thus there is no way of predicting who the few susceptible individuals might be.

Similar surveys on the incidence of hypospadias in male offspring of mothers treated with progestogens for pregnancy salvage are not available in the published literature. However, there must have been some cases of hypospadias among such offspring, since the background incidence of this abnormality in the United States is relatively high (15). Currently, approximately one in 200-250 males are noted to have hypospadias at birth. Some cases of hypospadias in offspring of mothers given DMPA were, in fact, noted in a small survey conducted by the Upjohn Company and submitted as

part of the application for an NDA for the use of Depo-Provera as a contraceptive in 1967 [16]. Six out of 204 male offspring of mothers who received DMPA for pregnancy salvage exhibited some abnormality of the genitalia. Four of these were in the 182 males that had been exposed to the DMPA during the first trimester, the period critical for masculinization of the external genitalia. Of these, two had isolated hypospadias, one bilateral undescended testes and one bilateral hydrocele. The two remaining cases of genital abnormalities, bilateral hydrocoles, occurred in the group of 55 males whose mothers had been treated with DMPA during the second trimester, that is, after the period of organogenesis. The incidence of 2 cases of hypospadias in the DMPA treated group would appear to be high. However, whether this represents a statistically significant increase cannot be deduced from this report because there were no controls and the sample size was small. By the same token these data cannot serve to support the reason why they had been submitted in the first place, that is, to provide evidence that DMPA used as a contraceptive is unlikely to increase the frequency of congenital malformations in general.

Whether progestogens do or do not increase the incidence of hypospadias is still a subject of controversy, 14 years after such an association was first suggested by Aarskog [17]. Progestogens have been identified as a significant risk factor in some studies but not in others [17-23]. Thus,

a causal association between progestogens and failure of masculinization is less clear cut and, in fact, is likely to prove more difficult to establish than virilization in the female. Unlike the latter abnormality, minor degrees of hypospadias, without indentifiable cause, occur relatively frequently in the U.S.A. [15]. The number of etiological factors that could interfere with the process of masculine differentiation are also much greater than those that can be implicated in abnormal masculinization of females. Masculinization requires adequate production of testosterone by the fetal testes and normal functioning of the mediators of the differentiating action of testosterone on its target organs. The latter includes the androgen receptor as well as steroid metabolizing enzymes [9]. Several mechanisms have been identified through which progestogens may act as antiandrogens and, thereby, intervene in the normal process of masculinization [24-29]. These include, inhibition of enzymes involved in the synthesis of testosterone [24] or in its conversion to active metabolites in target cells including 5 alpha reductase, the enzyme required for the formation of dihydrotestosterone, the mediator of the differentiating action of testosterone on the external genitalia [9, 26]. Progestogens can also interfere with and influence testosterone's interaction with its receptor [27-29].

Interestingly several congenital defects have also been identified that could be responsible for defective masculinization [9]. There are some clues on factors that may make some fetuses susceptible to the antiandrogenic actions of progestogens. For example, several genetic defects have been identified that, like progestogens, effect specific enzymes in the pathway of biosynthesis of testosterone or enzymes responsible for its conversion to active metabolites at its target organs [9]. These abnormalities may be responsible for some cases of congenital failure of masculinization, such as is manifested by hypospadias. Since these genetic defects appear to be autosomal recessive in nature, they would find overt expression only in individuals that inherit a defective gene from both parents. The superimposition of a progestogen on such an abnormality could make overt an abnormality in a heterozygous individual in whom it would otherwise remain latent and could exaggerate the abnormality in a homozygous individual. Similarly synergism between the progestogen and other xenobiotics effecting one of the many steps in the process of masculinization could be the basis of susceptibility in others. These are clearly only hypotheses. They are advanced only to provide an example of the types of underlying factors that may make some male fetuses susceptible to exogenous progestogens. Like the hypotheses advanced by others to explain the susceptibility of a small

number of female fetuses to the masculinizing actions of progestogens, they need to be tested. However, since there is no way to identify individuals who may be susceptible to progestogens for whatever reason, it is essential that all precautions be taken to avoid administering DMPA to women who may be pregnant and not to underplay the teratogenic potential of the progestogens.

5.3 INFLUENCE OF PROGESTOGENS ON SEXUAL DIFFERENTIATIONS: FUNCTIONS MEDIATED BY THE CENTRAL NERVOUS SYSTEN (CNS)

A legitimate concern with respect to the exposure of developing humans to drugs and other xenobiotics has to be whether they effect the future functional capacity of the individual, in particular the expression of CNS mediated functions.

Traditionally, teratology has been concerned with structural abnormalities affecting major organ systems. Such abnormalities are readily identifiable within the first few years of birth. Information available on human embryology also makes it possible to pinpoint times in development when specific events in the formation of major organ systems occur and could be disrupted by teratological agents. Structural malformations of major organ systems can only be induced by teratological agents during the period of organogenesis, within the first trimester. However, there is increasing recognition of important functional changes and defects that

may be induced by agents acting on the developing organism after completion of organogenesis when more subtle anatomical and biochemical developmental events take place. Interference with these so called organizational events may lead to permanent functional changes, deficits and abnormalities in the offspring. This phenomenon has been identified and defined in some detail relation to the CNS and has given rise to the concept of behavioral or neurobiological teratology.

Sex steroids have been among the first agents recognized as having important organizational effects on the developing mammalian CNS. They are known to act as determinants of the functional capacity of the individual with respect to a wide range of sexually dimorphic behavioral functions [30]. Specifically, in males masculinization of sexually dimorphic functions mediated by the CNS require that testosterone acts on the developing brain during critical periods of its development. Progestogens, by acting as androgens, could cause inappropriate masculinization of these functions in females. Conversely, since progestogens are also antiandrogenic, they could interfere with the normal masculinization of brain by endogenous testosterone in males. The extensive literature on findings on experimental animals, including subhuman primates, provides the basis for the questions that need to be raised concerning the long term effects that DMPA may have on the developing CNS in the human

during later stages of fetal development. Specifically, can they cause any masculinization of CNS mediated functions in females or interfere with normal masculinization of such functions in males? As in case of the genital structures, it will be necessary to keep in mind that there may be certain individuals who, either because of genetic or environmental factors, may be particularly susceptible to the androgenic and antiandrogenic actions of progestogens. There are considerable problems involved in obtaining meaningful data to answer these questions [30]. They include selection of appropriate behavioral end points for study, their the quantification, and the need for detailed, long term follow-up of affected individuals and matched controls by scientists experienced in the field.

There is one ongoing study of the behavioral and intellectual development of a small group of male and female offspring of mothers who have received DMPA therapeutically during pregnancy [30]. The females are ones born with virilized external genitalia as a result of this treatment. The tests being administered aim to identify consequences of both the androgenic and antiandrogenic effects of the progestogen. This study, though small, is of considerable value because of the care taken in its design and execution. The findings to date have been reassuring in that no major differences from controls have been detected in the indices of behavioral, psychosexual or cognitive functions selected

for study. Considering the difficulties attending such studies, it is unlikely that very much additional information will become available in the near future, in particular, since no adequate provisions appear to have been made to obtain detailed information and to follow prospectively offspring exposed in utero to contraceptive doses of DMPA. It is only through adequately designed prospective studies that the more subtle effects that drugs may have on CNS mediated functions in the human may be identified. That these may be unexpected and likely to remain unrecognized without adequately designed studies is illustrated by recent findings on the influence of exposure to DES in utero on the incidence of psychiatric illness in later life [31]. The uncertainties that are likely to remain with respect to whether DMPA can cause any permanent functional changes in the CNS of fetuses and that these may be variations in individual susceptibility to its actions, underscore once more the importance of taking all precautions to avoid injecting women who may be pregnant with contraceptive doses of the drug.

The concern over potential functional changes that might be caused by DMPA in the CNS of the developing human has to be extended to the postnatal period. This issue and the need for additional studies to identify any such effects has been addressed in a report by WHO [32]. One specific area of concern is a continued role that androgens may have in the

postnatal period in shaping sexually dimorphic functions of males. This suggested by the marked elevation in plasma testosterone in boys during the first three months of life [33, 34]. Medroxyprogesterone acetate is known to be excreted into milk were its concentration is comparable to that in maternal serum [32, 35]. It has been estimated that the amount absorbed by "a theoretically average infant" and the levels of the drug in its circulation are likely to be small [35]. However, direct measurements still have not been carried out to test the appropriateness of the assumptions on which these calculations are based. Nor have testosterone levels been measured in blood of males ingesting MPA and its metabolites via the maternal milk to determine if the amount of the drug or its active metabolites transferred to the neonate is sufficient to have a biological effect. Such information is needed to provide a more rational basis for choices among contraceptives during the period of lactation.

5.4 PROGESTOGENS AND EXTRAGENITAL ABNORMALITIES

The epidemiological data relating to the question whether progestogens can be held responsible for causing congenital abnormalities in extragenital structures is far from conclusive. The problem is not so much in the quality of the date but in the nature of the problems associated with investigating this question. It is likely to prove difficult

to establish by means of standard epidemiological approaches whether a causal relationship does or does not exist between progestogens and the various abnormalities implicated. The number of organ systems implicated in some reports is large, and without an understanding of underlying mechanisms there is no rational basis for grouping the various abnormalities. The background incidence of the different abnormalities implicated is low, considerably lower than that of hypospadias [15] and the increase in risk that could be attributed to the steriods, even in the most positive studies, is small [2-5]. A wide variety of progestogens have been administered at different doses and at different times during pregnancy. In retrospective studies there have been serious problems of ascertainment of drug exposure. Under the circumstances, it is doubtful if further analyses of the existing literature and data base can shed any new light on the subject. Experimental data on animals are also scant, as is our knowledge of how progestogens might cause extragenital defects. This is in clear contrast to the situation with respect to the effect of progestogens on genital structures and on sexual differentiation. However, even if one accepts the possibility that progestogens are teratogenic for extragenital structures, it is evident that the risk of DMPA causing the birth of a child with extragenital abnormalities is small, provided the drug is used appropriately as a contraceptive. The risk is not a sufficient reason to reject

using the drug as a contraceptive when indicated or for aborting a fetus that has been exposed to it inadvertently. However, the seriousness of the abnormalities implicated reinforces the need to ensure that all precautions are taken to avoid administering DMPA to women who may be pregnant.

The absence of known mechanisms by which progestogens might cause abnormalities in extragenital structures has led some reviewers to consider such risks to be negligible or nonexistent [2]. Specifically, it has been stated that only genital structures should be considered targets for the teratogenic effects of progestogens, since only in these structures have receptors, through which progestogens might exert an effect, been identified during the period of organogenesis. This proposition needs to be questioned on several grounds. First, the mechanisms through which progestogens may act are not restricted to those mediated by receptors. For example, as discussed in relation to the affects of progestogens on sexual differentiation, these steroids can also act via non receptor mediated mechanism by a direct interaction with the enzymes [24-26]. It is also difficult to explain on the basis of receptor mediated mechanisms alone the remarkably high concentrations of labeled steroid found in the adrenal gland of human fetuses following the administration of radioactive MPA to the mother [36]. The significance of this observation, made close to two decades ago, is still obscure. Second, progestogen can

interact not only with the progesterone receptor but also with the receptors for glucocorticoids and androgens. In fact, the interaction of MPA with the glucocorticoid receptor has been held responsible for the ability of progestogens to cause cleft palate in rabbits [37] and its interaction with the androgen receptor for the ability of progestogens to masculinize female fetuses, as discussed previously. It would require detailed knowledge of the ontogenic pattern of all three classes of receptors in the various extragenital organs to exclude the possibility of progestogens having any receptor mediated teratogenic effects on organogenesis. The application of sensitive and discriminating techniques, both biochemical and autoradiographic, have revealed the presence of receptors for sex steroids in a number of unexpected sites in adults (e.g., androgen receptors in the heart muscle, kidney and fibroblasts [27-29, 41]). Similar, sensitive methods have not yet been applied in any systematic manner to study steroid receptors in various organs of the mammalian fetus throughout the period of organogenesis. Thus there is no theoretical basis for discounting the possibility of progestogens influencing organogenesis.

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THE COMMISSIONER'S QUESTION #6:

WHETHER, IN VIEW OF DEPO-PROVERA'S ADVERSE SIDE EFFECTS OR PHARMACOLOGICAL EFFECT, ESTROGEN THERAPY IS LIKELY TO BE PRESCRIBED, IN ADDITION TO DEPO-PROVERA, IN A SIGNIFICANT NUMBER OF PATIENTS?

