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**REPORT TO USAID OF THE  
AD HOC CONSULTATIVE PANEL ON  
DEPOT MEDROXYPROGESTERONE ACETATE**

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July, 1980

AD HOC CONSULTATIVE PANEL ON DMPA

Chairperson

Allan Rosenfield, M.D.  
Center for Population and  
Family Health  
College of Physicians and Surgeons  
Columbia University  
New York, New York

Guiseppe Benagiano, M.D.  
Special Programme of Research,  
Development and Research Training  
in Human Reproduction  
World Health Organization  
Geneva, Switzerland

Rebecca Cook  
Georgetown University Law Center  
Washington, D.C.

William Hansel, Ph.D.  
College of Veterinary Medicine  
Cornell University  
Ithaca, New York

Dwight Janerich, M.D.  
Cancer Control Bureau  
New York State Department of Health  
Albany, New York

Patricia King, J.D.  
Georgetown University Law Center  
Georgetown University  
Washington, D.C.

Suporn Koetsawang, M.D.  
Faculty of Medicine at Siriraj Hospital  
Mahidol University  
Bangkok, Thailand

Tapani Luukkainen, M.D.  
State Maternity Hospital  
University of Helsinki  
Helsinki, Finland

Daniel Mishell, M.D.  
Women's Hospital  
LAC/USC Medical Center  
Los Angeles, California

Roger Rochat, M.D.  
Bureau of Epidemiology  
Center for Disease Control  
Atlanta, Georgia

Ruth Roemer, J.D.  
School of Public Health  
University of California  
Los Angeles, California

Judith Rooks, C.H.M., M.P.H.  
Office of Population Affairs  
Department of Health, Education  
and Welfare  
Washington, D.C.

William Spellacy, M.D.  
College of Medicine  
University of Florida  
Gainesville, Florida

Consultant

C. Wayne Bardin, M.D.  
Center for Biomedical Research  
The Population Council  
Rockefeller University  
New York, New York

Observers

Stephen Joseph, M.D.  
Agency for International Development  
Washington, D.C.

James Shelton, M.D.  
Agency for International Development  
Washington, D.C.

Agency for International Development  
Library  
Room 146, SA-18  
Washington, D.C. 20523

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REPORT TO USAID OF THE  
AD HOC CONSULTATIVE PANEL ON DEPOT MEDROXYPROGESTERONE ACETATE

New York City, December 7-8, 1978

I. Summary Statement

An Ad Hoc Consultative Panel on Depot Medroxyprogesterone Acetate (DMPA) has reviewed the results of animal toxicology studies and currently available information on the use, benefits and risks of DMPA in humans in the U.S. and abroad. In addition, it has reviewed the conclusions of the World Health Organization (WHO) Toxicological Review Panel. Based on these reviews and the information available to it, the Ad Hoc Consultative Panel (with one dissenting vote) recommends that the United States Agency for International Development (USAID) make DMPA available to nations which request it.

II. Introduction

At the request of USAID, an Ad Hoc Consultative Panel on DMPA was formed to review a variety of issues relating to DMPA and its possible provision in the international programs of USAID, despite the present U.S. Food and Drug Administration (FDA) ruling. The Panel met for two days (December 7-8, 1978) in New York and included members who had expertise in the fields of obstetrics and gynecology, animal physiology and toxicology, epidemiology, pathology, law and health policy. The deliberations of the Panel are presented herein.

DMPA has been used both for clinical gynecologic and contraceptive purposes since the early 1960s.<sup>1</sup> At the present time it is approved in the U.S. for the treatment of endometrial cancer, but not for use as a contraceptive. It is, however, approved for contraception in 76 developed and developing countries and has been demonstrated to have unusual popularity as a contraceptive method in many settings.<sup>2</sup>

Initial experience with this drug was gained through its use for treatment of two conditions, one benign (endometriosis) and one malignant (endometrial carcinoma). In both instances high dosages of the drug were used for long periods of time.<sup>3</sup> In some instances these dosages were as much as 50 to 75 times the dosage currently recommended for contraceptive use, and treatment at these high dosages was maintained in some instances for several years. Thus, in addition to animal toxicologic studies there was the unusual opportunity to have available high dose human data to review. However, it must be added that no systematic studies have been published which specifically reported on long-term follow up of these women.

The review of this drug by the FDA has taken place over a long period of time and has been unusual in many regards. In 1967, a new drug application (NDA) for approval of DMPA as a contraceptive was filed by the Upjohn Company.<sup>4</sup> In 1973, following a favorable recommendation of its Advisory Committee on Obstetrics and Gynecology, the FDA announced its intention to give qualified approval for contraceptive use for those women who: 1) refused or were unable to accept the responsibility demanded by other contraceptive methods; 2) were incapable or unwilling to tolerate the side effects of conventional oral contraception; 3) had repeated

failures with other contraceptive methods.<sup>5</sup> Because of concern about reversibility, it was recommended that it be used only for women who had completed their childbearing. The FDA further recommended that women be informed of the possible risk of breast cancer.

In September, 1974 the FDA announced in the Federal Register its proposed final form of approval, which was to take effect from October 15, 1974.<sup>6</sup> Letters to this effect were sent to physicians throughout the country. At approximately the same time, however, a House Subcommittee on Intergovernmental Relations held hearings which resulted in a letter from the chairman of that committee to the Secretary of HEW, who then stayed the approval of the drug.<sup>7</sup> Among the issues raised by the subcommittee were concerns about potential carcinogenic effects on cervix and breast. In 1975, the FDA convened a joint meeting of its Advisory Committees on Ob/Gyn and on Biometric and Epidemiological Methodology. These committees, in turn, jointly constituted a subcommittee task force which, after open hearings, subsequently recommended that the FDA approve DMPA with the earlier limitations. After continued review, however, the FDA made a decision in March, 1978, to deny approval of the Upjohn application for the following five reasons:<sup>8</sup>

1. Safety questions, raised by studies in dogs showing an increased incidence of mammary tumors associated with the drug, have not been resolved;
2. A number of safer alternative methods of contraception are available in this country, and no clear evidence has been submitted to show that a significant patient population in need of the drug exists in the U.S.A.;

3. Irregular bleeding disturbances caused by the drug may necessitate administration of estrogen, imposing an added risk factor and decreasing the benefits of a progestogen-only contraceptive;
4. Exposure of the fetus to DMPA, if the drug fails and pregnancy occurs, poses a risk of congenital malformations, a risk potentially enhanced by the prolonged action of the drug;
5. Serious reservations about the ability of the postmarketing study for breast and cervical carcinoma, proposed by the Upjohn Company, to yield meaningful data.

This decision has been appealed by the Upjohn Company and the FDA announced in July, 1979, that this appeal will be heard by an FDA-appointed Board of Inquiry.<sup>9</sup>

USAID, as part of its program of population and family planning assistance in developing countries, provides contraceptive commodities. At present, the methods provided include oral contraceptives, IUDs, condoms and vaginal methods. Recently, the agency has received requests for DMPA from a number of countries, since local purchase in bulk is very costly.<sup>10</sup> USAID policy, however, has prohibited it from providing other countries with drugs which are not approved by the FDA for use in the U.S. Because this is a policy of the agency and not a legal regulation, and also because of reviews of the Drug Act which are currently taking place in Congress,<sup>11</sup> USAID requested that this Panel be constituted. Its task is to review the risks and benefits of DMPA, to advise USAID on appropriate action the agency can take in response to requests for DMPA from developing countries, and to recommend additional studies, ongoing monitoring and postmarketing evaluation which should be undertaken, if indeed the agency does provide the drug. The

following report will discuss the benefits of DMPA, review various actual and hypothetical side effects and complications, and make a series of recommendations.

