

Origins and Evolution of Children's Environmental Health

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We all witness the miraculous development of newborns and young children as they undergo great physical and mental changes in just a few years. But sometimes a child tragically loses, or never attains, his or her ability to speak or interact socially.

Kenneth Olden
(NIEHS/U.S. EPA Press Release 2001)

Children's health is, to a large extent, a function of the environment in which they live. This concept, which has its origins in ancient history, has never been more obvious than it is today. Infectious agents remain a leading cause of death and disability in the world, but the major causes of disease and disability in industrialized countries—cardiovascular disease, diabetes, obesity, respiratory ailments, and injuries—are due to noninfectious environmental factors or gene-environment interactions (Willett 2002; Lichtenstein et al. 2000; Valent et al. 2004). Moreover, many of the “new morbidities” of childhood—intellectual impairments, behavioral problems, asthma, and preterm birth—are linked with remarkably low-level exposures to environmental pollutants [Wisborg et al. 2001; DiFranza and Lew 1996; Murray and Lopez 1996; Ness et al. 1999; England et al. 2001; National Research Council (NRC) 2000; Weitzman et al. 2002; Windham et al. 2000; Windham et al. 1999; Torres-Sanchez et al. 1999; Needleman et al. 1990; Baghurst et al. 1992; Bellinger et al. 1992; Eskenazi and Trupin 1995; Grandjean et al. 1997; Schantz et al. 2003; Jacobson and Jacobson 1996; Wasserman et al. 2000; Dietrich et al. 2001; Olds and Henderson 1994; Noland 2003; Kahn et al. 2003; Borja-Aburto et al. 1999; Jaakkola et al. 2001; Wakschlag et al. 2002; Needleman and Gatsonis 1990; Longnecker et al. 2001; Whyatt et al.

Thus, while questions remain, existing data support the hypothesis that exceedingly “low-level” exposures to certain prevalent environmental toxicants are associated with substantial health effects.

2004; Eskenazi et al. 2004; Berkowitz et al. 2004; Fried et al. 1998; Williams et al. 1998; Chiodo et al. 2004; Stewart et al. 2003; Sood et al. 2001].

Children’s environmental health—the study and prevention of disease and illness in children due to exposure to social, physical, biologic, and chemical agents—has emerged as a new field of research, policy, and clinical practice (Landrigan et al. 1998). It has its origins in environmental disasters, but this new field has flourished during Dr. Kenneth Olden’s tenure as director of the National Institute of Environmental Health Sciences (NIEHS). The growth of children’s environmental health has been fueled by evidence that the fetus and child are particularly vulnerable to environmental influences, the development and validation of biomarkers (Perera 1997; Lanphear and Bearer 2005; Links et al. 1995), and research linking environmental exposures to prevalent diseases and disabilities in children. It is also an outgrowth of a profound attachment to our own children and community outrage about our inability to protect children from recognized environmental threats.

Environmental Disasters

Epidemics of overt poisoning from widespread environmental contamination of commercial products heralded the discovery of children’s enhanced vulnerability to environmental toxicants and pollutants (Rogan 1995). In a series of disasters beginning in the 1880s, coal smoke and other industrial pollutants blanketed cities and towns, causing a surplus of deaths from respiratory disease and asthma (Bell and Davis 2001). One hundred years ago, an epidemic of lead poisoning was described among children in Australia who ingested leaded house paint (Gibson 1904; Turner

1908). The children, who were weakened and pale from anemia, suffered from encephalopathy, paralysis, and blindness. In the 1950s, in a Japanese fishing village on methyl mercury-tainted Minamata Bay, children’s bodies were twisted by cerebral palsy, limb defects, and mental retardation (Harada 1977). In Taiwan and Japan during the 1960s and 1970s, the ingestion of PCB-contaminated rice bran oil by pregnant women led to fetal wasting and cola-colored, dull, and apathetic children (Chen et al. 1992). During the past century, widespread tobacco use has led to an epidemic of undersized, premature babies and children afflicted with respiratory infection and repeated bouts of wheezing (Wisborg et al. 2001; DiFranza and Lew 1996; Murray and Lopez 1996; Ness et al. 1999; England et al. 2001).

