Endocrine Disruption—History, Fact, and Fantasy of Gender Bending Chemicals

by Raphael J. Witorsch, Ph.D.

Hormones control all reproductive processes such as gender determination before birth, sexual maturation during adolescence, and reproductive function in adulthood. Certain chemicals have the capacity to behave like hormones or their antagonists. In so doing, these substances can potentially produce reproductive birth defects like gender ambiguity and penile deformities, abnormalities in sexual development and adult reproductive function, as well as alterations in the incidence of hormone-dependent cancers of the prostate, uterus, and breast. Such chemicals have been referred to as endocrine disruptors or "gender benders."

Diverse arrays of environmental substances (e.g., dioxins, PCBs, alkyl phenols, DDT derivatives, certain pesticides, pharmaceuticals, and plant and fungal agents) mimic or inhibit hormone activity, usually through an interaction with the estrogen receptor. The estrogen receptor is a protein within the target cell that binds estradiol, the principal female (or estrogenic) sex hormone. Hormone reception is the first step in a hormone-induced biological response of the cell. Hormone receptors account for "hormone specificity," where a cell can respond to a particular type of hormone (e.g., estrogen) and not another.

A recent study reported that almost 100 compounds from varying classes of chemicals could bind to the estrogen receptor.[1] This "promiscuity" of the estrogen receptor appears to be the major reason for endocrine disruption. Accordingly, chemicals that interact with the estrogen receptor are referred to as environmental estrogens, xenoestrogens, or estrogen mimics. A hormone receptor contains a region called a "binding pocket" that can accommodate the three-dimensional structure of the hormone, analogous to a key (hormone) fitting into a lock (receptor). Many xenoestrogens contain chemical features that resemble parts of the estradiol molecule, so the binding pocket of the estrogen receptor can accommodate these molecules, even though the fit is usually less than perfect and the binding to the receptor is weak. As a result of this weak binding, xenoestrogens usually exhibit low biological activity compared to estradiol, and relatively large amounts are required to produce biological effects.

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Several observations in wildlife and humans suggest environmentally-induced endocrine disruption. Grazing livestock exhibit "clover disease" or impaired fertility, which has been attributed to the consumption of plants containing estrogenic substances (or phytoestrogens). Contamination of bodies of water with xenoestrogens has been causally associated with demasculinized alligators in Lake Apopka, Florida, and reproductive abnormalities in aquatic birds of the Great Lakes.

Treatment of pregnant women with diethylstilbestrol (DES), a potent synthetic estrogen used therapeutically prior to its prohibition in 1971, has been associated with vaginal cancer in offspring. A composite study (or meta-analysis) of over 60 published studies between 1940 and 1990 suggested a 50% decline in sperm production worldwide during this time period. The authors of that study attributed the trend to exposure of male embryos during pregnancy to a "sea of estrogens" that pervaded the environment.[2] A positive correlation was reported between tissue levels of estrogenic compounds and the incidence of human breast cancer. Increasing trends of endocrine-related disorders such as penile deformities, prostate cancer, obesity in children, and precocious puberty also has been attributed to endocrine disruptors.

In the laboratory, bisphenol A, a constituent of plastics and dental restorative materials that has estrogenic activity, reportedly has produced enlargement of the prostate in adult mice that were exposed to low (or environmentally relevant) doses of the substance prior to birth. This phenomenon has been referred to as the "inverted U" effect because it appears to occur within a narrow dose range. It has been suggested that this effect observed in mice might have relevance to the etiology of prostate cancer in humans.

Media coverage of the phenomenon has raised public awareness and concern about endocrine disruption. At congressional hearings in 1993, Professor Louis Guillette of the University of Florida, the leading researcher of the Lake Apopka study, commented in reference to the report of sperm count declines that "every man in this room is half the man his grandfather was." In March 1995, a *Newsweek* magazine

article entitled "The Estrogen Complex" suggested that societal decreases in sperm production could be the result of "chemical pollutants in water and food." Awareness of endocrine disruption was intensified by the 1996 publication of the book, *Our Stolen Future,* by Dr. Theo Colborn of the World Wildlife Fund and co-authors, who strongly advocated that endocrine disruption posed a serious threat to humans and wildlife.

Numerous books and Internet websites now address the issue of endocrine disruption. In view of the chemical diversity of potential "gender bending" chemicals and their health implications, endocrine disruption has become an issue of particular interest to numerous industries, such as plastics, food packaging, petroleum, pesticides, agricultural products, soy products, pharmaceuticals, and chemicals.

As a consequence of congressional action, the Food Quality Protection Act[3] and the Safe Drinking Water Act[4] mandated that the Environmental Protection Agency (EPA) implement the Endocrine Disruptor Screening Program (EDSP) to test for endocrine disruptive effects in over 87,000 substances or mixtures. The mandate mainly dealt with compounds exhibiting estrogenic activity, although other hormone effects (e.g., androgens, thyroid hormone) also were considered. The EDSP was launched in 1999, and the majority of the program to date has been focused on validating biological assays for hormone activity.

In May 2002, the Hormone Disruption Research Bill was introduced to Congress, authorizing the National Institute of Environmental Health Sciences (NIEHS) to spend $100 million per year over five years to "fund necessary research to protect vulnerable mothers and children from harmful chemicals."[5] Endocrine disruption also is likely to be an issue with respect to the reproductive toxicity provisions of California's Proposition 65.[6] In addition to U.S. activity, in February 2001 the Commission of the European Communities published a White Paper entitled *Strategy for a Future Chemicals Policy*.[7] This strategy, which is guided by the "Precautionary Principle," considers endocrine disruptors as "substances of very high concern" on the basis of their association with such conditions as breast and prostate cancer, decreased sperm production, and genital deformities.