### III. Benefits

DMPA has certain benefits not possessed by any other contraceptive. It has a higher use effectiveness than any other reversible method<sup>12</sup> and is the only available long-acting injectable contraceptive which is highly effective and can be provided at three-month intervals.<sup>13</sup> Further, its effectiveness continues even if the user is a few weeks late in obtaining a repeat injection.<sup>14</sup>

It is a uniquely acceptable method for some women because of the preference for injection over other approaches to contraception. It is not used in relation to coitus, requires infrequent administration, is provided outside the home and requires no supplies to be left around the home, thus giving the user a high degree of privacy. Further, it can be administered by any person who normally gives injections in a health care system and does not require a clinical setting for administration.<sup>15</sup>

DMPA does not suppress lactation and thus, in comparison to oral contraception, has been considered for use among postpartum women.<sup>16</sup> This would be a major advantage in the developing world, where successful and prolonged breastfeeding is of critical importance in helping to lower existing high rates of infant morbidity and mortality. However, there is inadequate information presently available on possible effects on the nursing infant of the DMPA in the breast milk; this is an area requiring further study.

Among women in whom iron deficiency anemias are common, the development

of oligomenorrhea and secondary amenorrhea following use of DMPA may help to decrease the incidence of this problem.

Based on information available to the Ad Hoc Panel at the time of its meeting, there appear to be few, if any, contraindications to the use of DMPA, other than pregnancy. Because it is administered periodically by injection and has few potentially harmful metabolic side effects,<sup>17</sup> DMPA may be the preferred method for several groups of women who desire effective, reversible contraception, but who have special medical needs which contraindicate the use of other methods, and for whom sterilization is not legal or desired. The Panel did not agree with the FDA that there is not a significant population of potential users for this method in the United States; it felt that no data were available which would allow one to draw such a conclusion.

Although, as with the pill and the IUD, different DMPA continuation rates have been reported in different studies, even within similar cultural settings,<sup>18</sup> the Panel felt there were no physiological reasons to explain this. Rather, it was felt that differences in patient education, preparation and understanding of the potential side effects, as well as different physician responses to these effects, probably explain most of these differences. As with all contraceptive methods, clear and understandable consumer education and information is essential to method choice, effective and safe use, and, where possible, consumer identification of contraindications. Other causes of the continuation rate variations might include age and parity differences, as well as differences in availability and price of subsequent injections.

#### IV Metabolic Effects

As judged by laboratory findings, DMPA appears to have a mild effect on carbohydrate tolerance in women, although this effect is apparently less severe than that caused by oral contraceptives.<sup>19</sup> In a relatively small percentage of women using DMPA, weight gain occurs, which occasionally can be significant.<sup>20</sup> Data also suggest a possible effect on the adrenal glands, with a resultant decline in cortisol levels, although this has not been shown to be of clinical significance.<sup>21</sup> Studies have not identified any effect of DMPA on liver function or lipid metabolism.<sup>22</sup>

The effect of DMPA on blood pressure is unclear. While the number of users is probably still too small, there is no evidence of thromboembolic phenomena or other circulatory diseases, as are seen with estrogen-containing oral contraceptives in the United States and Britain.<sup>23</sup> The Panel urged further monitoring of this aspect since, if the lack of cardiovascular effects is confirmed, DMPA will have an important advantage over estrogen-containing oral contraceptives.

In contrast to oral contraception, DMPA does not appear to produce a decrease in either the quality or quantity of milk in lactating women.<sup>24</sup> To the contrary, the data suggest that it stimulates an increase in the quantity of milk. The effects of DMPA and its metabolites on the growth and development of the nursing infant, however, are still unknown.

#### V. Menstrual Side Effects

Among minor side effects, the most significant relate to menstrual irregularities. During the first six to twelve months, the most common irregularities are spotting, staining and bleeding. Later, as many as 40 to 60% of women become amenorrheic. Heavy bleeding requiring estrogen

therapy is rare, and almost never is severe enough to require operative procedures such as dilatation and curettage.<sup>25</sup> During the 1960s, estrogens in low dosages were occasionally used to treat spotting and staining<sup>26</sup> but the results were equivocal and this therapy is no longer recommended by most physicians. If amenorrhea is not acceptable to a woman, cyclical estrogens may be used to cause monthly withdrawal bleeding. However, this is not recommended. Menstrual irregularities virtually never necessitate the use of estrogen. The Panel, therefore, felt that the FDA's concern about the potential administration of estrogen to women using DMPA could not be substantiated by available reports and experience. Further package labelling for physicians could caution against the supplemental use of estrogens.

#### VI Return of Fertility

One injection of DMPA provides reliable contraception for a period of three months, with continuation of contraceptive effect for a varying period thereafter. While this is an advantage for the woman who may be late for her next scheduled injection, this does lead to a delay in the return of fertility for some women. Thus, there appears to be a delay in the percentage of women who become pregnant after terminating DMPA use, when compared to women discontinuing use of other reliable contraceptive agents such as the pill or the IUD. However, available data suggest that by 24 months, over 90% of DMPA users who have discontinued use in order to become pregnant have indeed conceived.

The following table compares a series of 756 DMPA users with 437 oral contraceptive users in Thailand.<sup>27</sup> The women in both groups had discontinued

use in order to become pregnant. The mean gravidity of the DMPA users was 1.5, roughly double that of oral contraceptive users, suggesting more of the DMPA users had proven their fertility prior to beginning contraception. The mean time for establishment of pregnancy after the discontinuation was 5.1 months for DMPA users, as compared to only 2.5 months for pill users. The table demonstrates that there is a delay in return of fertility, with substantial differences at 6 and 12 months. By 24 months, however, there was no significant difference.

	<u>Prior DMPA Users</u>	<u>Prior O.C. Users</u>
Number	756	437
Mean Age	24.5	22.3
Mean Gravidity	1.5	0.7
Proven Pregnancy		
6 months*	53%	75%
12 months	75%	85%
24 months	92%	94%
Mean months	5.5 months	2.5 months

(Source: T. Pardthaisong, 1978)

\* Months after stopping contraceptions; contraception was considered stopped after last cycle of O.C. was taken or 3 months after last injection.

Another analysis of data from this same population in Thailand found that the proportions of women who had become pregnant were almost identical at 12, 18, and 24 months among women who had discontinued DMPA and those who had an IUD removed in order to conceive.<sup>28</sup>

Because of these data and other studies from the U.S with similar findings,<sup>29</sup> Panel concluded that, while there is a delay in the return of fertility the vast majority of women desiring a pregnancy were able to conceive within a two-year period of time. Thus, concerns about irreversibility, or chemical sterilization, do not appear to be substantiated.

The same Thai study did suggest an abnormal sex ratio (more males

than normally expected) among children born to prior DMPA users, but the number of infants was small and this may have been a chance finding.<sup>30</sup> However, this finding should be assessed in additional studies.

### VII. Teratogenic Potential

Laboratory experiments have shown that exposure in utero to very large doses of DMPA can have a virilizing effect on rat and rabbit fetuses, but this is not so in humans.<sup>31</sup>

Several epidemiologic studies suggest that prenatal exposure to exogenous sex hormones may rarely produce various types of congenital abnormalities in a developing fetus.<sup>32</sup> However, there is very little information on the possible effects of progesterone alone.<sup>33</sup> Nonetheless, the possibility of an effect is of concern, since some women starting to use DMPA may have an unrecognized early pregnancy and women stopping DMPA may conceive before DMPA is completely cleared. Because of the depot or long-term action of DMPA, this could possibly be of concern even beyond the three months of contraceptive effectiveness. Information about such conceptions and their outcome should be collected, perhaps in an international registry, as an extremely large series would be necessary to refute or prove this possible relationship, as discussed below.