Estrogens, including DES, have been used in an attempt to counter irregular bleeding, the most frequent short-term side effect of DMPA. In addition, they have been used to arrest heavy bleeding, a rare but serious complication of the drug. There is no adequate documentation of how effective or ineffective estrogen has proved to be in controlling these undesirable side effects. However, there appears to be a concensus among those with extensive experience in the use of DMPA as a contraceptive that estrogen is ineffective in either regulating or arresting uterine bleeding caused by DMPA [1-4]. Consequently, it is unlikely that estrogens would be used in conjunction with DMPA in any significant number of subjects. Moreover, estrogen is not likely to be prescribed for the particular groups of subjects for whom the use of DMPA is indicated, that is, for those with contra-indication to the use of estrogens, and in those who do not wish or cannot be relied on to take a medication on a daily basis.

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INFLUENCE OF DMPA ON PLASMA LIPIDS AND BONE

The focus in the controversy surrounding the general marketing of DMPA as a contraceptive has been on the carcinogenic potential of the drug. In this section we address briefly two additional issues relevant to an assessment of the long term safety of the drug, both of which have been raised during the course of this inquiry. The first of these, the effect of MPA on plasma lipoproteins, was the subject of an extensive discussion at the public hearing [1, 2]. Its importance relates to findings that some synthetic progestogens can cause the types of changes in the pattern of plasma lipoproteins that have been found in epidemiological studies to be associated with an increased risk of atherosclerotic cardiovascular disease [3, 5]. The second, the influence of prolonged use of DMPA on bone integrity, relates to one of the questions we addressed to the parties before the public hearing [6]. Specifically, we requested information on the status of estrogen dependent structures in long term users of DMPA and whether there is any evidence of hypoestrogenism in such subjects. The consequence of hypoestrogenism on bone is of particular concern because it could predispose the individual to osteoporosis. Both atherosclerosis and osteoporosis are serious, essentially irreversible conditions. Therefore, for the sake of completeness we are including a brief section on

these two issues, although they were not specifically addressed by the questions of the Commissioner, and our findings on these issues have not been considered by us in our decision.

As indicated above, some synthetic progestogens have been found to alter the profile of plasma lipoproteins [3-5]. Specifically, they may reduce the concentrations in blood of high density lipoproteins (HDL) and elevate the concentration low density lipoproteins. In epidemiological studies, decreased levels of high density lipoproteins and increased levels of low density lipoproteins have been found to be associated with an increased risk of atherosclerotic heart disease. These observations provide the basis for the concern that synthetic progestogens may be a predisposing factor to atherosclerotic cardiovascular disease and, therefore, the need to evaluate the effects of MPA on plasma lipoproteins.

The direction of the changes caused by the progestogens is similar to that caused by androgens [3, 5], specifically by testosterone, the hormone considered to be one of the factors responsible for the higher incidence of atherosclerotic cardiovascular disease in males. Estrogens, in contrast, change plasma lipoprotein profiles in the opposite direction. Consequently, they are considered to be one of the factors protecting females from such diseases. Based on these considerations it is reasonable to propose

that synthetic progestogens effect plasma lipoproteins by virtue of their potential to act as androgens and/or as antiestrogens, and in case of DMPA, also by causing a decrease in the levels of estrogens in blood. However, progestogens could influence plasma lipoproteins not only by acting as androgen agonists but also by acting as progestins or progesterone agonists. This has been proposed by some investigators on the basis of a comparison of the influence of various progestogens with different relative androgenic, antiandrogenic and progestational potencies (see discussion in [7]). That progesterone may act directly on fat cells and influence the disposition of lipids is suggested by findings in experimental animals [8]. In the rat, fat cells have been found to have both estrogen and progesterone receptors, and both these steroids appear to play a role in the regulation and distribution of the bodies' metabolic resources in part by acting on peripheral metabolic tissues including the lipid compartment [8]. It is also of interest to note that the weight gain experienced by many women receiving DMPA appears to be attributable to changes in the lipid compartment [9]. The statement found in reviews that progesterone itself appears to lack effects on lipid metabolism [4] are referenced by publications that pre-date some of the more sophisticated methods that have since become available for establishing plasma lipoprotein profiles.

As discussed in relation to the teratogenic effects of progestogens, the various synthetic progestogens differ greatly in their relative potencies with respect to their actions as androgens, antiandrogens, antiestrogens and progestins. There have been insufficient systematic studies of the influence of different progestogens on plasma lipoprotein patterns to evaluate the relative importance of these different potential mechanisms of action of these drugs. Consequently, there is no adequate basis for predicting what the consequences of the long term use of DMPA on plasma lipoprotein profiles might be. The question needs to be resolved by direct experimentation, specifically, by systematic, longitudional collection of data from women receiving DMPA as a contraceptive.

There have been two reports on plasma lipoproteins in women receiving DMPA as a contraceptive [10, 11]. In a cross sectional study from Holland, 23 women receiving three monthly injections of 150 mg DMPA for one year or longer had significantly lower concentrations of plasma high-density cholesterol levels than a matched group of 23 women using IUD [7]. The time elapsed since the last injection did not appear to effect the findings. Plasma triglyceride levels were not significantly different in the two groups. In the second study, in 12 Thai women receiving three monthly injections of 150 mg DMPA, there were no changes in the concentrations of serum cholesterol, phospholipids or

triglycerides either three weeks after initiation of treatment or after three and 12 months of treatment [10]. The number of subjects in both studies was small and in neither were all the relevant lipoproteins measured. Consequently, they do not provide an adequate basis for evaluating whether the long term use of DMPA affects the profile of plasma lipoproteins.

A much more detailed analysis of the influence of MPA on different plasma lipoprotein fractions is to be found in a report from Finland [12]. Oral administration of MPA to 8 healthy women for two weeks during the luteal phase of the cycle was found to have no effect on plasma high density lipoprotein fractions. In contrast, the more androgenic progestin, levonorgestrel, a nortestosterone derived steroid, caused under the same conditions a significant reduction in HDL. However, the value of this more detailed study for resolving the issue at hand is limited for two reasons. First, the subjects were exposed to the progestins for only two weeks and second, the drug was administered orally rather than parenterally. Duration of treatment is an important consideration since certain effects of progestins on antiandrogens lipoprotein profiles may take time to become manifest [3]. The route of administration of the progestogen is important since it can affect the potency and actions of the drug. When the drug is administered orally, it is acted on by the liver before reaching other target organs, and it

also acts in a high concentration on the liver, one of its major target organs with respect to metabolic effects (first pass effect). The same limitations apply to some of the other studies in which MPA was reported to have statistically significant effect on plasma lipoproteins when given orally either alone or in combination with estrogens [12, 13].

Clearly, additional studies are needed to determine what changes may be associated specifically with the use of MPA in these putative indicators of atherosclerotic cardiovascular disease, when the drug is administered parenterally and over at least one year. This should be possible to accomplish relatively easily. More long term epidemiological studies will be needed to find out how any changes that may be identified relate to the long term risk of atherosclerotic carciovascular disease. Clarification of these issues is especially important, in particular, since one of the proposed indications for the use of DMPA is for subjects with other risk factors for cardiovascular disease, such as hypertension, which might be exacerbated by estrogens.

The need to evaluate the consequences of the long term use of DMPA on bone is based on the following considerations. In women receiving 150 mg DMPA at three monthly intervals the concentration of estrogens in blood is maintained at the level found during the early follicular phase in women with normal menstrual cycles [14]. These levels, though higher than those found after menopause, are lower than the

concentration of estrogens at any other stage of the menstrual cycle. The net effect is that estrogen dependent tissues in women using DMPA as a contraceptive are exposed to a lower integrated dose of estrogens than normal. There is insufficient information to predict whether these levels are sufficient to maintain the integrity of bone. If not, this could result in diminished bone mass and an increased predisposition to osteoporosis in susceptible individuals. There is some evidence to suggest that this effect of DMPA might be counteracted by the drug having, like other synthetic progestins, a direct anabolic action on bone [15, 18]. The data available is, however, insufficient to provide the definitive evidence needed to resolve this issue. There have been only few attempts to evaluate the influence of progestogens in general on calcium balance and on bone, and we have only been able to identify one very limited study in which women actually using parenteral DMPA as a contraceptive have been the subject of such an investigation [19]. Altogether, in only two studies was an attempt made to evaluate directly the consequences of the administration of progestogens on bone, in addition to indirect indices of calcium balance, that is, blood levels or urinary excretion of calcium, urinary excretion of proline.

To evaluate the influence of MPA on bone, Simpson and Dale compared serum levels of phosphorus, calcium and magnesium in women using DMPA with those of subjects using

Ovulen, or mechanical devices for contraception and with pregnant women in 35th week of gestation [19]. In the women receiving DMPA, calcium levels were reported to be elevated in the first three months of treatment but then returned to levels comparable to those not receiving any steroids. The DMPA treated women also had higher than normal levels of serum phosphorus and magnesium levels that did not vary with duration of use of the drug. Clearly this study does not provide much insight into what may be happening to bone integrity in these subjects. In another study, the influence on bone of the prolonged use (3-13 years) as a contraceptive of another progestogen, lynestrenol, was evaluated in 104 women by applying radiogrammetric methods to x-rays of the hand [17]. Tne authors report finding an increase in bone mass in those using lynestrenol and conclude that this progestin, like estrogens, has a protective effect on bone mass. It should be noted that norethisterone is one of the major metabolites of lynestrenol. This raises the question whether the anabolic effect observed in this study might not be attributable to the androgenic aspect of norethindrone's action. A related steroid, norethisterone, was found to lower plasma calcium concentrations as well as urinary calcium/creatinine and urinary hydroxyproline/creatinine ratios in hypoparathyroid subjects, a finding which led the investigator to propose a protective role of progestogens on bone [15].

Finally, there have been two studies in which the influence of medroxyprogesterone acetate on bone integrity was examined [16, 18]. In both only indirect indices were used and only the acute effects of the drug evaluated. Both studies provide an indication that DMPA may have an anabolic effect on bone. This conclusion is based, in the earlier study by Dompani et al [16], on a decrease in calcium excretion following acute administration of MPA to patients with senile osteoporosis and in the recent one by Mandel et al [18] on the basis of a decrease in ratios of calcium and hydroxyproline to creatinine ratios in postmenopausal women following four weeks treatment with MPA administered orally. As Mandel et al state in their concluding remark to the abstract of their publication, "Long term studies of bone density will be required to confirm these apparent, beneficial effects of DMPA on bone metabolism in postmenopausal women." Such long term studies are equally necessary to establish definitively that bone integrity is maintained in subjects using DMPA as a contraceptive for an extended period of time.

In conclusion, the questions concerning MPA's influence on plasma lipoproteins and bone have a legitimate basis. Women using DMPA as a contraceptive have not been the subject of any systematic investigation with respect to these issues. The available data on the effect of various progestogens on plasma lipoproteins is too incomplete and contradictory to

provide an adequate basis for concluding whether DMPA is or is not likely to effect the incidence of atherosclerotic cardiovascular disease. The data on the influence of synthetic progestogens on bone may be considered encouraging in that, at least according to certain indirect indices of bone metabolisms, they appear to have an anabolic effect on bone. To establish this definitively will however, require additional studies.

As stated previously, our analysis of the data of the influence of DMPA on plasma lipoprotein profiles and on bone integrity has not been considered in making our final decision. There are two reasons for this. First, these were not issues addressed directly by the Commissioner's questions. Second, their importance in contrast to that of DMPA's carcinogenic potential, has only come to be recognized relatively recently. The data from large scale epidemiological studies, establishing an association between high and low density plasma lipoprotein concentration in blood and atherosclerotic cardio-vascular disease, only became available in the late 1970's. The prevelance of post menopausal osteoporosis in the U.S.A. has also become recognized only relatively recently. We have addressed these issues since they were raised during the inquiry. Moreover, they represent valid questions and concerns that, now that they have become clearly identified, will need to be resolved promptly by appropriately designed studies.

