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The intersection of neurotoxicology and endocrine disruption

Bernard Weiss *

Department of Environmental Medicine, University of Rochester, School of Medicine and Dentistry, Rochester, NY 14642, United States

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ABSTRACT

Endocrine disruption, the guiding theme of the 27th International Neurotoxicology Conference, merged into the neurotoxicology agenda largely because hormones help steer the process of brain development. Although the disruption motif first attracted public health attention because of reproductive anomalies in both wildlife and humans, the neurobehavioral implications had been planted decades earlier. They stemmed from the principle that sex differences in behavior are primarily the outcomes of differences in how the brain is sexually differentiated during early development by gonadal hormones (the Organizational Hypothesis). We also now understand that environmental chemicals are capable of altering these underlying events and processes. Among those chemicals, the group labeled as endocrine disrupting chemicals (EDCs) offers the clearest evidence of such selectivity, a consequence of their actions on the endogenous sex steroids, androgens and estrogens. Two EDCs in particular offer useful and intriguing examples. One is phthalate esters. The other is bisphenol A. Both agents are used extensively in plastics manufacture, and are pervasive in the environment. Both are produced in immense quantities. Both are found in almost all humans. Phthalates are considered to function in essence as anti-androgens, while bisphenol A is labeled as an estrogen. Their associations with brain sexual differentiation are reviewed and further questions noted. Both EDCs produce a wider spectrum of health effects, however, than would be extrapolated simply from their properties as anti-androgens and estrogens. Obesity is one example. Further complicating their assessment as health risks are questions about nonmonotonic dose–response functions and about transgenerational effects incurred via epigenetic mechanisms. All these facets of endocrine disruption are pieces of a puzzle that challenge neurotoxicologists for solutions.

1. Introduction

Endocrine disruption, the global theme of the 27th International Neurotoxicology conference, can trace its connections to neurotoxicology from the first stirrings of the environmentalist movement. Rachel Carson's *Silent Spring* (1962) sounded alarms about the decline of bird populations (Fig. 1) but touched peripherally on implications for human health. Her message arrived in the midst of rising concerns about environmental contamination, and the erosion, not only of avian populations, but of aquatic mammals and various fish species from both marine and freshwater habitats. Reproductive anomalies were also observed in terrestrial mammals such as mink fed fish from the Great Lakes. Bald eagle populations were declining at disturbing rates. Around the Great Lakes, herring gulls displayed peculiar developmental anomalies such as twisted bills. Participants in the first Rochester Conference on Environmental Toxicity (Berg and Miller, 1969), trying to explain the evidence that eggshell thinning might explain diminished eagle populations, offered the proposition that pesticides such as DDT could be responsible because of their estrogenic properties, while others saw a connection with dioxins and allied chemicals (reviewed in Schecter et al., 1994). The growing swell of such information, and the puzzling changes taking place in wildlife populations spurred the 1991 Wingspread Conference (Markey et al., 2002), led by Theo Colborn, to its conclusion that these phenomena could be the result of environmental contamination by chemicals that altered hormone status and function. Endocrine disruption was later featured as a theme for neurotoxicology, especially as a developmental neurotoxicant, at the 1995 International Neurotoxicology Conference (Tilson, 1998; Weiss, 1997).

Endocrine disruptor describes those chemical agents that interfere with the biological actions of hormones by blocking, mimicking, displacing, or acting through a variety of other mechanisms to subvert their natural roles. Like some other neurotoxicants, they present a special challenge to traditional toxicology because, rather than expressing their effects in the form of tissue pathology, clinical disorders, or death, they may simply distort or shift the organism's normal or characteristic patterns of response to environmental or internal conditions.

* Correspondence address: Department of Environmental Medicine, University of Rochester Medical Center, Rochester, NY 14642, United States.
Tel.: +1 585 275 1736; fax: +1 585 256 2591.
E-mail address: bernard_weiss@urmc.rochester.edu.

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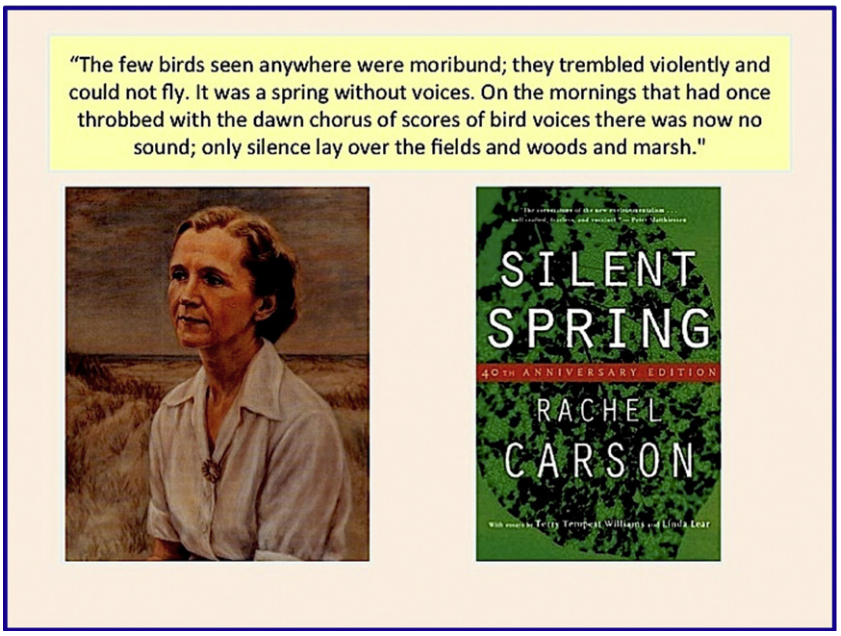