A review of the evidence in recent studies concerning the possible teratogenic effects of exogenous sex hormones showed that, although all of the available studies have methodologic deficiencies, the data suggest an association between prenatal exposure to these hormones and a variety of congenital abnormalities, especially cardiac defects, with a relative risk probably in the range of two-fold.

Since effective contraception prevents both normal and abnormal pregnancies, it can be shown that even if a two-fold increase in con-

genital defects were associated with prenatal exposure to DMPA widespread use of the drug would result in a net decrease in the number of anomalies. Because of this, only a very small number of fetuses would be exposed to the two-fold increased risk associated with maternal use of the drug.

The Panel felt that continued surveillance was essential to evaluate potential teratogenic effects, but stated that no human data was available to suggest that DMPA increases the risk over that which may be associated with other hormonal contraceptives.

#### VIII. Carcinogenic Potential - Cervix

There is no strong evidence linking DMPA with cervical disease.<sup>34</sup> Furthermore, it is virtually impossible to conduct a good scientific study to persuasively identify a relationship between the use of any hormone and cervical cancer, unless the increased risk is at least four-fold. The major reason for this is that the risk of cervical cancer is strongly associated with sexual behavior variables, which are difficult to control. Many past studies, including those reported to the FDA by the House Subcommittee in 1974, have been confounded by failure to deal with these difficult-to-measure, but critical sexual variables. The development of invasive cervical cancer lags 5 or more years after the development of presumed cancer precursors, which can be detected by pelvic examination and Pap smear.<sup>35</sup>

It appears that any effect of hormones on cervical cancer incidence, if present, is unlikely to affect the risk of cervical cancer to a degree

which can be measured with current medical and epidemiologic evaluation techniques. Pathologists differ significantly in their interpretation of cervical biopsies, so that it is nearly impossible to conduct comparative studies in the large populations required to detect differences of less than a four-fold magnitude in relative risk.

The Panel felt that there was no evidence presently available to suggest a relationship between the development of either cervical cancer or its precursors and the use of DMPA; thus there is no contraindication of its use for this reason. Given the long delay in human carcinogenicity, however, continued data collection was recommended.

#### IX. Carcinogenic Potential - Endometrium

In December, 1978, several weeks after the Ad Hoc Panel had adjourned, it became known that the required 10-year studies of DMPA in monkeys had been completed, and the preliminary results of the autopsies contained the surprising finding that two of the monkeys which had been receiving 50 times the human dose had endometrial cancer.<sup>36</sup> No other neoplasia were found. The Chairperson of the Panel, after consultation with Panel members, arranged for a special toxicology committee to consider this information and the reports of consultant toxicologists (to the Upjohn Company) who reviewed the microscopic specimens of all the test monkeys. (See Appendix I for the Toxicology Committee's full deliberations.) In brief, the Committee concluded that the meaning of the finding of endometrial cancer in two of the monkeys subjected to extremely high doses of DMPA for many years is far from clear, for the following reasons:

1. There is no baseline information on the incidence or natural history of endometrial cancer in monkeys.

2. There is a substantial body of literature which shows that progestogens do not promote endometrial cancer in women. In fact, there is some preliminary evidence that they may even be protective.

3. DMPA does not cause hyperplasia in either monkeys or women; it causes atrophy. Hyperplasia is the state believed to be favorable for the development of endometrial cancer in women.

4. There is considerable doubt among toxicologists and pathologists that it is valid to extrapolate from the experience of animals given extremely high doses.

5. There is no evidence, in the few and preliminary data available, of an increase of endometrial cancer among long-term users of DMPA.

Weighing these factors against the considerable benefits of DMPA, the Committee was unanimous in supporting the original recommendation of the Ad Hoc Panel that DMPA should be made available to developing countries, upon request, as a part of its assistance program, provided that careful study of the possible health effects of DMPA continues. Thus, the Committee was in agreement with the WHO's Toxicology Review Panel.

#### X Carcinogenic Potential - Breast

Of great concern to the Panel were data from toxicologic studies of DMPA in beagle dogs, in which the treated animals have manifested more mammary gland tumors than control animals, and some of the tumors have become malignant.<sup>37</sup> Data from a series of studies were

reviewed in which varying dosages, ranging from the human contraceptive dose to 25 times this dose, were used over a varying period of years.<sup>38</sup>

Because of the complexity of the issues involving the beagle dog and its relevance to humans, much time was spent discussing both similarities and differences in the beagle dog response to the exogenous sex hormones, particularly progesterones. In both beagle dogs and humans, progesterone prevents the LH surge, prevents ovulation, decreases plasma cortisol, and causes a mild disturbance of carbohydrate metabolism.<sup>39</sup> Beagle dogs and humans, however, differ in their response to progestogens three important ways:

1. The beagle dog endometrium is stimulated by DMPA, producing dilated secretory glands, leading to a condition of mucometra and/or pyometra (the latter, in some cases, causing death).<sup>40</sup> In the human, on the other hand, there is an initial stimulatory effect, followed by a quiescent stage, leading to atrophy of the endometrium.<sup>41</sup>
2. With higher doses an acromegalic-like condition is seen in the beagle dog which becomes conspicuous in many of the animals tested.<sup>42</sup> At the present time it appears that this may be related to a stimulatory effect on growth hormone, although the data on this particular point are not yet conclusive. In the human no acromegalic changes are seen.<sup>43</sup>
3. Finally, many beagle dogs that were treated with high doses of DMPA, many of whom developed mammary gland tumors, died from causes other than breast cancer (usually pyometra).<sup>44</sup> No deaths in humans receiving high dosages of DMPA have been reported.

Studies comparing beagle dog responsiveness to DMPA with that of other test animals and humans show significant species differences in the metabolism and progesterone receptor responses.<sup>45</sup> In all the reported studies mammary gland nodules developed in almost all treated beagle dogs that lived beyond the first few years of treatment. In 2 of 16 animals receiving high doses of DMPA, mammary gland tumors metastasized to other parts of the body.<sup>46</sup> In animals which were hysterectomized in order to prevent death from pyometra, and then received high doses of DMPA, widespread vascular changes were noted, with increases in platelets and many had massive thromboses.<sup>47</sup> Serious renal changes were observed with early deposition of PAS-positive material, together with some instances of amyloidosis and diabetic glomerular changes.<sup>48</sup> These effects have not been seen in the human. In other studies, using lower doses of DMPA, liver adenomas were found in the beagle dog, together with an increase in gallbladder stones.<sup>49</sup> Progesterone itself, at physiologic dose levels, produced no such changes in these particular experiments.

There is little doubt that C-21 steroid derivatives with progestational activity, including progesterone itself, produces a series of toxic manifestations in the beagle dog. All progestogens, including 19-NOR derivatives, also produce mammary changes in beagles, if given in high enough doses. A probable explanation of differences between progestogens in tumorigenic potential relates to the wide variation in relative affinities of synthetic progestogens for the progesterone and estrogen receptors of various species.\* There have been problems

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\* For this reason, the Committee on Safety of Medicines in the United Kingdom no longer requires beagle dog studies for contraceptive drugs.<sup>50</sup>

however, for technical reasons, in the ability to precisely measure progestogen receptors in the normal human breast.

Finally, since the Ad Hoc Panel meetings, new information bearing on this subject has come to light. (See Appendix II for summaries of relevant information released in the year following the Panel meetings). Most importantly, data from nine years of prospective study of thousands of contraceptive users in Britain found absolutely no excess of breast cancer among women using contraceptives containing progestogens closely related to DMPA.<sup>51</sup>

As mentioned earlier, the various committees that have reviewed the effects of DMPA in the human had available to them the unique opportunity to review human data in which DMPA had been used for long periods of time at much higher doses than the contraceptive dose. With some fifteen years of experience, there have been no known fatalities related to DMPA administration in the human, nor any of the endometrial, acromegalic, vascular or mammary gland changes shown to occur in the beagle dog.

