8. The DES story: long-term consequences of prenatal exposure

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8.1. Introduction

In 1970, Herbst and colleagues reported an unprecedented finding; they had diagnosed a rare vaginal cancer (vaginal clear-cell adenocarcinoma) in seven young women, a cancer that had never before been seen in this age group in this hospital (Herbst and Scully, 1970). The following year, these authors published the startling finding that seven of the eight cases (one more had been identified), but none of 32 matched controls, had been prenatally exposed to the synthetic oestrogen diethylstilboestrol (DES) (Herbst *et al.*, 1971). Seven months after this publication, the US Food and Drug Administration (FDA) withdrew approval for use of DES by pregnant women, for whom this potent synthetic oestrogen had been prescribed since 1947 in the mistaken, but widespread, belief that it prevented spontaneous abortion (miscarriage). In fact, this apparently innocent treatment proved to be a time bomb for the infants exposed during the first third of pregnancy. The discovery that DES was a transplacental carcinogen (and was shown after 1971 to also be a teratogen — causing birth defects) occurred only 10 years after the awful discovery (James, 1965) that the use of thalidomide by women in early pregnancy caused severe limb reductions. These tragic lessons forced scientists to abandon their commonly held view of the foetal environment as a safe place, protected by the placental 'barrier', and replace it with an understanding of the extreme vulnerability of the developing foetus, for whom any maternal exposure that occurred during critical periods had the potential to alter development, even long after birth.

8.2. Optimistic beginnings

Oestrogens are steroid hormones, made primarily in the female ovaries and the male testes, that act by binding to oestrogen receptors. Oestrogens, together with the other so-called sex hormones (progestins and androgens), are required for the regulation of reproduction and the development of secondary characteristics in both males and females. In 1938, Charles Dodds and colleagues formulated DES, the first orally active synthetic oestrogen (Dodds *et al.*, 1938). This synthetic (non-steroidal) oestrogen has been estimated to be five times as potent as oestradiol, the most potent naturally occurring oestrogen in mammals (Noller and Fish, 1974). DES is inexpensive and simple to synthesise and the developing pharmaceutical industry quickly began worldwide production; DES was marketed under more than 200 brand names. Like other pharmaceuticals produced at that time, DES underwent very limited toxicological investigations. It rapidly became popular in a wide variety of treatments, including those for menopausal symptoms and prostate cancer. Other therapeutic uses were suppression of lactation, post-coital contraception (morning-after pill) and post-menopause syndrome (Noller and Fish, 1974). It was later used as a growth promoter in chicken, sheep and cattle (Aschbacher, 1976).

Among the multiple uses of DES was that for the prevention of spontaneous abortion (miscarriage). It was believed in the 1940s that spontaneous abortion was the result of a decrease in oestrogen levels, now recognised as a consequence, not a cause (Smith, 1948). As early as 1941, Karnaky and others began experimenting with the use of very high doses (100 mg administered intramuscularly into the cervix daily) in women 'threatening to abort', and deemed the drug effective for this purpose, stating that there were no adverse consequences to mother or foetus (Karnaky, 1942). The use of DES for prevention of miscarriage was further promoted by the work of Olive and George Smith, who conducted multiple (uncontrolled) trials of DES for use in pregnancy throughout the 1940s and published extensively regarding its effectiveness (Smith, 1948; Smith *et al.*, 1946).

Paradoxically, Charles Dodds, the scientist who first synthesised DES, a discovery for

which he was later knighted, speculated years later about the minimal testing of new drugs at that time. Reviewing the history of stilboestrol (another common term for DES), suggested by Dodds himself (Dodds *et al.*, 1938), he noted that no long-term toxicity tests of this synthetic oestrogen had been conducted. He stated: 'I suppose we have to be very thankful that it (DES) did prove to be such a non-toxic substance.' (Dodds, 1965) Unfortunately, when Dodds wrote this the long-term consequences of DES had not been discovered.

