

**Prenatal Exposure to Diethylstilbestrol (DES)
in Males and Gender-Related Disorders:
Results from a 5-Year Study**

by

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Abstract

For many years, researchers and public health specialists have been assessing the human health impact of prenatal exposure to the estrogenic anti-miscarriage drug, diethylstilbestrol (commonly known as DES or "stilbestrol"). The scope of adverse effects in females exposed to DES (often called "DES daughters") has been more substantially documented than the effects in males ("DES sons"). This paper contributes three areas of important research on DES exposure in males: (1) an overview of published literature discussing the confirmed and suspected adverse effects of prenatal exposure in DES sons; (2) preliminary results from a 5-year online study of DES sons involving 500 individuals with confirmed (60% of sample) and suspected prenatal DES exposure; (3) documentation of the presence of gender identity disorders and male-to-female transsexualism reported by more than 100 participants in the study.

Prenatal Exposure to Diethylstilbestrol (DES) in Males and Gender-Related Disorders: Results from a 5-Year Study

Introduction and Background

During the 1970s and 1980s an increased amount of public and scientific attention was paid to the health and medical problems of individuals whose mothers were prescribed diethylstilbestrol (DES). A potent synthetic nonsteroidal estrogen, DES was first developed in 1938 and initially became available in the U.S. for treating a range of gynecologic conditions in 1941 (Apfel and Fisher, 1984). A few years later its approval by the FDA was broadened to include treatment of pregnant women for the purpose of preventing miscarriages. Though its efficacy had long been questioned by some in the medical community (Bambigboye and Morris, 2003; Dieckmann, 1953), DES remained popular with doctors until discovery in the early 1970s of an apparent association between prenatal exposure to DES and a rare form of vaginal cancer in females whose mothers used DES (Heinonen, 1973; Herbst and Bern, 1981). Subsequent research confirmed the transplacental mechanism of DES transmission (Maydl, et al., 1983) and classified DES as a carcinogen and teratogen (Mittendorf, 1995) as well as a mutagen (Roy and Liehr, 1999; Stopper et al., 2005).

While DES usage with pregnant women was banned by the FDA in 1971, the drug continued to be used in several European countries into the early 1980s (Schrager and Potter, 2004). DES remained a popular option for treatment of advanced prostate cancer in aging males due to its ability to inhibit luteinizing hormone secretion by the pituitary and thus inhibit testosterone secretion (Scherr and Pitts, 2003; Whitesel, 2003), despite reports that adverse effects from this treatment could include feminization in males (B. C. Cancer Agency, 2005). Through the 1970s DES was also prescribed as an estrogen supplement for treatment of male-to-female transsexuals (Kwan, 1985; Ober, 1976).

It has been estimated that as many as four to five million American women were prescribed DES during pregnancy. Estimates of the numbers of "DES daughters" and "DES sons" born in the U.S. are between one million and three million each (Edelman, 1986). Hundreds of thousands of DES sons and daughters were also born in Canada, Europe and Australia between the 1940s and 1980s. Efforts to determine exact numbers of prenatally exposed individuals, and the dosage and exposure patterns, particularly during the years of prime DES popularity, 1947-55 in the U.S., have been largely unsuccessful (Duke, et al., 2000; Heinonen, 1973). Because DES proved popular as a growth-stimulant in the cattle industry (Raun and Preston, 2002) for more than forty years (McLachlan, 2001), many consumers have also been exposed to unknown amounts of DES as it entered the food chain through beef consumption.

Following the FDA restrictions on DES prescriptions in the U.S. in 1971, researchers began to document a range of confirmed and suspected adverse effects of prenatal DES exposure in females and males (Edelman, 1986). Compared with the volume of published research on adverse effects in DES daughters, however, relatively few primary studies of DES sons have been published. The scope of known and suspected health effects among DES sons discussed in literature published since the 1950s includes (1) reproductive tract abnormalities; (2) infertility; (3) testicular cancer; (4) prostatic hyperplasia and cancer; (5) psychosexual effects; (6) psychiatric effects; and (7) effects on hemispheric laterality and spatial ability (Giusti et al., 1995; Pillard, et al., 1993; Reinisch and Sanders, 1992; Verdoux, 2004).