After reviewing animal as well as human data, the Toxicology Review Panel of WHO, which met in September, 1978, and whose report was available to the Panel in draft form, concluded that:

Considerable reservations must be expressed over the relevance of the findings in the beagle dog to the possible toxicity of long-acting progestogens in humans. Significant differences in the response to progestogen treatment between dogs and women have demonstrated. . . . There is evidence that the healthy beagle dog's breasts contain a reservoir of microscopic neoplasms which may grow and occasionally become malignant in response to prolonged over-stimulation by progestogens, especially by those compounds particularly active in the canine species. Progesterone treatment stimulates progesterone receptors in the

breasts of the dog, but not in the rat nor in the human. The available evidence suggests that all investigated progestogens, including progesterone itself, are able to promote mammary tumors in the beagle dog. For these reasons the beagle dog does not appear to be an appropriate animal model for the evaluation of carcinogenic risks associated with progestogens.<sup>52</sup>

In addition to work on beagle dogs, studies have also been carried out in rodents and monkeys. The WHO Toxicology Panel reviewed these in depth. Included were several very high dose studies in both mice and rats, with doses up to 200 times the recommended human contraceptive dose. Results indicated no change in mortality rates and there was a similar incidence of neoplasms in both treated and untreated animals. In particular, no mammary cancer was observed. Growth hormone release was stimulated by DMPA, but there was no effect on prolactin. Benign hepatoma was seen rarely in test animals. The relevance of the rodent results to the human is difficult to assess in the absence of detailed comparative pharmacokinetic and pharmacodynamic data.

Studies on monkeys show no demonstrable differences between controlled groups and monkeys treated with low, middle or high doses of DMPA, in the development of mammary nodules, except for one study in which mammary nodules were noted in some of the animals receiving the middle but not the high dose.<sup>53</sup> These nodules were benign, with dilated ducts and alveoli, together with a slight proliferation of epithelial cells and connective tissue, but no indication of neoplasia.

#### XI. Monitoring and Research

While there has been an extensive literature published on the use of DMPA for both clinical and contraceptive uses in the United States and abroad, there is need for continued and additional data on the short- and long-term risks and benefits of DMPA in humans. In order to be able to more accurately continue to evaluate and assess risk/benefit, and to resolve

any continued uncertainties and doubts, there is a need to support both the organization of appropriate surveillance systems and the development of carefully focused research studies. Many of the steps to be suggested below are relevant to other contraceptive methods, as well, and should also strengthen the capacity for conducting risk/benefit analyses both in the United States and other countries when DMPA is used as a contraceptive.

A. Surveillance: Routine surveillance or reporting systems, such as those existing in the United States and Britain, are the source of much of the present epidemiologic information on the risks and benefits of contraceptives. Although these systems are costly, require a degree of technical expertise, and cannot easily be established, they are important if countries are going to be able to effectively monitor the use of agents such as hormonal contraceptives. Such systems might include the following:

1. Brief case reports of untoward and unusual illness among women in this reproductive years. Even if initially incomplete, such reporting, especially if followed up routinely, will improve reporting completeness, generate hypotheses for study, and allow for epidemiological assessment of potential and actual complications related to the use of DMPA and other contraceptive methods.
2. Periodic cross-sectional surveys of health care providers may reveal unusual or dramatic complications of an old or newly introduced contraceptive method like DMPA.
3. Formal registries, perhaps first organized on a limited geographic basis, also lay the foundation for further study. Since the issue of neoplastic disease has been

raised with the use of hormone contraceptives, cancer registries should be considered. This should be recognized as a long-term investment in disease control yielding potential benefits beyond the issues addressed by the Panel.

## B. Research Studies

1. In order to gather additional information relating to the potential teratogenic effects of DMPA (either when injected during an unrecognized pregnancy, or when conception occurs before DMPA is cleared from the woman's system), as well as to gain information on the potential risk to child development arising among infants exposed to DMPA and its metabolites in the mother's milk, prospective and retrospective studies are required to assess spontaneous fetal loss, stillbirth, birth weight, congenital abnormalities, sex ratio, early growth and development, and other pertinent measures of morbidity in infancy and childhood. Suitable non-exposed controls, matched on relevant reproductive characteristics, will be necessary.
2. While the data from Thailand on return of fertility following discontinuation of DMPA was felt by the Panel to be reassuring, differences in proven fertility of the two groups of women studied shows the need for continued assessment of this issue, especially regarding use of DMPA in women with unproven fertility and/or irregular menstrual cycles. In addition, there is a need for detailed workup of those women unable to become pregnant after discontinuing DMPA.

Further, one study noted a rather high male-female ratio among births to women conceiving after DMPA use and further evaluation of this finding is required.

3. Attempts to assess the possibility of malignant changes in the cervix related to hormonal preparations were felt by the Panel to be extraordinarily difficult for technical reasons, if only a small increased risk is involved. The problems described earlier in this report are thought to be significant; continued follow-up and observation are recommended, but no new controlled studies are proposed at this particular time because of the difficulties and costs.
4. The Toxicology Committee which reviewed the information on endometrial cancer and DMPA emphasized the need for further and more intensive investigation of this issue. Several studies are already planned by the World Health Organization and by the International Fertility Research Program. These will be carried out in areas where DMPA has been established as a popular method of contraception for years. It was suggested that a variety of research approaches be utilized, including: registries of pathology where unusual types of tumor would be noticed; case control studies in areas where use is common; and cohort studies (perhaps based on an initial cross-sectional study of a population that could be followed).
5. The potential for development of breast cancer in humans remains one that requires continued follow-up because the latent period between exposure and appearance of cancer may be long

in the human. It is urgent that observational case control studies begin now. Clinical studies to assess the metabolic effects on DMPA in humans should be continued both here and abroad. In addition, studies should be continued on the beagle dog, until explanations of the causes of the mammary tumors, as well as the acromegalic-like syndrome, are available.

## XII. Conclusions

Based on the testimony and discussion of Panel members with expertise in various areas of concern related to DMPA use, on review of the extensive bibliography on the subject, and on review of WHO materials (most particularly the findings of the Toxicology Review Panel of the WHO Special Program of Research in Human Reproduction), the Ad Hoc Consultative Panel on DMPA has drawn the following conclusions:

1. DMPA has been used rather widely for clinical gynecologic uses (for endometriosis and endometrial carcinoma) at doses significantly higher than that recommended for contraception, and as yet the Committee knows of no reports of significant adverse effects.
2. DMPA is the only widely available long-acting injectable contraceptive and has a higher use effectiveness than any other reversible contraceptive method, particularly since it has no relation to coitus, requires infrequent administration, and is provided outside the home.
3. Metabolic Effects: While laboratory findings suggest a mild effect on carbohydrate tolerance and a mild adrenal suppressive effect, these are probably less than similar effects caused

oral contraceptives. There appears to be no circulatory system effect, although it would be premature to make definitive statements in this regard at the present time.

