Diethylstilbestrol (DES) in the US

Diethylstilbestrol (DES) is an artificially created hormone first synthesized in the late 1930s. Doctors widely prescribed DES first to pregnant women to prevent miscarriages, and later as an emergency contraceptive pill and to treat breast cancer. However, in 1971, physicians showed a link between DES and vaginal cancer during puberty in the children of women who had taken DES while pregnant. Consequently, the US Food and Drug Administration (FDA) banned its use during pregnancy. In the late 2000s, several studies showed that the grandchildren of women who had consumed DES also suffered medical issues. By the early decades of the twenty-first century, roughly ten million people in the US had been exposed to DES, and three generations of individuals had suffered medical issues due to DES exposure. Researchers class DES as an endocrine disruptor, which affects the form and function of the hormone (endocrine) system.

In the early 1900s, scientists worked to isolate estrogen, a female sex hormone, and to produce it in the lab. Estrogen, or estrogen-like chemicals, stimulate the female reproductive system and the development of female sex characteristics like breasts and pubic hair. Scientists said that the production of a synthetic estrogen would enable them to treat hormonal problems caused by lack of estrogen, like various cancers and difficulty getting pregnant.

Sir Edward Charles Dodds specialized in biochemistry and worked at the University of Oxford in Oxford, England. His biographer and colleague, Francis Dickens, said that Dodds aimed to create artificial estrogen to simulate the effects of the natural hormone. In 1934, Dodds and colleagues synthesized the first artificial estrogen with a chemical base almost identical to that of the natural hormone. However, the compound was minimally effective and had to be administered to subjects through injection, making its widespread use unfeasible, because it required individuals to visit a physician for frequent injections.

In 1938, Dodds's lab, along with the lab of Robert Robinson at Oxford, synthesized a new synthetic estrogen, called stilbestrol, and soon called DES. DES acted three times more powerfully then natural estrogen and was effective when subjects took it orally. Researchers produced it as a lightweight powder, and many of the male workers in the lab developed breasts due to inhaling DES. DES cost about two dollars per gram to produce, rather than the three hundred dollars to produce natural estrogen. Furthermore, because DES was synthesized in a laboratory that was publically funded, the product could not be patented, further reducing its cost.

Several months after the synthesis of DES in 1938, Dodds published a paper showing that DES, when given to rats and rabbits, could prevent or end pregnancies, making it a viable birth control or emergency contraceptive pill. However, Dodds said that the human female reproductive cycle was too delicate to introduce foreign substances into it, and he denounced the use of DES to prevent or end pregnancies. Dodds stressed the possible cancerous effects of DES and other synthetic estrogens.

Even with early signs of problems that arose when women took DES, such as miscarriages, many people used the hormone to treat a variety of hormonal problems. In 1941, the US FDA, headquartered in Silver Spring, Maryland, approved DES as a treatment for menopausal symptoms, postpartum lactation suppression, gonorrheal vaginitis, and atrophic vaginitis. That same year, physicians Charles Huggins and Clarence V. Hodges at the University of Chicago in Chicago, Illinois, used DES to treat metastatic prostate cancer. Huggins won the Nobel Prize in Physiology or Medicine in 1966 for his use of hormones like DES to treat prostate cancer.

In 1949, scientists observed that pregnancy complications, like premature birth and fetal death

in the womb, correlated with low estrogen levels in the urine of pregnant women, indicating that women with a history of miscarriages could be treated with an estrogen mimic like DES to prevent those complications. Many used DES to treat what they deemed as excessive height in adolescent girls during the 1950s, and in 1960 researchers showed that DES helped treat breast cancer in postmenopausal women. Physicians around the world prescribed DES to millions of individuals.

However, the use of DES quickly became problematic, as Dodds had predicted. A 1953 study conducted by researchers at the University of Chicago in Chicago, Illinois, found that the use of DES during pregnancy did not prevent miscarriages. In 1970, researchers linked DES to the development of clear cell adenocarcinoma of the vagina in the daughters of those women who ingested DES while pregnant. Throughout 1971, researchers published more studies that linked DES to the development of irregularities in the glands of the daughters of DES users and, in November of 1971, the FDA banned the use of DES during pregnancy in the US. However, that year, a study reported that DES was an effective post-coital contraceptive, spurring the off-label use of DES as an emergency contraceptive pill on many college campuses.

In 1975, to prevent its off-label use, the FDA approved DES as a contraceptive in emergency situations such as rape and incest. Later that year, the FDA withdrew that approval. It removed the large dose prescriptions of DES from the market, and it required DES manufacturers to label both the DES container and the physician insert, an insert included with the drug that tells physicians what the drug can be prescribed for, with a statement prohibiting the use of DES as an emergency contraceptive. However, during the 1970s, researchers created a non-estrogen emergency contraceptive that largely replaced DES prior to the FDA's actions.