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THE COMMISSIONER'S QUESTIONS 1, 4 AND 7 REFORMULATED:

WHETHER THE RATIO OF BENEFIT TO RISK OF DEPO-PROVERA WHEN USED AS A CONTRACEPTIVE WARRANTS ITS APPROVAL UNDER CONDITIONS OF GENERAL MARKETING? WHETHER APPROVAL FOR GENERAL MARKETING AS A CONTRACEPTIVE MIGHT INCREASE ITS USE FOR UNAPPROVED INDICATIONS? AND, IF NOT APPROVED FOR GENERAL MARKETING, ARE THERE CONDITIONS FOR CONTROLLING THE LIMITED DISTRIBUTION OF THE DRUG AS A CONTRACEPTIVE FOR CERTAIN PATIENTS WITH SPECIAL NEEDS?

The available evidence presented fails to provide an adequate, scientifically justifiable basis for concluding whether the use of DMPA as a contraceptive does or does not pose any long term risks. The collection of data from the women who have been using DMPA as a contraceptive world wide over the last 15 years has been too haphazard and uncoordinated to provide evidence of the nature and quality required to resolve major outstanding questions concerning the drug's long term safety. The theoretical arguments and hypotheses offered why MPA is unlikely to be carcinogenic in the human or why the findings of neoplasias in the test animals are not to be considered relevant to the human do not substitute for the lack of data. In the absence of adequate data there is no basis for concluding that the benefits of the drug as a contraceptive outweigh its risks, a requirement which is inherent for approval of an NDA in the U.S.A. [1]. Neither the obvious benefits offered by the drug nor the fact that it appears to be devoid of short term serious and

irreversible adverse effects can compensate for the lack of data on the long term consequences of its use as a contraceptive.

Depo-Provera represents the first successful large scale application to contraception of the concept of using a pure progestational agent, and of a formulation of a chemical contraceptive that provides convenient long-term protection from pregnancy. DMPA is a highly effective contraceptive. Method failure appears to be as low as that with oral contraceptives, but with DMPA, failures due to lack of patient compliance can be reduced or eliminated. Consequently, it is possible to achieve with DMPA lower overall lower failure rates than with any other currently available reversible contraceptive. The convenience and the privacy afforded to the individual user, as well as the relief from the burden of daily pill taking are some advantages of DMPA that have been stressed. The absence of any estrogen in the formulation and the lack of any obvious estrogenic action of MPA can also be of importance to certain subjects.

The short term, immediate, and reversible side effects of DMPA have been well studied and documented. While some of these side effects, such as excessive bleeding or spotting, depression, headaches, weight gain, and loss of libido, are not trivial, the drug has proved acceptable to a large number of women. Some of the side effects may prove intolerable to

certain subjects leading to an overall discontinuation rate for DMPA at least as great as that for oral contraceptives. One obvious, regrettable omission in the literature on the immediate side effects of DMPA is information on how long it takes for potentially serious complications, such as depression, to disappear after the last injection. However, there is no evidence that following short term use DMPA causes serious, irreversible side effects, such as the thromboembolic complications associated with oral contraceptives. Serious bleeding requiring surgical intervention is reported to be rare. Fetal abnormality is the one potentially serious and irreversible consequence of DMPA that may occur at any time during DMPA use. But, as discussed in relation to question 5, this can be considered a rare and largely avoidable risk. Thus, neither the short term side effects of the drug nor its teratogenic potential should constitute a reason for not proposing to use DMPA as a contraceptive, provided that these risks are communicated clearly to potential users. They do not constitute significantly greater problems than are posed by oral contraceptives.

In contrast, the possibility that DMPA may have serious irreversible effects that become evident only after its long-term use or after a period of latency must continue to pose a problem to the approval of the drug for general marketing as a contraceptive. Concerns over DMPA's

carcinogenic potential was why in 1974 questions were raised about the advisability of approving the supplemental NDA for use of the drug as a contraceptive. The questions arose because an analysis of the data then available from the initial IND studies indicated increased incidence of carcinoma of the cervix in women receiving DMPA as a contraceptive [see pp. 101-108]. While the findings can not be considered conclusive, since data on appropriate controls were not available, they did provide a clear indication for a need to carry out controlled studies. Yet no such studies were undertaken, at least not until recently. Therefore, there are no additional data at this time to either confirm or dispell the suspicions raised by these early observations that DMPA may be carcinogenic in the human. In the interim, the suspicion that DMPA may be carcinogenic has been reinforced by the findings of neoplasias in DMPA treated dogs and monkeys, the two species selected to study the long term effects of the drug. During the same period of time, data that could have served to evaluate the significance to the human of the findings in test animals were not being collected in any purposeful and systematic manner. Only recently have appropriately designed epidemiological studies been initiated to follow the very large number of women receiving contraceptive doses of DMPA. Nor has any significant new information been added to help resolve the long-standing controversy whether the dog is, or is not, an

appropriate species for studying the influence of progestogens on the human breast (see pp. 36-54). This failure to accumulate relevant, scientifically valid, new information is unfortunate and frustrating. If the fear of carcinogenesis is unfounded, this needs to be established lest an important addition to the options available for fertility control be condemned unnecessarily. If, on the other hand, such a risk does exist, its magnitude must be defined, and the use of the drug limited accordingly. Data are also inadequate on the effect of DMPA on bone and on plasma lipoprotein patterns to provide a basis for deciding whether the long term use of the drug does or does not increase the subsequent risk of osteoporosis or atherosclerosis. Thus, while the benefits of the drug are clear, there is insufficient basis for evaluating the risks associated with its use.

The questions raised concerning the long term risks of DMPA relate, for the most part, to diseases to which women in the United States are already at increased risk. This applies to carcinoma of the breast and uterus, postmenopausal osteoporosis and atherosclerosis. Should DMPA prove to cause even a relatively small increase in the risk of any one of these diseases, this would carry a different significance in the United States than in countries where the background incidence of these diseases is markedly lower. Consideration of the specific circumstances of each country and population

of subjects can, we think, effect not only the benefit but also the risk side of the equation on which the decision whether or not to use the drug must depend.

Approval of a drug for general marketing implies that questions raised concerning major side effects and risks associated with its use have been adequately investigated and resolved. In this context, resolution, like the term safety, does not necessarily mean that the drug has been shown to be entirely without major undesirable effects, but that these side effects have been defined and the frequency of their occurrence established within reasonable limits by scientifically acceptable methods. This information is needed to enable health care professionals and the subjects they treat to arrive at an informed decision concerning the risk vs benefits associated with the use of a drug and to make an informed choice among drugs. This is a reasonable expectation for a drug that has been approved for general marketing and one that also conforms to the legal requirements. Such information is not available for DMPA and in its absence there is no valid basis for comparing the risks of DMPA with those of other contraceptives.

The immediate benefits of DMPA as a contraceptive, combined with the fact that no immediate life-threatening complications appear to be associated with its use, may make questions of possible delayed, serious adverse effects of the drug appear, to some, a theoretical exercise. We reject this

view. In certain situations the immediate benefits may, indeed, outweigh any unknown long term risks. However, the long term risks need to be defined before a decision can be made on the level of safety of a contraceptive intended for use by essentially healthy women, possibly for long periods of time.

The immediate risks posed by pregnancy, the problems of unwanted pregnancies and the risks of abortion, are well documented (testimony of E. Connell [1]). The importance for women of achieving control over their fertility is also recognized. These considerations have been rightly stressed by those involved in the important social task of family planning. Additional options for contraception are unquestionably needed. But the risks of unwanted pregnancy and the benefits of DMPA as a contraceptive can not obscure the fact that the factual information available on DMPA fails to provide adequate, scientifically valid information on the major outstanding question of the drug s long term side effects. To imply by approval of the drug for general marketing that such data exist would be misleading.

The fact that the available scientific evidence on DMPA is, in our opinion, insufficient to warrant its approval as a contraceptive under conditions of general marketing in the United States makes the question whether such an approval would lead to increased use of the drug for unapproved indications largely irrelevant. In any case, it would seem

that the decision on approval of DMPA as a contraceptive should, in any case, not be influenced by what consequence a decision would have on the use of the drug for other, unapproved indications. Physicians in the United States may and are using DMPA for a variety of unapproved indications either as part of an approved new drug investigation or as part of their own practice of medicine. It is, we understand, FDA policy not to regulate the physician's practice of medicine in prescribing approved drugs for unapproved indications.

Since our analysis leads us to conclude that the data available are insufficient to warrant approval of DMPA for general marketing in the United States, the next consideration is whether the drug should or could be made available as an approved drug for certain patients with special needs. There are, unquestionably, individuals with special needs for whom using DMPA as a contraceptive may indeed provide a reasonable and desirable option. They include those in need of the degree of protection from pregnancy offered by chemical contraception but for whom the use of oral contraceptives is contraindicated for medical reasons. Similarly, there may be compelling personal reasons why DMPA may need to be considered as a contraceptive for some individuals. These include subjects who can not rely on themselves or can not be relied on to take a pill regularly or need the privacy offered by the drug.

Upjohn provides in its final brief a more extensive list of 10 categories of patients for whom it considers the risk/benefit ratio to be particularly favorable [2].8/ Seven of these 10 categories of indications (#'s 1, 2, 3, 5, 7 and 8) would essentially cover the subjects we have identified, and listed above, as having special needs that would warrant considering using DMPA as a contraceptive. Two of the categories refer to subjects for whom the use of DMPA may be indicated for very special reasons and which, in our opinion, are not relevant to the more general issue of the use of the drug for contraception, specifically, subjects with sickle cell anemia (# 4) and those for whom amenorrhea would be advantageous (# 10).

In persons with sickle cell anemia, the indication for using DMPA rests on a study in which DMPA was found to improve the hematological status of patients with this disease [3]. Confirmation of these interesting observations

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8/ 1) Patients who have medical contraindications to other highly effective methods and who are unwilling or unable to terminate pregnancy due to method failure;
2) who have a high risk of infection from IUDs;
3) who have a risk of cardiovascular problems, regardless of age and smoking habits;
4) who have sickle cell anemia;
5) who can not tolerate the side effects of estrogens;
6) who have had repeated failures with other methods;
7) who have had repeated abortions;
8) who need a contraceptive method that provides a high degree of privacy;
9) for whom anovulation would provide relief from dysemenorrhoea and premenstrual syndrome;
10) for whom amenorrhea would be advantageous.

is needed on a larger number of subjects. Subjects for whom amenorrhea would be advantageous presumably refers to those mentally retarded for whom the drug would be used for hygenic reasons. Finally, it is not clear why Upjohn considers that DMPA would be "uniquely well suited" for women needing relief from dysmenorrhoea or premenstrual tension, since oral contraceptives may be equally effective in such cases.

Whether it is desirable and feasible for the FDA to approve the use of DMPA as a contraceptive for a limited, defined population of subjects under controlled conditions, is a subject on which there was some divergence of opinion among the three members of the PBI. Two of us (Drs. Stolley and Weisz) do not think it desirable that the FDA set up broad categories of indications for use of DMPA as a contraceptive since the use of the drug is likely to be appropriate only for selected patients within each category. It is, in our opinion, preferable if the indications and the risk/benefit evaluation are arrived at on an individual basis, and with informed choice and consent being arrived at by the physician and the patient or those responsible for her. We do not think that indications should be considered routine. In those instances in which the physician and his or her patient should come to the conclusion that DMPA is the drug of choice for that patient, this option is available under the practice of medicine without any additional action on the part of FDA since DMPA is currently approved in the

United States for use for other indications. A minor inconvenience is that the dose of the injectable formulation on the market for the approved indication, i.e., for endometrial cancer, is larger than that needed for contraception and needs to be adjusted accordingly.

Two of the Board members (Drs. Stolley and Weisz) also question whether there is, at this time, any effective mechanism by which FDA can limit the distribution of the drug to a specific population of subjects or by which information on subjects receiving the drug as a contraceptive can be collected in a systematic fashion in the U.S.A.

Dr. Ross, on the other hand, suggests that, if feasible, approval should be given for use of the drug for two broad categories of patients, the mentally retarded and drug addicts (see Dr. Ross' letter, p. 181).

A summary of our Findings of Fact and our Conclusions of Law follow.

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FINDINGS OF FACT

I. DATA AVAILABLE ON THE LONG-TERM RISKS OF DMPA ARE INSUFFICIENT AND INADEQUATE TO PROVIDE A BASIS FOR A DECISION WHETHER THE BENEFITS OF THE DRUG AS A CONTRACEPTIVE OUTWEIGH ITS DISADVANTAGES UNDER CONDITIONS OF GENERAL MARKETING IN THE USA.

