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THE TICKING TIME BOMB: DIETHYLSTILBESTROL

WARSH, CHERYL
HISTORY DEPARTMENT
VANCOUVER ISLAND UNIVERSITY
NANAIMO, BRITISH COLUMBIA
CANADA

Dr. Cheryl Warsh
History Department
Vancouver Island University
Nanaimo, British Columbia
Canada

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Synopsis:

1940s researchers claimed artificial hormones (e.g.diethylstilbestrol) combatted pregnancy's ills, including morning sickness, diabetes and miscarriage, and they were widely prescribed. 1950s research disproved those claims, but exposed thousands of infants to congenital malformations. While child research then was avoided, the problem of 'orphan drugs' remained. FDA needed to balance risks of child drug research with reality of widespread use of medications on children without prior testing.

The Ticking Time Bomb: Diethylstilbestrol

Riddle #1: what does a synthetic hormone have to do with mink coats?

Riddle #2: how did a taste for chicken necks lead to a need for male brassieres?

(Read below for the answers)

In the 1970s, Dr. Frances Oldham Kelsey and her Bureau of Drugs co-workers at the Food and Drug Administration, along with colleagues at the National Cancer Institute and other federal agencies, navigated around politicians, medical researchers, university administrators, litigators, advocacy groups and agricultural lobbies to provide protection and redress for women and their children. What was remarkable about the Diethylstilbestrol [DES] tragedy was that it was a case of good science gone wrong. A 1940s research team were so optimistic about the hormone's prospects, they recommended it become as common a part of the prenatal experience as pickles and ice cream. A 1950s researcher mounted an excellent study to disprove the original claims, yet was so reckless about dosages that the study subjects were ground zero for the cases of birth defects which manifested themselves almost two decades later.

DES, a non-steroidal compound with estrogenic activity, had been synthesized in the 1930s by the English pharmaceutical firm, E. C. Dodds and Associates. Inexpensive, easy to prepare, and available in pill form, it was a popular estrogen replacement for post-menopausal women. University of Chicago researcher Dr. Charles Huggins won a Nobel Prize with his discovery of DES's efficacy in the treatment of prostate cancer. DES was also used in the meat industries; it caponized (castrated) chickens, tenderizing the meat, and fattened beef animals. Kelsey noted that its use for caponizing chickens virtually wiped out the mink industry. When

the furry creatures were fed chicken parts containing residues from DES capsules, they were rendered sterile.[1] In the 1940s, a wife-and-husband research team, biochemist Olive Watkins Smith and gynecologist George van Seclin Smith, of Boston's Free Hospital for Women, advocated the use of DES in cases of gestational diabetes, risk of miscarriage, and other prenatal complications.[2] So enthusiastic were they about the powers of DES, in 1946 they recommended that "increasing amounts of diethylstilbestrol should be administered to all women during pregnancy to prevent or decrease the hazards of the late complications of pregnancy for mothers and babies."[3] This sweeping claim was based upon the supposition that complications were the result of a deficiency of progesterone and other steroids in the placenta. DES was widely used in the 1940s and 1950s, and to a lesser extent in the 1960s and 1970s. It was estimated that at least 20,000 individuals were exposed in utero to DES every year it was available, that is, over approximately 25-30 years, 500,000 Americans were exposed to the drug. This was a conservative estimate; others reached as high as several millions.[4]

Despite these high numbers, the Smiths' blanket claim was controversial and other researchers undertook studies to prove the Smiths' findings. The largest study was undertaken by University of Chicago researcher William Dieckmann, sponsored by an NIH research grant. Dieckmann criticized the Smiths' research due to lack of adequate controls, since patients given trial medication "inevitably receive more meticulous study and medical care than other patients."[5] He resolved this structural flaw by including in his project every woman who registered at the Chicago Lying-in Hospital's prenatal clinic, who were estimated to be 6-20 weeks pregnant, within a 1951-1952 period.[6] These included healthy women as well as those with chronic high blood pressure, diabetes mellitus or repeated miscarriages. The women had come to the clinic for state-of-the-art prenatal care to ensure the best possible outcomes for their

pregnancies. The total sample was about 1,600 women (as well as their babies), half of whom were given diethylstilbestrol and half placebos. Upon registering, each patient was offered a box of tablets "without charge." If she stayed on the programme, the doses ranged from 5 milligrams to a maximum dose of 15 milligram tablets during later pregnancy. To avoid cheating and subterfuge (at least on the part of the mothers), the tablets were coated with a red dye that was excreted in urine. If the mother's routine urine tests were clear, it was evident she was not taking the tablets as promised and she would be removed from the study. To avoid any biases, the patients' identities, as well as that of the tablets, were carefully coded and the code held by a lab technician. At check-in, each expectant mother was informed that there was medical evidence that the tablets helped to prevent some complications of pregnancy, and that "they would cause no harm to her or the fetus. No coercion was used but she was asked to return the tablets if she did not wish to cooperate. No special clinics or procedures were instituted."[7] There were just nurses and physicians in crisp white lab coats at a world-class institution offering possible wonder drugs, free of charge, to nervous expectant mothers. No coercion indeed. Dieckmann's team did not find significant variations in the incidence of pregnancy complications of the DES sample and the control group, although they did not consider DES to be particularly harmful to the pregnant women or their foetuses.