In 1959, a single case study of pseudohermaphroditism in a male with prenatal DES exposure was reported (Kaplan, 1959). Reports of urogenital abnormalities in DES sons first appeared in the medical literature during the 1970s (Andonian and Kessler, 1979; Bibbo et al., 1977; Cosgrove et al., 1977; Gill et al., 1979; Gill, et al., 1988; Henderson et al., 1976), consistent with results of experiments with prenatal DES exposure in male mice reported by McLachlan et al. (1975) and Newbold et al. (1987). These effects include epididymal (benign) cysts, hypoplastic or undescended testes (cryptorchidism), microphallus or underdeveloped penis, and hypospadias. Using data from DES sons participating in the DES cohort studies funded by the National Cancer Institute (NCI), researchers have examined possible links between prenatal DES exposure and greater risk of male infertility but have reached inconclusive findings (Wilcox et al., 1995). Although heightened testicular cancer risk has long been associated with prenatal DES exposure in males, researchers using the NCI cohorts to track cancer outcomes among DES sons claim to have measured no statistically significant increases in testicular or other forms of cancer (Strohsnitter, et al. 2001).

John McLachlan (2001), a pioneering DES researcher whose studies have assessed the effects of DES exposure in laboratory animals and mechanisms of DES toxicity for the past three decades, was among the first researchers to classify DES within a broader family of chemical compounds called "environmental estrogens", "xenoestrogens", or "endocrine disrupting chemicals" because of their common ability to mimic and interfere with normal hormonal processes associated with reproductive development. He has observed:

Developmental feminization at the structural or functional level is an emerging theme in species exposed, during embryonic or fetal life, to estrogenic compounds. Human experience as well as studies in experimental animals with the potent estrogen diethylstilbestrol provide informative models (2001).

The evolving research on endocrine disruptors has implicated DES in a variety of sexual differentiation disorders of the brain and body in males (Colburn et al, 1993; McLachlan et al., 2001; Sharpe, 2001; 2004; Sultan et al, 2001; Toppari et al., 1996), including testicular dysgenesis syndrome (Boisen, et al., 2001; Skakkebaek, Meyts, and Main, 2001). In 1993, Sharpe and Skakkebaek observed:

Treatment of several million pregnant women between 1945 and 1971 with a synthetic oestrogen diethylstilbestrol (DES) is now recognized to have led to substantial increases in the incidence of cryptorchidism and hypospadias and decreased semen volume and sperm counts in the sons of these women. DES exposure may also increase the incidence of testicular cancer and cryptorchidism. The similarity between these effects and the adverse changes in male reproductive development and function over the past 40-50 years raises the question of whether the adverse changes are attributable to altered exposure to oestrogens during fetal development. This possibility is not unlikely given the view that 'humans now live in an environment that can be viewed as a virtual sea of oestrogens' (Sharpe and Skakkebaek, 1993).

However, in a recent Danish meta-review of published epidemiological studies involving the association of prenatal indicators of estrogen exposure (including prenatal DES) and the deleterious impact on human male reproductive health such as reduced sperm counts, cryptorchidism, hypospadias and testicular cancer, Storgaard et al. (2005) reached this conclusion:

With the possible exception of testicular cancer there is no strong epidemiological evidence to indicate that prenatal exposures to estrogen are linked to disturbed development of the male reproductive organs. It is unlikely that phytoestrogens and several environmental xenoestrogens play a role unless exposures are extremely high (which is not expected), the dose-response relation is U-shaped or mixtures of xenoestrogens have synergistic actions. Low exposure levels for xenoestrogens may, however, operate by means of other toxicological mechanisms (Storgaard, et al., 2005).