There are adequate data to assess the efficacy and benefits of DMPA as a contraceptive. There is also sufficient information on its short term side effects and risks. The drug is clearly a highly effective contraceptive with certain specific advantages, and it does not appear to pose any immediate irreversible serious side effects. However, the facts relating to the long term consequences of the use of the drug are inadequate and insufficient to provide a basis for risk assessment. This is a serious deficiency in light of the specific questions that have been raised that the drug may have major adverse effects following its long term use or that may become evident only after a latent period. Most important among these has been the concern over the drug's carcinogenic potential.9/

The long term consequences of the use of DMPA on neoplasias, in particular of the breast and uterus, as well

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9/ Data are also inadequate to establish effect of MPA on bone and on the profile of plasma lipoproteins, information needed to evaluate whether the long term use of the drug will or will not predispose the individual to osteoporosis or to atherosclerosis. Our Conclusions of Law do not rely on this finding.

as osteoporosis and atherosclerosis are of particular relevance for any risk/benefit assessment of the drug's use in the United States because of the susceptibility of the population in this country to these diseases.

In the absence of adequate data on the long term consequences of the drug it is not possible to arrive at any scientifically defensible conclusion whether or not the benefits of the drug, when used as a contraceptive, outweigh its risks for the average healthy individual in the United States. It also makes it impossible to compare the risk/benefit ratio of DMPA with that of other drugs available for contraception.

II. DATA FROM THE STUDIES OF RHESUS MONKEYS AND BEAGLE DOGS CAN NOT BE DISMISSED AS IRRELEVANT TO THE HUMAN WITHOUT CONCLUSIVE EVIDENCE TO THE CONTRARY. SUCH EVIDENCE IS NOT AVAILABLE AT THIS TIME. THEREFORE, THE FACT THAT MALIGNANT NEOPLASIAS DEVELOPED IN TWO SPECIES IN TARGET ORGANS OF SEX STEROIDS MUST BE CONSIDERED AS AN INDICATION OF A POTENTIAL OF PROGESTOGENS, INCLUDING DMPA, TO PROMOTE THE DEVELOPMENT OF MALIGNANCIES IN TARGET ORGANS.

The findings from animal tests implicate DMPA as a potential promoter of neoplasias because:

1) Chronic administration of DMPA was associated with the development of malignant neoplasias in two mammalian species.

2) The neoplasias developed in target organs of sex steroids.

3) There is good evidence to support the conclusion that in both species the malignancies were drug related.

4) There is no evidence to support the conclusion that the effect of the drug is to be attributed only to the administration of excessively high doses and that the effect of lower doses would differ qualitatively from those of higher doses.

Therefore, DMPA in these experiments exhibited the characteristics of a potential carcinogen according to generally accepted criteria. Under the circumstances, to dismiss the findings as irrelevant to the human would require conclusive experimental evidence of fundamental differences among the species in the basic mechanisms of action of the hormone or in the responses of target cells. There is as yet no such evidence at hand. Specifically, there are no data on the histogenesis of the neoplasias nor on the mechanism of action of progestogens on the presumed cells of origin of the neoplasias in the test animals. Therefore, there is no evidence to support the claim that the malignancies developed either in cell types unique to the species or as a result of a species specific response of target cells to progestogens. Conversely, data on women who have been exposed for prolonged periods to the relatively unopposed action of progestogens are inadequate to warrant the conclusion that their response to this hormonal state in terms of neoplasias would differ in

some fundamental way from the two species of test animals.

III. THE DATA ON THE HUMAN ARE INSUFFICIENT AND INADEQUATE TO EITHER CONFIRM OR REFUTE THE IMPLICATION OF THE ANIMAL DATA THAT DMPA MAY INCREASE THE RISK OF CANCER IN WOMEN USING DMPA AS A CONTRACEPTIVE.

The available data on the human can not provide a basis for concluding whether DMPA, used as a contraceptive, does or does not influence the incidence of carcinomas in general or of the accessory organs of reproduction in particular, because:

1) They fail to provide information on an adequate number of long term users of DMPA, or on ex-users who have been followed for a long enough period of time. There are only minimal data on subjects that have used DMPA for 5 years or longer with most of the data reported having been obtained from women who have used the drug for 2 years or less.

2) In the majority of the studies there were no controls followed in parallel with those using DMPA. In many studies from developing countries there is not even information on the background incidence of the diseases being studied in DMPA users that could serve as a basis for comparison.

3) In a number of the retrospective studies there is reason to question the adequacy of the record keeping on

subjects receiving DMPA and, therefore, of the possibility of retrieving the data subsequently for any valid analysis.

To obtain the direct evidence needed to resolve the issue would have required purposeful, systematic collection and recording of data on users of DMPA and appropriate controls with consideration of the natural history of the diseases being monitored. Not until recently have such studies been initiated. Until they are completed and full reports of them available their value as evidence is limited.

IV. IN CASE OF CONTRACEPTIVE FAILURE WITH DMPA, THE RISK OF A MOTHER GIVING BIRTH TO A MALFORMED CHILD IS UNLIKELY TO BE MEASURABLY GREATER THAN THAT POSED BY THE ORAL CONTRACEPTIVES. THE CHANCE IN EACH CASE CAN BE ESTIMATED TO BE SMALL ENOUGH NOT TO POSE AN OBSTACLE TO THE USE OF THE DRUG AS A CONTRACEPTIVE WHEN OTHERWISE INDICATED.

Data have not been systematically collected on offspring that have been inadvertently exposed to DMPA *in utero*. Conclusions, therefore, can only be based on the body of epidemiological data obtained on the effects of a variety of sex steroids, including progestogens, on the developing human fetus. In these cases, the drugs had been administered for a variety of indications and at various times during pregnancy. This is clearly a less than ideal data base. Nonetheless it can provide some general estimate of the magnitude of the risk.

According to these data the risk of various malformations attributable to protestogens for the various malformations implicated is low. The rate of contraceptive failure with DMPA when used appropriately is also low. Consequently, the chance of a mother bearing a malformed child following contraceptive failure can be estimated to be small. However, because DMPA is a long acting depot preparation, the exposure of any susceptible fetus to the drug is likely to be more prolonged than with oral contraceptives. Consequently, the range of critical and vulnerable events that may come under the drug's influence may also be expected to be greater than with oral contraceptives. It should be possible to counter balance this disadvantage of DMPA by ensuring that contraceptive failure is kept at a minimum and taking the necessary steps to avoid injecting women already pregnant. As with oral contraceptives this risk should not, in itself, constitute a reason for not using the drug if otherwise indicated.

There have been no direct determinations of the concentrations of MPA in the blood of breast fed infants of mothers receiving DMPA as a contraceptive nor if the amount of the drug transferred passed onto the infant is sufficient to have a biological effect. This information is needed before advocating the use of DMPA as a contraceptive to lactating mothers in the postnatal period and before it is

possible to conclude that the drug does not pose any risk of functional teratogenicity.

CONCLUSIONS OF LAW

Accordingly, Upjohn's supplemental new drug application for Depo-Provera (DMPA) sterile aqueous suspension for intramuscular injection as a contraceptive agent in humans does not contain reports of investigation adequate to show that the drug is safe for use under the conditions prescribed, recommended or suggested in the labeling as required by § 505(d)(1), (2) and (4) of the Federal Food, Drug, and Cosmetic Act, and the information contained in the supplemental new drug application, combined with other information about the drug, does not provide sufficient basis from which FDA can determine that DMPA is safe for general marketing in the United States.

Dated this 17th day of October, 1984.

Judith Weisz MB BChir.

Judith Weisz, MB BChir.
Chairperson

Paul D. Stolley, MD.

Paul D. Stolley, M.D., M.P.H.

The University of Texas
Health Science Center at Houston

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July 23, 1984

Dr. Judith Weisz
The Pennsylvania State University
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500 University Drive
Hershey, Pennsylvania 17033

Dear Judith:

I am disappointed to inform you that deterioration in my health prevents my participation in drafting and parsing the final report of the Public Board of Inquiry. Since my appointment to the Board in September, 1982, I have participated in both of the public hearings and in the various meetings we have held to review the evidence presented at the hearings. As a result, I have formed an opinion about the quality of the information in the record, which I wish to summarize briefly, and suggest a "Bottom Line" for the decision.

The quality of the data submitted in writing and orally is inadequate to provide a scientifically valid basis to either affirm or deny the long term safety of the drug for use in human subjects. As I understand the law, approval of a drug for marketing requires test results scientifically adequate to show that the drug is safe for use.

While I concur with you and Paul that the data submitted are inadequate to show that Depo Provera is safe, these also fail to show that the drug is unsafe for human use. Accordingly, as an alternative to outright disapproval, I would recommend that the Commissioner consider approval, if practicable, for limited use in two populations of patients for whom satisfactory alternatives do not exist. These populations are:

1. Oliogophrenic (mentally retarded) women and
2. Women using drugs abusively.

Moreover, such a course of action would make it possible for physicians to participate with these persons or their agents in reaching decisions about the use of the drug for contraception.

This course of action would be consistent with the fact that nothing we have seen or heard established the concept of intolerable risks following use on human subjects, and allow time for further tests to be performed and results analyzed.

Sincerely,

Griff T. Ross, M.D., Ph.D.

GTR:bmc

From Dept. of Public Sft. of Inquiry on Depo-Provera Oct '84 (copy + copy for shelf)

APPENDIX 1

DMPA USE AND RISK OF BREAST CANCER: HUMAN DATA

Reference	Number of Women Studied, Dose and Duration of DMPA Use	Findings	Comments
Greenspan, A.R., Hatcher, R.A., Moore, M., et al. The Association of Depo-Medroxyprogesterone Acetate and Breast Cancer. Contraception 21:563, 1980 DMB Vol. 285 Tab #320	Case-control study of breast cancer in the Grady Memorial Hospital Family Planning Clinic, Atlanta, Georgia. Thirty women with breast cancer, age 55 or younger, who were enrolled in the Clinic between 1967 and 1979 and 6 controls per case, not known to have breast cancer, and matched to the case for age (±2 years), race, and date of visit to the clinic (±6 mos), had their contraceptive history ascertained via the medical records in the Clinic. Average parity was 3.3 in cases and 4.6 in controls. 70% were older than 30 years of age The mean number of DMPA injections (150 mg) was 2.8 in cases and 3.3 in controls (i.e., short term users).	1) Used DMPA: Cases with breast Cancer (16.7%) 5; Controls without breast cancer (17.9%) 32 Did not use DMPA: 25; 147 Total: 30; 179 Matched relative risk estimate = 0.92. (95% CI:0.33-2.58). Controlling for parity did not alter this result. 2) For all 5 exposed cases, DMPA exposure preceded diagnosis of breast cancer by an average of 4 years (range 2-5 yrs) (i.e., short latency).	1) Short average exposure to DMPA. 2) Short latency period. 3) The study did have the power to detect a RR of 3-fold or 4-fold (with 80% and 95% chance, respectively).
Liang, A.P., Greenspan, A.R., Layde, P.M., et al. "The Risk of Breast, Uterine Corpus, and Ovarian Cancer in Women using DMPA" JAMA, 249:3909, 1983 DMB Vol. 283 Tab G-628	5000 Black women attending the Grady Clinic during 1967-1976 were followed up through 1980 for occurrence of cancer. The followup period ranged from 4 years (for women whose initial injection was in 1976) to 13 years (for women whose initial injection was in 1967). The median length of followup was 9 years. In the 1981 stratified random sample of GMH Clinic attendees, 72% of DMPA users could be contacted. (28% not contacted). Duration of Use / Number of Women: < 13 mos. 2,934 (58.7%) 13- 36 mos. 1,438 (28.7%) 37- 60 mos. 425 (8.5%) 61-114 mos. 206 (4.1%) N=5,003 (100%)	1) Based on the National Cancer Institute SEER age-specific incidence data for Black women 1973-1980, the expected number of breast cancer cases was 10.07. This compares to 7 cases of breast cancer actually observed at Grady. The RR = 0.69 (95% CI: 0.3-1.4) 2) 6 out of 9 cases with cancer (7 breast cancer, 1 uterine corpus, 1 ovary) in this series of women had only 1 or 2 injections of DMPA. Authors suggest it is unlikely that the cancers of these women were causally linked to DMPA.	1) Short average duration of DMPA use. 2) Incomplete ascertainment of occurrence of cancer. Deceased persons obviously not contacted. 3) Authors state that "although these data are not conclusive, they are reassuring. This study indicates that there is unlikely to be a strong association between DMPA use and breast cancer." 4) Evidence exists from other sources of incomplete initial recording of data (See FDA Audit).