These environmental disasters seem quite remote. But considerable evidence has accumulated during the past two decades indicating that low-level exposure to these and other environmental toxicants and pollutants continue to affect contemporary children. Indeed, exposure to exceedingly low levels of environmental toxicants are often associated with adverse effects such as lowered intelligence, diminished school performance, increased rates of behavioral problems, asthma, lowered birth weight, and preterm birth (Baghurst et al. 1992; Bellinger et al. 1992; Jacobson and Jacobson 1996; Needleman and Gatsonis 1990; Canfield et al. 2003; Stewart et al. 1999; Needleman et al. 1979; Steuerwald et al. 2000; Thacker et al. 1992; Dietrich et al. 1993; Lanphear et al. 2000; Yolton et al. 2005). Concurrently, there is a growing awareness and, for some diseases, a rising prevalence of these childhood morbidities (Branum and Schoendorf 2002; Demissie et al. 2001; Yeargin-Allsopp et al. 1995; Zito et al. 2000; Akinbami and Schoendorf 2002).

Diseases of Industrialization

Many diseases of contemporary society are linked with environmental pollutants and toxicants. This is not a new concept; there was heated, but largely unresolved debate about the contribution of environmental risk factors of cancer (Doll and Peto 1981). But we are discovering these concepts anew as we shift our focus to diseases and disabilities afflicting children. Some argue that “lifestyle”—a term used to indicate that our interactions with the environment are largely voluntary—is a more potent predictor of disease and disability than involuntary environmental influences. But the obesity epidemic and innovative research exposing the insidious role of the tobacco industry’s marketing efforts to convert children to tobacco users has largely eliminated any false barriers separating lifestyle and environment (Bero 2005; Sargent et al. 2004).

The New Morbidities of Childhood

There is considerable evidence that children are more vulnerable to certain toxins and pollutants than adults. The fetus and young child frequently express signs and symptoms of toxicity that fail to produce any outward indications of disease or disability in adults. The central nervous systems of the fetus and young children, which are undergoing rapid changes during the first 3 years of life, are particularly vulnerable to some toxicants. The fetus is a recipient of toxicants through placental transfer (Perera et al. 2003; Whyatt and Perera 1995; Bearer 2003). In some cases, such as methyl mercury, the fetus is exposed to a larger dose than the mother (NRC 2000; Ramirez et al. 2000). In other cases, such as organophosphate pesticides, the fetus may lack critical enzymes to metabolize environmental toxicants (Chen et al. 2003). Toddlers are often at greater risk for exposure to many environmental toxicants because they have a high degree of hand-to-mouth activity, and they absorb some toxicants more efficiently (Lanphear et al. 2003; Bearer 1995; Lanphear et al. 1998). Young children often exhibit higher concentrations of pollutants such as lead, cotinine, and pesticides because of differences in metabolism, mouthing behaviors, and respiratory rates [Bearer 1995; Centers for Disease Control and Prevention (CDC) 2003].

Over the past 50 years, the morbidity and mortality from infectious diseases in children have declined dramatically. At the same time, there is increasing

recognition of new morbidities of childhood. One in six children have one or more developmental disabilities, from a subtle learning disability to overt behavioral or emotional disorders (Boyle et al. 1994). Exposures to environmental toxicants have been linked with higher rates of mental retardation, intellectual impairment, and behavioral problems, such as conduct disorder and attention deficit hyperactivity disorder (ADHD) (Needleman et al. 1990; Baghurst et al. 1992; Bellinger et al. 1992; Eskenazi and Trupin 1995; Grandjean et al. 1997; Schantz et al. 2003; Jacobson and Jacobson 1996; Wasserman et al. 2000; Dietrich et al. 2001; Olds et al. 1994; Noland 2003; Kahn et al. 2003; Wakschlag et al. 2002; Needleman and Gatsonis 1990; Fried et al. 1998; Williams et al. 1998; Chiodo et al. 2004; Stewart et al. 2003; Sood et al. 2001; Canfield et al. 2003; Needleman et al. 1979; Steuerwald et al. 2000; Thacker et al. 1992; Dietrich et al. 1993; Lanphear et al. 2000; Yolton et al. 2005). Asthma, the most disabling disease of childhood, has escalated for reasons that are largely unexplained (Akinbami and Schoendorf 2002). One in 10 children in the United States is reported to have doctor-diagnosed asthma (Lanphear et al. 2001). Numerous environmental risk factors, including environmental tobacco smoke (ETS) exposure, indoor allergens, and air pollution have all been implicated in asthma development or exacerbations [Institute of Medicine (IOM) 2003]. Each year, > 400,000 babies, representing about 12% of all births, are born prematurely in the United States (Branum and Schoendorf 2002; Demissie et al. 2001). From 1981 to 1998, rates of preterm birth increased by > 30% (Branum and Schoendorf 2002; Demissie et al. 2001). Despite years of intense efforts to reduce the rates of preterm birth, the underlying mechanisms for low birth weight and preterm birth have not yet been identified (Klebanoff et al. 1998).