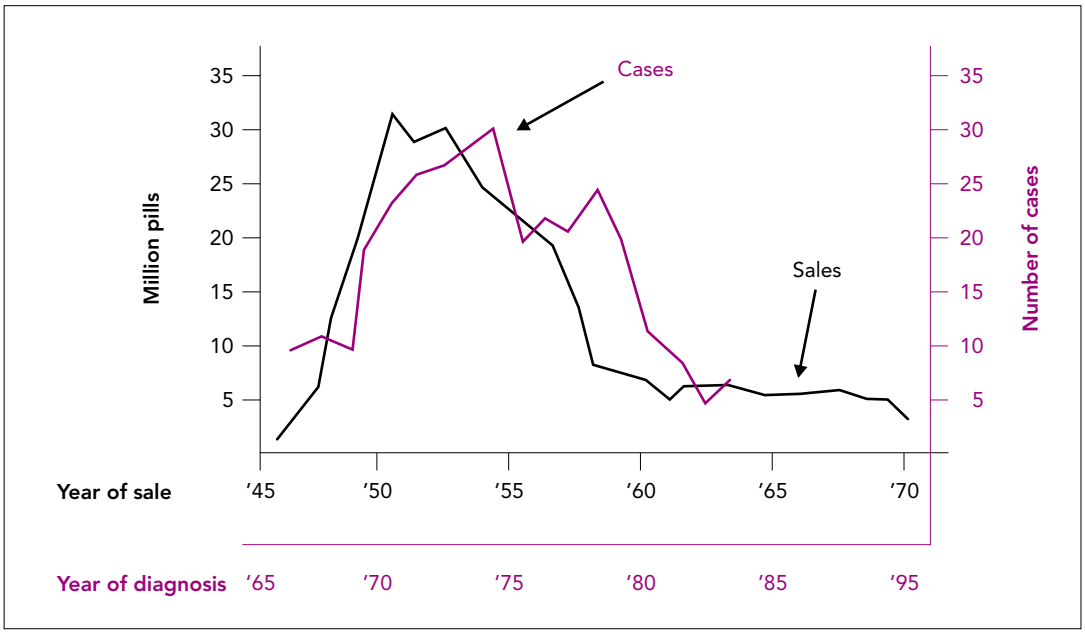
8.3. Tragic consequences

Reports that DES increased cancer incidence in laboratory animals appeared as early as 1938 (Lacassagne, 1938; Geschickter, 1939; Shimkin and Grady, 1941; Greene and Brewer, 1941). Since those early reports, extensive research has demonstrated an increased incidence of cancer of the mammary glands, cervix and vagina in multiple rodent species in response to DES.

However, until 1971 there was little evidence suggesting that maternal use of DES could result in cancer and reproductive abnormalities in humans, 20 years after exposure.

The 1971 case-control study of Herbst and colleagues identifying prenatal exposure to DES as the likely cause of a rare and often fatal vaginal cancer in young women was startling and unprecedented. This case-control study was followed within a few months by a second, corroborative, case-control study (Greenwald *et al.*, 1971). The relationship between DES use by pregnant women and the occurrence of vaginal clear-cell adenocarcinoma is clearly apparent in Figure 8.1. As can be seen, there is a remarkable correspondence between sale of DES (represented here by market sales figures produced by a large and representative US manufacturer during litigation) and diagnosis of this cancer 20 years later (Melnick *et al.*, 1987).

Market sales of 25 mg DES vs. cases of clear-cell cancer by year of diagnosis Figure 8.1.



Source: D. Ibarreta and S. H. Swan

This shocking finding finally raised a red flag concerning the dangers of DES use by pregnant women, as well as providing convincing evidence of the potential hazards that exposure of the pregnant woman to pharmaceuticals (and other chemicals) pose to the foetus. As a result of this study, the FDA released a bulletin in November 1971 stating that DES use was contraindicated (must not be used) during pregnancy (US Department of Health, E. and Welfare, 1971). Tragically, the use of DES by pregnant women continued even after 1971 outside the United States and in some countries was reported many years later (Direcks and t'Hoen, 1986). The number of women who took DES is known imprecisely, but the National Institutes of Health has estimated that it was used by 4.8 million pregnant women in the United States alone. Total exposure (to mothers, sons and daughters) worldwide has been estimated to be 10 million (see Box 8.1.).