It has been hypothesized that prenatal DES exposure may also have led to behavioral effects in humans (Meyer-Bahlburg and Erhardt, 1986; Meyer-Bahlburg, et al., 1995). Primary studies exploring possible behavioral and psychiatric effects of prenatal DES exposure in males first appeared in the literature during the 1970s. DES exposure has been associated with increased potential for major depressive disorders and other psychiatric effects in males (Katz, et al., 1987; Meyer-Bahlburg et al., 1985; Pillard et al., 1993; Saunders, 1988; Vessey et al., 1983). Recent discussions of potential psychiatric effects of prenatal DES exposure, including gender-related effects and schizophrenia, have been presented by Verdoux (2000; 2004) and Boog (2004). Verdoux summarizes the research on DES in the psychiatric literature this way:

Sparse findings suggest that exposure to xenoestrogens such as diethylstilbestrol may be a risk factor for psychiatric disorders, mediated by a possible deleterious impact of the substances on foetal neurodevelopment, but this hypothesis is speculative owing to the small number of studies and their methodological limitations (Verdoux, 2004).

Among the possible effects associated with prenatal DES exposure that have been discussed in the literature is impact on psychosexual development (Giusti et al., 1995). Research investigating possible psychosexual impact in human males was first published in the 1970s (Yalom, Green, and Fisk, 1973). Studies by Kester et al. (1980), Reinisch and Sanders (1984; 1992) and Reinisch, et al., (1991) attempted to assess various dimensions of "masculine" and "feminine" behavior and spatial ability among DES sons. In their meta-analysis of 19 studies on the behavioral effects of prenatal exposure to hormones administered for the treatment of at-risk human pregnancy (including the Yalom et al., 1973 and Kester et al., 1980 studies of DES-exposed males), Reinisch et al. (1991) concluded:

The data on prenatal exposure to synthetic estrogen derive primarily from subjects exposed to diethylstilbestrol (DES). DES-exposed male subjects appeared to be feminized and/or demasculinized, and there is some evidence that DES-exposed female subjects were masculinized.

A study of "psychosexual characteristics" (limited to questions regarding "handedness", "age at first sexual intercourse", "number of sexual partners", "percent having exclusively heterosexual partners", "percentage ever married") was conducted in 1994 with responses from DES sons and DES daughters participating in the National Cancer Institute's long-term DES combined cohort studies (Titus-Ernstoff, et al. 2003). Although Udry (2003) critiques the Titus-Ernstoff study for not examining "gendered behaviors," no primary research investigating gender-related outcomes of DES-exposed males has been published since the Reinisch et al. review of 1991.

While it is not possible in this paper to review the extensive array of experimental animal research involving prenatal and neonatal DES exposure, two recent wildlife studies of the effects of DES on the reproductive function and behavior of male Japanese quail are notable. One study by Halldin et al. (2004) included DES in a primary assessment of the effects of estrogenic chemicals administered during the sexual differentiation phase in Japanese quail. They summarize:

We conclude that the Japanese quail is well suited as an animal model for studying various long-term effects after embryonic exposure to estrogenic compounds. Depressed sexual behavior is proved to be the most sensitive of the variables studied in males and we find this endpoint appropriate for studying effects of endocrine modulating chemicals in the adult quail following embryonic exposure.

A separate study of sexual behavior in male quail by Viglietti-Panzica et al. (2004) led to the conclusion:

The present data demonstrate that embryonic treatment with diethylstilbestrol induces a full sex reversal of behavioral phenotype as well as a significant decrease of vasotocin expression in the preoptic- limbic region in male Japanese quail.

These findings are consistent with those of Walker and Kurth (1993), who experimented with DES in laboratory mice and concluded that abnormal sexual differentiation of the fetal hypothalamus is the most common by-product of DES exposure.

Many questions remain as to how extensively the results of wildlife and animal behavioral studies involving DES can be extrapolated to measurable effects in humans (Vandenbergh, 2003; Zala and Penn, 2004). Questions with regard to the full impact of prenatal DES exposure on the genetic aspects of sexual differentiation have also been raised in recent years (Fielden, et al., 2002; Mericskay et al., 2005). These issues validate the importance of continued study and documentation of the developmental effects of DES exposure in animals as well as humans.

Researching DES Sons: An Internet Study

In July 1999, the U.S. National Cancer Institute, National Institute of Environmental Health Sciences, Office of Research on Women's Health and the Centers for Disease Control jointly sponsored a two-day conference, "DES Research Update 1999: Current Knowledge, Future Directions" (NCI, 1999). The event brought together leading DES research scientists, public health specialists, and DES-exposed advocacy group representatives for an evaluation of what was known and what still needed further investigation in the realm of human health effects of DES exposure. Among the notable conclusions of this conference was that DES sons had been insufficiently studied, and that more studies were needed to document the full range of adverse health consequences in DES sons.