Nevertheless, once this study was published, DES use began to lose favour in the obstetrical community, although perhaps not soon enough. In his 1958 presentation to the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Dr. E. D. Colvin of Emory University concluded that the general acceptance "of the prophylactic value of hormone and vitamin therapy in threatened or habitual abortion are apparently unwarranted."[8] Colvin's paper had the unfortunate title, "Salvage Possibilities in Threatened Abortion," as if a

pregnant woman could be equated with a rusty freighter – a revealing choice of words given the extent of chemicals blithely prescribed to and ingested by parturient women in the middle third of the 20th century. However, as distinguished paediatric surgeon Helen Taussig would later warn young women, the fault was not always that of the attending physician. In his comment upon Colvin's paper, Los Angeles Dr. Bernard Hanley approved of the former's treatment of bed rest and sedation, which was "exactly what most of us would like to prescribe for our patients, but few of us have the courage to do so for fear of criticism by other physicians or by the patient and her relatives and friends … However, the patients should not be hoodwinked into believing that the giving of expensive injections, vitamins or other medications will surely lead to full-term delivery of a normal infant." Yet Hanley also was following the fashion, or more likely the market, when he stated that "at the present time the giving of estrogen in the form of diethylstilbestrol seems to be the most popular method of treatment. During the past two years I have run a fairly large series of these cases in which doses of 15 milligrams to 100 milligrams stilbestrol daily have been given" - and this was by a skeptic.[9]

Anomalies soon appeared. In 1966, the Mayo Clinic's Dr. Kenneth Fawcett reported 14 cases of clear-cell cervical adenocarcinoma, previously a very rare form of cancer, of which 5 sufferers were under age fifteen. At this point, no connection was made with possible maternal risk factors. In 1970, Dr. Arthur Herbst and team described an unusual cluster of this adenocarcinoma at Massachusetts General Hospital, and patient interviews revealed that all of their mothers had taken DES during pregnancy.[10] Prior to determining possible actions, such as changing the labelling and distribution of DES, FDA needed follow-up studies completed to track additional cases of injury arising from the drug's use. Because Kelsey recalled the Dieckmann study, she was "roped in" as Project Officer for two proposed contracts: at the

original University of Chicago site, and at the Mayo Clinic, which maintained excellent patient records and had a standing agreement with FDA to do such follow-ups.[11]

In March 1972, Kelsey contacted University of Chicago pathologist Dr. Robert Wissler to initiate the research, and was directed to Dr. Frederick Zuspan, chair of the department of obstetrics at the Pritzker School of Medicine. They were "most receptive" for FDA assistance, having discussed pursuing a follow-up study for some months. Kelsey found Zuspan to be "very enthusiastic" and developed a good working relationship with him.[12] The Chicago team wanted a full-time nurse or social worker to search the records and do the telephoning, and hoped to use the FDA field resources for follow-ups.[13] When the wheels of FDA bureaucracy rattled along too slowly for Chicago's administration however, Zuspan and his team found funding elsewhere, but shared their findings promptly with Kelsey and the Bureau of Drugs.[14]

The first task was to find the 1,661 computer punch cards which supposedly were the case records of the 1950s trials. During the summer, Fred Zuspan hired his college-aged daughter and her friend to root through the long-deceased Dr. Dieckmann's dusty filing cabinets, and the girls did find the punch cards, but the only notes were that the patients had taken drug A or drug B. There was no identification of which was the stilbestrol and which the placebo. A visit to Russell Pottinger, the retired laboratory technician who had recorded the information was in order, and Zuspan and company located him at his northern Illinois farm.[15] Pottinger recalled the study well, and the fact that there was an even-odd separation of trial subjects, but "which was which escaped him."[16] Pottinger did, however, think he had some of the original drugs. He had intended to give the leftover stilbestrol to his chickens, creating some tender caponettes. A few days later he dropped by the Chicago laboratory with the drugs still in their original packaging. When they were analyzed, one batch turned out to be diethylstilbestrol, while the

other was inert. The researchers tried to match the punch cards to the birth records, but there were no dates on the cards. Finally, after matching even study numbers, female babies and medical charts in the hospital archives, they found that some noted stilbestrol administration, while none were recorded in a sampling of odd numbered charts. Fred Zuspan had cracked the code.[17] Zuspan then contacted eighty of the original subjects. One of those patients happened to be at a cocktail party and mentioned the Chicago letter in the presence of a reporter. The subsequent publicity led to Zuspan receiving over 400 nervous phone calls and contacts from women who had been administered DES at the Chicago Lying-in Hospital or elsewhere.[18] The follow-up study determined that not only were 1,719 foetuses exposed to DES, but 384 of these were also exposed to progesterone. An additional 436 pregnant women were administered progestin from 1940 to 1970.[19] Along with cases of clear-cell adenocarcinoma, Zuspan's study found that the mothers who were given stilbestrol were at a higher risk of breast cancer than the general population, and that early age of first pregnancy, which had been thought to be protective for breast cancer, was not protective for DES exposed women.[20] DES was harming not only the babies but the mothers as well.

In April 1972, Kelsey contacted Dr. Robert Miller at NIH, asking about the possible relationship of DES and cancer in offspring. He had just written an editorial for the *Journal of the National Cancer Institute*, stating that the association of high doses of the hormone to cancer was "pretty clear," and that puberty might be the predisposing factor, but he did not think DES to be hazardous at other times. He did, however, have reservations about high doses of DES being used as a morning-after pill.[21] In May 1972, Herbst was awarded a $91,000 one-year contract to perform a follow-up study of 350 young women and men whose mothers had taken stilbestrol 20 years earlier.[22] The cases were piling up, and the prospect of litigation got FDA's legal

department involved. In June 1972, Bureau of Drugs Director Henry Simmons wrote to General Counsel Peter Barton Mott regarding a newspaper article linking DES to over 70 cases of vaginal cancer. Simmons noted that Herbst's findings, as well as the reported cases of Dr. Peter Greenwald, provided a "statistical inference" that DES produced vaginal cancer in some offspring, but that a "cause/effect relationship has not been established." Simmons added that several studies were underway to assess the quantitative risk of DES, including an FDA sponsored study at the Chicago Lying-in Hospital as well as a feasibility study to help determine the risk. They had asked Herbst for his findings to date, so that they could use them in the evaluation. FDA also wrote to the governments of Sweden, Great Britain, Australia and Canada for information regarding any linked cases in those countries. At that point, however, Simmons said that FDA was "not prepared to issue further warnings and/or recommendations to the practicing physician."[23] However, they did establish a task force comprising NIH, National Cancer Institute and FDA officials.