Reference	Number of Women Studied, Dose and Duration of DMPA Use	Findings	Comments
McDaniel, E.B. and Pardthaisong, T. Incidence of Breast Nodules in Women Receiving Multiple Doses of Medroxyprogesterone Acetate J. Biosoc. Sci. 5:83, 1973 DMB Vol. 170 Tab #66	Cross-sectional study of 1527 Thai women: 257 were new patients presenting for contraceptive services (i.e. controls). 1270 already received 1 to 25 consecutive 3-month DMPA (150 mg) together with monthly oral DES supplement. Duration of DMPA Use: — Number of Women 1- 4 consecutive injections (1 yr.) — 503 (39.6%) 5- 9 consecutive injections (2 yrs.) — 417 (32.8%) 17-20 consecutive injections (5 yrs.) — 315 (24.8%) 21-25 consecutive injections (6 yrs.) — 35 (2.7%) N=1270 100%	1) the incidence of mammary nodules was 1.2% in the controls (3 out of 257 IUD patients or first-timers OCS or DMPA) vs. 0.8% in DMPA users (8 out of 1270). 2) on re-examination of 6 of the 8 women, 3 had definite breast masses (1 galactocele; 1 scar tissue from old breast abscess; 1 large mammary dysplasia with chronic inflammation). 3) Authors noted that in over 6 years of experience with DMPA and estrogen supplement in 13,418 patients (with 18,890 women yrs. of use and 74,086 injections), the formation of breast nodules has never been a patient complaint.	1) No information on how controls on IUD compare with the DMPA users on risk factors such as, age, parity, previous oral contraceptive use. 2) A latency period of a maximum of 6 years may not be sufficiently long for a breast tumor to develope. 3) The use of estrogen supplement (DES) is a confounder. 4) No nodules in the breast were observed in a series of 13,418 women. 5) If the incidence of breast cancer is low in Thai women, these data may not be relevant to U.S. women in whom the incidence of breast cancer is much higher. There are marked international variations in the rates of cancer. e.g. the age-standardized incidence rate for breast cancer is: 19.4/100,000 Chinese women in Singapore. 17.6/100,000 Malayan women in Singapore. 25.5/100,000 Indian women in Singapore. vs. 76.1/100,000 white women in U.S. 56.5/100,000 black women in U.S. 44.0/100,000 Chinese women in U.S. (based on Waterhouse J, Muir C, Correa P. et al. Eds. Cancer Incidence in 5 Continents, Leon, IARC, 1976) 6) Sampling bias because patients too ill to travel to the city or who had died, did not have an equal chance of being sampled.

APPENDIX 1

DMPA USE AND RISK OF BREAST CANCER: HUMAN DATA

Reference	Number of Women Studied, Dose and Duration of DMPA Use	Findings	Comments
Ory, H.W., Rubin, G., Jones, V., et al. "Mortality among young black contraceptive users" 1982. (unpublished) DMB Vol. 283 TAB #190C G-629	Comparison of mortality rates in black women using one of four contraceptive methods (OCS, DMPA, IUD, Barrier). Death certificates for 218 women whose names, addresses and birthdates matched the Grady family planning records were analyzed for cause of death. (ages 10-44 yrs. old). Person-months of observation were computed from the date of first visit to the family planning clinic to the date of death or to Dec. 1977 (which-ever came first). On average, women were followed up for 8.2 years. Person-years of contraceptive use were computed from the date of first clinic visit to the date of last visit for that method + 6 months (ignoring switching between methods). All rates were age-standardized because of different age distributions in the 4 groups.	1) The rates of death per 10,000 years of follow up from all causes among the 4 groups were: 12, 30, 30, 0 for users of IUDs, OCs, DMPA and barrier methods, respectively. 2) The cause specific death-rates show a risk of death from cancer for OC users 3 times higher than the risk for ever use of IUD or DMPA.	1) Misclassification bias because women were considered users on only 1 method of contraception, the one chosen at the first clinic visit. If switched to other contraceptive, women were still counted in original grouping. 2) No information on former contraceptive use, before attending the clinic. 3) No information on duration of contraceptive use. 4) Type of cancer not specified. 5) The computerized name-matching system may not have identified the total number of deaths.

		Death rate/10,000 women per yr. Use Ever of			
Cause of Death	Total Number	OC	IUD Ever	DMPA	Barrier
Cancer	17	1.1	0.3	0.3	0.0
Circulatory	51	2.1	1.4	2.0	2.5
Total Medicine	134	5.4	5.3	6.7	4.5
Accident & Violence	84	3.5	2.9	2.9	3.1
All Deaths	218	8.9	8.1	9.6	7.6

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Reference	Number of Women Studied, Dose and Duration of DMPA Use	Findings	Comments
Pena-Delgado, J., Aleman-Herrera, M., and Baez-Reyes, A. Long-term Use of Medroxyprogesterone Acetate in Contraception *Sem. Med. Mex.* 98:331, 1981 DMB Vol. 221:95)	Study of 1% random sample (N=1025 cases) out of 71,188 new clients who chose DMPA (150 mg) and who used the method continuously for 3 to 8 1/2 years. Duration of DMPA Use: < 12 doses — Number of Women: 85 (8.3%); 13-24 doses: 738 (72%); 25-36 doses: 199 (19.4%); 37-38 doses: 3 (0.3%); N=1025 (100%)	1) "No sign of any greater tendency to occurrence of benign breast nodules or mammary cancer under DMPA" (compared to what??) 2) 6 out of 1025 had mammary nodules with 5 breast biopsies negative. No information on the sixth. 3) "In all 6 cases, it was not possible to verify that the presence of nodules was due to use of the drug." 4) In some instances, mammary tension was decreased by the medication.	1) Basically, a follow-up study of long-term users of DMPA without controls. 2) No information on previous contraceptive use, parity, etc. 3) No information on background incidence of breast cancer in this population of Mexican women.
Rall, H.J.S., Van Niererk,W.A., et al., Comparative Contraceptive Experience with Three-Month and Six Month Medroxyprogesterone Acetate Regimens *J. Reprod. Med.* 18:55, 1977 DMB Vol. 161A	Cross-sectional study of 19,875 women (migratory, low-to-middle socioeconomic population) in South Africa, treated in 2 hospitals between 1970-1975 with 150 mg/3 mos or 450 mg/6 mos DMPA. Duration of DMPA Use: < 13 mos. — Number of Users: 13,922 (70.0%); 13-36 mos.: 5,715 (28.8%); ≥ 37.mos.: 238 (1.2%); N=19,875 (100%)	1) No mammary tumors were diagnosed in the 3-month or 6-month DMPA groups. (i.e., 0 out of 19875 women seen over 5 years!!)	1) Complete ascertainment of mammary tumors is questionable in this migratory population. 2) No information available on the incidence rate of mammary tumors in a comparison group in South Africa. 3) Short-term use and short follow-up.

APPENDIX 1

DMPA USE AND RISK OF BREAST CANCER: HUMAN DATA

Reference	Number of Women Studied, Dose and Duration of DMPA Use	Findings	Comments
Schwallie, P.C. Experience with Depo-Provera as a Injectable Contraceptive J Reprod Med. 13:113, 1974 DMB Vol. 135A pp. 58-62 and See Also	Pooled data from 11,500 women worldwide (all ages, all dose-regimen, U.S. and non-U.S., black and white) who were treated with DMPA during 1963-1973.	1) 14 women among the 11,500 studied either developed mammary nodules or had an enlargement of previously existing nodules. 8 of the 14 received 150 mg DMPA 2 received 250 mg 2 received 300 mg 1 received 400 mg 1 received 500 mg Their age range was 20-45, para 1-7, and number of injections 1-24. 2) 3 of the 14 had also received estrogen supplements.	1) No control data available and therefore cannot - estimate degree of excess risk posed by DMPA. Note: heterogeneity of subjects from different countries with different breast cancer incidence. 2) No adjustment for confounding risk factors (e.g., parity, obesity, etc.)
Schwallie P.C., and Mohberg N.R. Medroxyprogesterone Acetate: an injectable contraceptive Adv. Planned Parenthood 12:35, 1977 DMB Vol. 161A G-513	Review of same data on women as in the above.	1) 24 women either developed mammary nodules or had an enlargement of pre-existent nodules. 2) 5 of the 24 had carcinoma, but 3 of these received also concomitant estrogen therapy.	

APPENDIX 1

DMPA USE AND RISK OF BREAST CANCER: HUMAN DATA

Reference	Number of Women Studied, Dose and Duration of DMPA Use	Findings	Comments
Zanartu, J., Onetto E., Medina, E., Dabancens A. Mammary Glands Nodules in Women Under Continuous Exposure to Progestagens Contraception 7:203, 1973 DMB 93A pp. 635-644	Prospective study of the mammary gland in 2418 women using DMPA (250, 300, 500 mg/3 mos. or 1000 mg/6 mos.) and 932 women using chlormadinone acetate (CA) in Chile. Women were given estrogen supplement in cases of amenorrhea Duration of DMPA Use / DMPA Users < 13 mos. 491 (20.3%) 13-36 mos. 671 (27.8%) 37-60 mos. 923 (38.2%) 61-84 mos. (5-7 yrs.) 333 (13.8%) N=2418 100%	1) the incidence of breast nodules was 10 out of 3350 women treated with DMPA or CA between 1965 and 1971. (i.e. 3 per 1000) 2) Of the 10 cases with mammary nodules, 2 received 150 mg. DMPA, 6 received 250 mg. DMPA, 1 received 1000 mg. DMPA, 1 got CA. 3) 7 of the 10 received also cyclic estrogen during 1 month to 3 years. 4) 2 cases of these 10, (the 250 and 1000 mg. DMPA) were mammary carcinomas. 2 was chronic mastitis 1 fibroadenoma and 5 adenosis. 5) All 10 cases with nodules were long-term users of DMPA or CA (46 to 72 months); the 2 carcinomas occurred in users for 60 and 66 months. 6) These 10 cases ranged in age from 23 to 37 years old, and had 1 to 15 pregnancies.	1) An adequate control group of similar age and parity, never exposed to progestagens is not available for comparison. 2) Use of estrogen is a confounder as is the high number of pregnancies in these women. 3) The follow up study comprised breast examination twice a year. It is not clear if, and how, women who stopped using the drug were examined if they didn't return to the clinic., i.e., question of complete followup and ascertainment.

APPENDIX 1

DMPA USE AND RISK OF BREAST CANCER: HUMAN DATA

Reference	Number of Women Studied, Dose and Duration of DMPA Use	Findings	Comments
Zarfas, D.E., Fyfe, I., Gorodzinky, I., The Utilization of Depo Provera in the Ontario GovernmentFacilities for the Mentally Retarded: A Pilot Project, 1981. (unpublished) DMB Vol. No. 203 G-550	Questionnaires were completed by the staff of 9 facilities for the mentally retarded on all 533 woman for whom DMPA had been prescribed. Duration of DMPA Use / No. Women < 3 yrs. 218 (41%) 3-5 yrs. 67 (13%) > 5 yrs. 208 (39%) Unknown Duration 40 (8%) Total N-533	(1) Of 533 females who received DMPA, 21 had died. (2) Of the 21 deaths, 3 died of breast cancer. (3) Information on all deaths of female residents in those facilities since 1965 for ages 15 and over produced an additional cohort of 342, 3 of which were due to breast cancer. Breast Cancer Mortality in DMPA Users 3/21 (ages 32,33,40) in DMPA Nonusers 3/342 (ages 53,66,77)	1) The information based entirely on reports from the staff of the facilities for the mentally retarded; no independent verification of the data attempted by the authors. 2) Duplication of cases may have occurred since most Centers use case numbers rather than names to identify individual questionnaires, and record linkage between Centers was impossible. 3) No adjustment made for confounders such as nulliparity, use of other drugs, etc., which may increase risk of breast cancer in this group. 4) Complete ascertainment of breast cancer questionable because post-mortem examination of breasts is not required unless there is apriori evidence of breast cancer. Therefore, some cases may have been missed. 5) NOTE the younger ages at which breast cancer occurred among the DMPA users!