This present study was initially conceptualized as an Internet-based outreach campaign for locating DES sons from around the world and inspired by the need for more primary research involving DES sons. During the same month as the NCI's DES conference, the DES Sons online network was launched at <http://health.groups.yahoo.com/group/des-sons>. Scott Kerlin, a DES son born in 1953, founded the network after extensive review of existing DES research and following a series of discussions with DES Action USA, the largest advocacy group representing

DES-exposed individuals in the United States. In 2003, the network's name was updated to "DES Sons International Network" in order to reflect the inclusion of DES sons located in Canada, Europe, and Australia. An extensive online reference library was also developed and maintained at <http://health.groups.yahoo.com/group/des-sons/links>.

The perceived advantages of utilizing the Internet for conducting this study included:

- Opportunities for greater anonymity and privacy among participants
- Ability to include participants in research activities in a more convenient fashion (asynchronous, ongoing communication) than in traditional face-to-face interviews or one-time surveys
- Ability to enroll study participants in a "virtual support group environment" (i.e., network-associated private discussion list) that enabled the researcher to present questions pertaining to DES exposure or effects which stimulated group discussion and deeper levels of self-disclosure than in traditional interview formats (Murray, 1997)
- Opportunity for participants to develop a greater comfort level with participation in the research, which can lead to increased willingness to self-disclose about health, medical, or psychological issues of great sensitivity.

The network's goals at the outset included (1) locating individual males who could confirm their prenatal DES exposure (i.e., confirmation that they are "DES sons"); (2) documenting the range of self-report indicators of lifetime health, medical, and behavioral concerns reported directly by DES sons; (3) promoting interpersonal support among DES sons; (4) expanding investigation of the confirmed and suspected adverse effects of prenatal DES exposure in males by surveying DES sons who had never participated in the NCI's DES cohort studies.; (5) attempting to document the length of prenatal drug exposure including determination of the trimester of mother's initial use of DES during pregnancy; and (6) assessing the level of public awareness about DES sons.

The revelation in the early 1970s of heightened cancer risk among DES daughters led to a public advocacy movement among DES daughters and their mothers for increased research on DES and women's reproductive health concerns along with greater accountability among the drug companies (Seaman, 2003). However, DES sons have historically remained relatively isolated from one another and their health concerns have been largely unknown to the public. Among the activities of the DES Sons International Network was to document the most common patterns by which DES sons learned of their prenatal exposure. Researchers had long recognized that among DES daughters, the most common form of notification regarding DES exposure was from mothers (Apfel and Fischer, 1984; Seaman, 2003). Less has been known about communications and relationships between DES sons and their mothers although it is believed that lower percentages of DES sons than DES daughters have been informed of their exposure (NCI, 1999).

Sample Development

Upon launch of the DES Sons online network in 1999, announcements about the network were made through a variety of DES print and online outreach resources from DES Action USA, DES Action Canada, and DES Action Australia. Other announcements about the sons' network and its web site were posted in male reproductive health resource networks where outreach was thought to provide greatest likelihood of reaching individual males with evidence of prenatal exposure.

Online requests for network memberships and listserv subscriptions became the mechanism by which, over time, the sample of DES sons was developed for the subsequent research study. Each request was carefully screened for (1) evidence or confirmation of prenatal DES exposure; (2) confirmation of birth between the late-1940s and early 1970s in all requests from individuals born in the U.S.; (3) confirmation that the subscriber was born as a male and thus qualified to be considered a "DES Son". There was no cost to participants who joined the network and all participation in subsequent interviews, surveys, and online discussions involved voluntary consent of the study participants. Members were asked to preserve the "closed" nature of all online discussions (i.e., access to list discussions was only for individuals who had become network members). In order to participate in the network's discussion list, each membership applicant was asked by the researcher to provide a summary history of principal health, medical, and psychological issues that had occurred across the lifespan.

In accordance with recommended best practices in online health and medical research methodology, all health histories and online interview data gathered in this study were preserved confidentially offline and appropriate steps were followed to assure privacy (Duffy, 2002; Eysenbach, 2002; Sheehan and Hoy, 1999; Stone, 2003).

