Will reducing chemical exposures combat the obesity epidemic?

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Introduction

Obesity has reached epidemic proportions in many countries around the world. This is especially evident in the United States, where by 2002 30% of adults met the criteria of 'clinically obese' (Hedley *et al*. 2004). After two decades of sharp growth in the final fifth of the 20th Century, one in six US adolescents is now obese (Ogden *et al*. 2010).

How serious is this trend? Enough to engage the White House, with First Lady Michelle Obama launching a campaign in February, 2010, to curb childhood obesity. Unfortunately, it appears that the focus of that campaign may be missing some very big opportunities.

Interventions to combat the obesity epidemic, including the new White House effort, have targeted what are widely believed to be the two principal contributors to obesity: insufficient caloric expenditure, and excess caloric intact ("the big two", Keith *et al*. 2006). Yet despite widespread and expensive efforts focused on "the big two" by public health agencies, private foundations, educators and medical practitioners, the high prevalence in youth has remained steady for the past 10 years (Ogden *et al*. 2010).

A recent review of "the big two" concluded that undue attention was being devoted to reduced physical activity and excessive caloric intake "leading to neglect of other plausible mechanisms and well-intentioned but potentially ill-founded proposals for reducing obesity rates" (Keith *et al*. 2006).

Since publication of that review, substantial evidence has emerged that increases the plausibility of one of the alternative mechanisms suggested by Keith *et al*.: disruption of weight regulation by endocrine-disrupting chemicals (EDCs) in the environment. Plausible mechanisms have emerged from animal and cell research, and some epidemiological studies have suggested associations between certain contaminants and obesity (Newbold *et al*. 2007; Heindel and vom Saal 2009).

This is potentially very good news for the fight against obesity. If EDCs are contributing to the epidemic, then measures taken to reduce exposures may offer a practical means to alleviate some portion of this disease burden. Several of the implicated contaminants are not persistent, and are eliminated relatively quickly from human fluids and tissue. Previous experience demonstrates very clearly that policy interventions can lead to dramatic declines in US contamination levels, even with highly persistent compounds (e.g., lead, DDT, hexachlorobenzene).

Developmental origins of adult disease

Concerns about the potential contribution of EDCs to childhood obesity build from two considerations, one out of human biology, the other from animal experiments:

First, it is now well established that events early in human life, particularly in the womb, can have long-term consequences for health, including increased risks of heart disease, obesity and type 2 diabetes. Studies of people clearly show that fetal nutrition plays a vital role in setting risk to these chronic diseases (Gluckman *et al*. 2007).

Second, while research on 'developmental origins' initially focused largely on nutrition, animal research proves that early life is also a window of sensitivity to chemical exposures, which can powerfully affect the course of development and cause chronic diseases later in the life of the animal.

Prior to 2005, the experimental literature is peppered with scattered examples in which animals in the experimental group show weight gain compared to controls (Baille-Hamilton 2002), but these experiments were never designed to test for weight gain *per se*. Indeed viewed through the lens of traditional toxicology, weight gain is good; it implies health. The toxicologists were concerned more with weight loss, which was seen as an adverse outcome.

In 2005, Newbold *et al*. published results of an experiment expressly designed to test the hypothesis that early life exposure to an EDC could cause adult obesity (Newbold et al. 2005). Newbold had noticed that experimental animals (mice) used in her research on the synthetic estrogen diethylstilbestrol (DES), often developed into morbidly obese adults following exposure to DES right after birth. In the experiment Newbold *et al*. treated the animals with approximately one part per billion of the animal's body weight per day (1µg/kg/day) for days 1-5 of neonatal life. While the females did not differ from controls during treatment, by adulthood the DES-treated female mice were obese (Fig. 1).

A series of studies now unequivocally demonstrate that obesity in adult animals can be caused by exposures to specific chemicals in the womb (reviewed in Newbold *et al*. 2009; Heindel and vom Saal 2009). They also shed light on the potential molecular mechanisms underlying the effect: many of these chemicals alter the behavior of specific genes that are involved in determining the number of fat cells (adipocytes) an individual will have as an adult. Animals exposed to contaminants that increase the activity of these genes wind up with more fat cells and thus are at greater risk to obesity. Contaminants that have this effect have been termed "obesogens" (Grün *et al*. 2006). Studies also suggest other mechanisms, including interference with neurochemical signals that provide information to the brain about hunger.

The list of contaminants implicated by animal studies is substantial, including several estrogenic EDCs like DES (bisphenol A, soy phytoestrogens [particularly

important given widespread use of soy-based infant formula]), certain phthalates and a family of compounds called organotins.

It is particularly troubling that human exposure to these is quite widespread, if not ubiquitous, and the exposure is at levels capable of causing obesogenic effects in animals. For example, the U.S. Centers for Disease Control reports that bisphenol A can be measured in over 90% of Americans, with higher levels in youth.

Almost no human data are available to test the obesogen hypothesis in people. No epidemiological evidence exists, because the hypothesis is so new. A few studies associate chemical levels measured in adults with obesity (e.g., Stahlhut et al. 2007) but these are not relevant to a developmental model. One *in vitro* experiment, however, has demonstrated that exposure to obesogens increases the rate of conversion of human stem cells to adipocytes (Kirchner et al. 2010), confirming the validity of the basic mechanism and the relevance of the animal studies to people.

Conclusion

Chronic diseases are rarely the result of a single risk factor (Kirchner et al. 2010). Such is almost certainly the case for obesity. Given the failures of current intervention attempts that focus on "the big two", and the serious health and economic burden that obesity is imposing on people around the world, the obesity epidemic challenges public health and medical professionals to look widely at potential causes, including those that at first might seem 'outside-the-box.' These emerging studies, summarized briefly above, indicate that a substantial—but as yet undetermined—portion of the obesity epidemic may be caused by endocrine-disrupting chemicals. At the very least, this argues for urgent investment in additional research designed to test the obesogen hypothesis. It may also point toward interventions that are far more practical and effective than those indicated by a focus on "the big two." That would be a big win for medicine and public health.

References

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Figures

Fig 1. Mice exposed around birth to 1 part per billion diethylstilbestrol (1µg/kg/day) for days 1-5 after birth become obese in adulthood (Newbold et al. 2007). Figure courtesy of Retha Newbold, NIEHS. Control animal on left, exposed animal on right.