APPENDIX 1

DMPA USE AND RISK OF BREAST CANCER: HUMAN DATA

Reference	Number of Women Studied, Dose and Duration of DMPA Use	Findings	Comments
Spellacy, W.N., Buhi, W.C., Birk, S.A., Stimulated Plasma Prolactin Levels in Women Using Medroxyprogesterone Acetate or an Intrauterine Device for Contraception Fertil. Steril. 26:970, 1975	Study of plasma prolactin levels in women using DMPA. 12 women who had been receiving MPA (150 mg.) for 4-5 years were compared to 9 women who had been using an IUD for 1 year) and none of these women was taking other drugs. MPA women were older than the IUD women (mean age: 33.3 yrs. vs. 26.4 yrs.) MPA women has a higher parity (mean: 4.5 vs. 1.5). Blood samples were drawn before and after chlorpromazine stimulation.	1) Although less prolactin was released after the chlorpromazine stimulation in the MPA group, the differences were not significant. 2) There was no significant difference also in basal blood prolactin concentrations between the two groups.	1) Authors' conclusion was that since breast neoplasia may be related to chronically elevated prolactin levels, these data are reassuring. But, relationship of prolactin to breast cancer in humans, unlike in the rodent, is not known.
Zanartu, J., Aguilera, E., et al., Effect of Long-Acting Contraceptive Progestogen on Lactation Obstet. Gynecol. 47:174,1976 DMB Vol. #	Prospective study on the duration of lactation in 406 mothers injected postpartum for contraception with DMPA (150 mg./3 mos. or 250-300 mg./6 mos.) compared with 173 nontreated controls. The follow up period was 18 months. Average age and parity reported to be comparable in both groups.	1) no pathologic breast conditions were observed in mothers during the study.	1) Only 1 or 2 injections, i.e. short-term use. 2) The objective of the study was to examine effect on lactation. The observation on breast pathology was incidental.

APPENDIX 2

THE ASSOCIATION BETWEEN DMPA USE AND DEVELOPMENT OF ENDOMETRIAL CANCER

REFERENCE	STUDY DESIGN	FINDINGS	COMMENTS
Cervantes, A., Azcona, Bribiesca, Aguirre, Velasco. "Effect of Medroxyprogesterone acetate on human endometrium after five or more years of use as a contraceptive," 1982 (unpublished) DMB Vol. 213 Tab #U-20(a) see also Upjohn's response to questions on this study April 15, 1983. pp. 2-4 DMB Vol. 343 Tab #506	Phase I of the study involved histophatological examination of biopsies taken from 76 women who used DMPA (150 mg) for ≥5 years. (40 active patients and 36 who discontinued use). Phase II of the study involved the examination of all death certificates of women above 20 years of age between 1967-1978 in Coahuila, Mexico, to identify the cause of death, and then inquire from relatives or last attending physician about prior contraceptive use.	The histophatology findings: 1) No anaplasia was found in any of 40 active patients: 9-"simple hyperplasia" 27-"slight to severe atrophy of endometrium" 4-"normal secretory or proliferative endometrium" 2) Among the 36 inactive patients (on average discontinued use for more than 1 1/2 years): 17-"normal active endometrium" 11-"simple hyperplasia" 8-"slight to severe atrophy of endometrium" The epidemiological findings: 1) 12,356 total deaths in the 12-year period 1967-1978. Of these, 172 women died of genital cancer during this period: 146-cervical cancer 12-ovarian cancer 6-endometrial cancer 8-undiagnosed 2) The history of contraceptive use in these women was: 6-cases of endometrial cancer who never used any kind of steroid contraceptives. 12-cases of ovarian cancer who never used any kind of steroid contraceptives. 6-of 146 cases of cervical cancer used combined oral contraceptives at one time during lifetime.	1) Question concerning confirmation of histopathology (for detailed discussion see text). 2) Possibility of difference in coding cause of death. 3) Ascertainment of drug use questionable. Interview with next-of-kin about contraceptive use may cause mis-classification. 4) No information on background incidence of either breast or endometrial cancer in comparable Mexican population. Note high degree of international variations in incidence rates of cancer. e.g., the age-standarized incidence rate of cancer of the corpus uteri for Spanish women is: 9.5/100,000 in El Paso 8.4/100,000 in New Mexico 6.1/100,000 in Puerto Rico The incidence rate for white women is: 33.3/100,000 in Alameda, CA 20.1/100,000 in Detroit For black women, the rate is 13.6/100,000 in Alameda. CA 10.5/100,000 in Detroit (Based on Waterhouse and Muir, 1976).

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THE ASSOCIATION BETWEEN DMPA USE AND DEVELOPMENT OF ENDOMETRIAL CANCER

REFERENCE	STUDY DESIGN	FINDINGS	COMMENTS
Greenspan, A.R. Chap. 8: "The endometrium and DMPA," in The Grady Experience, 1978 (unpublished) DMB Vol. 221 and DMB Vol. 279 Tab 295	832 current users of DMPA at the Grady Clinic were asked to respond to the question: "If you have used the shot before, have you had a D&C since you started using it?" 34 replied "yes." Out of 34 responders, the medical charts of 26 were reviewed for a history of D&C or endometrial biopsy done anytime after having at least 1 DMPA injection. 21 of the 26 patients answering "yes" didn't have history of D&C or endometrial biopsy. Patients misinterpreted question or did not know what D&C meant.	1) No patients were found to have had cancer based on the pathology reports.	1) Serious misclassification problems (e.g. only 19% agreement between medical record and patient report). 2) Serious problems of ascertainment, since only the charts of those who responded "yes" were reviewed while among those responding "no" there may have actually been some D&Cs.
Pitts, H., Endometrial biopsy series, 1979 (cited in above)	Examination of endometrial biopsies from 8 patients who had used DMPA for > 3 years.	(1) 6 had inadequate endometrial tissue for biopsy; 2 had evidence of atrophic endometrium (2) These results suggest hypo rather than hyperplastic changes in the endometrium following long-term administration of DMPA	1) Study of consequences of DMPA on endometrial histology, not of incidence of endometrial cancer.

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THE ASSOCIATION BETWEEN DMPA USE AND DEVELOPMENT OF ENDOMETRIAL CANCER

REFERENCE	STUDY DESIGN	FINDINGS	COMMENTS
Williams, O. The endometrium after prolonged use of DMPA, 1975. (cited in above)	The names of all women having hysterectomies at Grady Memorial Hospital between 1967 and 1974 were obtained and their drug histories were reviewed.	1) 7 women (out of how many?) who had hysterectomy were found to have a history of DMPA use of 1 year or longer. 2) duration of DMPA use by these patients was 19-39 months; mean duration of use was 25 months. 3) 6 of the 7 patients had received DMPA at 60 or fewer days prior to surgery; 1 patient had received DMPA 120 days prior to surgery. 4) No cases of endometrial cancer were found in this group. Author states that these patients had cervical dysplasia and DMPA may have been used as palliative treatment.	1) Study uninterpretable. 2) No information provided on the size of the denominator in the study. 3) Cervical dyplasia is not a usual indication for DMPA use. 4) Uncertainty about reason for administration of DMPA in these women suggests serious problems in record keeping.

APPENDIX 2

THE ASSOCIATION BETWEEN DMPA USE AND DEVELOPMENT OF ENDOMETRIAL CANCER

REFERENCE	STUDY DESIGN	FINDINGS	COMMENTS
Stamm, H., deGrandi, P. Adenocarcinoma of the Endometrium Following Treatment with Medroxyprogesterone For Contraception Rev. Med. Suisse Romande 101:913, 1981 DMB Vol. 234 Tab #1	Case report of endometrial cancer in a 44-year-old woman after use of DMPA (150 mg) for 2-1/2 years. Patient history: - father who died from cancer of the esophagus - patient smoked 1 pack of cigarettes daily - had menarche at age 14, 2 pregnancies - at age 38 (1975) started oral contraceptive use for 2 months - then IUD use for 2 years - in 1978 started DMPA use - severe bleeding appeared in 1980.	1) Stage I endometrial carcinoma diagnosed in 1980 and a hysterectomy performed.	1) Endometrial cancer diagnosed while on DMPA.
Behary, C.M., Dollberg, L., Czernobilsky, B. Endolymphatic Stromal Myosis in Two Patients on Progestagen Therapy Contraception 13:1-6, 1976 DMB Vol. #	Case report of 2 women, in Israel, who were found to Shave massive endolymphatic stromal myosis after receiving DMPA (50 mg and ethinyl estradiol) for > 1 year and for > 8 years, respectively. Case 1: 20 year-old, unmarried, given progestagen for severe menorrhagia and dysmenorrhagia. Case 2: 44 year-old, 2 pregnancies, suffering from meno-metrorrhagia for 8 years while receiving Metrulen (ethynodiol diacetate and mesteranol).	(1) The authors speculate that growth of these lesions was stimulated by the progestagen therapy.	

THE ASSOCIATION BETWEEN DMPA USE AND DEVELOPMENT OF ENDOMETRIAL CANCER

REFERENCE	STUDY DESIGN	FINDINGS	COMMENTS
McDaniel,E.B., Potts, M. International forum update: depot medroxyprogesterone acetate and endometrial cancer. Intl. J. Gynecol. Obstet. 17:297, 1979 DMB Vol. 222	Retrospective survey of all hospital admissions for proven endometrial cancer in two Thai provinces where DMPA (150 mg or 450 mg/4 mo.) has been widely used since 1965.	1) Total number with discharge diagnosis of endometrial cancer, 1974-1978, in seven hospitals in the two provinces with over four million population....= 49 2) Total number with confirmed pathology of endometrial cancer.....= 39 27 proven diagnosis 12 presumptive diagnosis 3) Of 27 with proven diagnosis, only 16 came from the two provinces where DMPA was widely in use..... (27-16=9 were not followed up because assumed to be nonusers of DMPA.) 4) Of the 16 assumed to have had an opportunity to be exposed to DMPA, another 7 were not followed up because: - 4 were assumed too old (>50 years) to have used contraceptives - 1 had never married or borne children, so assumed not to have used DMPA. - 1 gave false address and could not be located - 1 had changed address and moved too far. 5) Of the 9 successful follow-ups: - 4 were alive - 5 were deceased and the information on drug use was obtained either by mail, or by personal interviews, either with the patient or with family members. (Why could not the clinic records be checked for verification??) 6) None of the 9 contacted cases reported use of DMPA ever.	1) Numbers dwindled fast from 49 to 9. 2) Assumes that all cases of endometrial cancer reach the hospital. 3) Ascertainment of drug use questionable. 4) Incidence of endometrial cancer in this population is not known.

APPENDIX 3

The Association between DMPA Use and Risk of Cervical Carcinoma in-Situ

Reference	Number Women Studied and Follow-up Period	Findings	Comments
Dabances, A.,Prado, R., Larraguibel, R., Zanartu, J. Intraepithelial cervical neoplasia in women using intrauterine devices and long-acting injectable progestogens as contraceptives. Am. J. Obstet. Gynecol. 119:1052, 1974 DMB Vol. #	A controlled prospective study of 2684 women receiving either DMPA or chlormadinone acetate, and of 2409 women given IUDs, in Chile. The follow-up period was (1965-1971), with women regularly evaluated for cervical neoplastic changes.	1) The group of women receiving the injectable contraception had a higher prevalence rate of preclinical cervical neoplasia at baseline as compared with women using IUDs (13.1/1000 vs. 7.3/1000 in the two groups, respectively). 2) The incidence rate (i.e. new cases) of preclinical cervical neoplasia were not different in the two groups after 4 years of followup. (1.26/1000 women-years with 95% CI: 0.4-2.06 in the DMPA/CA group vs. 1.82/1000 women-years with 95% CI: 04-3.33 in the IUD group).	1) The only study with relatively long follow-up of women receiving DMPA (4 years of prospective observations on these women). 2) The study includes a relatively large number of long-term users of DMPA. (1428 women were taking DMPA or CA f 3 years or longer. Of these, 443 women were taking injections for 5 years or longer). 3) Authors concluded that no significant difference seen in the risk of developing cervical carcinoma between the two cohorts of women taking DMPA or IUD.
Ide P, Wijnants P, Bonte J: Cytological observations of cervico-vaginal smears on hormone contraception. Revue Cytologic Clinique 5:105, 1972 DMB Vol. 244 Tab #219	Microscopic and cytologic examination of the cervix in Belgian women participating in a program for early cancer detection. 482 women were using continuous progesterone contraception (duration unspecified), 2,349 progesterone contraception, and 2,134 randomly chosen controls, matched on age and parity.	(1) 34% of the controls had cervical abnormalities (Pap I and II smears), compared to 47% in the continuous progesterone group, and 60% in the combined estrogen-progesterone group, based on clinical pathology.	1) Lacking details on duration of use contraception in the respective groups. 2) Demographic information on the controls not provided. 3) Authors attribute pathology only to effect of estrogens. 4) It is difficult to deduce either the study design or findings from this report.