During 2003, the U.S. Centers for Disease Control and Prevention (CDC) held a year-long "DES Update" public education and outreach campaign for providing information to DES-exposed individuals (online at <http://www.cdc.gov/DES/>). The DES Sons International Network served as a participating partner and was the largest organization of DES sons to join the campaign. As a result, nearly 100 DES sons ultimately joined the online network in subsequent months.

Primary research on DES sons' health issues conducted through the network included (1) documenting each member's self-report indicators of critical health, medical, and psychological events or issues across the lifespan; (2) periodic analysis and reporting of statistical data summaries of leading health concerns reported by DES-exposed members; (3) conducting several online surveys (open to network members only, and archived under the "polls" section of the DES sons network web site at <http://health.groups.yahoo.com/group/des-sons/polls>) on issues of reported greatest concern among network members; (4) follow-up interviews (open-ended) with individual DES sons, either online or by telephone when permission was granted for the researcher to make subsequent contact. Reports of research findings were posted annually to the DES Sons International Network in order to keep members aware of the range of primary health and medical concerns raised by network subscribers. A preliminary report summarizing what had been learned from research with DES sons during the first three years of the study, 1999-2002, was published by Kerlin and Beyer in 2003 (Kerlin and Beyer, 2003).

Study Statistics and Preliminary Findings

This paper's **Appendix** presents an overview of statistics from initial analysis of data gathered during the primary study of DES sons discussed in this paper. The period of the full study spanned five years, from July 1999 to July 2004. What follows is a brief summary of the results that have been determined so far, based on feedback from more than 500 study participants. Data analysis will continue until 2006, when a full report will be released.

- **Sample Size**
By July 2004, a sample of approximately 500 males with confirmed (60% of total) or "strongly suspected" DES exposure (40% of total) participated in the DES Sons International Network research and provided a summary of major health, medical, and

psychological issues they had encountered across the lifespan. Among the 60% of participants who indicated they had confirmed their exposure, the majority of confirmations came from the mother's verification of having been given DES at some time during the pregnancy. The total number of study participants who have confirmed their exposure through direct access to their mothers' medical records continues to be investigated (see Appendix, Part I).

- Nations of Origin
Approximately 85% of network members were born in the U.S., while 5% each indicated they were born in Canada, Europe (chiefly UK) or Australia.
- Core Health Concerns of DES Sons
Based on preliminary analysis of critical health issues reported by individual DES sons in the network, the three topics most frequently listed among the sample of 500 individuals with confirmed or suspected prenatal DES exposure are (a) gender identity concerns (at least 150 reports); (b) psychological/mental health issues, especially depression and anxiety disorders (at least 100 reports); and (c) hormonal/endocrine health issues (at least 75 reports) (see Appendix, Part II).
- Additional Reported Adverse Health Effects
Though identified less frequently in overall health reports provided by study participants, several participants listed histories of infertility, reproductive tract abnormalities (including reports of ambiguous or underdeveloped genitalia), epididymal cysts, cryptorchidism, hypospadias, gynecomastia, and erectile dysfunction. Statistics on the full extent of reporting of these concerns are still undergoing analysis.
- Prevalence of Male-to-Female Transsexual, Transgender, and Intersex Individuals
More than 150 network members with "confirmed" or "strongly suspected" prenatal DES exposure identified as either "transsexual, pre- or post-operative," (90 members), "transgender" (48 members), "gender dysphoric" (17 members), or "intersex" (3 members). These statistics are taken from self-report terms provided by individual participants in their health histories (see Appendix, Part III).
- Low Cancer Prevalence
Only 7 individuals with confirmed or "strongly suspected" prenatal DES exposure have reported experiencing some form of cancer. Most were testicular cancer survivors.