Despite some compelling observations, extensive media coverage, and aggressive government public health policy action, endocrine disruption has been the source of major scientific controversy. Certain key observations supportive of the concept have *not* been confirmed or are subject to debate. Among these are the observations of a marked decline in sperm production among men worldwide over a 50-year period, and the association between tissue xenoestrogen content and breast cancer. Reports of increasing trends of penile deformities, prostate cancer, obesity in children, and precocious puberty are not universally accepted, and may be artifacts of improved screening or flawed epidemiological methods. Finally, other laboratories have not reproduced the low-dose effect of bisphenol A in mice consistently.

In view of the importance of low-dose effects of environmental estrogens and controversy regarding the reproducibility of the inverted U effect, EPA and NIEHS cosponsored the formation of the Endocrine Disruptors Low-Dose Peer Review Panel to review the relevant studies. Comprised of experts from academia, industry, and government, the panel concluded somewhat ambivalently that the evidence for low-dose effects of bisphenol A was "credible," particularly with regard to the major effect—prostatic weight increase in mice. On the other hand, the panel concluded overall that the low-dose effect of bisphenol A had *not* been established as a "general and reproducible finding," on the basis of the number and power of studies in rodents that failed to confirm these effects, and speculated that discrepancies between the studies were due to numerous factors, such as weakness of the effect, animal diets, genetic differences among the animals used, animal housing, and seasonal differences.[8]

This author has questioned the relevance to humans of low-dose effects of bisphenol A in mice during pregnancy, on the basis of species differences.[9] The physiology of pregnancy in mice and humans differs markedly, particularly with regard to the regulation and amount of hormones secreted. Estrogen levels attained during human pregnancy are much higher (usually 100-fold or more) than those attained in the mouse. Furthermore, it would appear that exposure to low doses of a weak xenoestrogen like bisphenol A would have little, if any, impact in human offspring in view of the high estrogen levels attained during human pregnancy.

Although the promiscuity of an estrogen receptor explains why so many environmental chemicals bind to that receptor, it does not explain the nature of the biological response. A chemical that binds to the estrogen receptor can either mimic the action of estradiol or produce the opposite—an "anti-estrogenic" effect. The nature of the response (estrogenic or anti-estrogenic) of chemicals that bind to the estrogen receptor depends upon the specific chemical and target tissue involved. The reason for this diversity of response of xenoestrogens is not fully explained but appears to be a function of the xenoestrogen itself and the particular biochemical make-up of the target cell in question. Other factors also influence the potency and nature of the response of xenoestrogens, but their discussion is beyond the scope of this article.

The general issue of endocrine disruption and its health implications was reviewed in 1999 by two advisory bodies, the American Council on Science and Health and the National Research Council (NRC). Both groups arrived at similar conclusions. While they acknowledge that environmental substances exhibit hormonal activity and can produce endocrine disruption under extreme conditions (e.g., toxic spills or high-dose experimental exposures), both groups concluded that epidemiological studies do not support a consistent link between environmental pollutants and endocrine disruption in humans. Furthermore, most xenoestrogens exhibit low biological activity. In other words, there is little compelling evidence that adverse health effects are evoked by a sea of estrogens as suggested in a study alluded to earlier. The NRC also recommended that more research is needed on endocrine disruption because much is not known about the reproductive and developmental effects of hormonally active agents.

Because the biological effect of various xenoestrogens is difficult to predict at this time, the appropriateness of the Endocrine Disruptor Screening Program is questionable. This ambitious program, as well as the strategy proposed by the European Union, has not considered adequately the complexity of the estrogen receptor signaling pathway and related issues regarding endocrine disruptive mechanisms. Accordingly, such programs may be premature and may provide erroneous or misleading information.

Note: Unless otherwise specified, all information conveyed in this article has appeared and has been cited in one or both of the following papers: Raphael J. Witorsch, *Endocrine Disruption: A Critical Review of Environmental Estrogens From a Mechanistic Perspective*, 19 Toxic Substance Mechanisms 53 (2000); and Raphael J. Witorsch, *Endocrine Disruptors: Can Biological Effects and Environmental Risks Be Predicted?,* Reg. Toxicology and Pharmacology (in press).

[1] Robert M. Blair et al., *The Estrogen Receptor Relative Binding Affinities of 188 Natural and Xenochemicals: Structural Diversity of Ligands*, 54 Toxicol. Sci. 138 (2000).

[2] Richard M. Sharpe & Niels E. Skakkebaek, *Are Oestrogens Involved in Falling Sperm Counts and Disorders of the Male Reproductive Tract?*, 341 The Lancet 1392 (1993).

[3] Pub. L. No. 104-170, 110 Stat. 1489 (1996).

[4] Pub. L. No. 104-182, 110 Stat. 1613 (1996).

[5] Quote attributed to Rep. Louise Slaughter (D-NY) who introduced the bill. *See* News Release, May 9, 2002, *available at* http://www.house.gov/slaughter/ (last visited July 31, 2002).

[6] Safe Drinking Water and Toxic Enforcement Act of 1986, Cal. Health & Safety Code § 25249.5-13 (Deering 1986).

[7] White Paper on the Strategy for a future Chemicals Policy COM(2001)88, *available at* http://europa.eu.int/comm/environment/chemicals/whitepaper.htm (last visited July 31, 2002).

[8] NIEHS, National Toxicology Program (NTP), Final Report of the Endocrine Disruptors Low Dose Peer-Review (2001), *available at* http://ntp-server.niehs.nih.gov/htdocs/liason/LowDoseWebPage.html (last visited Sept. 3, 2002).

[9] R.J. Witorsch, *Low Dose in Utero Effects of Xenoestrogens in Mice and Their Relevance to Humans: An Analytical Review of the Literature,* 40 Food & Chem. Toxicology 905 (2002).