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Endocrine Disruption for Endocrinologists (and Others)

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On June 3, 2005, The Endocrine Society held an unprecedented full-day forum on endocrine-disrupting chemicals (EDCs). Sponsored through the generosity of The Endocrine Society, the National Institute of Environmental Health Sciences, and the Environmental Protection Agency, this forum brought together basic scientists, physicians, clinical scientists, epidemiologists, and others interested in discussing and learning about the importance of endocrine disruption in the context of endocrinology. This first-ever supplement to *Endocrinology* contains a special series of eight review articles on endocrine disruption, seven of which are authored by the forum's speakers, and the eighth providing an evolutionary perspective to epigenetics in endocrine disruption. As forum organizers, the three of us developed and directed the programming, but more importantly, we have this opportunity to summarize and integrate the outcomes of the forum for the endocrine community. The review articles that follow this introduction make it clear that the topic of endocrine disruption is pertinent to all endocrinologists. Moreover, a wide variety of chemicals exert endocrine-disrupting actions, including but not limited to industrial chemicals, pesticides, plant phytoestrogens, metals, and other environmental substances. Here we provide an overview of the highlights of the science at the forum, a synopsis of the open discussion, and we make recommendations for future research.

The Science of Endocrine Disruption

Three major themes were recurrent at the forum. First, the timing of exposure to exogenous hormonally active substances, *i.e.* endocrine disruptors, is critical to the outcome of that exposure, with early lifetime exposures (*e.g.* fetal or early postnatal) particularly detrimental because they produce permanent effects (1). Second, EDCs often act at environmentally relevant doses, have complex dose-response curves, and involve cellular mechanisms that often occur through multiple signaling pathways (2). Third, effects of EDCs not only impact the exposed individual but may also be transmitted to subsequent generations through the germ line, probably via epigenetic modifications (3–5). These topics are discussed here briefly; for details, we refer our readers to the review article series that follows.

The fetal/developmental basis of adult disease

This hypothesis postulates that exposures to exogenous (and in some cases aberrant exposure to endogenous) substances during developmental periods predisposes an individual to develop a disorder or disease much later in life (1, 6). Those life stages most vulnerable to endocrine disruption are the prenatal and early postnatal periods, because these are times when organ and neural systems are changing most rapidly. Pubertal and perimenopausal periods may also be sensitive windows of exposure because of the changing hormonal effects during these periods (7). Furthermore, research in endocrine disruption is focusing increasingly on the interactions of these early exposures with the individual's nutrition and genetics, including genetic polymorphisms and epigenetic modulation of gene activity. Thus, exposure of one individual to an environmental toxicant may have little effect, whereas another individual with identical exposure will develop overt disease or dysfunctions. Differences can be caused by the individuals' different genetic makeup as well as other lifetime exposures that can ensue. In this supplement to *Endocrinology*, the papers from the groups of Skinner (8), Crews and McLachlan (9), Fenton (10), Blumberg (11), Korach (12), Newbold (13), Petersen (14), and Welshons and vom Saal (15) provide strong examples of the fetal/developmental basis hypothesis for systems ranging from neural, mammary gland, and reproductive tract of males and females as well as neuroendocrine systems. Moreover, other studies show that this hypothesis is applicable to thyroid (16, 17), stress (18), growth (19), and metabolism and obesity (20).

Epigenetic, transgenerational effects

Effects of endocrine disruption may be manifested across multiple generations (*i.e.* transgenerationally), but the mechanisms often do not involve an overt gene mutation. Rather, epigenetic effects of EDCs may occur whereby an action is exerted upon the genome to alter gene expression, by methylation without modifying the sequence of the DNA itself (21) and/or histone modifications such as acetylation (22). Such changes can affect gene function and can be transmitted from generation to generation with a higher penetrance than

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Abbreviation: EDC, Endocrine-disrupting chemical.

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mutations themselves (3). Such mechanisms of EDCs are difficult to diagnose through simple means such as DNA sequencing. The timing of these exposures is crucial, because the receipt of a signal at an inappropriate developmental period may permanently influence gene expression by an epigenetic mechanism. Fortunately, new technology exists to study DNA methylation and acetylation that will likely be essential to identify public health consequences of EDC exposures (23). That epigenetic effects are inherited across multiple generations ties in very strongly to the fetal/developmental basis of adult disease hypothesis; not only what your mother but also what your grandmother or your great-grandmother were exposed to may affect you and predispose you for a disorder. This concept also extends to fathers (and their fathers, *etc.*), because transgenerational effects of EDCs have been reported for up to four generations of male rats via patrilineal germ-line transmission (8). The epigenetic, transgenerational effects of endocrine disruptors are also discussed in the review articles by Anway and Skinner (8), Crews and McLachlan (9), and Newbold *et al.* (13).

