ENDOCRINE DISRUPTORS AND HUMAN HEALTH - AN UPDATE

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Introduction

Colborn and coworkers (1) summarized multiple studies on developmental and reproductive problems in wildlife that may be associated with exposures to various environmental contaminants including organochlorine pesticides and industrial compounds or by-products. Some of these chemicals include the polychlorinated biphenyls (PCBs), dibenzofurans (PCDFs), dibenzo-*p*-dioxins (PCDDs), 2,2-bis(*p*-chlorophenyl)-1,1-dichloroethylene (DDE), and related metabolites. It was hypothesized that many of these responses may be related to exposure to endocrine-active compounds (endocrine disruptors) during critical *in utero*/early postnatal periods leading to male and female reproductive tract problems in the juvenile or adult offspring. This hypothesis is supported by numerous laboratory animal studies demonstrating that *in utero* and/or early postnatal exposure to estrogenic compounds, antiandrogens and aryl hydrocarbon receptor (AhR) agonists such as the highly toxic environmental contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) resulted in a host of problems in the offspring. Moreover, human and laboratory animal studies with the potent estrogenic drug diethylstilbestrol (DES) has also demonstrated the adverse effects on the male and female offspring of women who took this drug during pregnancy in the 1950s to early 1970s. Thus, the endocrine disruptive hypothesis, suggesting that male and female reproductive tract problems may be related to exposures from endocrine disruptors during critical periods of development, is biologically plausible and supported by results from wildlife, laboratory animal and high dose human studies. The major unanswered question is . . . are we currently exposed to levels of endocrine disrupting contaminants that are causing adverse responses?

Endocrine Disruptors and Male Reproductive Capacity

Carlsen and coworkers (2) analyzed 61 studies on male sperm counts published between 1938 and 1991, and linear regression of this data showed a decrease in sperm counts ($113x10^6$ to $66x10^6$/ml) and sperm production during this time period. These data, coupled with the increased incidence of testicular cancer in most countries and some reports of increased incidences of hypospadias and cryptorchidism in children, led to the hypothesis that environmental estrogens, possibly DDE (an antiandrogen), and other endocrine disruptors may be responsible for a worldwide decrease in male reproductive capacity (3, 4). This hypothesis has subsequently received worldwide media and press attention and has also stimulated intense research, particularly on sperm counts.

Sperm Counts. Since 1992, a large number of sperm count/quality studies have been published on various cohorts from hospitals and clinics throughout the world and particularly from developed countries. Some studies reported sperm count declines over the last 15 to 25 years, whereas other studies reported no decline and possibly small increases. More importantly, an new variable has emerged in the sperm count debate, namely the effects of demography. Recent studies have reported that within countries such as the United States, Denmark, France and Canada, there are remarkable demographic variations in sperm counts, and some of these differences within the same country are higher than the reported decrease in sperm counts in the original meta-analysis by Carlsen and coworkers (2). For example, in the Canadian study, sperm count differences varied from 48.6 to 104.5×10^6/ml among the 11 centers involved in this study (5). A recent critical review by Saidi and coworkers (6) concluded that "Sperm concentrations are highest in New York compared to other U.S. cities. When accounting for this geographic difference and examining all available data, there appears to be no significant change in sperm counts in the U.S. during the last 60 years." However, it was also pointed out that "Further studies addressing the causes of geographic variations are needed" (6). It should be noted that variations of organochlorine contaminants within most developed countries/regions are minimal and it is unlikely that these compounds will correlate with region-specific differences in sperm counts. Other factors including weather, diet, other lifestyle differences and possibly chemical exposures may be important for explaining the sperm count variability, and the relative contributions of these and other unknown variables have yet to be determined.

Testicular Cancer. There is much less controversy regarding the incidence of testicular cancer (particularly in young men) which is increasing in most countries. However, like sperm counts, testicular cancer incidence also exhibits high geographical variability. For example, the incidence/10^5 (1985-1986) in Denmark, Norway, Sweden and Finland in 1985-1989 was 14.5, 12.6, 8.3 and 3.6, respectively (7). Although Denmark and Finland are highly developed countries located within the same region, there is a > 4-fold difference in their incidence of testicular cancer in young men. Sharpe (4) hypothesized that the antiandrogen DDE may contribute to testicular cancer; however, it was shown that DDE levels within the Scandinavian countries were not significantly different and, therefore, did not correlate with the differences in testicular cancer incidence in these countries (7). Moreover, the 80-90% decrease in DDE levels observed in most developed countries over last 30 years is inversely related to the increase in the incidence of testicular cancer. Thus, it is likely that organochlorine pollutant levels correlate with testicular cancer and identification of "lifestyle or environmental" contributions to this disease require further study.

Hypospadias and Cryptorchidism. It is well-recognized that *in utero* exposure to estrogenic compounds (e.g. DES) can lead to displacement of the urethral opening

(hypospadias) and failure off the testicles to descend into the scrotum (cryptorchidism). Some papers have described an increase in hypospadias and cryptorchidism; however, a recent review (8) reports that both increases and decreases have been observed and that demographic differences between and within countries were also evident. However, "Among all systems showing an increase, rates tended to level off after 1985" (8). Thus, results obtained for hypospadias and cryptorchidism, two endocrine-related responses, do not support a hypothesis that there is a global decline in male reproductive capacity; however, the familiar demographic variability in hypospadias/cryptorchidism suggest that unknown genetic and environmental factors may play a role in these problems.

Breast Cancer in Women

Since endogenous exposure to estrogens is a risk factor for breast cancer, it was not surprising that it was hypothesized that xenoestrogens were a preventable cause of breast cancer in women (9). Reports that DDE or PCB levels were higher in two small cohorts of breast cancer patients vs. controls (10) were used as evidence to support the xenoestrogen hypothesis even through the estrogenic activities of these chemicals were highly questionable (11). Subsequent larger studies in Europe, North America and Mexico have shown that neither PCB or DDE levels were elevated in breast cancer patients vs. controls and has also been pointed out that xenoestrogens form only a small component of the overall dietary intake of natural endocrine-active chemicals many of which exhibit both estrogenic and antiestrogenic activities (10, 11).

Dioxins

Occupational and accidental exposures to PCDDs/PCDFs *in utero* and as juveniles/adults clearly leads to a multitude of adverse heath effects. However, there are still many differences between various studies that will eventually be resolved after further monitoring. For example, Bertazzi and coworkers recently reported "an excess of diabetes cases" (12), whereas in an industrial cohort, diabetes "showed a negative exposure-response trend" (13). In a recent commentary on environmental disease research, Bertazzi stated that "Open-minded inquiry almost inevitably pays off. Skepticism, instead may curb scientific curiosity" (14), and this author fully agrees with the first part of this statement. However, in assessing the adverse health impacts of trace levels of organic pollutants in a diet containing much higher levels of naturally occurring endocrine-active compounds, a little skepticism may be warranted.

Summary

The endocrine disruptor hypothesis has initiated multiple new areas of research (and research funding) and has further demonstrated the importance of testing endocrine-active chemicals during critical exposure periods. In the opinion of this author, most evidence from human studies does not support the endocrine disruptor hypothesis; however, important new insights from wildlife and animal studies suggest that this area of research should be pursued.

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