# Genital Tract Anomalies and Cancer in Females Exposed in Utero to Diethylstilbestrol

## *Brief report on the DESAD Project*

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IN 1938 THE ENDEAVORS of Dr. E. C. Dodds, Courtauld Professor of Biochemistry, Middlesex Hospital, London, and his colleagues culminated in the synthesis of a most effective nonsteroidal estrogen—diethylstilbestrol (DES) (*1*). Their achievement in endocrinologic research, which in the 1930s was focused on the sex hormones, was reviewed in 1974 by Noller and Fish (*2*).

DES gained clinical acceptance almost immediately. In most tests, it was fully as active as estradiol, one of the major estrogens responsible for significant physiological effects resulting in the human female's sexual maturation (*3*). DES could be sythesized at low cost; its purity, and thus its quality, was excellent; and most important, it could be administered orally. These characteristics contributed to its popularity and, consequently, DES was promptly used as a substitute for endogenous estrogen in estrogen-deficient persons, for example, post-menopausal women. This popularity has not abated; DES continues to be synthesized by pharmaceutical companies and prescribed by physicians as a substitute for natural estrogen.

The 1976 Physicians' Desk Reference (*4*) gives the following list of conditions for which the use of DES is of value: menopause or female castration, postpartum breast engorgement, carcinoma of the prostate (for palliation), breast cancer (for palliation), senile vaginitis (inflammation of the vagina occurring in old age), kraurosis vulvae (dryness and shriveling of the vulva).

Based on the published reports of Morris and van Wagenen (*5*) and Kuchera (*6*), the Food and Drug Administration in the February 5, 1975, Federal Register (*7*) approved the use of DES as a postcoital contraceptive as a "measure to prevent pregnancy in an emergency, for example after rape." It is not, however, to be used as a routine or frequent method of contraception.

### DES Used for Complications of Pregnancy

The focus of this paper, however, is not on the present uses of DES but on an historical one. During the 1940s, 1950s, and perhaps as late as the 1960s, DES was, commonly prescribed to prevent threatened abortion. Its use for this purpose was proposed in 1946 by O. W. Smith and co-workers (*8*). They described an investigation of DES as a possible therapeutic agent in preventing complications of pregnancy such as premature delivery, intrauterine death, pre-eclampsia (development of hypertension with proteinuria, edema, or both, due to pregnancy or the influence of recent pregnancy) and eclampsia (occurrence of one or more convulsions, not attributable to other cerebral conditions, in a patient with pre-eclampsia).

It was believed that these complications, characteristic of late pregnancy, arose from a deficiency in

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the production of two placental steroid hormones, estrogen and progesterone. DES served to prevent these complications by stimulating the placenta's secretory cells to synthesize the deficient hormones. Consequently, DES was not administered for its own estrogenic activity, but rather for its stimulatory action on the placenta.

Administration of DES was assumed to be beneficial in any abnormal situation in pregnancy. In 1948 Smith recommended that DES be used as therapy for threatened abortion and complications of late pregnancy including premature delivery, hypertension, and diabetes (*9*). The recommended drug dosage was to begin with 5 mg per day in the 6th to 7th week of pregnancy and was to be escalated at fixed intervals ending in the 35th week of pregnancy; however, all physicians did not adhere to this recommended regimen. They frequently prescribed various doses of DES for time intervals based on the severity of the patient's complications. As a result, it is difficult to make comparisons among persons having received the drug initially.

The specific number of women to whom DES was administered for this purpose has never been accurately determined, but it is generally estimated that between 500,000 to 2 million were exposed to DES—at least, that number was reported in 1974 (*2*).

Although Dieckmann and co-workers in 1953 questioned the therapeutic value of DES in preventing threatened abortion (*10*), it was not until 1970 that a paper by Herbst and Scully (*11*) implicated DES as a carcinogen in human beings. They reported that eight female patients (ages 15–22 years), examined at Massachusetts General Hospital between 1966 and 1969, were diagnosed with clear cell adenocarcinoma of the vagina. Cancers of this site and histological type had not previously been diagnosed in women of that age group at that hospital.

In a case-control study of these patients, it was reported that the mothers of seven of the eight females had taken DES during pregnancy, but none of the mothers of the 32 females in the control group took DES, although some of the mothers of controls had experienced bleeding during pregnancy and had had previous miscarriages (*12*). An additional study confirmed these results (*13*), and in another study (*14*) it was noted that clear cell adenocarcinoma of the cervix was also associated with exposure to DES in utero.

## National Cancer Institute-DESAD Study

It was in this climate that the National Cancer Institute's Division of Cancer Control and Rehabilitation issued a Request for Proposal in December 1973 entitled "Study of the Incidence and Natural History of Genital Tract Anomalies and Cancer in Offspring Exposed *in Utero* to Synthetic Estrogens (DES)." The resulting study was set up as a field test to answer questions concerning incidence, prevalence, and natural history of vaginal epithelial changes. The study required the cooperation of at least four organizations to develop jointly a common protocol for the satisfactory study of female offspring of mothers who received the synthetic estrogen during pregnancy. It became known as the DESAD (DES-Adenosis) project.