APPENIDX 3

The Association between DMPA Use and Risk of Cervical Carcinoma in-Situ

Reference	Number Women Studied and Follow-up Period	Findings	Comments
Litt BD., FDA Statistical Review of Carcinoma-in-Situ Among Contraceptive Users of Depo-Provera. June 17, 1974 DMB Vol. G-161	A re-analysis of the Upjohn data for 127 U.S. women with a Grade III Pap smear.	1) 11 (of 127 women with Grade III Pap smear) had carcinoma-in-Situ. Specifically, the 11 cases of carcinoma in situ reported by Powell and Seymour. 2) Comparison of rates for cervical cancer in Depo Provers users with those of the third National Cancer Survey showed for DMPA users a rate 4.9 times higher than the general population in white women, and 3.1 times higher in non-white women.	1) Source of denominator is ambiguous. 2) The effect of detection in a screened population may account for the apparent tripling of rate in the treatment group compared to that reported by the 3NCS which draws from the general population. 3) Illustrates the difficulties of attempting to derive epidemiological information from a study that was not designed as an epidemiological study in the first place.
Powell, L.C. and Seymour, R.J. Effects of Depo-Medroxyprogesterone Acetate as a Contraceptive Agent. Am. J. Obstet. Gynecol. 110:36, 1971 FDA Vol. 116A	1,123 women in a hospital in Galveston, Texas given DMPA (150 mg) for contraception, together with estrogen supplement. Cervical cytology was done on 1,107 patients. Duration of use / No. of Women: < 12 months: 756 (67.3%) 13-36 months: 300 (26.7%) 37-54 months: 66 (5.9%) > 54 months: 1 total: N=1,123 100.0% Hospital population is approximately 80% Black; older age-group; higher parity; lower socio-economic status group with a higher than usual incidence of cervical malignancy.	1) 23 (out of 1107) had suspicious and positive smears. (Abnormal cytology rate of 21/1,000 patients in DMPA group). This compared to an abnormal cytology rate of 12/1,000 patients with repeat smears over 3 years in general population in this hospital. 2) In 82 patients who had the cervix evaluated histologically: Histopathology / No. women: no malignancy: 58 dysplasia: 11 (13.4%) carcinoma in-situ: 11 (13.4%) invasive carcinoma: 0 other pelvic malignancy: 0 Unknown: 2 Total: 82 3) Authors observed that the rate of carcinoma in-situ in the DMPA group (9.8/1,000) was twice as high as the rate occurring in previously screened patients in past 3 years in their hospital (5.02/1,000).	1) Observations made in course of a study carried out under an IND. primarily to establish efficacy and side effects. No controls included in the protocol. 2) Confounders for risk of cervical cancer not controlled for (e.g. age, parity, sexual activity). 3) The detection rate of cervical cancer in a screened population may be expected to be higher than that in the general population, i.e. close surveillance under an IND.

APPENDIX 3

The Association between DMPA Use and Risk of Cervical Carcinoma in-Situ

Reference	Number Women Studied and Follow-up Period	Findings	Comments
Schwallie PC. Experience with Depo-Provera as an Injectable Contraceptive J. Reprod. Med. 13:113, 1974 DMB Vol. 135A pp. 58-62 and Upjohn Responses to the PBI Questions 1982; p. 81 DMB Vol. 244 Tab #219	Pooled data from U.S. and non-U.S. studies on DMPA. 11,500 women treated with various dosage regimens during 1963-1973.	1) 35 patients (out of 11,500) diagnosed cervical carcinoma in-situ. (Papanicolaou smears were done at 6 month to yearly intervals on all patients). 2) Upjohn Report to the PBI, referring to Schwallie's data, adds that on further analysis it was shown that 33 cases were diagnosed among 6,378 U.S. women studied for a total of 8504 woman-years. (does it mean that only 2 cases were observed in 5122 subjects from other countries?)	1) Information on dose and duration not available. 2) No controls and no information on background incidence for the different populations. 3) Race - specific rates not provided. 4) International variation in the rates of cancer not controlled for. (e.g., age-standardized incidence rates for cervix uteri are: 27.5/100,000 in Brazil, 62.8/100,000 in Colombia, 25.5/100,000 in Puerto Rico, 16.2/100,000 in Osaka, Japan compared to: 14.0/100,000 for White females 32.1/100,000 for Black females in Detroit. (based on Waterhouse and Muir, 1976).

APPENDIX 4

REVIEW OF TERATOGENICITY ASSOCIATED WITH DMPA EXPOSURE: ANIMAL STUDIES

Reference	Study Design	Findings
Andrew, F.D. and Staples, R.E. Prenatal toxicity of medroxyprogesterone acetate in rabbits, rats, and mice. Teratology 15:25, 1976. FDA Vol. 302 Tab - D1	Post-implantation study: MPA given daily for 3, 6 or 9 consecutive days during gestation days 7-15 to mice and rabbits and to rats on days 8-16. (at least 6 animals were included in each group). Glucocorticoids cause cleft palate in rabbits.	1) Malformations attributable to MPA did not occur in fetuses of mice or rats exposed to the largest dosage tested. 2) But 1, 3 or 10 mg/kg on days 13-15 to rabbits resulted in 6, 28, and 42% cleft palate, respectively in each dose. Comparable cleft palate frequencies were not seen in untreated control fetuses. 3) A significant dose-related increase in fetal mortality occurred in rabbits given MPA at all periods tested, but not in mice or rats.
Chang, M.C. Effect of medroxyprogesterone acetate and estrogen on the development of the early rabbit embryos. Contraception. 10:405, 1974. Vol. 239(A) Tab - A15	Injection of high dose DMPA given to artificially inseminated mature female rabbits on Day 1. All 6 rabbits (with MPA treatment before or after insemination) were examined on Day 11.	1) The injection of MPA on Day 1, 4, or 5 had no effect on the development of early rabbit embryos.
Eibs, H.G., Spielmann, H. Hagele, M. Teratogenic effects of cyproterone acetate and medroxyprogesterone treatment during the pre - and postimplantation period of mouse embryos. I. Teratology, 25:27, 1982. FDA Vol. 247 Tab - G598	Pregnant mice treated with a single injection of MPA on Day 2 of pregnancy, or days 1-12 of gestation.	1) 1st experiment: MPA treatment on day 2 was followed by sporadic increases in dead and resorbed fetuses, a decrease in fetal weight, an increase in the rates of cleft palate and malformed or abnormally developed fetuses. 2) None of these effects, however, were dose dependent. 3) 2nd experiment: MPA treatment on one day between 1-12 days revealed a high rate of respiratory and urinary tract abnormalities only on day 9. 4) Cleft palate was significantly more frequent in all treated groups, though days of peak sensitivity were not detected. 5) All these effects were observed at massive doses, i.e. the lowest dose in this study is 2 times the human dose. 6) It differs from the Andrew Study above in strain of mice studied, time of injections in relation to implantation and dose level.

APPENDIX 4

REVIEW OF TERATOGENICITY ASSOCIATED WITH DMPA EXPOSURE: ANIMAL STUDIES

Reference	Study Design	Findings
Kimmel, G.L., Hartwell, B.S., Andrew, F.D. A potential mechanism in medroxyprogesterone acetate teratogenesis. Teratology, 19:171, 1979. FDA Vol. 302 Tab - D25	Female rats and rabbits studied to show a distinct species difference in the binding of MPA to gluco-corticoid receptor.	1) Conclude that MPA may be teratogenic in rabbits by binding with specific glucocorticoid receptors.
Revesz, C., Chappel, L.I., Gaudry, R. Masculinization of female fetuses in the rat by progestational compounds (abstract) Endocrinology 66:140, 1960. FDA Vol. 239(B) TAB - A67	Rats treated with MPA during 15th - 20th days of pregnancy. 4 received daily dose of 0.25 mg. 4 - 1 mg daily. 5 - 2 mg daily. 4 - 2.5 mg daily. 3 - 5 mg daily. (small numbers of animals per treatment group).	1) Delivery was delayed after large doses of these compounds and the pups were removed by Cessarian Section on Day 22. 2) Masculinization of female fetuses in the rat was observed. There were 151 males, 18 females, and 25 intersexuals born to the 17 MPA treated rats. At the lowest dose of MPA, masculinization was seen in 2 out of 17 females at 20 days of age. At 2.0 and 2.5 mg, all females were pseudohermaphrodites; externally all appeared like males. The effects are related to the androgenecity of the compounds.
Satayasthit, N., et al. The effect of medroxyprogesterone acetate, administered to the lactating ration the subsequent growth, maturation, and reproductive function of the litter. J. Reprod. Fert. 46:411, 1976. FDA Vol. 30 G-458 Abstract Vol. 68A	28 control and 32 experimental female rats plus 19 control and 19 experimental male rats. The experimental animals were produced by rats given 5 mg. MPA/g body weight On Day 3 after parturition (i.e. study the effect on lactating young rats.)	1) No difference in growth rates between experimental and control animals observed until Day 60. 2) All the experimental rats became pregnant, and no abnormalities seen at birth. i.e. MPA is not obviously androgenic. 3) Treatment of lactating females with MPA did significantly delay the onset of vaginal opening and of the first oestrus cycle in the young. (i.e. delay in sexual maturity). This effect was observed at 2 1/2 the human dose. 4) What is missing in this study is a sufficiently long follow up to see if polycystic ovary develops, a sign of androgenization.

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APPENDIX 5A

EFFECT OF MPA ON OFFSPRING:
EXPOSURE OF FETUSES TO CONTRACEPTIVE DOSES OF MPA

Reference	Number of Women and Condition Studied, Dose and Duration of MPA Use	Pregnancy History	Pregnancy Outcome and Effects on Fetus
Dodds, G.H. The use of sterile medroxyprogesterone acetate suspension as a contraceptive during a three-year period. Contraception 2: 15, 1975 FDA Vol. 74A p. 319-323	3 year follow-up of 1883 women treated with DMPA (250 mg/3 mos) in Hong-Kong.	1) Out of 736 women who discontinued DMPA, 279 (38%) were lost to follow up or used other contraception during the 10 month follow-up. 2) One contraceptive failure: injection given between 6-10 weeks of conception (i.e. high dose early in gestation period). 3) 40 out of 60 women who discontinued DMPA to get pregnant, conceived within 18 months after last injection. 4) 144 planned & unplanned pregnancies occurred within 1-28 months after last injection in women receiving 1-9 injections.	1) Out of 184 pregnancies (at tail-end of injection): 137 were live births 3 were stillbirths 26 abortions 3 ectopic pregnancies 9 currently pregnant 6 lost-to-follow-up, unk. outcome 2) In the one case of drug failure, a living infant with no abnormalities was born, sex not stated.
Mohberg, N.R. and Greenspan, A. Depo Provera and exogenous estrogen at the Grady Memorial Family Planning Clinic. Technical Report, Sept., 1980 FDA Vol. 214 Tab U-29	Family planning clinic chart review of random sample of 708 DMPA contraceptive users from the Grady Hospital in Atlanta, GA. [Mean months of DMPA use was 24].	1) 167 DMPA users (24%) of the sample became pregnant subsequent to DMPA use. 2) Mean time elapsed from last DMPA injection to conception was 18.2 months median time was 16.0 months. 3) 2 possible contraceptive failures, i.e. injection given after conception.	1) No information provided on pregnancy outcome because "the records of the status of the babies born to former DMPA users were sparse and cryptic. We would need a more thorough follow-up system to allow claims to be made concerning these infants" (p. 9).