In July, the DES Task Force needed Kelsey's team to provide evidence regarding the following questions: should DES be marketed at all? If so, should it be restricted to certain populations? If unrestricted, should the labelling be changed? Does DES have any post-coital use? The FDA's Obstetrics/Gynaecology Advisory Committee had a variety of opinions. Five members believed that DES should remain on the market, although two of these members recommended some revisions on the label. The sixth member believed the product should be removed from market. A few days later, the DES Task Force was surveyed with the same questions, and their responses also were mixed, ranging from use restricted to postmenopausal and cancer indications and removal from the market. The inconsistencies were due to insufficient data at that time. Kelsey laid out her department's position regarding the safety of DES to the

Task force, in a survey of the pharmacological and clinical studies. She stated that it was "reasonable" to conclude the existence of a "causal relationship" between the administering of DES to a pregnant woman and vaginal cancer in the offspring. Pharmacological studies supported the association of DES and reproductive abnormalities. For instance, a 1972 Emory University study demonstrated that when sixteen adult squirrel monkeys had DES implanted subcutaneously, 30 percent experienced the formation of polyovular follicles, many of which contained up to nine oocytes. Some developed greatly enlarged labia and uteri and thickened vaginal mucosa.[24] Almost ten years earlier, Drs. Thelma Dunn and A.W. Green determined that stilbestrol induced vaginal cancer and cancer of the uterine cervix in female mice, and multiple cysts of the epididymis in male mice.[25]

Furthermore, Kelsey noted that even though estrogens had been used for thirty years for uterine bleeding in pregnancy, many researchers still were in doubt regarding its efficacy. Of those female children who had been born subsequent to their mothers' bleeding episodes, for which no estrogen had been administered, very few cases of carcinoma had been reported similar to that associated with the use of DES. Therefore, the administration of DES in these pregnancies was both unsafe and ineffective. However, she added, the science did not justify a total ban of DES. It had been an inexpensive therapy in "reasonably high doses" for the treatment of prostate cancer, although there was some association of early death from cardiovascular disease. A "reasonably high degree of risk" also was tolerated for prostate cancer sufferers, as well as post-menopausal women, who were prescribed the estrogen to lessen menopausal symptoms. DES also was used as a hormone replacement for younger women who had hysterectomies. Kelsey did not find cancer reports among these cohorts to be convincing, and added that there was no evidence that natural estrogens would be any less carcinogenic to the foetus than DES.

Therefore, she concluded, it would be "hard to justify" the banning of the use of DES in the above three categories without assurances that any substitute would be safer. She noted, however, that there was "no justification" for continuing studies of high doses of DES as a "morning-after" pill.[26]

The Task Force's opinions also reflected the public and political scrutiny surrounding DES. Dr. Charles Anello, for instance, advocated removal of the drug immediately: "if the findings of Dr. Herbst are confirmed, we most certainly will not have acted prematurely. On the other hand if the findings of Dr. Herbst are spurious … the product can be returned to the marketplace. Action to take the product off the market can only be applauded as a strong gesture of consumer protection."[27] The growing public outrage about the hidden health risks of clinical trials led to the introduction of legislation by Senator Hubert Humphrey on September 5, 1972, to establish a national Human Experimentation Standards Board as an amendment to the National Research Act.[28] In his speech, Humphrey cited the "barbaric" Tuskegee syphilis study, the controversial early parole of Nathan Leopold because of his involvement in the anti-malarial studies, and the Dieckmann DES research, as he superbly advocated for the need for true consent:

> Consent is often granted under duress, as in cases where a family member is critically ill, and permission is given to try anything. In general, however, it is not clear that where consent is granted, most people know what they have consented to. In fact, the reverse appears to be true… What are the people who have been the subjects of medical experiments? ... The powerless, the poor, the least educated, and members of minority groups are the likeliest human subjects… Those who are confined, and for whom the experiment at least appears to be a way out of confinement, volunteer their bodies … It is

> those who cannot understand what is being done to them that constitute by far the largest numbers among human experimentation subjects. Children, the institutionalized and even mentally retarded, they too are the subjects of human experimentation.[29]

In February 1973, Kelsey made a site visit to the Mayo Clinic in Rochester, Minnesota, where the FDA-sponsored follow-up study was under way. Their comments revealed the uncertainty of current knowledge about DES and the range of therapeutic responses. Epidemiologist Dr. Anne Lanier reported that they had identified 1,722 pregnant women who had attended the clinic between 1943 and 1959, and who had received estrogen in doses ranging from 10-14 milligrams, which was on the conservative side of therapies. Of the traced offspring, 432 girls living in the Rochester area were urged by letter to have a physical examination, and 269 were examined. No clear cell adenocarcinomas were detected, but 26 cases of vaginal ectopy, or patches of adenosis in the vagina, were discovered. Mayo Drs. Decker and Fry did not consider the growths to be malignant, and disagreed with the actions of Dr. Sherman of Detroit, who claimed that fully 80 percent of the DES offspring he examined had adenosis for which he performed radical surgery. The Boston study by Herbst had 'only' found a 30 percent rate of adenosis. Fry and Decker then made a remarkable observation that if there actually was so great a discrepancy between the Detroit cases and those at the Mayo Clinic, perhaps Sherman's patient population was more promiscuous than that seen in Rochester, so that the Detroit cases were the consequence of socially transmitted diseases.[30] Kelsey added no comment about the relative friskiness of women in the Motor City.