Later studies, including follow-up of a large cohort of DES-exposed women (DESAD cohort, for DES-adenosis) showed that these 'DES daughters' exhibited a wide range of reproductive tract abnormalities. These included epithelial changes (such as vaginal adenosis) as well as structural changes such as cervical stenosis (narrowing of the cervical opening) and uterine malformations. Unlike vaginal clear-cell adenocarcinoma, which was extremely rare among DES-exposed women, these abnormalities were common, particularly in women whose mothers had been prescribed DES in early pregnancy. These changes, at least some of which were found to be prevalent even before birth (Johnson *et al.*, 1979), resulted in serious reproductive consequences for those affected. The risk of all adverse pregnancy outcomes, including ectopic pregnancy (embryo attachment outside the uterus), spontaneous abortion and premature delivery, were significantly increased (Swan, 1992). While studies on 'DES sons' have been much more limited, several have demonstrated increased rates of genital abnormalities in these men (Goldberg and Falcone, 1999).

8.4. DES ineffective for prevention of miscarriage

After the first claims of the effectiveness of DES for the prevention of miscarriage, several studies were carried out to assess its efficacy, with mixed results. As these studies became more rigorous, the support for the use of DES declined. Finally, in the early 1950s, two randomised, placebo-controlled trials were conducted. The larger of these trials, conducted by Dieckmann *et al.* (1953), reported no statistically significant differences in adverse pregnancy outcomes when DES was compared to a placebo. The authors concluded (as did the authors of the second, smaller trial) that DES was ineffective in the prevention of miscarriage and complications in late pregnancy. In spite of this, the drug continued to be prescribed even to women without previous pregnancy problems. An advertisement for one of the DES congeners (DesPlex) read, 'Recommended for routine prophylaxis in all pregnancies' (see Figure 8.2.).

A reanalysis of Dieckmann's data was published in 1978, after the long-term carcinogenic and teratogenic effects of DES were known (Brackbill and Berendes, 1978). The authors reanalysed Dieckmann's published data and found that DES actually increased the risk of the endpoints it was sold to prevent. The methods used in the reanalysis were not new, and had been available in 1953. As the authors noted, had the data been properly analysed in 1953, nearly 20 years of unnecessary exposure to DES might have been avoided. The fact that this drug was prescribed for two decades after its lack of efficacy was clearly demonstrated illustrates a massive failure of the system.

In fact, it was not the lack of efficacy that triggered the end of DES marketing for use in pregnancy, but a fortuitous accident. If the seven cases originally detected by Herbst and colleagues had been diagnosed in several different medical centres, rather than at Massachusetts General Hospital (where DES use had been high because the Smiths had conducted their early experiments on DES there), the dangers of DES might well have gone unrecognised. The cancer that DES caused in young women (vaginal clear-cell adenocarcinoma) is extremely rare. It is estimated to have occurred in less than one in every 1 000 exposed daughters (Melnick *et al.*, 1987). In fact, the registry established by Herbst in 1972 to actively register all cases of adenocarcinoma of the genital tract in young women has identified fewer than 800 cases worldwide. Thus, this cancer and its link to DES could well have gone undetected. Had this occurred, it is unlikely that DES-associated genital tract changes, which can only be identified by a physician conducting

a special DES examination, and the multiple reproductive consequences of DES exposure, would ever have been identified.