The National Cancer Institute originally awarded contract funds in 1974 for 3 years to four institutions. During a recent review of the project, a peer review committee recommended to the Institute that the study continue to be supported to answer fully questions posed by the aims of the project.

The institutions and principal investigators to whom funds were awarded are Massachusetts General Hospital (Dr. Ann Barnes and Dr. Stanley Robboy), Baylor College of Medicine (Dr. Raymond H. Kaufman), University of Southern California (Dr. Duane Townsend), and Mayo Clinic (Dr. David Decker). Dr. Leonard Kurland and staff of the Mayo Clinic serve as the coordinating unit for the project.

The DESAD study's basic purpose is to assess the magnitude and severity of the health hazard to DES-exposed female offspring. To accomplish this aim, a population of these females has been identified and are being clinically examined according to a standard procedure agreed upon by all participating centers.

A publication by the DESAD group which describes the project's complete methodology and design will be published in 1977. The article will include, among other items, a definition of the target population, the eligibility criteria, location, and recruitment of participants, and details of the clinical examination.

The first group in the target population are those offspring with documented exposure in utero to any dosage of DES for any duration at any stage of fetal life for any indication. The one exception is that if the exposure occurred only during the week of pregnancy before delivery, the offspring is not considered to have been exposed. Participants who were exposed are classified in four categories:

1. Participants identified by systematic review of a collection of prenatal records.
2. Persons with documented exposure referred by a physician who is not a project participant.

3. Persons with documented exposure coming to the centers. (This category was closed on September 29, 1976.)

4. Persons recruited after they were located in an active search by DES center staff.

The two categories of the control population are nonexposed siblings and matched controls.

Both control and experimental groups are gynecologically and colposcopically examined at regular intervals—usually on an anniversary basis or more frequently if deemed necessary by the examining physician. The examination includes iodine staining of the vagina and cervix and biopsy of suggested abnormal areas.

The data being collected include the participant's prenatal record review, female health history, drug history, and results of colposcopy, cytology, and pathology. They will be used to derive answers for the questions posed by the following six protocol aims of the DESAD project.

1. To estimate the prevalence and incidence rates of vaginal epithelial changes and other vaginal, cervical, and other abnormalities in the lower reproductive tract among the general population of exposed females.

2. To determine the upper bound or limit for risk of adenocarcinoma.

3. To estimate the frequencies of dysplasia (alteration in size, shape, and organization of adult cells), squamous carcinoma, and adenocarcinoma in the course of followup in DES-esposed offspring with and without vaginal epithelial changes.

4. To determine if DES-exposed females are at higher risk than unexposed females for the abnormalities referred to in aims 1 and 3.

5. To study the progression and outcome of vaginal epithelial changes, including the subsequent occurrence of dysplasia, squamous cell carcinoma, and adenocarcinoma and to evaluate the effect of risk factors such as contraception and pregnancy. Treatment protocols may be developed in the course of followup; if so, these will be studied.

6. To study the value of cervical and vaginal cytology, histology, colposcopy, palpation, and vaginal staining in the screening of the DES-exposed offspring with respect to subsequent outcomes.

These aims are being accomplished through identification and enrollment of a minimum of 2,000 females with documented exposure to DES in utero. Of these, 500 were identified from review of prenatal records. An enrollment of 750 nonexposed controls is expected.

## Results

Late in 1977, the project's researchers will publish the first baseline findings. They will report on the rates of neoplasia in the experimental group com-

### DES-Type Drugs That May Have Been Prescribed to Pregnant Women

#### Nonsteroidal Estrogens

| | | |
|---|---|---|
| Benzestrol | Estrosyn | Palestrol |
| Chlorotrianisene | Fonatol | Restrol |
| Comestrol | Gynben | Stil-Rol |
| Cyren A | Gyneben | Stilbal |
| Cyren B | Hexestrol | Stilbestrol |
| Delvinal | Hexoestrol | Stilbestronate |
| DES | H-Bestrol | Stilbetin |
| DesPlex | Menocrin | Stilbinol |
| Diestryl | Meprane | Stilboestroform |
| Dibestil | Mestilbol | Stilboestrol |
| Dienestrol | Methallenestril | Stilboestrol DP |
| Dienoestrol | Microest | Stilestrate |
| Diethylstilbestrol | Mikarol | Stilpalmitate |
| Dipalmitate | Mikarol forti | Stilphostrol |
| Diethylstilbestrol | Milestrol | Stilronate |
| Diphosphate | Monomestrol | Stilrone |
| Diethylstilbestrol | Neo-Oestranol I | Stils |
| Dipropionate | Neo-Oestranol II | Synestrin |
| Dethylstilbenediol | Nulabort | Synestrol |
| Digestil | Oestrogenine | Synthoestrin |
| Domestrol | Oestromenin | Tace |
| Estilben | Oestromon | Vallestril |
| Estrobene | Orestol | Willestrol |
| Estrobene DP | Pabestrol D | |