There are profound racial and ethnic differences in the rates of disease and disabilities that are linked with environmental toxicants and pollutants. African Americans are at higher risk for many diseases and disabilities that have been associated with exposure to environmental toxicants, such as low birth weight, preterm birth, asthma, delinquency, and intellectual delays (Dietrich et al. 2001; Branum and Schoendorf 2002; Demissie et al. 2001; Yeargin-Allsopp et al. 1995; Lanphear et al. 2001; IOM 2003.; Richie et al. 1997; CDC 1998). Moreover, African American children have, for a given exposure, significantly higher blood lead levels,

cotinine and DNA adducts (Lanphear et al. 1996; Wilson et al., in press; Hecht 2003). African Americans also have a higher body burden of polychlorinated biphenyls (PCBs) and mercury than other ethnic groups (CDC 2003). In contrast, Mexican Americans have higher serum dichlorodiphenyldichloroethene (*p,p'*-DDE) concentrations [a metabolite of dichlorodiphenyltrichloroethane (DDT)] than other Americans (CDC 2003). Differences in exposure, metabolism, and absorption of environmental toxicants undoubtedly underlie many of the racial health disparities (Lanphear et al. 2003). But there are too few studies linking biomarkers of exposure and genetic susceptibility with diseases and disabilities in children of diverse racial and ethnic groups to draw any firm conclusions about their relative contribution.

The Role of Biomarkers

Numerous studies have shown that serious health consequences occur not only from heavy exposure, they also occur from low-level, chronic exposures to environmental pollutants. Many of these pollutants are widely dispersed in the environment and can readily be found in the blood, body fluids, or tissues of children and pregnant women (CDC 2003). The impairments are often subtle for an individual child, but the damage can be substantial at the population level, especially for prevalent exposures (Rose 1992). Exposures to putative causative agents are difficult to characterize because of the complexity of accurately quantifying exposure, estimating the timing of exposure, and measuring the effect of environmental toxicants (Links et al. 1995). But biomarkers are enhancing our ability to link environmental exposure and susceptibility with disease and disability in children.

The development and validation of biomarkers is one of the main reasons for the growth of children's environmental health (Lanphear and Bearer 2005; CDC 2003; Sexton et al. 2004; Bearer 1998). Historically, scientists and clinicians have relied on indirect markers—housing condition, questionnaires, and community-level monitoring of water and air—to quantify the effect of environmental influences on children's health (Sexton et al. 2004). Similarly, we have relied on family history to assess genetic susceptibility for a particular condition or disease. The emergence of biomarkers is enhancing our ability to study and test causal association in the same way serologic tests transformed the study and control of infectious agents.

The expanding number of biomarkers not only enhances our ability to link environmental toxins with disease and disability, they also make epidemiologic research more complex. There are, for example, both human and experimental research indicating that children who are exposed to multiple environmental agents may be at particular risk for disease or disability (Stewart et al. 2003; Bemis and Seegal 2000; Roegge et al. 2004; Gilliland et al. 2004). Children who have high exposure to methyl mercury or PCBs, for example, are at risk for adverse neurodevelopmental effects (Jacobson and Jacobson 1996; Stewart et al. 2003). But children who are exposed to both methyl mercury and PCBs appear to be at greater risk for adverse neurodevelopmental outcomes, even at lower levels of exposure (Stewart et al. 2003). The plethora of biomarkers will make longitudinal studies too costly and complex to conduct, induce us to increase the resources for studies of environmental hazards, or convince us to alter the way we regulate environmental chemicals and pollutants.