APPENDIX 5A

EFFECT OF MPA ON OFFSPRING:
EXPOSURE OF FETUSES TO CONTRACEPTIVE DOSES OF MPA

Reference	Number of Women and Condition Studied, Dose and Duration of MPA Use	Pregnancy History	Pregnancy Outcome and Effects on Fetus
Parveen, L. et al. Injectable contraception in rural Bangladesh Lancet, 1:946, 1977 FDA Vol. 82A pp. 129-130	1601 women using DMPA for up to 3 yrs. in Bangladesh. 1020 of these were breast-feeding at time of first injection. (150 mg. with estrogen supplement).	1) only one pregnancy due to method failure. 2) 3 women received first injection while already pregnant. 3) 5 women received injection while already pregnant expecting it would cause an abortion. 4) Therefore, a total of 9 cases with exposure to maximal dose of DMPA early in gestation. 5) 21 women became pregnant after dropping out, i.e. tail-end of the injection.	1) Of the total 30 pregnancies, 10 had normal deliveries; 2 had spontaneous abortions; 18 currently pregnant. 2) No specific information on the fate of offspring exposed early in fetal life to DMPA. 3) No information on effect on the breast-fed children.
Powell and Seymour Effect on depo-medroxyprogesterone acetate as a contraceptive agent. Am J Ostet Gynec 110: 36, 1971 FDA Vol. 126A pp. 150-155 and see also Seymour, R.J., Powell, L.C. Depot-medroxyprogesterone acetate: A contraceptive. Obst Gynecol. 36:589, 1970. FDA Vol. 126A pp. 202-209	752 patients followed over 44 months in Galveston, Texas.	1) 4 patients had already conceived when first injection was given. 2) 2 additional patients missed an injection and were exposed to DMPA when already pregnant. 3) 1 case of method failure. 4) Therefore, a total of 7 patients where maximal dose (150 mg/3 mos.) occurred during early pregnancy. 5) 47 additional pregnancies occurred after DMPA had been discontinued, i.e. tail-end of the injection.	1) Among the 7 patients who inadvertantly received DMPA while pregnant: 4 had full-term, normal deliveries: 1 normal premature; 2 abortions. Sex of infants not stated. 2) The outcome of the 47 pregnancies after DMPA discontinuance (i.e. at recovery of fertility) was: 29 full-term 5 premature 1 immature 1 ectopic pregnancy 8 abortions 3 lost to follow-up

APPENDIX 5B

TRANSFER OF MPA TO FETUS OR NEONATE

Reference	Number of Women and Condition Studied, Dose and Duration of MPA Use	Pregnancy History	Pregnancy Outcome and Effects on Fetus
Besch, P.K., Vorys, N., Ullery, J.C. In vivo metabolism of H^3-medroxyprogesterone acetate in pregnant and nonpregnant women and in the fetus. Am. J. Obstet. Gynec. 95:228, 1966. DMB Vol. 302 Tab D4	4 pregnant patients were administered 40 mg. MPA 8 hours before therapeutic abortion to ascertain transplancental mechanism and to study fetal metabolism of MPA.	1) 4 male fetuses delivered at 11, 12, 16, and 22 weeks were removed by standard procedures.	1) The fetal adrenal contained the bulk of the radioactivity recovered. Larger amounts of radioactivity were in the adrenals compared to other tissues. 2) There appears to be a doubling in concentration between the 16th and 22nd wks. in the amniotic fluid to blood ratio and in kidney to blood ratio for MPA.
Crist, R.D., Krantz, K.E., Warren, J.C. Placental transfer of synthetic progestins Obstet. Gynecol. 25:89, 1965. DMB Vol.	Term placentas obtained at normal deliveries were exposed to samples of progestins including MPA (110 mc/mg) to study placental transfer.		1) Significant quantities of MPA were found to cross the in vitro perfused term placenta. 2) Since the quantity of unchanged MPA recovered was never as much as originally added, this suggests alteration of the MPA to unrecognized metabolites or binding within the placenta. e.g. the mataboites of MPA contained less than 5% of the radioactivity on the initial chromatograms. Five metabolites of MPA were present.
Saxena, B.N., Shrimanker, K., Grudzinkas, J.G. Levels of contraceptive steroids in breast milk and plasma of lactating women. Contraception 16:605, 1977 DMB Vol. 82A pp. 167-175	Blood and milk samples were collected at regular intervals from 7 lactating women given DMPA (150mg) one week after delivery for contraception.		1) In all 7 women the MPA levels in breast milk were similar to plasma concentrations. The ratio of MPA inplasma to milk was 1:1 throughout the study period up to 87 days. 2) No information given on effects on the suckling infants.

APPENDIX 5B

TRANSFER OF MPA TO FETUS OR NEONATE

Reference	Number of Women and Condition Studied, Dose and Duration of MPA Use	Pregnancy History	Pregnancy Outcome and Effects on Fetus
Turner, S.J., Mizock, G.B., Feldman, G.L.: Prolonged gynecologic and endocrine manifestations subsequent to administration of medroxyprogesterone acetate during pregnancy. Am J Obst Gynecol 95: 222, 1966. FDA Vol. 16 pp. 1888-1893	20 ward service patients (ages 15-25) 10 being controls and 10 given DMPA (100 mg. weekly) from 30th to 36th week of gestation (cum. total of 500 mg DMPA). Additionally, 77 patients treated with DMPA during pregnancy.		1) 32 of the 77 patients conceived again subsequently: Of these, 28 had normal deliveries and 4 had abortions in 1st trimester. 4 (out of the 77) were lost to follow-up. No information on offspring exposed to DMPA in utero. 2) The objective was to study MPA effects on fertility, not effects on the fetus.
Zanartu, J., Aguilera, E., Munoz, H., et al Effect on a long-acting contraceptive progestogen on lactation. Obstet Gynecol 47: 174, 1976 FDA Vol. 16 pp. 2049-2051	406 nursing mother receiving DMPA every 3 or 6 months (150 mg or 250-300 mg, respectively) for contraception. 339 mothers were given DMPA within 3 months postpartum; 133 within the first 30 days postpartum; 67 between 3 and 6 months postpartum.	1) Two mothers became pregnant at the 12th and 21st months postpartum while under the regimen of 250 mg DMPA/6 months.	1) No adverse iatrogenic effects were observed in the breast-fed children from mothers on MPA. No information on how newborn were tested or duration of follow-up. 2) Authors caution that a more careful evaluation is required on its effects on weight, growth, health, since MPA or its metabolites are expected to be excreted in the milk. 3) No information is provided on the two pregnancies where fetuses were exposed to high dose MPA.

APPENDIX 5C

RELATIONSHIP BETWEEN PROGESTINS AND HYPOSPADIAS

Reference	Study Design	Findings	Conclusions and Comments
Aarskog, D. Maternal Progestins as a Possible Cause of Hypospadias. New Eng. J. Med. 300:75-78, 1979. See Also Aarskog, D. Clinical and cytogenic studies in hypospadias. Acta Paediatr. Scand. (Suppl) 203:1-62, 1970. DMB Vol.	Case-control study. 130 hypospadic patients and 111 patients with oral clefts born during the same period were studied retrospectively with reference to pathogenetic mechanisms that might have interferred with testicular differentiation of function during fetal life.	1) In 11 out of 130 cases of hypospadias (8.5%) there was a history of maternal progestin intake in early pregnancy: 6 - for threatened abortion. 5 - for pregnancy test (with estrogen). 2) In contrast, 2 mothers of 111 infants with oral clefts (1.8%) had a history of progestin intake in early pregnancy.	1) There appeared to be a relationship between time of exposure to progestin treatment (i.e. week of gestation) and the degree of hypospadias. progestins: + / −; hypospadic cases: (8.5%) 11, 119, 130; controls: (1.8%) 2, 109, 111 RR = 5.04 (95% CI: 1.09-23.24)
Czeizel, A. Toth, J., Erodi, E. Aetiological studies of hypospadias in Hungary Hum. Hered. 29:166-171, 1979 DMB Vol.	Case-control study: 294 cases with simple isolated hypospadias in Budapest, Hungary born during 1970-1972 and a comparison group of healthy children matched on place and time of birth.	1) Sex hormone therapy for threatened abortion was significantly more frequent among mothers of cases of hypospadias than among controls ($\chi^2_1 = 9.00$, $p < 0.01$). 28 of 294 cases with hypospadias (9.5%) vs. 12 of 294 controls (4.0%) were exposed in utero to progestogens (RR = 2.4) 2) More mothers of cases of hypospadias took also sedatives.	1) Significant seasonality was documented, with hypospadias more frequently occurring in children born between August and December. [Roberts and Lloyd, 1973, and Neto et al, reported similar findings.] sex hormones: + / −; cases: (9.5%) 28, 266, 294; controls: (4.0%) 12, 282, 294 RR = 2.47 (95% CI: 1.23-4.96)

APPENDIX 5C

RELATIONSHIP BETWEEN PROGESTINS AND HYPOSPADIAS

Reference	Study Design	Findings	Conclusions and Comments
Mau, G. Progestins during pregnancy and hypospadias Teratology 24:285-287, 1981 DMB Vol.	Cohort study: A sample of 3,602 male newborns who were examined five times (at birth, at 6 weeks, and at 9, 18 and 36 months). Detailed information was available about the intake of drugs throughout pregnancy by the mothers of these newborn.	1) 33 of the total cohort of 3602 male newborn had hypospadias (1%). 2) Mothers of this cohort of newborns were exposed to progestins either for hormonal pregnancy test (4.2% or 151/3602) or for treatment for threatened abortion (11.3% or 408/3602). 3) Of the 33 cases with hypospadias, 13 mothers had used in addition to progestins other drugs during the first trimester. 4) The frequency of exposure to high doses of progestins during early pregnancy was 15% in the group with hypospadias (5 of 33) compared to 11.3% in the group without hypospadias (403 of 3569). This high dose intake was due to treatment for threatened abortion. 5) The frequency of exposure to progestins used as a pregnancy test was 9% in the group with hypospadias (3 of 33) compared to 4.1% in the group without hypospadias (148 of 3,569). 6) The combined exposure to progestins was 24% in the group with hypospadias (8/33) compared to 15% in the group without hypospadias (551/3569). The relative risk = 1.75 (95% CI: 0.5-4.4).	1) Author concludes that if a risk exists, it is a low risk, but nonetheless a distinct possibility.

APPENDIX 5C

RELATIONSHIP BETWEEN PROGESTINS AND HYPOSPADIAS

Reference	Study Design	Findings	Conclusions and Comments
Neto, R.M., Monteleon, R.R. Castilla, E.E., Paz, J.E. Hypospadias: An Epidemiological Study in Latin America Am. J. Med. Genet. 10:1-10, 1981 DMB Vol.	Case-control study of liveborn in six Latin American countries during 1967-1975. 324 male fetuses with hypospadias were compared to a control group consisting of the first nonmalformed child born after each "case", matched for sex, place, and time of birth.	1) Drug intake during the first trimester of pregnancy was higher among mothers with hypospadias than among control mothers (34.4% vs. 20.4%). 2) Among the ingested drugs were sex hormones. Specifically, 24 of 314 cases (7.6%) vs. 12 of 319 controls (3.8%) had been exposed to sex hormones in utero. 3) The overall frequency of hypospadias was 7.6 per 10,000 live births. In 13.6% (44/324) of cases, hypospadias were associated with another malformation, most often in the genital area. The frequency of hypospadias by country was: Brazil 17.7/10,000 Venezuela 11.5/10,000 Chile 6.6/10,000 Argentina 6.2/10,000 Ecuador 5.0/10,000	1) No information is provided on dose and timing of exposure, nor is any progestin uniquely identified. 2) Authors state that the difficulty in detecting an association between exposure to sex hormones and hypospadias may be due to the fact that the relative risk is low (but statistically significant) whereas the spontaneous incidence of hypospadias is high. Sex hormones Cases with hypospadias: Yes (7.6%) 24; No 290; 314 controls: Yes (3.8%) 12; No 307; 319 RR = 2.1 (95% CI: 1.1-4.3)
Sweet, R.A., Schrott, H.G., et al. Study of the incidence of hypospadias in Rochester, Minnesota, 1940-1970, and a case-control comparison of possible etiologic factors. Mayo Clin. Proc. 49:52-58, 1974. DMB Vol.	Case-control study: 113 cases of hypospadias were identified in a review of records of 13,776 live male infants (8.2 per 100 live male births) and for each case two controls were matched on hospital of delivery, last menstrual period of mother (±1 month), and maternal age (±1 year).	1) Hydroxyprogesterone caproate, intramuscularly, was given to 4 mothers of cases of hypospadias but to only 1 control mother. 3.7% (4/107) vs. 0.4 (1/226). 2) 9 mothers of cases of hypospadias vs. 5 mothers of controls had taken combination oral contraceptives within 9 months of their last menstrual period.	progestins Cases with hypospadias: + (3.5%) 4; - 112; 113 controls: + (0.4%) 1; - 225; 226 RR = 8.04 (95% CI: 0.89 - 72.74)