All of the Mayo Clinic patients with vaginal ectopy had received DES in utero and likely at a high dosage. In the total sample of about 1600 patients, nine malignancies were reported. Dr. Lanier also reported 230 cases of major or minor anomalies, which was a significant amount.

They included serious cardiac anomalies, hip dysplasia, polycystic kidneys, hypospadias, undescended testes, and an absence of the uterus and vagina.[31] Heart lesions had been associated with the use of hormones to diagnose pregnancy, but Decker noted that the hormone test had only been used at the Mayo when the mother had some bleeding, and that the bleeding per se might be related to the anomaly, rather than the drug use. Of course, as Kelsey noted, the same association might be made concerning the patients they were surveying, i.e. the daughters who had been born of mothers who were patients at the Mayo Clinic due to uterine bleeding might have had damaged hearts associated with the bleeding, rather than the hormone treatment they received. The Mayo group were exchanging data with Dr. Herbst, but they concluded that if there were a real association between DES and vaginal changes, the incidence was very low. They pointed out that in their own research on clear cell carcinomas, not all of the mothers had a history of estrogen therapy during pregnancy. Therefore, the Mayo researchers and Kelsey agreed that a control population study needed to start as soon as possible.[32]

The Mayo study revealed that male offspring did not escape damage, which contradicted a poor yet generally accepted early study from the Chicago Lying-in Hospital. In 1948, Drs. Edward Davis and Edith Potter concluded that the administration of DES or testosterone to mothers in early pregnancy did not produce "any demonstrable changes in the appearance of the gonads or genital organs of six male fetuses." They concluded from this tiny sample that these drugs would not "affect aversely the development of the genital organs of the human male fetus."[33] In December 1971, Kelsey attended a meeting in New York where she was told a follow-up study on males exposed in utero to DES had shown a "high degree of feminization, both behavioral and anatomical." The mothers had been prescribed DES due to gestational diabetes.[34] The following year, Dr. William Gill, part of the team performing the retrospective

study of Dr. Diekmann's patients, found that fully one-fourth of males exposed in utero to DES were likely to have genital tract abnormalities, including cysts on the testes, hypoplastic (underdeveloped) testes or penises, and severe sperm abnormalities resulting in sterility.[35]

The possible threat to public health caused by DES was not limited to exposure in prenatal clinics, and laid bare the political clashes that would emerge in the early 1970s between the nascent environmental movement and the powerful agricultural lobby, and was rooted in the Delaney Clause of the *Food, Drug and Cosmetics Act*. Enacted in 1958 and named for New York Congressman James Delaney, the clause stated that FDA "shall not approve for use in food any chemical additive found to induce cancer in man, or after tests, found to induce cancer in animals."[36] DES had been approved as a cattle feed additive in 1954, with the proviso that it be withdrawn from feed 48 hours before slaughter so that none remained in the beef. FDA was to recommend a measurement tool for DES, while USDA was to perform the meat inspection. Until 1965, neither agency checked beef on a regular basis, although in 1959, the National Cancer Institute had warned that this "known potent carcinogen" should be eliminated from the human food supply. In that year, pharmacologist Eugene Geiling had come out of retirement to act as an consultant with FDA. His first task was to prepare a statement on the "big business" aspects of adding potent drugs, in this case estrogens such as diethylstilbestrol, to the feed of cattle, swine, lambs and poultry. FDA had just declared estrogens as potential carcinogenic agents.[37] By then, there was a medical report of a 1950s New York restaurant worker who was so fond of chicken, he ate the necks left over by the patrons every night. The chicken was known as a caponette, very tender meat due not to castration but to the implantation of a pellet of DES in the neck. The restaurant worker grew female-sized breasts.[38]

The first test of the Delaney clause was at Congressional hearings in 1960 over food colour additives. Thomas Carney, Vice-President of Research for Eli Lilly, the manufacturer of DES, spoke against the enforcement of the clause by citing the example of DES, which, he argued, had been prescribed to 300,000 women with no side effects.[39] The Delaney clause suffered a setback in 1969, when studies linking cyclamate with cancer, resulted in FDA banning the artificial sweetener. So great was the public outcry about the loss of their diet pop that FDA was forced to recant the ban.[40] In 1962, pro-agricultural forces in Congress engineered the passage of section 512(d)(1)(h) of the *Act*, permitting carcinogens to remain in cattle and sheep feed as long as "no residue is left in the meat when the chemical is used according to label directions that are 'reasonably certain to be followed in practice.'" As reporter Nicholas Wade drily added, "in other words, if you find DES in meat, that's the fault of the farmer for disobeying the 'reasonable' regulations. So don't ban DES, jail the farmer."[41]

In 1965, the U.S. Department of Agriculture (USDA) began regular inspections of cattle for DES. John N.S. White, one of the inspectors, found that cows fed very heavy doses of DES developed "anatomical abnormalities." When he was reprimanded for "conduct embarrassing to the Department for seeking permission to publish his findings, he resigned and published it in a scientific journal. The USDA's inspection tools were imprecise in the 1960s and inspections were spotty. In 1966, DES was found in 1.1 percent of 1,023 samples. This was not a particularly large sample, although extrapolated to the 30,000,000 cattle annually slaughtered at that time, it meant potentially that the meat from over 322,000 cattle could have contained DES residues. Banning of DES from cattle feed, however, would have cost the industry $90 million annually in grain and maintenance, since hormone use sped the fattening process.[42]

