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Our Stolen Future: A Decade Later.

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Who would have predicted 10 years ago that:

- An environmental contaminant, bisphenol A, would cause insulin resistance in adult mice after only 4 days exposure (Alonso-Magdalena *et al*., in press) at concentration levels comparable to that found in tissue and fluid of virtually every American tested by the Centers for Disease Control (Calafat *et al*. 2006)?
- Or that this same molecule is equipotent with estradiol at stimulating calcium influx and prolactin release in pituitary tumor cells in vitro, in concentrations of less than 1 part per billion (Wozniak *et al*. 2005). Increasing calcium can initiate signaling cascades that lead to a variety of cellular changes.
- Or that the gene that produces amyloid precursor protein—a protein implicated in Alzheimer's Disease-- would be upregulated during old age in mice after behaving normally throughout most of the animal's life, following perinatal exposure to environmentally-relevant levels of lead? And that the same lead exposure in adulthood has no comparable effect (Basha *et al*. 2005)?

We published *Our Stolen Future* in 1996, drawing widespread attention to the scientific discovery that low doses of some contaminants can interfere with hormonal signaling, thereby altering fetal development.

When we wrote *Our Stolen Future*, there was strong evidence from laboratory animals and from studies of wildlife, but at that time there were few human studies to confirm what the animal research predicted could be happening. The issues raised by the animal research were so serious that governments in Asia, North America and Europe over the next decade invested hundreds of millions of dollars in research on endocrine disrupting chemicals (EDCs) in the environment.

In the aftermath of those research investments, new scientific discoveries like those described above are now flooding into the scientific literature (Myers 2005). Thousands of scientists have become engaged in research on endocrine disruption, from university and government laboratories around the world, and thousands of research

papers have been published. The laboratory studies of animals and mechanistic studies using cell culture strongly confirm the scientific results we reviewed in *Our Stolen Future* and raise many additional concerns that were not perceived just 10 years ago. And some human studies are now finding patterns consistent with the predictions that we made based on animal research.

Taken together, these studies are the building blocks of a scientific revolution, with profound implications for public health. There are many elements to this revolution:

- Very low doses of some contaminants can alter hormone signaling and by doing that, alter gene expression. These changes can have wide ranging impacts upon development; the specific effects will depend upon gene, tissue and timing of exposure (e.g., Muñoz de Toro *et al*. 2005, Timms *et al*. 2005, Zsarnovszky *et al*. 2005).
- The range of hormonal signaling systems vulnerable to endocrine disruption has been widened dramatically, well beyond the initial focus on steroid hormones such as estrogen. Every component of the endocrine system that has been studied carefully has been shown to be affected. Specific contaminants are known to alter signaling pathways controlled by estrogens, androgens, glucocorticoids, thyroid, progesterone, insulin, and retinoids.
- Recent research has also demonstrated that a new class of receptors associated with cell membranes can be disrupted by estrogenic contaminants. This has been especially important because several of the contaminant molecules studied, like bisphenol A, are just as powerful as estradiol (a natural form of human estrogen) when changing cell signaling via this pathway (Quesada 2002, Wozniak *et al*. 2005). In this context, these contaminants are not just weak estrogens, as critics of endocrine disruption have asserted; they are equally as powerful as endogenous estradiol and estrogenic drugs.
- A recurring pattern in animal and cell research is dose-response curves that are non-monotonic, that is, shaped like a U or an inverted-U. These demonstrate that low doses can have qualitatively different effects than high doses, and that the low dose effects cannot be predicted on the basis of high dose results (Welshons *et al*. 2003).
- The range of health endpoints of concern has broadened dramatically beyond the initial focus on reproduction and infertility. Intellectual development, behavior, disease resistance, auto-immune disease and even weight regulation (obesity) are now areas of research on the impacts of EDCs.
- It had traditionally been thought that one contaminant was likely to influence a relatively small number of health endpoints, for example, the ability of asbestos to cause mesothelioma. This is now clearly a false assumption. Because some endocrine disrupting compounds affect the expression of a wide array of genes, it would not be unexpected to see them emerge as causal agents in disease endpoints that are associated by human genetic studies with those genes. Research with bisphenol A, for example, shows this compound alters the expression of many different genes involved in multiple biochemical pathways (e.g., Singleton *et al*. 2006). Genetic research has established links between some of those genes and a wide array of human health problems, including infertility, behavioral abnormalities, memory problems, senility and obesity.

- Fetal development is the most vulnerable period of life, and impacts on the fetus can cause effects all through life, with the effects sometimes not visible until adulthood. A new field of research has emerged, called 'fetal origins of adult disease.' Testicular cancer is one example, where hormonal imbalances in the womb appear to cause abnormal development of cells within the fetal testes. These abnormal cells then become cancerous in adulthood.
- Mounting evidence indicates that testicular cancer is one part of a syndrome of male reproductive disorders in people called 'testicular dysgenesis syndrome' (TDS) (Skakkebæk *et al*. 2001). Other elements of TDS are reduced sperm quality, undescended testes and hypospadias. Animal experiments show close parallels with a syndrome that can be produced in laboratory experiments by exposing fetal male rodents to a class of plasticizers call phthalates, which suppress testosterone synthesis and interfere with genes involved in testicular descent in fetuses. Recent epidemiological work confirms associations in baby boys with phthalate exposure in the womb, using techniques designed explicitly to test predictions in people based on results from animals (Swan et al. 2005).
- Chemical mixtures of environmental hormones are ubiquitous, and they can have greater impacts than single contaminants. Several careful laboratory studies show that mixtures of contaminants, each at concentrations where they individually cause no detectable effect, in combination cause large effects (Rajapakse *et al*. 2002, Brian *et al*. 2005). These experiments, conducted typically with up to a dozen contaminants simultaneously, have begun to explore what it may mean for people to be exposed simultaneously to hundreds of chemicals. For example, a recent study tested human umbilical cord blood for contaminants and found 287 chemicals of the 413 contaminants that were measured (Environmental Working Group 2005).

One lesson learned from laboratory studies is that that most human studies testing the effects of environmental hormones have inadvertently been designed in ways that weaken their ability to find impacts. Few epidemiological studies incorporate the scientific points summarized above, especially: possible effects of fetal exposures on adult diseases; simultaneous exposures to many different chemicals; and effects at low levels of exposure differing qualitatively from effects at high levels. They also often ignore human and animal data showing large differences within populations in sensitivity to exposure, a failure that further weakens the power of epidemiological research. Because of these and other study design failures, it is highly likely that the epidemiological literature is full of what statisticians call 'false negatives": concluding a compound is safe when it really is not safe. Insisting that there be conclusive evidence from human studies before taking regulatory action is highly likely to be putting people at risk.

Some epidemiologists are responding to this challenge by changing their study designs to reflect the advances in animal science. These new studies are beginning to show strong effects in people.

While these scientific results raise questions about the safety of many products in widespread use today, they are also a source of hope. They point toward a future in which steps to reduce exposures may help prevent diseases that until recently many may have never imagined

were preventable.

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