By the late 1970s, the FDA approved DES in the US only to treat postmenopausal breast cancer, post-partum lactation repression, and metastatic prostate cancer. In 1977, the FDA approved a new drug, tamoxifen, to treat breast cancer, which produced better results than DES. Tamoxifen had fewer side effects, and it replaced DES. In 1978, the FDA banned the use of DES for post-partum lactation suppression. Later, in 1985, a new drug, GnRH agonist leuprolide, which mimicked DES, replaced DES as a treatment for prostate cancer. Finally, in 1985, the FDA listed DES as a known carcinogen.

Between 1938 and 1971, an estimated four million women in the United States took DES while pregnant. DES affected women who took DES while pregnant, the daughters and sons exposed to DES prenatally, and the children of those daughters and sons. But for many years, researchers could little explain the long-term effects of DES, either on those who had ingested DES or on those exposed to DES as fetuses of pregnant women who had taken DES.

One effect seen in women who took DES while pregnant is a higher risk for breast cancer. In 1978, research indicated a link between those women who took DES during pregnancy and breast cancer. However, subsequent studies found no increase in breast cancer rates in DES mothers. Over the next twenty years, researchers published studies both supporting and refuting the link between DES ingestion and breast cancer. In 2001, researchers found a modest association between breast cancer and DES mothers.

Researchers found that DES seems to cause more adverse effects in daughters exposed to DES prenatally than in daughters not exposed to DES prenatally. Daughters exposed to DES as fetuses had an increased risk for certain cancers of the vagina, cervix, and breasts. The first effects of DES on female offspring were documented in 1970, when Arthur L. Herbst and Robert E. Scully at the Vincent Memorial Hospital in Boston, Massachusetts, found a link between prenatal exposure to DES and the development of clear cell adenocarcinoma of the vagina and cervix in the daughters of women who had taken DES. Vaginal clear cell adenocarcinoma is a cancer that causes lesions in the vagina and cervix, and the cells of those lesions the cells look clear under a microscope. Usually, that kind of cancer develops in postmenopausal women, but in DES daughters, the cancer begins during puberty and into the early twenties, though some cases manifest in women in their thirties and forties. Researchers said that one in every thousand DES daughters will develop clear cell adenocarcinoma of the vagina. As of 2014, studies also showed an increased risk of breast cancer in DES daughters.

Within the reproductive tract of DES daughters, several structural abnormalities are common, and

those abnormalities often make pregnancy more difficult than normal, both in terms of getting pregnant, and in carrying a pregnancy to term. A quarter of DES daughters are infertile, which is often due to abnormal reproductive tracts. Approximately one third of DES daughters have cervical abnormalities and vaginal adenosis, an abnormal tissue found on the surface of the vagina. A T-shaped uterus is also common in DES daughters, where the uterine cavity is shaped like a T, as opposed to a pear-like shape. This structural difference causes two thirds of the infertility seen in DES daughters. DES daughters also have higher than normal rates of miscarriages, premature births, and ectopic pregnancies, pregnancies where the embryo implants outside the uterus.

Compared to DES daughters, researchers found fewer health effects in males exposed prenatally to DES, though some health effects do exist. DES sons have an increased rate of epididymal cysts (lumps on the epidydimus) compared to the general population. Scientists also indicated that other genital abnormalities, like the underdevelopment of the testes (testicular hypoplasia), the absence of one or both testes (cryptorchidism), and a penis under two inches in length (microphallus), may link with DES exposure. However, in animal studies, older subjects showed more of the effects of prenatal exposure to DES in males, leading many researchers to claim that testicular and other cancers will become more prevalent as DES sons age. The fertility of DES sons is normal.

Research about DES in animals showed that DES can cross the placenta and enter the fetal blood stream, where it accumulates in the reproductive tract of fetuses. DES can then affect the chromosomes of the cells that it comes into contact with, causing aberrations, which later cause the medical conditions seen in DES daughters and sons.

The medical conditions caused by DES spurred many lawsuits, including 1980's Sindell v. Abbott Laboratories, a California Supreme Court case. In Sindell, two DES daughters, Judith Sindell and Maureen Rogers, sued a group of DES manufacturers and alleged that their mothers' ingestion of DES caused injuries to Sindell and Rogers. They could not specify a manufacturer due to the amount of time that had passed between when their mothers ingested DES and the appearance of symptoms in Sindell and Rogers. Furthermore, their mothers had used of a generic brand. The women won their case against the drug manufacturers when the court established the precedent of market share liability, for which an entire market is responsible for a share of a settlement when the individual manufacturer cannot be identified.

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