

# DES timeline

The story of DES began in 1938, when British physician and chemist Charles Dodds and his team of scientists synthesized DES from a coal-tar derivative. DES, the first synthetic oral form of estrogen, mimicked the effect of natural estrogen. There was enormous excitement around unlocking the secret of hormones, and DES was considered a great discovery. Until then, estrogen was extracted from animal urine, a painstaking process. In contrast, DES could be made cheaply and manufactured as pills or tablets.

Dodds advocated DES solely for menopausal symptoms. But, by the early 1940s Harvard Medical School obstetricians George and Olive Smith were extolling the merits of DES for use during pregnancy-in the mistaken belief that higher estrogen levels could prevent miscarriage. Medical students further spread the word about DES, and pharmaceutical sales reps boosted its sales. The popularity of DES spread to Canada, Europe, Australia, and beyond.

DES was so popular it became a wonder drug-widely prescribed to prevent miscarriage, given as "vitamins," and prescribed, "just in case," to make stronger, healthier babies. DES was used to treat over 100 conditions. It was fed to livestock as a growth stimulator, then showed up in hamburger, veal, and chicken. It was prescribed to suppress lactation after childbirth, distributed by college clinics as the morning-after pill, given to tall teenage girls to stunt height, and to transsexuals to prepare for sex change. It was used for treatment of acne, gynecological disorders, breast cancer, and prostate cancer. DES was used so broadly, it begs the question: How many of us are DES-exposed?

In the early 1970s, doctors in Boston identified a rare, sometimes fatal, vaginal cancer in teenage girls. The cancer had never been seen in women so young. The common denominator was the DES prescribed to the girls' mothers during pregnancy. The implications were terrifying. Millions of young people might experience disease, after an unknown period of time, from exposure before birth to a carcinogenic prescription drug. The media billed DES "The Time Bomb Drug." As doctors began seeing exposed daughters and sons, they discovered that DES also causes a wide range of reproductive tract injuries.

Since then, over 1500 papers have been published about the effects of DES. Researchers have found increased incidence of breast cancer in mothers; increased cancer, pregnancy problems, infertility, and autoimmune disorders in daughters; and urogenital anomalies in sons. Yet, no one knows the full story of DES. Fortunately, collaborative efforts are resulting in continued research and education programs. These initiatives will contribute to public knowledge about the lifelong effects of DES exposure.

## 1930s

**1938**-British physician and chemist Charles Dodds discovers DES.

■DES is the first synthetic oral estrogen and more powerful than estrogen occurring in the body. It causes such a sensation that over 200 scientific papers are published about it in the three years following its synthesis. DES is registered for sale in the U.S. and several European countries.

**1939**-Researchers at Northwestern University discover that offspring of DES-exposed rats develop uterine defects. Researchers at Johns Hopkins University report that mice injected with DES develop breast cancer.

## 1940's

**1941**-FDA approves DES for suppression of lactation and relief of menopausal symptoms.

**1941-1947**-Harvard Medical School obstetricians George and Olive Smith advocate the use of DES to prevent miscarriages and enhance pregnancies. No tests are run on pregnant animals. No tests are done on an unexposed, comparison group of women.

**1947**- FDA approves DES for use during pregnancy. DES is inexpensive to produce and profitable. It is never patented, so any manufacturer can make and bottle DES. DES use spreads.

**1947**- *USA Dispensatory*; a pharmacology encyclopedia, states, in reference to DES, "To date no national catastrophe has been recognized, but it is perhaps too early for any deleterious effect on the incidence of carcinoma of the female reproductive tract or breast to appear."

**1947-1971**-DES becomes a wonder drug. It is prescribed to an estimated 5 million pregnant U.S. women and hundreds of thousands more throughout the world. DES is used in some European countries until the mid '80s.

■ A popular DES regimen of 125 mg per day, recommended in the *PDR*, is the estrogenic equivalent of 700 birth control pills per day. Some women are given as much as 250 mg of DES per day.

## 1950's

■ 250 drug companies will eventually manufacture and market DES under 325 names. A brochure for pharmaceutical sales reps reads, "Deal yourself in . . . Play a winning hand. . . Diethylstilbestrol. . . Turn on the stream-and discover how good business really is."