4. Menstrual Effects: Menstrual side effects are the most important complaints related to the use of DMPA. Initially, there is irregular spotting, staining or bleeding, while later amenorrhea develops in as many as 60% of women. A review of the literature suggests that use of estrogens in the treatment of the spotting and staining are ineffective and are no longer recommended for this reason. FDA's concern that estrogen will be prescribed frequently to DMPA users does not seem to the Panel to be justified in fact.
5. Return of Fertility: Data were presented from Thailand, in which a series of women who discontinued use of DMPA in order to become pregnant was compared to a similar group of women who discontinued use of oral contraceptives and IUDs for the same reason. These data suggest that, while the return of fertility was delayed in the previous DMPA users, by 24 months there was no significant difference in pregnancy rates between women who discontinue DMPA use in order to become pregnant and prior pill or IUD users. The mean gravidity in DMPA users, however, was slightly higher than that of the oral contraceptives users, suggesting that more of the DMPA users had proven their fertility prior to contraception.

6. Teratogenic Effects: There is suggestive evidence that a two-fold risk of certain congenital anomalies is associated with prenatal exposure to some exogenous sex hormones. With DMPA there is concern that a woman with an unrecognized early pregnancy may receive an injection of DMPA, or that conception may occur before the effects of DMPA have cleared from the woman's system. The weight of available epidemiologic data suggest that there may indeed be a small association between prenatal exposure to all exogenous hormones and a variety of congenital defects, with a relative risk, perhaps in the range of two-fold. However, because data have not been found specifically identifying DMPA as a causative teratogen, it is impossible to state that it poses a greater or lesser risk than other hormones. Further, the teratogenic risk, if it exists at all, is small, and the risk of pregnancy is also very small, thus making this potential risk an extraordinarily rare one. The Panel recommended continued evaluation, but did not feel that the available data suggest DMPA should be held off the market because of this possible risk.
7. Cancer - Cervix : There had been some concern that DMPA might produce premalignant changes in the cervix. However, review of the available data suggest that there is no demonstrable effect on cervical disease. Further, studies to identify a small increase in risk (less than four-fold) were deemed to

be extraordinarily difficult for a variety of technical reasons, including differences in pathologists' interpretation of cervical biopsies, together with the need to control for a range of sexual behavior factors, for which information is difficult to obtain.

8. Cancer - Endometrium: The Committee of experts, which reviewed the data on cancer of the endometrium associated with DMPA among monkeys, concluded that, while continued studies are imperative, the data available at this time do not warrant discontinuing use of DMPA for this reason. The full Ad Hoc Panel reviewed the Committee's report (Appendix I) and was in agreement with the Committee's conclusions.
9. Cancer - Breast: Of great concern to the Panel was the development of breast nodules, some of which have been malignant, in beagle dogs subjected to varying doses of DMPA. Assigning a different order of magnitude to the possibility of an association between DMPA and breast cancer from that assigned to non-threatening risks, the Panel spent a great deal of time reviewing this particular issue and felt that, while studies must continue to assess the meaning of beagle dog data, there are significant differences between the beagle dog and the human in the response to progestogens and in the histology of the mammary gland. These differences include a different response of the endometrium, which is stimulated in the beagle dog and which atrophies in the human; the development of acromegalic changes

in the beagle dog and no similar changes in the human; the latent neoplastic foci in the beagle mammary gland, which do not exist in the human; and death of beagle dogs due to pyometra, secondary to the hyperstimulation of the endometrium, which, again, does not occur in the human. The Panel concluded that while studies should continue, the evidence suggests that the response in humans is different and that the beagle dog data are not sufficient reason to withhold DMPA.

### XIII. Recommendations

1. After a review of the various materials and information described earlier, and after as thorough as possible an assessment of the risks versus benefits of DMPA use in humans, the Panel recommended that USAID make DMPA available to those nations that request it for use as a contraceptive. One Panel member, Dr. William Hansel, does not concur with this final recommendation. (The majority of Panel members also felt that this drug was appropriate for use in the United States as a general contraceptive agent but this was beyond the purview of issues the Panel was asked to address).
2. This recommendation holds even if the FDA does not change its present stance at the time of its hearing in response to the Upjohn Company's request, unless new or additional adverse data or information become available.
3. USAID should inform nations to which it provides financial and commodity assistance of the availability of DMPA, but should take care to avoid influencing the choice of DMPA within a

country's program. It should not promote DMPA as a contraceptive method, as long as the drug is not approved for contraceptive use in the United States by the FDA.

4. USAID should provide as much information as possible about the risks, benefits and use effectiveness of DMPA as a contraceptive, to enable other nations to assess, in light of their own health needs, whether DMPA should be used in their respective countries. This recommendation may be minimally satisfied by providing information obtained for this purpose from both the FDA and the WHO.
5. If DMPA is provided this should be done through the normal channels through which USAID provides such commodities, including direct bilateral distribution and distribution through intermediaries. The Panel did not feel that there should be any special distribution channel for this drug that would be different from AID's procedures with other such commodities.
6. The Panel did not feel that USAID should place restrictions on use of this drug, feeling instead that this was the role of the requesting nation, which, after its own review, should make such decisions.
7. As with other forms of contraception, consumer information and education on DMPA should be an integral part of programs providing contraception. The methods of providing this information should be decided within each country according to its own practices, but the Agency should recommend that consumers

- be as fully informed as possible about the benefits, risks and side effects of all forms of contraception and provide contraceptives only where such consumer safeguards are in place.
8. A series of recommendations are included in the body of the report concerning the establishment of appropriate surveillance and monitoring procedures, together with suggestions as to the types of research studies that should be undertaken. The Panel did not feel that these could be conditions for provision of the drug, but, rather, that AID should be prepared to support such activities upon request and should encourage surveillance, monitoring and research studies wherever appropriate. It should also work in close collaboration with WHO, (which is involved in developing and conducting a number of the types of studies listed in the body of the report), and also with the UNFPA, IPPF and other donor agencies.
  9. If USAID does elect to distribute DMPA, despite the present FDA ruling, this should not be seen as a precedent for the more general provision of other drugs not approved by the FDA. If exceptions are deemed of importance in the future, careful review of all related issues should first be carried out, through the mechanism of an expert and ad hoc panel.
  10. In order to monitor, on an on-going basis, data on DMPA, as well as data on other contraceptives, the Panel recommends the establishment by USAID of a continuing Scientific Advisory Committee.

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**APPENDIX I**

**REPORT OF THE TOXICOLOGY COMMITTEE**

## Committee Members

C. Wayne Bardin, Director  
Center Biomedical Research  
The Population Council  
Rockefeller University  
York Avenue and 66th Street  
New York, N.Y. 10021

Col. Harold W. Casey, Chairman  
Department of Veterinarian Pathology  
Armed Forces Institute of Pathology  
Washington, D.C. 20306

Alex Ferency, M.D.  
Department of Pathology  
Jewish General Hospital  
3755 Cote Ste Catherine Rd  
Montreal 249  
Quebec, Canada

Saul Gusberg, M.D., Chairman  
Department of Obstetrics and Gynecology  
Mt. Sinai Hospital  
1176 5th Avenue  
New York, N.Y. 10029

Dwight Janerich, M.D., Director  
Cancer Control Bureau  
New York State Department of Health  
Room 565 - Tower Building  
Albany, New York 12237

Ms. Patricia King  
Associate Professor of Law  
Georgetown Law Center  
600 New Jersey Avenue, N.W.  
Washington, D.C. 20001

Ralph W. Richart, M.D.  
College of Physician & Surgeons  
630 West 168 Street  
New York, N.Y. 10032

Judith Rooks, CNM, MSPH  
Expert Consultant  
Office of Population Affairs  
Department of Health, Education and Welfare  
Washington, D.C.

