Hormones, Daughters and Death:

The DES Disaster

Courtesy DES Action USA

By Lawrence Segel, MD

Patients readily accept the risks and side effects of prescription medications. But how many women would do so if they knew the drug prescribed during their pregnancy was not only ineffective, but would expose their children to birth defects, infertility and cancer?

Diethylstilbestrol (DES), a synthetic estrogen, was first produced in 1938 by British scientist, Sir Charles Dodds. It was championed as a cheap, potent and ingestible alternative to injectable estrogens. Of notable advantage to the American pharmaceutical houses was the lack of patent protection. Such a boon allowed them to jump on the hormonal bandwagon and begin mass production of the drug.

Unfortunately, lost in the initial exuberance was a frightening harbinger of things to come. Between 1938 and 1940, early studies on DES-exposed mice demonstrated the development of breast cancer and rodent offspring with congenital malformations of the reproductive tract.

In 1941, DES was approved by the FDA in the U.S. for medical use in the treatment of vaginitis, gonorrhea, menopausal symptoms and suppression of lactation. At that point in time, there were no indications outlined for its use during pregnancy. In 1947, however, the FDA approved DES for use in pregnancy, despite the lack of controlled clinical trials warranting

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such confidence in its safety. Once approved for use in pregnancy, DES began to balloon in popularity. It was recommended for women with problematic gestations (*i.e.*, those with diabetes), and for those at high risk of miscarriage. At the height of its acceptance, it was prescribed almost as if it were some sort of panacea or "vitamin" supplement. It was sold under scores of different proprietary names in Canada and the U.S.

What caused such irrational exuberance about an unproven drug, given that doctors are generally conservative and cautious?

The unchallenged acceptance of DES couldn't have come to full fruition without some high-level academic support. Researchers from Harvard Medical School theorized that low levels of estrogen contributed to miscarriage, and, therefore, advocated the use of DES. In 1948, an article from its investigators appeared in *The American Journal of Obstetrics and Gynecology*, endorsing the use of DES in such scenarios.

By 1953, however, not all the new evidence about DES was positive. A study at the University of Chicago showed DES had no beneficial effect in the prevention of miscarriage, and, in fact, had just the opposite effect. Women who had used it during pregnancy had a higher percentage of miscarriages and premature deliveries. By the 1960s, the tide had fully turned. Most obstetric textbooks taught that DES was ineffective in preventing miscarriages. Still, the real bombshell was yet to drop!

In 1971, the unraveling of what can only be described as an unmitigated obstetrics disaster, came to the forefront. The *New England Journal of Medicine* published an article that year on a rare form of malignancy — clear cell adenocarcinoma — which was occurring at an alarming rate in young women in their teens and twenties. The common thread was shocking. Their mothers had all been exposed to DES during pregnancy. Later that year, the FDA reversed itself, and issued a warning against prescribing DES during pregnancy.

A DES information poster. Courtesy DES Action Canada

In 1975, a study by the National Cancer Institute on DES was initiated and continues to provide chilling data:

- One in 1,000 DES-exposed daughters will develop clear cell adenocarcinoma. The usual age of onset is about 20, but it has occurred into the 30s and 40s.
- DES-exposed daughters have higher rates of infertility, miscarriage, ectopic pregnancy, premature delivery, and structurally malformed reproductive organs.

- DES-exposed sons may have structural abnormalities of the reproductive organs.
- DES-exposed mothers have a higher risk of breast cancer.
- The effect on the third generation (grandchildren) is currently under investigation.

In 1992, the U.S. congress recognized the importance of the DES issue. It passed the DES Education and Research Amendment, providing funding to the National Institutes of Health for continuing research on mothers and children exposed to DES, and for public and physician education campaigns.

DES has left a chilling legacy. It is a virtual metaphor for the dangers of using any drugs, even physician-prescribed ones, during pregnancy. It is estimated that five to 10 million mothers, daughters and sons were exposed to DES. Regrettably, many were not even aware they were on the hormone. Complicating the awareness of each clinical case are fading memories, old and discarded medical records, and the deaths of involved individuals and physicians.

Vexing questions remain as to what went wrong. Were the pharmaceutical companies too quick in marketing this unproven drug, despite regulatory approval? And what of the regulatory agencies? Was there complacency? Was there a failure in requesting the necessary safety studies? Finally, what of the front-line physicians? Were they deluded victims themselves, or must they also accept some guilt for prescribing an ineffective drug to a misled public?

The DES disaster was a painful lesson for those in medicine. It will go down in history as an appalling global medical blunder. In response to the large number of affected individuals, DES action groups have sprung up throughout Canada, the U.S. and the rest of the world.

For more information on the DES disaster, some Web sites to visit include:

- *www.desaction.org* (DES Action USA)
- *www.web.net/~desact/* (A Canadian affiliate of DES Action USA.) Dx

DES Pamphlets. Courtesy DES Action Canada.