**1953**-Dieckmann study at the University of Chicago concludes that DES "has no beneficial effect whatsoever on the prevention of miscarriage." Approximately 800 pregnant women are given DES and 800 pregnant women are given a placebo. The women who took DES have more miscarriages and lower-weight babies.

**1954**-Livestock industry begins to use DES in animal feed to fatten veal, chickens, and cattle. By 1957, an estimated three out of every four hamburgers, steaks, and roasts on American dinner tables comes from livestock given DES-laced feed.

**1959**-Mink livestock are stripped of fur and rendered sterile after eating chickens with DES neck pellets. Mink farmers sue the federal government.

**1959**-DES is banned in chickens and lambs but not in pregnant women.

## 1960's

**1962**-FDA declares DES ineffective for pregnancy.

■ DES becomes the contraceptive "morning-after pill," distributed in college clinics throughout the U.S. Many young women prescribed the five-day regimen have already been exposed to DES in utero.

■ DES is prescribed to tall teenage girls in Australia to stunt growth.

**1964**-Charles Dodds is knighted by the Queen of England for his pivotal role in medical research.

## 1970's

**1971**-Alarming occurrence of vaginal cancer cases in young women, ages 14-22, puts the medical community on alert. The rare cancer had not been seen in women so young. Clear cell cancer of the vagina or cervix can spread to the lungs, liver, and bone. Despite radical treatment removing the vagina, uterus, and other reproductive organs, some of the girls do not survive.

■ *New England Journal of Medicine* publishes seminal report establishing link between DES and clear cell cancer in daughters of women prescribed DES. (Herbst, et al.)

■ Surgeon General warns against DES use during pregnancy, but DES is not banned.

■ Physician Arthur Herbst establishes Registry for Research on Hormonal Carcinogenesis, an international record of clear cell cancer cases. DES daughters have a one in 1000 chance of developing clear cell cancer of the vagina or cervix. They are at least 100 times at greater risk for developing the cancer compared to a young woman not exposed to DES.

■ DES explodes into national view. Newspapers call DES The Time Bomb Drug. *Wall Street Journal* headline reads Stalking a Killer: How Cancer in Women Was Linked to a Drug Their Mothers Took.

■ Controversy surfaces as physicians, researchers, and pharmaceutical industry question validity of evidence linking DES to cancer and reproductive tract injuries.

■ DES earns notoriety as the first transplacental carcinogen. First proof that an estrogen can cause cancer; first proof that an estrogen can cause reproductive anomalies; and evidence of a prenatal chemical exposure with a decades-long latency.

■ DES is used for dozens of treatments over the next decades, including: hormone replacement treatment, lactation suppressant, breast and prostate cancer treatment, morning-after pill, treatment of acne and gynecological disorders, for transsexuals preparing for sex change, to stunt or increase height in teenage girls and boys, and as growth stimulator in livestock.

**1974**-*Wall Street Journal* article reports 11,000 U.S. prescriptions were written for DES in 1974 "to guard against miscarriage" despite 1971 FDA warning

**1975**-National Cancer Institute funds the DES- Adenosis study, to follow medical conditions in DES daughters, at five major medical centers in the U.S.

**1975**-Scientists are able to cause developmental abnormalities in male mice exposed to DES in utero, suggesting laboratory studies may be a predictor of DES effects in humans. A 1980 study in female mice shows similar results. (McLachlan)

**1975**-Dutch doctors are warned not to prescribe DES during pregnancy, after an estimated 440,000 are exposed. DES prescriptions stop in France in 1977 after an estimated 150,000-450,000 are exposed. DES is prescribed to pregnant women in Spain until 1980, Italy until 1981, Hungary until 1983. Worldwide, DES was prescribed most extensively in the U.S., France, The Netherlands, Canada, and Australia. Dozens of other countries show record of DES use; estimates of use are based on pharmaceutical sales records, physicians' recall, and number of registered cases of clear cell cancer.