Allan Rosenfield, M.D., Director  
Center for Population & Family Health  
Columbia University  
60 Haven Avenue  
New York, N.Y. 10032

Bruce V. Stadel, M.D.  
Medical Officer  
Contraceptive Evaluation Branch  
Center for Population Research  
National Institute of Child Health  
and Human Development  
Bethesda, Maryland 20205

Observer  
Dr. James Snelton  
DS/POP/R  
RPE, Room 309 (AID)  
Department of State  
Washington, D.C. 20523

Staff  
Deborah Maine  
Center for Population and  
Family Health  
Columbia University  
60 Haven Avenue  
New York, N.Y. 10032

## I. INTRODUCTION

In December, 1978, at the request of the U.S. Agency for International Development, an Ad Hoc Consultative Panel on Depo Medroxyprogesterone Acetate (DMPA) was convened in New York. After review of animal toxicology studies and available information on the use, benefits and risks of DMPA, the Panel was prepared to recommend, unanimously, that USAID make this drug available, as part of its assistance program, to those countries which, after reviewing the available information, wish to use it.

Prior to finalizing the Panel's report, however, information was received indicating that endometrial carcinoma had developed in two test monkeys which had been receiving 50x the therapeutic dose of DMPA. A research firm under contract to the Upjohn Pharmaceutical Company, at the end of required ten-year studies, had carried out routine postmortem examinations on animals which had been receiving 1x, 10x, and 50x the therapeutic dose, as well as a group of controls. Two of the 10 monkeys receiving the highest dose were found to have endometrial carcinoma, while none of the seven control animals had this disease, nor did any of the 20 monkeys receiving other doses. (A number of animals in the study died from various causes before completion of the 10-year study period. None of them had endometrial disease).

As a result of the monkey data, the Panel agreed to table its report until more information was available, so as to be better able to interpret the findings. The Upjohn Company sent the monkey's endometrial slides to a number of leading human and veterinary pathologists for their interpretation.

With the reports submitted by these pathologists to Upjohn, and after telephone conversation with Panel members, the Panel chairperson organized a special, one-day committee meeting to review the data and make recommendations to the Panel for its final report. A group of experts was recruited for this meeting from a variety of relevant fields, including obstetrics and gynecology, gynecologic pathology, veterinary pathology and reproductive physiology. Committee members trained in these fields all had experience with endometrial disease in either primates or humans. In addition, other Committee members had experience in cancer epidemiology, international public health programs, and one was a lawyer with experience in ethics. (See Appendix for a list of Committee members.) The Committee reviewed materials provided by Upjohn, including the outside pathologists' assessments of the microscopic specimens. Committee members also reviewed the draft of the Ad Hoc Panel's original report, a summary of relevant literature published during the year since that report was written, and materials provided by the World Health Organization (WHO).

In October 1979, the WHO's Toxicology Review Panel issued its final appraisal of the DMPA monkey study. After reviewing all the data the Panel concluded "that the adenocarcinoma in these two monkeys were the result of massive overdosage. The Panel felt that the current and planned WHO studies of the health effects of DMPA should continue, and that there is no reason to recommend discontinuation of the use of DMPA in national family planning programmes."<sup>1</sup>

## 2. PATHOLOGIST'S REVIEW

Dr. Ralph M. Richart, Director of Obstetric and Gynecologic Pathology at the Sloane Hospital for Women, reviewed the reports submitted to the Upjohn Company by five consulting pathologists who examined the histological sections taken from the monkeys in the study of DMPA. The pathologists were Drs. Arthur T. Hertig, Ralph Heywood, John M. Morris, D. L. Moyer, and Marion G. Valerio. Dr. Richart's report to the panel follows:

There was uniform agreement among the consultants that in the majority of the monkeys the endometrium was atropic with a pseudo-decidual transformation of the endometrial stroma similar to the alterations commonly seen in women receiving DEPOPROVERA at contraceptive doses. They also agreed that the neoplasms noted in two of the high-dose monkeys were endometrial adenocarcinomas and that one was metastatic. Although there were some variations in the histological description of the two cancers, particularly with regard to differentiation, there was no greater variability than would be expected based on past experience, and the differences were not thought to be significant. Because of the small number of animals in the study, the relative paucity of data regarding the occurrence of endometrial carcinoma in older monkeys and the lack of accompanying endometrial hyperplasia, it was difficult for the reviewers to make a determination as to the possible relationship of the endometrial cancers to the administration of DMPA."

### 3. COMMITTEE'S DELIBERATIONS

The Committee members stressed the difficulty of interpreting the information because so little is known about endometrial disease in monkeys: Few institutions keep monkeys for such prolonged periods of time (10 years in the Upjohn study). There is no information on the baseline incidence of endometrial cancer in monkeys.

However, it does appear to be uncommon. For example, the San Diego zoo performs autopsies on all animals. Of 46 female macaque monkeys examined, none had endometrial abnormalities.<sup>2</sup> However, the zoo's Director of Research, Dr. Kurt Benirschke, who gave the Committee this information, cautioned that there is great variation among the many species of macaques, and there were less than a dozen rhesus monkeys (the species of macaque used in the DMPA test) in their sample. The Armed Forces Institute of Pathology does not have any cases of uterine cancer in its collection of primate neoplasia. On the other hand, Committee members said that they knew of two cases of uterine abnormality in monkeys, neither of which had been administered hormones. Dr. E.S. Gerard of the Upjohn Company provided the Committee with information on these cases:

At this time we are aware of three long-term monkey studies that have been completed. These are our own Depo-Provera study, a Population Council study utilizing the Tatum T intrauterine device, and a Wyeth study utilizing their marketed contraceptive steroids. The Population Council study had one control animal with endometrial adenocarcinoma in situ and the Wyeth study had one control animal with atypical adenomatous hyperplasia which is considered to be a premalignant lesion. Thus, each of the three studies has abnormalities of the endometrium: in a treated group in our study and in the control groups in the other two studies.

Dr. Bardin of the Population Council pointed out that the endometrial cancer in this control monkey would probably not have been detected on routine autopsy. The endometria of animals in their experiment were especially carefully scrutinized because it was an IUD study.

Dr. Gerard noted that there are a number of long-term trials underway on the effects of contraceptive steroids on monkeys. Perhaps when these are completed they will provide more information on endometrial lesions in monkeys.

It was suggested by the Committee that the monkeys' endometrial cancer could have arisen by any of three routes: through hormonal action of the DMPA; through some nonhormonal, toxic action of the DMPA; and independently of the DMPA, by chance.

If the hormonal action of the DMPA caused the cancers, then they are unusual in several ways: (1) They were associated with the superficial layers of the endometrium; whereas in women, cancer usually arises from deeper layers of the endometrium. (2) Endometrial cancer in women is usually associated with hyperplasia, such as that caused by estrogen. There was no evidence of hyperplasia among the DMPA treated monkeys. (3) The endometria of the monkeys treated with DMPA were atrophied, a condition which has been thought to decrease the risk of carcinoma developing. In short, the theory that the hormonal action of DMPA caused the endometrial cancer in the test monkeys is contrary to what is known of the natural history of endometrial cancer in women.

Additional evidence against the hormonal action of DMPA having caused the endometrial cancer is found in a variety of clinical and epidemiologic studies. Excess estrogen is known to increase a woman's

risk of developing endometrial cancer. There is evidence that progestogens neutralize this effect. For example, while use of estrogens by postmenopausal women increases the rate at which they develop endometrial cancer, use of a combination of estrogen and a progestogen does not increase the rate of disease.<sup>3</sup> Similarly, while use of sequential oral contraceptives (which emphasized estrogenic action) may have increased the risk of this disease among young women, use of oral contraceptives (which contain estrogen and a progestogen in each pill) does not have this effect.<sup>4</sup> In fact, there is new evidence from a case control study which suggests that women who use combined oral contraceptives may even have less risk of endometrial cancer than do women who do not take oral contraceptives -- in other words these preliminary data suggest that progestogens may even protect against endometrial cancer.<sup>5</sup> Finally, DMPA and other progestones have been used clinically to slow the growth of advanced endometrial cancer in women. While none of these findings rule out the possibility that DMPA may have caused the cancer found in the monkeys, they do call into question the meaning of that finding.