8.5. Assessing the extent of the damage

The young age of the women affected made the need for early detection of vaginal clear-cell adenocarcinoma critical. It was of crucial importance to identify the exposed population so that screening and early detection could help prevent fatal consequences. To assemble data on this rare cancer, Herbst and co-workers established the Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females in 1972 (Herbst *et al.*, 1972). Because it became evident, from several studies in which DES cohorts had been screened, that DES also had caused extensive non-cancerous DES changes of the female genital tract, in 1976 the National Cancer Institute established a cohort of over 3 000 DES-exposed women and close to 1 000 unexposed controls for long-term follow-up. This DESAD has proved invaluable for identifying the range of adverse consequences of DES exposure. Unfortunately, no comparable cohort of 'DES sons' has ever been established.

The exact number of individuals exposed to DES *in utero* is unknown, but estimates range from 2–10 million (see Box 8.1.). A study funded by the European Commission and published in 1991 (Direcks *et al.*, 1991) attempted to estimate the prevalence of DES-affected women in Europe. Eighteen countries were surveyed by means of questionnaires. This study found that use was greatest in Great Britain, France and the Netherlands, followed by Belgium, Ireland, Portugal and Spain. The survey concluded that DES had been prescribed during pregnancy, to a greater or lesser extent, in all countries surveyed except Sweden and Hungary.

Box 8.1. Use of DES to prevent miscarriage in Europe and the United States

Country	Period prescribed	Approximate number of pregnancies	Source: Direcks *et al.*, 1991, unless otherwise indicated
Belgium	1950–65		
Czechoslovakia	1958–76	63 000	
France	1950–77	200 000 60 000-240 000	Pons *et al.*, 1988 Direcks *et al.*, 1991
Germany	–1977	200 000	
Ireland	1950–76		Wingfield, 1992
Italy	– 1960 (?)		
Netherlands	1947–75	189 000–378 000	Hanselaar *et al.*, 1991
Norway	1948–72		Palmlund *et al.*, 1993
Portugal	1960–70		
Spain	1953–77 (1983?)	25 000	Garcia-Alonso *et al.*, 1988
United Kingdom	1940–71 (1973?)	7 000–8 000	Kinlen *et al.*, 1974
United States	1943–71	2–6 million	Goldberg and Falcone, 1999

The story of DES is far from over. Many of the youngest women exposed *in utero* are not yet 30. The known consequences of its use will continue to appear as this cohort ages. In addition, the cohort must be followed to identify unknown consequences, including a possibly increased cancer risk with age. The use of experimental animal models may help address some of these concerns about the future since the mouse appears to be a good model in which to study the effects of developmental exposure to DES (McLachlan, 1993). Such studies on ageing mice may be useful in predicting DES-effects as the exposed human population ages, as will continued follow-up of exposed cohorts.

What will happen to subsequent generations of the DES-exposed women? There is considerable interest in monitoring the grandchildren of DES-treated women. Studies in mice have shown an increased

susceptibility to tumour formation in the third generation (Newbold *et al.*, 1998), suggesting the DES grandchildren may also be at increased cancer risk (Miller, 1999). This is a question that will take many years to resolve.

8.6. Lessons from the DES story

It is worthwhile asking how this tragic event might have been prevented and what lessons can be learned from it. First, the DES story demonstrates that long-term and hidden effects of hormonal exposure (as was learned from the thalidomide story and other chemical exposures) are possible, and that such consequences may be devastating. Therefore, extreme caution should be taken before exposing pregnant women to substances that may alter the endocrine system, especially during foetal development. The DES episode also demonstrated that the absence of visible and immediate teratogenic effects cannot be taken as proof of the absence of reproductive toxicity. DES represents not only the first transplacental human carcinogen, but also the clearest example of human endocrine disruption. Although the doses of DES administered to pregnant women were far higher than usual environmental levels of synthetic chemicals, DES remains a clear warning of the consequences of perturbing the endocrine system through synthetic chemicals.