**1976**-Study of DES sons shows 4x greater prevalence of epididymal cysts and hypoplastic testes in exposed men, and more semen disorders. (Gill) A 1984 study on DES sons finds no significant differences between exposed and unexposed men. (Leary, et al.) A 1995 study shows increased genital problems in DES sons. (Wilcox)

**1978**-Study reports abnormalities in size and shape of uterus in DES daughters, causing pregnancy loss. Daughters with lower reproductive tract structural abnormalities are more likely to have upper genital tract changes. (Kaufman)

**1978**-DES Action, a national educational organization for DES-exposed people, is founded.

**1978**-National Cancer Institute publishes a report on DES after a federal task force investigates DES injuries. Surgeon General sends letter to over 400,000 U.S. physicians to recommend notification of patients if they were prescribed DES. No national registry, or program to notify people of exposure, is established.

## 1980's

**1988**-A study on autoimmune impairment among DES-exposed people shows higher risk for autoimmune diseases. (Noller, et al.)

**1988**-A study shows 33% infertility in exposed daughters compared to 14% in unexposed. (Senekjian)

**1989**-European DES Cancer Network is founded.

## 1990's

■An estimated 50% of exposed individuals remain unaware of their DES exposure. Researchers continue to find evidence of reproductive anomalies, cancers, possible autoimmune disorders, and possible skeletal changes in DES-exposed offspring. Recurrences of clear cell cancer in DES daughters raise concerns. New cases of clear cell cancer are reported in DES daughters in their '40s.

■DES attracts more media interest. Headlines read: Adult Years Bring New Afflictions for DES "Babies" (*New York Times*); You Could Be One of an Estimated 75,000 British DES Daughters (*London Times*); Diagnosis Meant Fear, Humiliation (*USA Today*); DES Twin Sold in Mexico (*Denver Post*); Banned Drug DES Could Haunt Children of Mothers Who Took It (*Corpus Christi Times*); Suit Filed for DES Daughters (*Cleveland Plain Dealer*); The Shocking Story of DES Sons (McCall's); A Private Pain and a Public Healing (*Los Angeles Times*); Manufacturers Criminally Accountable (*USA Today*); DES Nightmare for Millions (*Gannett Times Union*); DES Daughters and Children (*Washington Post*); Mother and Child (*New York Times*).

**1991**-DES consumer groups launch national campaign to revive flagging DES research and gain support on Capitol Hill.

**1991**-European Commission survey reports that DES was prescribed to pregnant women in Ireland, UK, Denmark, The Netherlands, Germany, Belgium, France, Spain, Portugal, Italy, Norway, Finland, Austria, Switzerland, Hungary, and Czechoslovakia. Personal correspondence cites DES use in Poland, USSR, and China. Other reports cite DES use in New Zealand, Mexico, Brazil, Peru, Costa Rica, Kenya, Rwanda, Uganda, Zaire, India, Asia.

**1991**-Study reports eating disorders and weight loss in DES daughters at 4x higher rate compared to unexposed women. (Gustavson)

**1992**-A research review shows DES daughters are more likely than unexposed women to have ectopic pregnancy (9x), miscarriage (2x), and premature delivery (5x). The risk for a DES daughter's pregnancy to not make it to full term is 3x greater than for an unexposed woman, and 5x greater if she has a genital tract abnormality. (Swan)

**1992**-Congresswoman Louise Slaughter and Senator Tom Harkin introduce the DES Education and Research Amendment, the first federal legislation for DES research.

**1992**-NCI convenes the first scientific conference on DES: Long Term Effects of Exposure to Diethylstilbestrol. Advocates, researchers, clinicians, and policy makers set a new model of multidisciplinary collaboration. Research recommendations are made in epidemiology, basic science, clear cell cancer, pregnancy outcomes, and education outreach.

**1992**-The *Los Angeles Times* quotes a pharmaceutical company spokesperson: "Eli Lilly & Co. believes that it acted responsibly in the development and marketing of DES, and we will continue to vigorously defend that position."

**1992**-DES legislation is passed. President Bush signs the DES Education and Research Amendment into law. NCI establishes the DES Combined Cohort Studies (DCCS) to update existing cohorts and investigate long-term health in the DES-exposed.

**1993**-A study of DES mothers confirms a 30% increased incidence in breast cancer, compared to unexposed women. (Colton)

**1994**-NIEHS holds Estrogens and Environment III conference. Conference concludes that the reproductive injuries found in wildlife and laboratory animals parallel those seen in DES-exposed humans, suggesting that chemicals in the environment may mimic estrogens and harm the reproductive system of second-generation offspring.