There is, of course, the possibility that the hormonal action of DMPA may increase the risk of endometrial cancer in monkeys through some unknown route. There is no way of knowing, with so few data, if this is the case. If it is, is this finding applicable to women? Some pathologists believe that DMPA, at very high doses, may affect tissues in the monkey endometrium which are known to react differently from those in women.<sup>6</sup>

It is also possible that the massive doses of DMPA may have affected the monkeys in the 50x group through some nonhormonal action -- i.e. as a toxin. The Committee members thought that this seemed unlikely because there was no evidence of a dose response: there was no higher mortality rate among

the monkeys receiving DMPA than among the control monkeys, nor any increase in mortality with increasing dosage. Neither was cancer found in sites other than in the uterus. However, these observations must remain speculative, because of the very small number of monkeys in the experiment.

Finally, the possibility that the two cases of endometrial cancer in the 50x group arose by chance cannot be ruled out. Using Fisher's exact test, the probability that the results of the monkey test could have occurred by chance ranged from one chance in three ( $P=0.33$ ), to one chance in four ( $P=0.28$ ), depending on whether only the monkeys left at the end of the trial or all monkeys ever in the trial were included. In addition, exploration with a variety of statistical techniques showed that these data lack both significance and power, even if margins of error (both Types 1 and 2) much larger than usual are allowed. For example even with an alpha as high as .30 (rather than the traditional .05), .80 power was not achieved unless the relative risk associated with DMPA use was assumed to be at least 6.6. In addition, even if four cases of endometrial cancer had been found among the monkeys in the 50x group (rather than the two cases which actually occurred), and the alpha level was set at .10, power did not reach .80 even assuming a relative risk with DMPA use of 10.

Several members of the Committee questioned the usefulness of testing contraceptives with massive doses. Dr. C. Wayne Bardin, Director of the Center for Biomedical Research at The Population Council, reported on the effects of very high doses of hormones, such as those used in the monkey experiments. His report can be summarized as follows:

One of the problems associated with current toxicologic studies for contraceptives is that steroids must be tested at 1-, 10-, and 50-fold the human dose. While this might be a reasonable approach for a chemical

carcinogen, it is not necessarily valid for hormones. The reason for this relates to the fact that there is not absolute specificity between various steroid hormones and their respective receptors. For example, a given progestin will bind to the progesterone receptor with high affinity ( $K_d=10^{-9}$ ). Progestins also bind to glucocorticoid, mineralocorticoid and androgen receptors with decreasing affinities. Thus, at physiological concentrations progestins bind to progestin receptors and produce progestational responses in organs that have these receptors. At slightly greater than physiological concentrations, progestins are also glucocorticoids by means of their interaction with the glucocorticoid receptors. At still greater concentrations progestins bind to the mineralocorticoid and androgen receptors. Over the enormous dose range tested in toxicologic studies, progestins would be bound to all of these hormone receptors and would exert many effects not related to the progestational activity seen at physiological concentrations of the hormone. (Almost certainly, many of the pathologic effects of MPA in the beagle dog related to their effects on other than progestin receptors).

Because progestins can interact with multiple hormone receptors when greater than physiological concentrations are present in the blood, unique and unexpected effects can be seen. One example of this is the interaction of progestins with the androgen receptor in kidney and prostate. MPA produces a moderate androgenic effect on the kidney, but only a slight androgenic effect on prostate. When administered in the presence of an androgen, MPA potentiates androgen action on the kidney but not on the prostate. This potentiating effect was unexpected and is still unexplained. Another progestin, cyproterone acetate, has no effect on kidney or prostate when administered alone. However, when administered with a low dose of testosterone it potentiates androgen action on the kidney but not on the prostate. When cyproterone acetate is administered with a large dose of testosterone, it inhibits androgen action both on the kidney and on the prostate. Many other progestins exert similar effects as described for MPA and cyproterone acetate. Thus, when progestins interact with the androgen receptor they may mimic, potentiate, or inhibit androgen action. Progestins are known to produce analogous effects when they interact with the glucocorticoid and mineralocorticoid receptors. It should be emphasized again that these unusual effects are seen when high doses of progestin are given, such as those that are present in animals treated with 50 times the human dose.

In conclusion, it is important to realize that these considerations on hormone action have been appreciated only in the last several years -- after the pattern of testing contraceptive steroids was well established. In view of these recent observations and conclusions, it is reasonable to reconsider whether contraceptive steroids should be tested at 50- and even at 10-fold greater doses.

In addition to trying to interpret the monkey data and assess their applicability to humans, the Committee considered the experience of women who have used this method of contraception. In response to the endometrial cancer finding at the conclusion of the monkey trial, Drs. Edwin McDaniel and Malcolm Potts have made an effort to determine whether there was an increase in endometrial cancer among women in Chiang Mai and Lumpoon provinces in Thailand, where DMPA has been used by more than 86,000 women since it was introduced in 1965.<sup>7</sup>

McDaniel and Potts report that a search of the records of all seven hospitals operating in these areas produced evidence of 39 cases of proven or presumptive endometrial cancer in 1974-1978. During these years, they note, ". . . there has been a steadily increasing patient load for diseases of all kinds." However, there was no clear increase in the number of cases of endometrial cancer seen each year, as Table I shows.

Table I. Proven and Presumptive Cases of Endometrial Cancer Reported in Chiang Mai and Lumpoon Provinces, Thailand, by Year of Diagnosis.

Year	Diagnoses		
	Proven	Presumptive	Total
1974	3	0	3
1975	8	1	9
1976	6	6	12
1977	7	3	10
1978	3	2	5
Total	27	12	39

Source: McDaniel and Potts

Of the 27 women with proven endometrial cancer, 16 came from Chiang Mai or Lumpoon province, where they could have received DMPA. Of these 16, four were too old to have received DMPA (63-84 years old at diagnosis), one had never been married, and two could not be located at the time of the report. Of the remaining nine women, none had ever used DMPA. Because the numbers are so small, the time too short, and the conditions of the study far from satisfactory, these findings cannot be construed as proof that DMPA does not cause endometrial cancer. Nevertheless, the authors note, the lack of a substantial increase in endometrial cancer -- in an area where hundreds of women are known to have used DMPA continuously for 10-13 years and many thousands for shorter periods -- ". . . is a reassuring preliminary observation."

The Committee members emphasized the need for further and more intensive investigation on this issue. Several studies are already planned by the World Health Organization and the International Fertility Research Program. These will be carried out in areas where DMPA has been established as a popular method of contraception for years. It was suggested that a variety of research approaches be utilized, including: registries of pathology where unusual types of tumor would be noticed; case control studies in areas where use is common; and cohort studies (perhaps based on an initial cross-sectional study of a population that could be followed).

#### 4. CONCLUSION

The assembled experts concluded that the meaning of the finding of endometrial cancer in two of the monkeys subjected to extremely high doses of DMPA for many years is far from clear, for the following reasons:

There is no baseline information on the incidence or natural history of endometrial cancer in monkeys.

There is a substantial body of literature which shows that progestogens do not promote endometrial cancer in women. In fact there is some preliminary evidence that they may even be protective.

DMPA does not cause hyperplasia in either monkeys or women; it causes atrophy. Hyperplasia is the state believed to be favorable for the development of endometrial cancer in women.

There is considerable doubt among toxicologists and pathologists that it is valid to extrapolate from the experience of animals given extremely high doses.

There is no evidence, in the few and preliminary data available, of an increase of endometrial cancer among long-term users of DMPA.