Genetic Susceptibility

Progress in mapping the human genome has created tremendous opportunities to enhance our understanding of the epidemiology and mechanisms of disease and disability. Innovative use of genetic information can help clarify the causal mechanisms linking environmental exposure to disease (Willett 2002; Umbach 2000). For example, prenatal smoke exposure has been linked with ADHD (Kahn et al. 2003), but the mechanism of toxicity is unclear. A genetic polymorphism in the dopamine transporter (the site of action for psychostimulants), was found to be associated significantly with adverse effects of prenatal smoke exposure on child behavior (Kahn et al. 2003). Because nicotine acts on the dopamine transporter (Drew et al. 2000), the specificity of the gene-ETS interaction can offer insight into the mechanism behind ETS effects. If confirmed, the specificity of the interaction can also help to counter concerns about confounding.

It is evident, largely from research funded over the past decade by the NIEHS, that the promises of decoding the human genome will only be realized if we examine the joint influence of genes and environment. The glutathione *S*-transferase (GST) enzymes (which are involved in the metabolism of xenobiotic compounds) and genes that determine their activity offer some

insight into the future of children's environmental health research (Gilliland et al. 2004; Wang et al. 2002; Nukui 2004). Wang showed that among pregnant women who actively used tobacco, only women who were exposed to active tobacco use and who had *GSTT1_{null}* (GST theta 1) were at higher risk for lower birth weight and preterm birth (Wang et al. 2002). Gilliland and co-workers have shown that only children who were exposed *in utero* to tobacco and who had *GSTM1_{null}* (GST mu 1) were at increased risk for persistent asthma and wheezing (Gilliland et al. 2004). Finally, Romieu showed that asthmatic children with *GSTM1_{null}* were more susceptible to the deleterious effects of ozone (Romieu et al. 2004).

Low-Level Toxicity

The findings from some of the most thoroughly studied and widely dispersed environmental contaminants indicate that exposure to exceedingly low levels of environmental toxicants are often associated with adverse effects; indeed, there is often no apparent threshold and, in some cases the effects appear to be greater at the lowest levels of exposure (England et al. 2001; Canfield et al. 2003; Lanphear et al. 2000; Yolton et al. 2005; Axelrod et al. 2004).

Despite dramatic reductions in emissions from industrial sources and improvements in pollution control devices on motor vehicles, air pollution remains a major cause of respiratory disease children. Gauderman and his colleagues found, in a longitudinal study of 1,759 children, that lung development was significantly reduced among children exposed to the highest levels of ambient air pollution, especially nitrogen dioxide, acid vapor, fine particulate matter [particulate matter with aerodynamic diameter of $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$)] and elemental carbon (Gauderman et al. 2004). There is also evidence that levels of some pollutants at levels considerably lower than existing standards are associated with asthma exacerbations. Gent and his co-workers found that ozone was associated with shortness of breath and chest tightness among children with asthma at levels below standards set by the U.S. Environmental Protection Agency (Gent et al. 2003).

There is emerging evidence that neurobehavioral effects linked with lower-level exposures to lead and tobacco are, for a given increment in exposure, greater than those found at higher levels. Studies show that environmental lead exposure in children who have

maximal blood lead levels $< 10 \text{ g/dL}$, the current "action" level set by the CDC and the World Health Organization, is associated with subtle but substantial intellectual decrements (Wasserman et al. 2000; Chiodo et al. 2004; Canfield, et al. 2003; Lanphear et al. 2000; Bellinger and Needleman 2003; Fulton et al. 1987; Schwartz 1994; Schwartz and Otto 1991; Walkowiak et al. 1998). Similarly, Yolton and her co-workers found an inverse relationship of ETS exposure with reading scores among U.S. children. For both environmental lead exposure and tobacco exposure, the decrements were, for a given change in exposure, greater at the lowest serum cotinine levels (Canfield et al. 2003; Lanphear et al. 2000; Yolton et al. 2005; Bellinger and Needleman 2003).

Low levels of tobacco exposure and air pollutants pose a risk for lower birth weight or preterm birth. England and her co-workers found that the largest decrements in birth weight occurred at lower levels of active smoking, equivalent to < 5 cigarettes per day (England et al. 2001). Moreover, ETS exposure—passive exposure of pregnant women to tobacco smoke—has been associated with low birth weight and preterm birth (Windham et al. 1999, 2000; Nafstad et al. 1998). Jaakkola and his co-workers found, using hair nicotine, that exposure to ETS was a risk factor for preterm birth. Pregnant women with $> 4 \text{ g/g}$ of nicotine in their hair were at a 6-fold increased risk for having a premature delivery compared with women in the referent group (Jaakkola et al. 2001). Jedrychowski and colleagues, in a prospective cohort in Poland, found that $\text{PM}_{2.5}$ was significantly associated with birth weight, length, and head circumference (Jedrychowski et al. 2004).