What precautionary action might have prevented the use of DES by pregnant women? First, no long-term toxicity tests were ever carried out. DES is a synthetic oestrogen and the carcinogenicity potential of oestrogens was already known even during the initial experimental use of DES (Cook and Dodds, 1933). Adverse effects of DES on animals had been published (Shimkin and Grady, 1941; Gardner, 1959; Dunn and Green, 1963), but they were largely disregarded. It was also known at the time that chemicals could cross the placental 'barrier'. There were early indications of adverse effects of exposure to oestrogens during development (Greene *et al.*, 1939) and Karnaky in his early experimentation with DES noted darkened areolae (the area around the nipple) and linea alba (the line running from the pubis to the navel) in exposed newborns, indicating the oestrogenic action of DES on the female offspring (Karnaky, 1945). This evidence remained largely ignored, although some modest attempts to pinpoint the risks can be found in the literature. For example, in 1948, Bernard Laplan, a physician who believed in the efficacy of DES, expressed reservations about possible long-term effects: 'The possibility of some latent effects on the reproductive and endocrine system of the infant resulting from the high dosage oestrogen therapy must be borne in mind as indicated by the work of Greene, Burrill, and Ivy in experimental animals. Furthermore, we would avoid this therapy in any patient with a family history of malignant disease.' (Laplan, 1948)

Second, it might have been recognised in premarket testing that DES was never effective for the prevention of miscarriage. The methods used in the clinical trials conducted in 1951–52 that demonstrated this had been available before 1947 when DES was put on the market for use in pregnancy without adequate proof of efficacy. A properly conducted and analysed clinical trial might have avoided the entire episode.

The fact that DES was not patented, and very inexpensive to produce, made it extremely profitable. This, plus the absence of obvious acute toxic effects, undoubtedly contributed to the rapidity with which its use spread worldwide. The widespread use of DES was undoubtedly furthered by the faith in the advances of science and the belief in man-made solutions to nature's problems that were prevalent during the post-Second World War era. Undoubtedly those prescribing DES believed it was safe and effective, and both 'modern and scientific'. In the Netherlands, for example, the use of DES was particularly prominent, aided in part by its endorsement by the Queen's gynaecologist (Brahams, 1988). Consequently, there was strong pressure on physicians to prescribe DES. In 1952, Robinson and Shettles found DES ineffective when compared to untreated cases and therefore discouraged its use. They discussed in their article the 'peer pressure' that doctors were subjected to: 'The synthetic oestrogen, diethylstilbestrol, has more recently become a popular form of therapy in threatened abortion. The public has been so frequently told of the virtue of this drug through articles appearing in lay journals that it now requires a courageous physician to refuse this medication. The mass of pharmaceutical literature, extolling the wonders of this drug, has also rendered most practitioners amenable to his patient's demands. This situation, together with the understandable desire to do something

positive toward rescuing a teetering pregnancy, has resulted in the widespread use of DES in threatened abortion.' (Robinson and Shettles, 1952)

The role of another important stakeholder in the wide use of DES, the pharmaceutical industry, should be examined. Pharmaceutical retailers and advertising promoted the effectiveness and safety of DES to doctors and consumers. The pharmaceutical industry ignored the lack of efficacy of their product and failed to assess its adverse health effects. In fact, some manufacturers promoted it as a panacea for use in all pregnancies (see Figure 8.2.).

Advertisement for DES — Figure 8.2.

Source: Des Plex, anonymous

The eagerness of the pharmaceutical companies to sell this profitable product was compounded by the failure of medical and regulatory agencies to react rapidly to the emerging evidence. While the FDA announced that DES was contraindicated for use in pregnancy only months after Herbst's publication in 1971 (US Department of Health, Education and Welfare, 1971), in Europe the delay to withdrawal was as long as 12 years. It was not until 1974 that the Dutch Ministry of Health advised that DES should not be given to pregnant women (Palmlund *et al.*, 1993); in France, it was not until 1977 that national authorities included the contraindication for pregnancy in the labelling of the drug (Epelboin and Bulwa, 1993). In some countries, such as Spain, there are reports of use as late as 1983 (Direcks *et al.*, 1991). In addition, underdeveloped countries remained an open market for DES for many years. As recently as 1985, DES products were used in maternity care in Brazil, Costa Rica, Kenya, Mexico, Peru, Rwanda and Zaire. In the early 1990s, it was still prescribed during pregnancy in Mexico, Uganda and Poland (Palmlund, 1996).