Weighing these factors against the considerable benefits of DMPA, the Committee was unanimous in supporting the original recommendation of the Ad Hoc Panel that DMPA should be made available to developing countries, upon request, as a part of its assistance program, provided that careful study of the possible health effects of DMPA continues. Thus, the Committee was in agreement with the WHO's Toxicology Review Panel.

It should be added that both this Committee and the original Ad Hoc Panel found no reason to support the FDA's decision not to approve use of DMPA as a contraceptive in the United States.

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## Appendix 2:

FROM: James D. Shelton, USAID

SUBJECT: Relevant information regarding the safety of Depo-Provera (DMPA) which has accrued during the last year, 1979.

Since the December 1978, meeting of AID's advisory panel on Depo-Provera, a notable number of important findings on the various safety considerations of Depo-Provera have become available. The most well-known of these was probably the finding of adenocarcinoma of the endometrium among two of the rhesus monkeys given 50 times the human dose of DMPA. The implications of this animal evidence for the human is as yet unclear. Some of the evidence described below, however, bears heavily on the endometrial cancer issue as well as other important issues and offers a good deal of encouragement. I think the information cited below is fairly complete, but would welcome information regarding data I may have omitted. Copies of cited studies are available on request.

### I. Breast Cancer

#### A. Human Data

1. Investigators at Emory University in collaboration with the Center for Disease Control have conducted a case-control study of breast cancer among contraceptive users.<sup>1</sup> From 1969 to 1978, over 11,000 women received DMPA. The study showed a relative risk of 1.0 (i.e., no increased risk vis a vis other contraceptive users). While the study was limited to 30 cases of breast cancer (because of the low incidence of breast cancer in this contracepting population), the authors calculated they would have had an 80% chance of detecting a three-fold risk and a 95% chance of detecting a four-fold risk.

2. Results regarding breast cancer and oral contraceptive users were published from the highly regarded "Oxford" study.<sup>2</sup> Breast cancers diagnosed over the decade from 1968 to 1977 were included. While the study looked at all oral contraceptive users, information was broken out on preparations containing chlormadinone acetate or megestrol acetate since these progestins belong to the same class of progestin as DMPA (17 $\alpha$ -hydroxy progesterone derivatives and the whole group has been particularly implicated as a cause of breast tumors in beagles. The British investigators found 30 cases of breast cancer among users of these preparations and 30 cases among controls. Thus, there was no increased risk and the relative risk was again 1.0.

3. Results on breast cancer became available from a 10-year double-blind prospective study of postmenopausal women receiving conjugated estrogens and cyclic oral medroxyprogesterone acetate (MPA) seven days in each month.<sup>3</sup> Other evidence has indicated that the oral MPA, if anything, gives higher blood levels than the injectable DMPA.<sup>4</sup> Although the sample size in the prospective study was relatively small, it showed a statistically significant lower incidence of breast cancer among women receiving the estrogen with MPA.

#### B. Animal Data

Published articles from Upjohn<sup>5</sup> and Schering<sup>6</sup> report a marked stimulatory effect on growth hormone when DMPA is administered to beagle dogs. This effect is known not to occur in humans. The data suggest that the profound effects of DMPA on the beagle mammary gland is a

species-specific effect related to its important effects on the dog's pituitary gland. Additionally, the British Committee on Safety of Drugs (equivalent to our FDA) has abandoned the beagle dog as a model for making judgments of the impact of contraceptive steroids on human beings.<sup>7</sup>

## II. Endometrial Cancer

### A. Human Data

1. McDaniel and Potts<sup>8</sup> have investigated confirmed cases of endometrial cancer hospitalized at the McCormick Hospital in Chiang Mai, Thailand. Between 1965 and 1979, the McCormick Hospital program provided Depo-Provera to over 86,000 users. Of the 16 cases of endometrial cancer from Chiang Mai and Lumpoon provinces, four were 63 years old or older. Nine of the remaining women were successfully followed-up and another had never married or borne children. None of the women followed-up had ever used DMPA or oral contraceptives. Furthermore, there has been no increase in hospital admissions for endometrial cancer over time, although there has been a steady increase in hospital admissions for other reasons. This negative result is, of course, not conclusive regarding DMPA use and endometrial cancer, but it certainly allays fears of any marked increase in risk.

2. A number of studies have reported that, whereas postmenopausal estrogens may induce endometrial cancer, addition of a cyclic progestin (usually MPA) nullifies this risk and may in fact provide protection.<sup>3,9-12</sup> This apparently occurs because MPA and other progestins suppress the endometrium whereas estrogens stimulate it.<sup>10-15</sup> One study of cyclic oral contraceptives and endometrial cancer also

showed no increased risk.<sup>16</sup>

#### B. Animal Data

The significance of the rhesus monkey findings remains elusive. WHO's expert toxicology panel has twice discounted the relevance of the monkey information although it appears true that endometrial adenocarcinoma is very rare in the rhesus monkey. The report of the advisory subpanel elaborates on this issue (Appendix 1).

### III. Metabolic Effects

#### A. Blood Clotting

British investigators report fewer abnormalities of blood coagulation among Depo-Provera users than among oral contraceptive users.<sup>17</sup>

#### B. Lipid Effects

Swedish researchers report markedly decreased effects of MPA on High Density Lipoprotein (HDL) and other lipid parameters associated with atherosclerosis. MPA might, therefore, be expected to have less theoretical effect on atherosclerosis than other progestins.<sup>18</sup>

#### C. Sex Hormone Binding Globulin (SHBG)

SHBG is a carrier blood protein which binds estrogens, progestins, and androgens. Steroid hormones which are bound to SHBG are generally not available for biologic activity. It has been known that the usual synthetic progestins (19-nor testosterone derivatives) bind strongly to SHBG whereas MPA does not.<sup>19-20</sup> Thus, these 19-nor synthetic progestins, by displacing estrogens and testosterone from SHBG, could contribute to the side effects attributed to these hormones. In addition to this theoretical advantage of MPA, British investigators in a recent study report that the 19-nor derivatives actually decrease SHBG while a progestin belonging to the MPA class

(megestrol acetate) slightly increases it. <sup>21</sup>

#### D. Vaginitis

An Egyptian study reports a decreased incidence of positive culture or smear for monilial (yeast) infection following use of DMPA. <sup>22</sup>

#### E. Blood Pressure

Careful blood pressure measurements before and after DMPA showed a small and statistically non-significant decrease.<sup>23</sup> Blood pressure measurements before and after any treatment should generally be evaluated with caution, however.

#### IV. Effect on Breast Milk and Child Growth

Some previous studies of the effect of DMPA on lactation have shown an increase. Others have reported no change. A recent study from Bangladesh goes beyond the usual breast milk measurements and actually looks at child growth among users of various methods of contraception.<sup>24</sup> Cross-sectionally, the average weight for height was remarkably similar for infants whose mothers used DMPA, oral contraceptives, sterilization, and no method. The caloric content of the breast milk was also remarkably similar. The DMPA group's weight/height percent improved significantly more than the non-hormonal group, but the authors caution that "socio-economic and other factors may have somewhat favored the injectable group."

#### Summary and Conclusion

Aside from the information regarding the endometrial cancer in rhesus monkeys, all of the latest information is favorable to Depo-Provera. The human epidemiologic studies, while not conclusive, are strongly reassuring. The metabolic data support other previous work which collectively shows a

superiority over oral contraceptives in a number of metabolic areas. This is not surprising since Depo-Provera contains only a single progestin rather than a progestin plus an estrogen and that single progestin is chemically more similar to the natural progestin (progesterone) than the 19-nor testosterone progestin generally found in oral contraceptives.

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