#### Nonsteroidal Estrogen-Androgen Combinations

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|---|---|
| Amperone | Teserene |
| Di-Erone | Tylandril |
| Estan | Tylosterone |
| Metystil | |

#### Nonsteroidal Estrogen-Progesterone Combination

Progravidium

#### Vaginal Cream-Suppositories with Nonsteroidal Estrogens

AVC cream with Dienestrol
Dienestrol cream

pared to the control group and on factors related to vaginal epithelial changes, such as drug dosage and duration of administration. (Vaginal epithelial change is defined as the presence of columnar epithelium, glands, Nabothian cysts, white epithelium, hyperkeratosis, and punctation of mosaic in the vagina.)

## NCI's Advice to DES Exposed Females

As a result of discussions with DESAD project physicians, the National Cancer Institute has issued an advisory. If a young woman suspects or knows that she was exposed in utero to DES, she should contact the physician who treated her mother in pregnancy for verification and for precise information about the specific kind of estrogen, dosage, period of pregnancy involved, and the condition for which the estrogen was prescribed.

Whether or not verification of DES exposure is possible, daughters past the age of puberty who think they may have been exposed are advised to obtain a complete pelvic examination by a gynecologist or other qualified physician. Such an examination should include (*a*) a complete inspection and palpation of the cervix and vagina, (*b*) a PAP test, (*c*) an iodine staining test, and (*d*) biopsy of selected areas if indicated. A colposcopic examination may be performed in certain areas. Daughters who are prepubertal are not usually examined unless they have symptoms such as abnormal bleeding or a vaginal discharge, which may indicate early puberty or some other condition.

Additional questions that DES-exposed offspring may have are answered in "Questions and Answers About DES Exposure Before Birth"—DHEW Publication No. (NIH) 76–1118. A second pamphlet, "Information for Physicians—DES Exposure *In Utero*"—DHEW Publication No. (NIH) 76–1119, is also available. Both pamphlets were compiled by members of the DESAD project and the Office of Cancer Communication. They are available free from the Office of Cancer Communication, National Cancer Institute, Bethesda, Md. 20014.

### *References*


1. Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R.: Estrogenic activity of certain synthetic compounds. Nature 141: 247–248, Feb. 5, 1938.
2. Noller, K. L., and Fish, C. R.: Diethylstilbestrol usage: its interesting past, important present, and questionable future. Med Clin North Am 58; 793–811, July 1974.
3. Murad, F., and Gilman, A. G.: Estrogens and progestin. *In* The Pharmacological basis of therapeutics, edited by L. S. Goodman and A. G. Gilman. Ed. 5. Macmillan Publishing Co., Inc. New York, 1975, ch. 68, pp. 1423–1440.
4. Physicians' desk reference. Ed. 30. Medical Economics Co., Oradell, N.J., 1976, p. 935.
5. Morris, J. M., and van Wagenen, G.: Postcoital oral contraception. *In* Proceedings of the Eighth International Conference, International Planned Parenthood Federation, Santiago, 1967, p. 256.
6. Kuchera, L. K.: Postcoital contraception with diethylstilbestrol. JAMA 218: 562–563, Oct. 25, 1971.
7. Subchapter D—Drugs for human use. Part 310—New drugs. Diethylstilbestrol as postcoital oral contraceptive: patient labeling. Federal Register 40: 5951–5955, Feb. 5, 1975.
8. Smith, O. W., Smith, G. V., and Hurwitz, D.: Increased excretion of pregnanediol in pregnancy from diethylstilbestrol with special reference to the prevention of late pregnancy accidents. Am J Obstet Gynecol 51: 411–415 (1946).
9. Smith, O. W.: Diethylstilbestrol in the prevention and treatment of complications of pregnancy. Am J Obstet Gynecol 56: 821–834 (1948).
10. Dieckmann, W. J., Davis, M. E., Rynkiewicz, L. M., and Pottinger, R. E.: Does the administration of diethylstilbestrol during pregnancy have therapeutic value? Am J Obstet Gynecol 66: 1062–1081 (1953).
11. Herbst, A. L., and Scully, R. E.: Adenocarcinoma of the vagina in adolescence: a report of 7 cases including 6 clear-cell carcinoma. Cancer 25: 745–757 (1970).
12. Herbst, A. L., Ulfelder, H., and Poskanzer, D. C.: Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 284: 878–881, Apr. 22, 1971.
13. Greenwald, P., Barlow, J. J., Nasca, P. C., and Burnett, W. S.: Vaginal cancer after maternal treatment with synthetic estrogens. N Engl J Med 285: 390–392, Aug. 12, 1971.
14. Noller, K. L., Decker, D. G., Lanier, A. P., and Kurland, L. T.: Clear cell adenocarcinoma of the cervix after maternal treatment with synthetic estrogens Mayo Clin Proc 47: 629–630 (1972).