Thus, while questions remain, existing data support the hypothesis that exceedingly low-level exposures to certain prevalent environmental toxicants are associated with substantial health effects. The consequences of exposure to many other chemicals such as insecticides—chemicals often specifically designed to be toxic—are largely unknown (Whyatt et al. 2004; Eskenazi et al. 2004; Berkowitz et al. 2004; National Academy of Sciences 1993.). Thus, not only do we need to explore how toxins and pollutants interact, we need to explore the effects at ever-lower levels of exposure. Moreover, given the increasing number of environmental chemicals, we need to expand our regulatory efforts to identify chemicals that are toxic before they are marketed or widely disseminated (Lanphear et al. 2005).

Challenges for Children's Environmental Health

In contrast with other biomedical research, the study of environmental risk factors raises unique challenges. Many of the new morbidities—asthma, learning disabilities, intellectual impairments, preterm birth, behavioral problems, and cancer—are linked with tobacco products, unsafe housing, and industrial pollutants. These hazards are more challenging to control than infectious agents because they invariably bring industry and public health into direct conflict. Many journals have set policy to prevent problems with competing interests in the publication process. But our scientific advisory committees, which ultimately review the research and translate it into policy, are now heavily contaminated with scientists hand-picked by industry (Kennedy 2003). In the end our efforts to understand and control environmental hazards using scientific methods will be futile if the final arbitrators—the scientific advisory committees—contain members who have competing interests.

Prevention

Despite the widespread recognition of low-level toxicity of prevalent environmental toxicants and pollutants, there is a paucity of data about the safety and efficacy of methods to reduce children's exposures. Even for childhood lead toxicity—often viewed as a problem that has largely been eliminated—there is a paucity of data indicating that interventions to control residential lead hazards are either safe or efficacious in reducing children's blood lead levels (Lanphear et al. 2003). Similarly, despite considerable evidence linking various environmental exposures with the development and exacerbations of asthma, there is considerable uncertainty about the safety and efficacy of various interventions (IOM 2003).

A new generation of study designs is needed to protect children from environmental toxins and pollutants. We have acquired considerable information from observational studies, but the next generation of studies will need to examine the interaction of multiple environmental toxins or pollutants at increasingly lower levels of exposure using biomarkers. We also need to expand the use of randomized controlled trials to test causal associations as well as the safety and efficacy of preventive interventions. It is not always possible or ethical to conduct randomized trials for environmental hazards. In that case, innovative studies are needed to make a convincing link between an

exposure and a disease or disability, such as those by Pope and Friedman (Pope 1989; Friedman et al. 2001).

Conclusions

Over the past century, increasing evidence has emerged linking chronic, low-level exposure to environmental influences and industrial pollutants with many of the new morbidities of childhood. But questions remain about the lowest levels of exposures linked with reproductive, respiratory, and neurobehavioral toxicity. Ultimately, the etiology and prevention of human disease can only be established in the context of both genetic susceptibility and environmental factors. Indeed, genetic factors may only be manifest once environmental exposures are taken into account. The use of biomarkers and innovative study designs—including experimental trials—offer us an opportunity to help resolve many of the unanswered questions about the toxicity and control of low-level exposures to environmental toxicants. Still, numerous challenges await us; perhaps none as daunting as how to translate research into policy to protect children from environmental hazards.

SUMMARY

Children's environmental health has burgeoned during the past decade, fueled by increased evidence that the fetus and child are vulnerable to environmental influences, the development and validation of biomarkers, and rigorous research linking exceedingly low-level exposure to prevalent diseases and disabilities in children. The growth of children's environmental health is also an outgrowth of a profound attachment to our own children and community outrage about our failure to protect children from recognized environmental threats. Finally, it is a testimony to Dr. Kenneth Olden's vision and his receptivity to the findings of scientists and the voice of the community. Despite the tremendous growth and expanding research, numerous challenges await us, including the translation of research into policy, identifying resources to conduct increasingly complex and costly research, and training a new generation of scientists, clinicians and policymakers.

NOTES

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