By 1971, advocacy groups such as Ralph Nader's Center for the Study of Responsive Law, as well as the National Cancer Institute, demanded that DES be banned from cattle feed.[43] By 1972, with more sensitive instrumentation, it became apparent that fully ten percent of test samples were laced with DES.[44] However, this highlighted the dilemma faced by FDA which could have ramifications for many other approved drugs. Commissioner Edwards argued that DES was no more carcinogenic than naturally occurring hormones and that a carcinogen, in small enough doses, could reasonably be considered safe. Section 512 (d)(1)(H) was directly challenged by the Delaney clause, which stated that any known carcinogen, regardless of level of toxicity, should be banned.[45] Nevertheless, as public opposition grew and levels of DES residue in cattle increased, in August 1972, Edwards was left with "no choice" but to ban DES as a cattle feed additive, despite the fierce opposition of the agricultural industry and the feed manufacturers.[46]

Then the victims had their say. By September 1972, with the national newspaper coverage of the Dieckmann study, the Chicago Lying-in Hospital was "deluged with inquiries relating to this study with some former patients hinting at possible legal action against the University."[47] The first class action suit was Abel v. Eli Lilly, in which 144 DES daughters sued 16 drug manufacturers. Many of the plantiffs had undergone surgery "in the belief that adenosis would inevitably lead to carcinoma."[48] Four lawsuits arising directly from the Dieckmann study were filed in 1977, including Mink v. University of Chicago and Eli Lilly, also a class action. As Dr. D.T. Chalkley, Director of the FDA Office for Protection from Research Risks wrote to NIH legal advisor Laurence Froelich, the Chicago study "has attracted more attention probably because of its size and apparent lack of consent procedures."[49] Patsy Takemoto Mink of Hawaii, (who would become a distinguished politician), along with two named co-plaintiffs, Gladys Lang

and Phyllis Wetherill, charged that while they were patients at the Chicago Lying-in Hospital, they were administered DES without their knowledge or consent. The plaintiff class was "so numerous that joinder of all members is impracticable."[50] Mink, Lang and Wetherill had been under the care of a University of Chicago obstetricians, from approximately one month after they had become pregnant until they gave birth, each to a daughter who later developed cervical adenosis. The mothers made regular visits to the Lying-in Hospital clinic.[51] From their first visits to a few weeks before delivery, each mother was given pills to take daily, which contained DES. The action stated that "no patients were told that the pills contained DES or a drug of any kind." Mink and Wetherill were told they were vitamin pills. Lang was told that the pills helped prevent complications in pregnancy, even though at this time, Dieckmann "personally believed" that previous research did not demonstrate DES's effectiveness for "any medical purpose" in pregnancy. Furthermore, the pregnant women were "intentionally misled" to believe that they were receiving individualized medical care rather than that they were part of a clinical trial.[52]

The lawsuit also noted that although FDA had ordered drug companies to cease marketing DES for use by pregnant women in November 1971, and that since 1973, it was known in the medical community that DES daughters should receive semi-annual pelvic examinations, Lilly had never notified the plaintiffs that they had been given DES. The University of Chicago sent form letters to the plaintiffs in 1975 and 1976, which "did not disclose that the drug had been administered without plaintiffs' knowledge as part of a medical experiment, nor did they inform plaintiffs of the precautions that their daughters should take to minimize the risk of cancer."[53] The letters were part of Dr. Marluce Bibbo's follow-up study on the effects of DES, financed by an NIH grant.[54] The letter stated that "it was only recently that some reports in medical literature have suggested that the use of the drug by women during

pregnancy may have some relationship to the development of some abnormal conditions in the genital tracts of their offspring, in particular, daughters, many years later."[55] This action was settled out of court for an undisclosed amount.

Other actions were filed from 1977 onwards on behalf of DES children. On the basis of an August 1977 case of Renslow v. Mennonite Hospital, the Illinois Supreme Court allowed for claims for damages for children born of women who had received DES during prior pregnancies, which created a new class of plaintiffs. This resulted from evidence that a woman who had received DES in the University of Chicago trials not only gave birth to a daughter with cervical adenosis, but that her son from a later pregnancy, for which she had not been given DES, was born with genital deformities.[56]

In 1978, HEW Secretary Joseph Califano Jr. formed another special task force of FDA, NIH, National Cancer Institute, and other officials to determine whether women exposed to DES during pregnancy should be warned about increased cancer risk, and what procedures they and their physicians should follow. The committee proposed to first discuss DES and then broaden its scope to include all estrogen-related cancer issues. The Task Force looked at breast cancer and other potential issues in DES mothers, cancer and other health issues in daughters, and reproductive abnormalities in DES sons. The scope was broadened to include all synthetic hormone use.[57] By that time, FDA had issued directives that DES, or any estrogen, should never be prescribed during pregnancy, and that there was no scientific evidence that DES prevented miscarriages. FDA's advisory committee also recommended that the use of estrogens for post-partum breast engorgement be deleted from drug labelling, and that DES was not to be marketed as a 'morning after' pill except for emergency situations such as rape and incest.[58] The Task Force published a pamphlet, "DES Exposure In Utero: Information for Physicians," which

recommended that DES-exposed young women avoid oral contraceptives, since these added "further hormonal variables to a complex situation."[59]

