

“Adenocarcinoma of the Vagina: Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women” (1971), by Arthur L. Herbst, Howard Ulfelder, and David C. Poskanzer

Published in 1971, “Adenocarcinoma of the Vagina: Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women,” by Arthur L. Herbst and colleagues, was the first piece of literature connecting maternal use of the drug diethylstilbestrol (DES), also called stilbestrol, with the development of a rare and severe form of vaginal cancer in young women. Diethylstilbestrol was later classified as an endocrine disruptor, a substance that disrupts the hormonal function of the body in those exposed to it during development or later in life. After Herbst and his team established the connection between DES and the occurrence of breast cancer, cervical cancer, infertility, and reproductive abnormalities, the US federal government banned use of the drug for pregnant women. The article was published in the *New England Journal of Medicine*.

Biochemist Charles Dodds synthesized diethylstilbestrol in the UK in 1938 with the help of chemist Robert Robinson. DES was a cheap and effective synthetic form of estrogen, a hormone that stimulates the female reproductive system. Physicians around the world adopted DES to treat a variety of hormonal problems, including menopausal symptoms, postpartum lactation suppression, gonorrheal vaginitis, and atrophic vaginitis. However, in 1949, researchers correlated low estrogen levels in urine with premature births and miscarriages. The research indicated that women with such conditions should be treated with a synthetic estrogen, like DES. Physicians prescribed DES, a synthetic hormone, to pregnant women in the 1950s and 1960s to prevent miscarriages and for a variety of other hormonal problems in non-pregnant individuals. In 1971, Arthur L. Herbst, Howard Ulfelder, and David C. Poskanzer of Massachusetts General Hospital in Boston, Massachusetts, published “Adenocarcinoma of the Vagina” linking maternal ingestion of DES to the development of vaginal cancer in eight women in their late teens and early twenties. The US Food and Drug Administration, headquartered in Silver Spring, Maryland, banned the use of DES during pregnancy in 1971. Between 1938 and 1971, five to ten million pregnant women and their fetuses were exposed to DES worldwide.

Between 1966 and 1969, prior to the publication of “Adenocarcinoma of the Vagina,” Arthur L. Herbst, a gynecologist at the Massachusetts General Hospital began treating young women showing signs of vaginal cancer. In 1969, Herbst and gynecologist Robert Scully published a study they had conducted on seven of those young women. In the study, Herbst and Scully discuss the rarity of vaginal cancer in women who had not yet gone through menopause. In follow-up appointments with those women and their mothers, Herbst noted that the mothers all reported taking DES during their pregnancies. Herbst communicated this link to Howard Ulfelder, the chief of gynecology at the Massachusetts General Hospital, who had reported similar findings. Herbst reports that he then spoke with David C. Poskanzer, epidemiologist and pediatric neurologist at Massachusetts General Hospital, about designing a study to test the hypothesis that DES exposure during development could be linked to the early development of vaginal cancer. Poskanzer, Herbst, and Ulfelder carried out the study and published their results in 1971 in “Adenocarcinoma of the Vagina.”

The three-page article starts with an abstract detailing the motivation for the study, the methods, and the results. After a short introduction about vaginal cancer, the authors detail the methods and results of their study. In the last section, the authors discuss the possible implications of their

study. Herbst and his colleagues start by categorizing the vaginal cancers observed in the seven patients from Herbst and Scully's original study, pointing to how rare it was to see vaginal cancer in women under the age of fifty. The young women Herbst and his team had examined showed signs of clear cell adenocarcinoma of the vagina, a rare tumor that forms in mucus-secreting glands in the cells lining the vagina. Such tumors are indicated by the presence of cells that appear clear under a microscope. The physicians at Massachusetts General Hospital had never recorded a case of vaginal cancer in a woman under the age of 50 until 1966. The tumors of the young women caused prolonged vaginal bleeding, which the physicians attributed to abnormal menstrual bleeding. The doctors examined the vaginal cells of the women that showed no abnormalities. Although when they viewed the cells under a microscope, they appeared clear with bulbous protruding nuclei (hobnail cells), a characteristic sign of adenocarcinoma. The seven young women had not been exposed uniformly to other factors that would cause early onset of adenocarcinoma. To determine the cause of adenocarcinoma in those women, the authors conducted a retrospective study by looking at events that had already occurred to identify factors that had caused the tumors.

In the methods section, Herbst and his team state that they worked under the hypothesis that maternal ingestion of DES was correlated with the development of adenocarcinoma in female children, a phenomenon that Herbst had clinically observed earlier at Massachusetts General Hospital. To test their hypothesis, the researchers needed to eliminate as many variables as possible. They conducted interviews to assess what factors could have caused the adenocarcinoma. The authors used the seven cases of early onset adenocarcinoma identified in the Herbst and Scully article as well as one identical case observed elsewhere. For each woman with adenocarcinoma in their study, they found four other women without adenocarcinoma who had been born at the same hospital within five days of the woman in the study. Herbst, Ulfelder, and Poskanzer, then interviewed the mothers of all women in the study, and they recorded facts about their pregnancies, namely the researchers were looking at what drugs those pregnant women had taken, whether they had experienced excessive bleeding, their ages during pregnancy, whether they had smoked during pregnancy, whether they had had prior miscarriages, whether they had breastfed, and whether they were exposed to x-rays during their pregnancies.

The researchers used statistical analyses to find correlations in their data. They found a significant association between pregnant women having taken DES and the development of vaginal cancer in their daughters. They found a lesser association between maternal bleeding during pregnancy or prior miscarriages and development of adenocarcinoma. The authors explain these findings as supporting evidence to their hypothesis because DES was often prescribed to women who experienced bleeding during pregnancy and had histories of miscarriages.

Although the correlation appeared strong, the authors note that the development of adenocarcinoma could also be linked to other factors. Of the eight women in the study group, five carried other female children to term during the same time period, and those children did not show signs of adenocarcinoma. But, among those women, only one mother had not taken DES during pregnancy. Further, physicians rarely saw the occurrence of adenocarcinoma in young women prior to the development and use of DES. The authors cite the example in which 675 patients of the Boston Lying-In Hospital in Boston, Massachusetts, were treated with DES. Looking at the hospital records, the authors claim that they found only one case of adenocarcinoma diagnosed in a young woman born between 1946 and 1951. Because of the conflicting data, the authors caution that the correlation they found between fetal DES exposure and later development of adenocarcinoma is not necessarily supported with evidence from other hospitals, and therefore it required further research.

In the discussion section, the authors briefly speculate on the effects of DES in utero. The women with adenocarcinoma also showed a higher occurrence of abnormal vaginal tissue (adenosis), which the researchers suggest could have been a preexisting condition. The authors hypothesize that DES may alter vaginal cells of the fetus in the womb, and that this alteration may not manifest until later in life. The authors predict more cases of adenocarcinoma in young women exposed to DES, but call for more patient data and experiments with DES on animals to determine the exact cause of such adenocarcinoma. The article ends with a statement that DES should not be administered to women during pregnancy.

The US Food and Drug Administration considered the results published in "Adenocarcinoma of the Vagina," and banned the use of DES in pregnant women. Researchers conducted further studies of adenocarcinoma in female children exposed to DES in the womb, and they confirmed the link that Herbst, Ulfelder, and Poskanzer found in their 1971 article. Later studies also found further reproductive, psychosexual, and immune abnormalities in male and female children of women who took DES during pregnancy, and higher rates of cancer in their children.

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