Discussion

- **Among the most significant findings from this study is the high prevalence of individuals with confirmed or strongly suspected prenatal DES exposure who self-identify as male-to-female transsexual or transgender, and individuals who have reported experiencing difficulties with gender dysphoria.**

In this study, more than 150 individuals with confirmed or suspected prenatal DES exposure reported moderate to severe feelings of gender dysphoria across the lifespan. For most, these feelings had apparently been present since early childhood. The prevalence of a significant number of self-identified male-to-female transsexuals and transgendered individuals as well as some individuals who identify as intersex, androgynous, gay or bisexual males has inspired fresh investigation of historic theories about a possible

biological/endocrine basis for psychosexual development in humans, including sexual orientation, core gender identity, and sexual identity (Benjamin, 1973; Cohen-Kettenis and Gooren, 1999; Diamond, 1965, 1996; Michel et al, 2001; Swaab, 2004).

- **Mental health and psychiatric issues (including depression and anxiety disorders) are relatively significant among the population of DES sons participating in this research.**

This study's findings provide fresh evidence of psychiatric disturbances among individuals exposed to DES. It is hopeful that future research on human health effects of exposure to endocrine disrupting chemicals (i.e., assessing neurotoxicity) can include psychiatric disturbances such as major depression, anxiety disorders, eating disorders, and psychoses as potential endpoints for analysis of the long-term effects from prenatal exposure. Additional questions may be explored as to whether psychiatric conditions such as increased depression and/or anxiety disorders in DES sons have a foundation in primary endocrine system disorders.

- **Endocrine system disorders such as hypogonadotropic hypogonadism in DES sons have been among the more common reported adverse health effects in this research study.**

Although the prevalence of endocrine system disorders among DES sons has not been discussed in any of the existing published epidemiological research on DES-exposed populations, both the Endocrine Society and the American Association of Clinical Endocrinologists (2002) have recognized prenatal DES exposure as a risk factor for endocrine disorders including hypogonadism. This study confirms that this issue needs further attention in future studies of DES sons.

- **Relative infrequency of reported cancer among the DES sons in this research is consistent with most existing long-term studies demonstrating limited cancer prevalence in males with prenatal DES exposure.**

While the rate of total cancer occurrence among members of the DES Sons International Network is uncertain, numerous efforts have been made to generate discussion about cancer risks and in particular, to encourage dialogue regarding testicular cancer experiences. Approximately seven members of the network between the study years of 1999 and 2004 indicated some past or present experience with testicular cancer. It appears that overall cancer outcomes among network members have been low, a finding consistent with research by Strohsnitter et al. (2001).

- **Based on the findings in this study, research into the human health effects of exposure to endocrine disrupting chemicals needs to focus on additional behavioral toxic endpoints besides those historically investigated.**

Implications

Although the scope of documented human health effects from prenatal exposure to various endocrine-disrupting chemicals continues to expand, the study of human behavioral effects is still in relative infancy (Ferguson, 2002; Swaab, 2004). This study's findings may offer new insights for the emerging field of neurobehavioral teratology relative to understanding disturbances of gender identity and sexual identity development.

Undoubtedly the results of this study--particularly the findings with regard to the prevalence of gender-related concerns among a significant number of individuals with confirmed and/or suspected prenatal DES exposure--will come as a surprise for some. It is worth noting that investigations regarding the *possible* effects of prenatal DES exposure on sexual differentiation (brain and body), and sexual orientation have been undergoing discussion for quite some time (Baron-Cohen, 2004; Hines, 1998; Hines 1999; Meyer-Bahlburg et al., 1995; Toppari and Skakkebaek, 1998), though more emphasis in the published research has tended to be placed on possible effects in DES daughters than in DES sons.

While prior to this current study there have been no primary research studies of DES sons which have documented the prevalence of transsexualism or other gender identity disorders, there *are* publications in which prenatal DES exposure is listed among the potential factors *associated* with transsexualism or sexual differentiation disorders. For example, Michel, Mormont, and Legros (2001) in their psycho-endocrinological overview of transsexualism observe the following:

Gender identity disorders may be the consequence of an atypical hormonal environment such as congenital adrenal hyperplasia, resistance to androgens or even exogenous hormonal impregnation (the absorption of diethylstilboestrol treatment during pregnancy). In the majority of cases, these subjects do not develop towards transsexualism (2001, p. 366).