**1994**-less than 50% of 3600 respondents to a California health survey have ever heard of DES. (Wingard)

**1995**-NCI renews five-year contract for the largest investigation of long-term health of DES-exposed daughters, mothers, and sons.

**1995**-Study on DES sons reports three times greater prevalence of urogenital abnormalities, but no decrease in fertility or impairment of sexual functioning. (Wilcox)

**1995**-DES education study reports that 91% of surveyed physicians know DES increases risk for clear cell cancer, but that only 39% know DES increases incidence of ectopic pregnancies in DES daughters. (Wingard)

**1995**-DES Third Generation Network is formed.

**1998**-Cancer biologists question whether DES affects gene regulation and expression, or if DES may disrupt cells' DNA and cause genetic change. (Sassoon)

**1998**-NCI study of DES daughters finds no increased risk for any cancers, other than clear cell cancer, although there is a suggestion of a possible increase in breast cancer risk among DES daughters over age 40. (Hatch)

**1998**-A federal project acts to evaluate 62,000 chemicals beyond their carcinogenicity to include potential for hormonal activity. The new direction is driven in part by the lessons of DES.

**1998**-DES advocates win renewed federal legislation. President Clinton signs the DES Reauthorization bill and Congress establishes the first national DES education program, to be carried out by the CDC.

**1999**-NCI holds second scientific conference on DES research: Current Knowledge, Future Direction. Recommendations are made for basic research, clinical/epidemiological research, and education and outreach.

■Reports on preliminary findings include a Belgian study citing evidence of DES in the bones of DES-exposed people over age 50, and a NY ophthalmologist suggesting a link between DES exposure and nearsightedness. Researchers stress the need for further research.

**1999**-Arthur Herbst emphasizes there is no age limit for the development of clear cell cancer. DES daughters should be monitored past age 40.

**1999**-U.S. meat shipment is seized by Swiss authorities after tests show traces of DES.

## **2000's**

**2000**-USDA begins testing U.S. beef for DES, for the first time since 1991.

**2000**-Estrogen, used in menopausal treatments and birth control pills, is rated a cancer-causing substance by the U.S. National Toxicology Program.

**2000**-NCI study confirms increased incidence of ectopic pregnancy, premature delivery, and miscarriage in DES daughters. (Kaufman, et al.)

**2000**-NCI study finds DES daughters are two times more likely to suffer infertility than unexposed women. (Palmer, Hatch, et al.)

■A Dutch study reports a 3x-5x increase in cervical cancer among DES daughters, compared to unexposed women. (Verloop, et al.)

■Increased incidence of reproductive tract tumors with no reduced fertility is found in male descendants of mice given to DES (grandson mice). A parallel study two years earlier on granddaughter mice showed similar results. Investigator concludes that in mice, "Increased susceptibility for tumors is transmitted from the DES 'grandmothers' to subsequent generations." (Newbold, et al.)

**2000**-NCI renews five-year contract for DES research on long-term health effects.

**2001**-NCI study confirms earlier findings of an increased risk of breast cancer in DES mothers. (Titus-Ernstoff)

**2001**-DES consumer organizations mark the 30th-year anniversary of the link between in utero DES exposure and clear cell cancer.

**2001**-CDC launches the first national public education campaign to educate public and physicians about DES.

## **Today**

■DES products are no longer on the market in the US. In some countries DES is still used as a treatment for prostate cancer. In others, it is found in vaginal creams and may still be bought over the counter for use during pregnancy.

- Clear cell cancer cases in DES-exposed women continue to be reported to the clear cell cancer registry at the University of Chicago.
- DES-exposed people show resiliency in coping with DES legacy, despite continuing health problems, reproductive dysfunctions, and concerns about the future.
- DES consumer organizations, led by DES mothers, daughters, and sons, influence public health education and social policy.
- Many people, worldwide, remain unaware of their prenatal exposure to DES; others are just learning of their exposure to DES.
- Urgent need remains for long-term investigation of health of DES daughters, sons, mothers, and grandchildren.
- DES-exposed people and DES consumer groups continue to advocate for public education and the promise of lifelong follow-up research.
- With continued efforts by DES advocates, educators, and policy makers, a new wave of studies will provide information on long-term health of the DES exposed, and offer an important scientific model about hormone action.