Fig. 1. Rachel Carson (1907–1964) lifted a nascent environmental movement into public awareness with the publication of *Silent Spring* (1962). It highlighted the environmental risks of pesticides such as DDT, which earlier had been overlooked.

Endocrine disruption offered a connection between environmental contaminants and human reproduction with publication of a 1992 article contending that semen quality had undergone a steady decline during the previous 50 years (Carlsen et al., 1992). It aroused a spirited debate about its validity and the underlying mechanisms. Sharpe and Skakkebaek (1993) interpreted these findings as evidence of exposure to estrogenic chemicals in the environment. To Skakkebaek (2003), viewing the landscape of male reproductive disorders 10 years later, they appeared to blend into an identifiable syndrome. He wrote, "There is evidence that poor semen quality, testicular cancer, undescended testes and hypospadias are symptoms of one underlying entity, testicular dysgenesis syndrome (TDS). Experimental and epidemiological studies suggest that TDS is the result of disruption of embryonal programming and gonadal development during fetal life." The syndrome is now presumed to arise from exposure to environmental endocrine disruptors at a critical stage of development (e.g., Sharpe and Skakkebaek, 2008; Wohlfahrt-Veje et al., 2009).

Neurotoxicology's main connection with endocrine disruption arose through what might be called the sexual brain. The same gonadal hormones that fashion the reproductive system are also fundamental in molding the brain. A connection between reproductive disorders and neurobehavioral function can be devised in a variety of mechanistic formulations, but a statement by Richard Sharpe (2008) frames the context in an engaging way:

"The difference between becoming a male rather than .a female is about as fundamental as you can get, as it will alter that individual's place in society, transform the shape of his body, reshape his inherent abilities, *his thought processes and his behaviors* [my italics]. While it is a constant source of debate and amusement as to whether this "transformation" process represents an improvement or not, when compared with the "set-up" program which would have led to a female, it is becomingly increasingly clear that "making a male" is a rather perilous process."

The publication of *Our Stolen Future* (Colborn et al., 1996) firmly placed endocrine disruption on the agenda of neurotoxicology. Theo Colborn, honored at the 27th Conference, had the insight to foresee this development. Many of the observations that created the book's thesis, that environmental chemicals had been fomenting turbulence in hormonal function, arose from puzzling instances of animal behavior. When George and Molly Hunt (1977) observed the presence of female–female pairings of western gulls on Santa Barbara Island, California, they invoked the term "lesbian gulls." Michael Fry (1995) attributed such pairings to both a reduced male population and anomalies in male reproductive structures and behavior. He proposed DDT and other "estrogenic" contaminants in the environment as causes. Because behavior is a reflection of events and processes in the brain, it became necessary to explain the coupling between aberrant behavior and endocrine disruption by determining how such environmental agents alter brain anatomy and function. In particular, to borrow Sharpe's term, how they proceed to alter the events that "make" a male. A succinct review of this sequence follows to help provide a context for the topics discussed at the conference.

2. Molding the sexual brain

Psychologists are responsible for establishing the principle that now governs how we conceive of sexual differentiation of the brain (Wallen, 2009). What came to be known as the *Organizational Hypothesis* first appeared in a publication by Phoenix et al. (1959). As recounted by Wallen (2009), "In the 50 years since its publication it has transformed common views of the actions of hormones on the nervous system. The notion that hormones could permanently alter the structure of the nervous system, radical when it was first published, is currently taught in high school and undergraduate classes in psychology and neuroscience. It has become the dominant explanation for the genesis of behavioral sex differences."

The differentiation process is largely controlled by the sex steroid hormones, that is, androgens and estrogens. Although these chemicals can apparently modify brain organization at other times of life, such as puberty (Mouritsen et al., 2010), the most critical phase occurs during pregnancy, when pronounced changes in the fetal brain are taking place almost hour by hour. Within this period lie specific temporal windows during which sexual differentiation proceeds most forcefully. For the genitals, this process in humans