In the 6th edition of the widely-consulted *Dictionary of Organic Compounds* (1996) the DES entry appears on pages 2175-2176 and includes within its array of documented adverse effects, "causes male impotence and transsexual changes particularly in offspring exposed *in utero*." In the text, *Human Embryology & Teratology, Second Edition* (1996), O'Rahilly and Muller list DES among their directory of hormonal teratogens, stating, "Exposure of a female conceptus to DES, which can act as an estrogen, can lead to bisexuality. In a male conceptus, the secretion of testosterone can be suppressed, resulting in hypomasculinization." (O'Rahilly and Muller, 1996, p. 111).

The term "gender-bending chemicals" has become relatively popular with the news media in their latest reports on the toxic effects of endocrine disrupting chemicals such as phthalates on male reproductive development (Sample, 2005; Swan et al., 2005). Scarcely more than a decade ago, the concept was almost unheard of. Its introduction into early news stories describing documented and suspected but unconfirmed effects of endocrine disrupting chemicals (EDCs) no doubt provoked both amusement and angst in the public imagination (see "Gender-Bending Pollution", 1995). By the time the World Health Organization's International Programme on Chemical Safety had released its "Global Assessment of the State-of-the-Science of Endocrine Disruptors" (IPCS, 2002), the story of DES had become part of the story of an entire group of environmentally-present toxic chemicals thought capable of creating a variety of reproductive abnormalities in humans as well as animal populations ("Alarm at Gender-Bending Chemicals", 2002). In that same year, Dutch researchers studying male and

female children's play behavior documented apparent "feminizing" effects in boys resulting from perinatal exposure to PCBs and dioxins (Vreugdenhil, et al., 2002). Undoubtedly, the issue of endocrine disruption and potential impact on gender identity and sexual development is an issue that merits wider investigation in the future (Johnson, 2004).

Historically, in the case of news stories about DES and its cancer-causing effects in DES daughters, many revelations first occurred in the 1970s (Berkson, 2000; Krinsky, 2000), but publicity regarding DES sons remained largely absent. And yet, there was no lack of recognition in the published medical literature that historically, at least some males prenatally exposed to DES were born with "structural and functional disorders of the reproductive tract" (Cosgrove, et al., 1977) or suffered psychiatric effects (Pillard et al, 1993).

If the results of this current study have pointed out anything significant, it is that we cannot relegate DES to the dustbin of "cancer-causing drugs no longer being used and therefore unworthy of continued investigation." And we cannot *afford* to limit the scope of our vigilance and public health information regarding long term effects of DES to cancer outcomes (Schrager and Potter, 2004).

Epilogue

A recent *Cochrane Library Review* of proposed medical protocols for evaluating future research identifying the relative risks and benefits (if any) of treating preterm infants with estrogens and progestins in order to prevent morbidity and mortality (Hunt et al., 2005) has recognized the history of adverse effects of prenatal DES exposure in sons and daughters. In discussing the history of adverse events associated with previous medical uses of estrogenic drugs for treatment of pregnancies, the authors observe:

Administration of sex steroids is not without risk. In the 1960's, women with high risk pregnancies were treated with diethylstilbestrol (DES). Epidemiological studies have since demonstrated strong associations between such therapy and abnormalities in the offspring of these pregnancies.

Perhaps most important relative to the findings presented in this current study of DES sons is the recommendation by Hunt et al. (2005) that future studies of preterm infants treated with estrogens and progestins need to carefully observe "evidence of any adverse events from hormone administration". Hunt et al. recognize two indicators of adverse events in this area:

- feminisation of males
- long term psychological morbidity, defined as any psychological disorder that meets diagnostic criteria of DSM-IVR

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APPENDIX

DES Sons International Network 5-Year Summary Statistics

Online Study Dates: July 1999 to July 2004

I. **Statistics on DES Sons Participating in the DES Sons International Network Between 1999 and 2004**

	<u>Totals</u>
(a) # of individuals requesting membership on DES Sons network listserv	600+
(b) # of individuals (after initial screening) with confirmed or "suspected" prenatal DES exposure who were allowed to join DES sons network	> 500
(c) % of (b) who confirmed prenatal DES exposure	60%
(d) % of (b) with "suspected" but unconfirmed prenatal DES exposure	40%
(e) % of (b) with direct access to mother's medical records	Unknown