What kinds of treatment were available for these victims of a "complex situation"? There were multiple answers and even greater numbers of patients. A 1972 study at Detroit's Sinai Hospital, which examined 528 women and girls exposed to DES in utero, found fully 346 of them to have lesions. "More startlingly, [Drs Saul Brown and Paul Goodman] found 'gross and microscopic abnormalities' in about 90% of the patients."[60] Similar findings were made in Milwaukee, and Boston's Beth Israel Hospital, and researchers concluded that the significantly higher numbers than Herbst's original study was due to the use of colposcopy, which detected abnormalities not caught by visual inspection or Pap smears. How to treat the adenosis was equally uncertain. Dr. Joseph Scott, at the University of Miami School of Medicine, didn't "believe in taking chances and he removes all abnormal epithelium from the top of the vagina, under colposcopic guidance, a little at a time, using a small Eppendorfer biopsy instrument, "much as one would weed a garden… This treatment is something I have been doing for years long before this stilbestrol thing was heard of. I nearly always remove abnormal epithelium. I can't prove that it's the right thing to do. Nobody knows for sure." He did boast a success rate of having only one invasive cancer in the genital tract out of over 10,000 private patients. The other gynecologists interviewed preferred to observe the patient and take no action until a "really suspicious-looking precancerous lesion appears," but they did not disapprove of Scott's proactive measures: "He may be right. I just don't know."[61]

However, Dr Duane Townsend, Chief of Gynecologic Oncology at the University of Southern California, totally disagreed with Scott's methods, arguing that adenosis "disappears through a normal physiologic process known as metaplasia." USC did not find clear-cell

adenocarcinoma in over 265 DES-exposed offspring, so Townsend saw no definitive proof that adenosis was the precursor to cancer. “It would require almost a total vaginectomy to remove the changes seen in some DES-exposed offspring, a rather formidable procedure for a teen-ager.”[62] Dr. Howard Ulfelder, chief of gynecology at Massachusetts General Hospital, considered the estimate of 500,000 DES exposed women to be “fair and conservative.”[63] By 1975, he was treating adenocarcinomas, usually in 18-year-old teenagers, through extirpative surgery and high-energy radiotherapy. During the surgery, the vagina was replaced with a skin graft over a mold. He reported performing 17 of these surgeries with technically satisfactory results, but the operations had a “serious emotional overlay.” Any less mutilating or sterilizing treatments, he argued, ran the risk of future cancer recurrence.[64]

DES daughters faced mutilation, sterilization, and for lack of a better word, terror. Dr. Ruth Schwartz, professor of obstetrics at the University of Rochester School of Medicine, was one of the few medical writers who focused upon the psychological impact of the DES diagnosis on the victims and their mothers.[65] According to the Task Force pamphlet, practitioners were advised to give a full pelvic examination to all girls who had been exposed to DES in utero when they reached menarche or at 14 years of age, or earlier if they developed abnormal discharges. The examination was to include inspection and palpation, a Pap smear and iodine staining test of the cervix and vagina. Abnormal areas were to be biopsied. The physicians were assured that the procedure could be performed in the office with “small biopsy instruments and without significant discomfort.”[66] This must have been a terrifying experience for children, as anesthesia was recommended for the “very young” patient. If an adequate examination was not possible at the first visit, the children were to use vaginal tampons for a few months to permit a proper examination without discomfort.[67]

Schwartz advised that practitioners would be seeing more DES victims, not only because they would present symptoms such as profuse bleeding or discharges, but because increasing public awareness, through the government-initiated campaigns, led many teenaged women or their mothers to their doctors after reading an article about DES. However, as Schwartz cautioned, "doing a pelvic on a teenager, let along someone [as young as eight years] poses the threat of tremendous psychological trauma so these youngsters require special handling. [The examination] involves treating them with respect, maturity, and, primarily, gentleness."[68] Another potential psychological minefield was informing the daughter of her exposure, which should always be done, Schwartz advised, by the mother "only if the mother and daughter have a good relationship to begin with." The daughters usually accepted the fact that their mother had taken the medication because they really wanted to have a child, and that acceptance amounted to "a life-long risk and the many, many years of follow-up." When a physician had to tell the daughter, they were to "let her ventilate whatever anger she might feel towards [the mother], toward the doctor who gave the mother the medication, toward life itself. Explain … that everyone meant well, that everyone wanted her to be born."[69] Dr. Schwartz's clinic offered photographs taken via colposcopy, and showed the girls their own bodies "so it isn't quite as frightening to them." Mothers, however, experienced "scalding guilt."[70] Schwartz advised any physicians who had prescribed DES to pregnant women to "ferret" the names out of their files, even if they feared a malpractice suit or had "irrational anger" against themselves. They needed to accept that they were not infallible. "We did it and therefore we have to try to do the best we can for the patients."[71]

For Frances Kelsey and the Bureau of Drugs, the best they could do was to continue to monitor and regulate synthetic hormones, as oral contraceptives remained exceedingly popular

and hormone replacement therapies were treatments of choice for menopausal symptoms in the last decades of the 20th century. In 1974, the Obstetrics and Gynecology Advisory Committee reviewed a study linking congenital limb reductions and spina bifida-anencephaly with women who had discontinued use of the pill immediately before becoming pregnant, or were pregnant as a consequence of oral contraceptive failure.[72] These cases echoed the instances of DES-linked deformities well after the mother had ceased taking the hormone.

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[1] FOK to JS, Memo, DES, n.d., Box 16, File 7, 1. Library of Congress. Kelsey Papers.