Mechanisms and dosage issues for EDCs

A major difficulty in the study of endocrine disruption is the apparent complexity of mechanisms of action. Often, nonmonotic dose-response curves are observed, such as U- or inverted U-shaped dose responses (9, 10, 13, 15). This has complicated the study of endocrine disruption and introduced some skepticism into such results. Nevertheless, endocrinologists should not be surprised by nonmonotonic dose-response curves, because these are common for hormone systems (*e.g.* Refs. 24 and 25). In addition, the mechanisms for EDCs are not only complex but also exerted upon multiple targets. For example, an EDC may be an agonist at one hormone receptor but an antagonist at another (26). It may also act at a different range of dosages from one system to another. Similarly, an EDC may act in different tissues differently. EDCs may also act as selected modulators of estrogen receptors, androgen receptors, thyroid receptors, and others. Furthermore, not only do EDCs act upon the nuclear hormone superfamily, which is most widely studied, but they can also act upon membrane receptors for steroids and neurotransmitters (*e.g.* Ref. 14). EDCs also act upon, or themselves are acted upon by, enzyme systems involved in hormone metabolism and biosynthesis. The combined effect of these multiple actions of endocrine disrupters can be difficult to interpret and can be misinterpreted as variability in the assay system. However, it is important to recognize that all hormones exert nonlinear actions on their targets and that the summation of multiple nonlinear dose responses is not predictable. Therefore, it is predictable that single compounds that interact with multiple endocrine systems will exert complex actions. Moreover, humans and wildlife are virtually never exposed to single compounds but rather to complex mixtures of chemicals that will increase this complexity. Finally, the endocrine state of the subject (experimental or human) during exposure may also influence the ultimate effect. These points need to be taken into consideration when interpreting studies and are discussed in the review articles by Crews and McLachlan (9), Grun and Blumberg (11), Henley and Korach (12), Newbold *et al.* (13), and Welshons, Nagel, and vom Saal (15).

The Discussion at the Forum

A one-hour panel discussion gave the participants of the forum an opportunity to ask questions of the meeting organizers and The Endocrine Society leadership. In attendance were ourselves and officers of The Endocrine Society at that time: Drs. Andrea Dunaif, President-elect; Margaret Shupnik, Co-Chair of the Research Affairs Committee; Glenn Braunstein, Chair of the Media Advisory Committee; and Daniel Spratt, Chair of the Government Relations Committee. A few of these points were: 1) how to increase funding for endocrine disruption from the National Institutes of Health and other federal funding agencies; 2) how to cross-fertilize endocrine disruption research among different scientific disciplines, for example, getting endocrinologists (basic and clinical), toxicologists, and epidemiologists to share insights and information; 3) how The Endocrine Society can continue to increase its leadership role in basic research and clinical understanding of endocrine disruption; and 4) how to get better insights into regulations and testing of industrial and pharmaceutical products.

Although we do not have the answers to these and other questions, we believe that the forum has increased the visibility of the problem of endocrine disruption and raised it to the forefront of The Endocrine Society's priorities.

Recommendations for the Future

As the meeting organizers as well as researchers and administrators actively engaged in endocrine disruption research, we propose the following recommendations to Endocrinologists.

1) Endocrinologists need to appreciate that EDCs and their effects should be grounded in endocrinology as their primary home because these agents act via alteration of the endocrine system, thereby altering any and all aspects of endocrinology, including basic mechanisms and the initiation, progression, and prognosis of disease and dysfunction. Thus, endocrinologists have a unique perspective and background to aid in understanding both the basic mechanisms of these agents and how they alter gene expression, as well as how they can lead to increased susceptibility to diseases and dysfunctions of endocrine systems.

2) Endocrinologists need to interact with other experts across other disciplines to fully appreciate the complex mechanisms of EDCs and the experimental strategies required to obtain credible results.

3) The Endocrine Society should continue to be a leader in research on endocrine disruption, including it in its annual program and hosting future meetings. It should also inform government policy and regulatory rules as well as scientists, physicians, the public, and the media.

4) The issue of endocrine disruption is global, and research and information need to be gathered from different exposure types and levels and disseminated appropriately.

5) There is a particular need for physicians to be knowledgeable about endocrine disruption and how to talk about these issues with their patients.

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Conclusions

Although the concept of environmental endocrine disruption had its origins in the observations of a variety of endocrinologists and toxicologists over the past several decades, we are now at a point where our understanding of endocrine mechanisms is sufficient and our experimental and epidemiological tools are sophisticated enough that we can begin to evaluate this concept in such a way that real answers will be forthcoming. However, this will occur only if we carefully consider the complexity of endocrine mechanisms, apply appropriate technologies to address important public health questions, and work across disciplines. Thus, we must have a central organization to bring the various disciplines together, and The Endocrine Society is a natural place for this to happen.

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