1. In the five years since formation of the DES Sons network in July 1999, approximately 600 individuals requested information or support through e-mail follow-up requests and/or requests to join the network. This is over and above all information that is freely available for visitors to the Network's web site (<http://health.groups.yahoo.com/group/des-sons>) which provides substantial information and resources on DES without subscription. Because the DES Sons International network does not maintain statistics on total Internet traffic to its web site, there is no accurate method to gauge how many other affected individuals may be utilizing this information.
2. Of the 600 individuals who have sought further DES information, approximately 500 indicated at the time of my initial screening that they had either actual confirmation (from mother, or direct access to medical records) or strong suspicions (based on unconfirmed information from other family members) that they had been exposed to DES in utero. These 500 individuals with confirmed or suspected prenatal DES exposure were members of the network sometime between 1999 and 2004.

II. DES Sons Reported Health and Medical Concerns: Frequency of Reporting¹

	<u>Totals</u>	<u>% of Total</u>
(a) Number of DES sons (confirmed exposure) participating in the online study between 1999 and 2004	300	60 %
(b) Number of individual males with "suspected but unconfirmed" prenatal DES exposure participating in study	200	40 %
(c) Numbers of DES sons (confirmed and suspected) reporting various health and medical concerns (percentages are of confirmed and suspected exposure):		
• Gender Dysphoria or Gender Identity Concerns	150+	30 %
• Major depression and/or anxiety disorders	100+	20 %
• Hypogonadism or other hormone-related disorders	75	15 %
• Infertility	30	6 %
• Testicular Cancer	7	1.4 %

1. Based on health history summaries received by the DES sons network between 1999 and 2004 from individuals with confirmed and suspected DES exposure, the three areas of greatest health concern among DES sons in the network appear to be (a) gender identity disturbances; (b) psychological/mental health issues including anxiety and depression; and (c) hormonal/endocrine health issues, especially hypogonadism. More than 150 members (all individuals who were born male) described histories of significant feelings of gender discomfort, and more than 90 identified as male-to-female transsexuals. More than 100 members described lifetime experiences with depression and/or anxiety disorders.
2. Somewhat lower proportions of members indicated concerns regarding autoimmune disorders, infertility, reproductive tract abnormalities, ambiguous or underdeveloped genitalia, epididymal cysts, testicular cancer, and erectile dysfunction. Because not every individual member has necessarily disclosed the full range of health issues or medical concerns by which he or she has been affected, the relative significance of reported health concerns among DES sons in this research study is an approximation, based on preliminary textual analysis of information which has freely volunteered by network members.
3. Cancer reports among DES sons were relatively rare (7 reported cases of testicular cancer).

¹ Figures are based on a preliminary analysis of response data. A final report will be available in 2006.

III. Statistics of Prevalence of Transsexualism, Transgenderism, Gender Dysphoria, or Intersex Among “Confirmed” and “Suspected” DES Exposed Individuals (N=158)

1. Among the population of DES sons joining the network who have discussed a history of gender identity concerns, personal stories and/or introductions have been received from more than 150 individuals with either confirmed or “strongly suspected” DES exposure.
2. Responses were received from at least 93 individuals with confirmed prenatal DES exposure who self-identify as either transsexual (male-to-female), transgendered (male-to-female), “gender dysphoric,” or intersex. The distribution of these 93 individuals is as follows:

Confirmed DES-Exposed and Gender-Related Issues (N=93)

(1) Confirmed Exposed and Transsexual:	54 individuals
(2) Confirmed Exposed and Transgender:	26 individuals
(3) Confirmed Exposed and Gender Dysphoric:	10 individuals
(4) Confirmed Exposed and Intersex:	3 individuals

3. There have been at least 65 individuals with “strongly suspected but not yet confirmed” exposure who indicated they are either transsexual (male-to-female), transgendered (male-to-female), “gender dysphoric,” or intersex. The distribution of these 65 individuals is as follows:

Strongly suspected, not confirmed DES Exposed and Gender-Related Issues (N=65)

(1) Suspected Exposure and Transsexual:	36 individuals
(2) Suspected Exposure and Transgender:	22 individuals
(3) Suspected Exposure and Gender Dysphoric:	7 individuals
(4) Suspected Exposure and Intersex	none reported