[2] Olive Watkins Smith and George Van Seclin Smith, "Use of Diethylstilbestrol to Prevent Fetal Loss from Complications of Late Pregnancy," *New England Journal of Medicine* 241, 15 (October 13, 1949): 562-68.

[3] Dieckmann, W.J., Davis, M.E., Rynkiewicz, L.M., and Pottinger, R.E. "Does the Administration of Diethylstilbestrol during Pregnancy have Therapeutic Value?" Final Report, 1-2. Box 16, File 3.

[4] "DES implicated in male genital and sperm abnormalities." n. journal, [1972?], p. 21. It was also available in other countries.

[5] Dieckmann, et al, "Administration of DES, 1-2.

[6] FOK to JS, Memo, DES, n.d., Box 16, File 7, 1.

[7] Dieckmann et al, "Administration of DES", 3.

[8] Colvin, E.D., Bartholomew, R.A., Grimes, William, and Fish, John. "Salvage Possibilities in Threatened Abortion." *American J. of Obstetrics & Gynecology*. June 1958: v. 39, 6:1221. Kelsey Papers Box 16, File 5, DES.

[9] Colvin, "Salvage Possibilities," p. 1223.

[10] DES Task Force First Report: Risk of Malignancy in Mothers Exposed to DES. May 30, 1978. Box16, file 8, DES Task Force, 1.

[11] FOK to JS, Memo, DES, n.d., Box 16, File 7, 1.

[12] FOK, Memo of Telephone Conversations, March 7-8, 1972, Box 16, File 2, DES.

[13] FOK, Memo of Telephone Conversation, March 9, 1972, Box 16, File 2, DES.

[14] "Chicago Women given DES in '52 are Sought." *OB-GYN News*, November 25, 1972. P. 29.

[15] FOK to JS, Memo, DES, n.d., Box 16, File 7, 2.

[16] "Progress Report No. 1." Summer Project: Diethylstilbestrol."July 31, 1972, Box 16, File 7, 1.

[17] "Progress Report No. 1." Summer Project: Diethylstilbestrol."July 31, 1972, Box 16, File 7, 2; "Progress Report No. 1: Follow-up." N.d., Box 16, File 7; FOK to JS, Memo, DES, n.d., Box 16, File 7, 2.

[18] Memorandum of Conference, FOK and Fred Zuspan, Dec 1, 1972, RE: U of Chicago DES study, 1-2. Box 16, File 2, DES.

[19] "Progress Report on Progesterone and Estrogen Project, DHEW Purchase Order # FDA 7837." Box 16, File 7.

[20] Task Force First Report, 8.

[21] FOK, Memo of telephone conversation with Dr Robert Miller, NIH, April 25, 1972

[22] FOK memo to Dr. Thaddeus Domanski, Deputy to Dr. Mordecai Gordon, NIH Re Contract with Dr. Herbst, May 5, 1972. Box 16, File 2, DES.

[23] Henry K. Simmons, Director, BD to Peter Barton Mott, General Counsel, Re: Diethylstilbestrol, June 25, 1972. Box 16, File 2, DES.

[24] Dr. C. Graham and Dr. Carolyn Bradley's Emory University study, published in J. *of Reproduction and Fertility*, 27:181-5, 1971 was abstracted as "Oogenesis Stimulation." *OB-GYN News*, May 15, 1972, n.p., Kelsey Papers, Box 16, File 6.

[25] Thelma Dunn and A.W. Green, "Cysts of the epididymis, cancer of the cervix, granular cell myoblastoma and other lesions after estrogen injection in newborn mice." *J. National Cancer Institute* 31: 425-455, 1963, as cited in Robert W. Miller, "Editorial: Transplacental Chemical Carcinogenesis in Man," *J. of the National Cancer Institute,* 47, 6, December 1971:1169-1171. Kelsey Papers, Box 16, File 6. DES.

[26] FOK, Memo to JS, 1/31/96 and "Comment", 1978?, p. 2. Box 16, File 7.

[27] Memo from William C. Drury, DES Project Officer to Director, Office of Scientific Evaluation, July 18, 1972, Re: DES. Box 16, file 2, DES.

[28] Memo D.T. Chalkley to Director, Scientific Investigations Staff, June 12, 1978, Subject: "DES and the Dieckmann Project."

[29] Senator Humphrey's introduction of a bill to establish a National Human Experimentation Standards Board (Congressional Record December 5 1972, Box 16, File 3, DES.

[30] FOK Project Officer. "Site Visit with Dr. Kurland of the Mayo Clinic." Typescript. 6 pp. c. Feb 12, 1973, 1-2.

[31] FOK, "Site Visit Mayo Clinic." p. 3. Their findings were published in Anne Lanier, Kenneth Noller, David Decker, Lila Elveback and Leonard Kurland, "Cancer and Stilbestrol: A Follow-up of 1,719 Persons Exposed to Estrogens in Utero and Born 1943-1959," *Mayo Clinic Proceedings*, November 1973, v. 48: 793-99.

[32] FOK, "Site Visit Mayo Clinic." 4.

[33] Davis, Edward and Potter, Edith. "The Response of the Human Fetal Reproductive System to the Administration of DES and Testosterone Propionate During Early Pregnancy." ? V. 42. May, 1948, p. 378. Kelsey Papers, box 16, File 6.

[34] FOK, Memo to Files, December 7, 1971. Box 16, File 2, DES.

[35] "DES implicated in male genital and sperm abnormalities." n. journal [1972?], p. 21. Kelsey Papers, Box 16, File 6, DES.