DES continued to be used for a variety of therapeutic uses for years after the evidence of its adverse effects had been widely publicised. This included use as a post-coital contraceptive. Since DES is less than 100 % effective in terminating pregnancy, the use of a chemical potentially carcinogenic to the foetus was not permissible. In 1973, the FDA discouraged the use of DES as a contraceptive, restricting it to emergency situations such as rape or incest (Mills, 1974). The use of DES as a growth promoter (see chapter on Hormones as growth promoters) began in the 1950s and ended after a heated battle in 1979. Gradually use for other therapeutic purposes decreased and in the spring of 1997 Eli Lilly, the last, and predominant, manufacturer of DES in the United States ceased production (Pat Cody, pers comm.).

There has been significant progress in most key areas of drug assessment since 1970, in part spurred by the consequences of DES and thalidomide. In fact, the entire field of teratology was established in response to these episodes. Toxicity testing is much more comprehensive and thorough and sound evidence of efficacy is now required before a drug is marketed. Regulatory authorities are also much more alert to reporting of adverse drug reactions and more inclined to take action than they were in the 1960s and 1970s. Nonetheless several areas of concern remain:

- drugs that were marketed prior to current more stringent regulations may not have been adequately evaluated with respect to efficacy or toxicity;
- monitoring and surveillance in patients taking drugs is neither consistent nor comprehensive. Moreover, it is difficult to demonstrate an association between a drug and a health outcome that is delayed and/or prevalent;
- formalised risk/benefit analyses of new drugs (as well as other chemicals) are not widely utilised;
- drug surveillance (and evaluation of human health risks from other chemicals) should not be limited to detection of gross

malformations and cancers; such limited surveillance would likely have missed most of the adverse effects of DES.

It is clear, in hindsight, that the concerns expressed by scientists regarding the marketing of a drug with known carcinogenic potential should have been heeded. Failure to do so reflects the prevalent attitudes towards health risks, and an absence of precautionary thinking. The lack of a timely response by manufacturers and regulators after DES was demonstrated to be a transplacental human carcinogen in 1971 cannot be excused so easily. Even after the tragic consequences of DES use in pregnancy were confirmed, economic interests predominated, resulting in a 'wait and see' approach.

Those considering the wisdom of precautionary action today would do well to consider the history of DES. This drug was a known animal carcinogen, a suspect human carcinogen and a drug that had been shown to produce observable changes in the offspring of women exposed in pregnancy. Even if marketing in 1947 could have been justified on the basis of insufficient evidence of harm, after DES was proven to be ineffective for use in pregnancy in 1953 a review of its risks and benefits should have resulted in immediate contraindication of this use. At that point there was no longer any justification for subjecting consumers to any carcinogenic risk in the absence of any benefit. Had DES been withdrawn for use in pregnancy at that time, the unnecessary and tragic exposure of millions of mothers, sons and daughters could have been avoided.

Table 8.1. **DES: early warnings and actions**

Source: EEA

1938	DES synthesised
1938	First report of increased cancer incidence in animals after DES administration
1939	First report of DES administered to patients
1942	Approval of DES by the American Council of Pharmacy and Chemistry
1942	First report of DES used for prevention of abortion
1947	US Food and Drug Administration (FDA) approves DES for the treatment of threatened or habitual abortion
1948	Use of DES increases following publication of large-scale study in the US
1953	First large placebo-controlled randomised trial shows DES ineffective in the prevention of miscarriage
1970	Published report of seven cases of vaginal clear-cell adenocarcinoma in young women
April 1971	Prenatal DES exposure is linked to vaginal clear-cell adenocarcinoma
November 1971	FDA withdraws approval of DES for use by pregnant women
1972	Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females is established
1978	Reanalysis of 1953 Dieckmann data shows that DES actually increased the risk of miscarriage and other adverse pregnancy outcomes
1985	Last reported use of DES by pregnant women world-wide

8.7. References

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