[36] J. H. Weisburger, "The 37 year history of the Delaney Clause," *Exp Toxicol Pathol*. 1996 Feb; 48 (2-3):183-8. doi: 10.1016/S0940-2993(96)80040-6. PMID: 8672873.

[37] Geiling, Hilltop House, Odessa, NY to FOK, June 16, 1959, July 16, 1959, September 5, 1959.

[38] Wade, Nicholas. "DES: A Case Study of Regulatory Abdication." *Science*. July 28, 1972. V. 177. NO. 4046: 335. Box 16, F. 5.

[39] Wade, "Delaney," 589.

[40] Wade, "Delaney," 590.

[41] Wade, "DES," 335.

[42] Wade, "DES," 335.

[43] Wade, "DES," 336.

[44] Wade, "DES," 336.

[45] Wade, "DES," 337.

[46] Wade, Nicholas. "Delaney Anti-Cancer Clause: Scientists Debate on Article of Faith." *Science*, v. 177, August 1972: 588. Box 16, File 5; DHEW, FDA, [Docket Nos. FD2-D-452, 494; NADA Nos. 11-295V, 9525, et al.] , Charles Edwards, Commissioner, July 31, 1972, "Diethylstilbestrol: Order Denying a Hearing and Withdrawing Approval of New Animal Drug

Applications for Liquid and Dry Premixes, and Deferring a Ruling on Implants," 1. Box 16, File 7. See also Federal Register. Part III. DHEW. FDA. "Diethylstilbestrol; Withdrawal of Approval of New Animal Drug Applications; Commissioner's Decision." September 21, 1979. V. 44, no. 185. Notices. Docket No. 76N-0002: 54852-54900.

[47] F.P Zuspan to Dr. Malone, Associate Director for Extramural Research and Training, NIH, Bethesda, MD, September 14, 1972. The articles included "Seek 840 in Cancer Drug Tie." *New York Daily News.* August 30, 1972; "Cancers traced to 1950 Experiment." *Evening News* [Newark, NJ] August 29, 1972. Box 16, File 1, DES.

[48] D.T. Chalkley, PhD, Director, Office for Protection from Research Risks, OD, FDA to Larry Froehlich NIH Legal Advisor, OGC (Office of General Counsel?) Subject: Mink v. University of Chicago and Eli Lilly, April 28, 1977, 1-2, Box 16, File 2, DES.

[49] Chalkley to Froehlich, 2.

[50] Action filed in the US District Court for the Northern District of Illinois Eastern Division, Mink, Lang, Wetherill v. University of Chicago and Eli Lilly & Company, April 25, 1977, attached to Chalkley to NIH legal advisor, Mink, memo, 1. Box 16, File 2, DES.

[51] Mink v Chicago, 4.

[52] Mink v Chicago, 6-7.

[53] Mink v Chicago, 9-10.

[54] Mink v Chicago, 12.

[55] Marluce Bibbo, MD, DES Program Director, Chicago Lying-in Hospital, DES Program, University of Chicago to Mrs. Patsy Takemoto Mink, Hawaii, January 29, 1976. See also Institute of Medicine, Committee on Ethical and Legal Issues relating to the Inclusion of Women

in Clinical Studies. *Women and Health Research*, vol. 1. National Academies Press, 1994. 241. https://books.google.ca/books?id=5upNplmdB78C&lpg=PP1&pg=PP1#v=onepage&q&f=false

[56] Legal memo, Allison Dunham and Raymond Busch, University of Chicago, September 7, 1977.

[57] DES Task Force Committee Meetings, Minutes, March 3, 1978, p. 2.

[58] *FDA Drug Bulletin*, March-April 1978, v. 8, 2 "DES and Breast Cancer", 10, and October-November 1978, "HEW Recommends Follow-up on DES Patients." 31. Kelsey Papers, Box 16, File 5. See Bibbo, Marluce, Gill, William, Azizi, Freidoon, Blough, Richard, Fang, Victor, Rosenfield, Robert, Schumacher, Gebhard, Sleeper, Kay, Sonek, Mojmir, and Wied, George. "Follow-up Study of Male and Female Offspring of DES-Exposed Mothers." *J. of Obstetrics & Gynecology* 49, 1, January 1977: 1-8; DES Task Force Committee Meeting, Agenda and Minutes, Appendix A, March 3, 1978, Box 16, File 8, DES Task Force.

[59] US. DHEW. PHS. National Cancer Institute. *Information for Physicians: DES Exposure In Utero*. Pamphlet, 2, 7.

[60] "Nine out of Ten 'DES Babies' have Vaginal Adenosis." *Medical World News*. November 9, 1973: 17. Box 16, File 5.

[61] "Nine out of ten," 18-19.

[62] Townsend, Duane. "Adenosis in DES Offspring." Letter to the Editor. *Medical World News*, 1974?, 12.

[63] "Experts discuss Problems of DES-related Cancer." *JAMA*, Nov 10, 1975, v. 234, n. 6: 585.

[64] "Experts discuss Problems," 585.

[65] "DES Daughters." *Emergency Medicine.* August, 1977, 107. Kelsey Papers, Box 16, File 6.

[66] *Information for Physicians*, 6.

[67] *Information for Physicians,* 7.

[68] "DES Daughters,"188.

[69] "DES Daughters," 188.

[70] "DES Daughters," 188.

[71] "DES Daughters," 189.

[72] D.T. Janerich, J. M. Piper, D.M. Glebatis, "Oral Contraceptives and Congenital Limb-Reduction Defects," *New England Journal of Medicine,* 291:697, 1974 as noted in Ob/Gyn Advisory Committee, 36th meeting, December 4, 1974. Box 16, File 3, DES