Seen in the context of globalization now under way, the vulnerability of children becomes one of the central public health problems for our time.

It's Time to Rethink Dose: The Case for Combining Cancer and Birth and Developmental Defects


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Toxicology, literally the scientific study of poisons, is a descriptive and experimental science that details the biological consequences of exposures to toxicants. The dose makes the poison—so goes the oft-repeated observation of the 16th-century progenitor of modern pharmacology, Theophrastus Paracelsus.

Over the past three decades a growing number of *in vitro* and *in vivo* studies shows that this widely accepted assertion has important variants and exceptions. Dose surely affects the toxicity of any substance, whether water, foods, or metals. However, it is increasingly evident that in determining the biological importance of any given exposure, the period of development (or the critical window during which exposure occurs) and the rate at which a dose is absorbed can be even more important than the total quantity of exposure.

Although birth defects, developmental defects, and cancers in children and infants remain rare, they sometimes fall into "clusters" and unfortunately remain largely unexplained. However, a spate of recent experimental and epidemiologic findings makes clear the exquisite sensitivity of prenatal and postnatal periods. Therefore, it is time for a new paradigm that takes into account the fact that some cancers and some birth and developmental defects stem from common exposures that occur early in life. Such a paradigm will improve the power of studies by combining the assessment of health end points that are likely to arise from exposures that take place during critical windows of development. In addition, such a paradigm will also challenge epidemiologic investigation of chronic diseases, for which early windows of vulnerability and long latencies are involved. For chronic diseases such as cancer and neurodegenerative disorders, it does not make biological sense to assess solely contemporaneous measures of exposure.

Like most cancers in children, neuroblastoma, the most common cancer in children under 1 year of age, is believed to arise as a terminal cell differentiation, reflecting prenatal influences or germ cell mutations. In a recent review of 95% of all children in the United States diagnosed with neuroblastoma (from trial groups of the Pediatric Oncology Group and the Children's Cancer Group) Daniels et al. (*1*) found that pesticide use in both home and garden significantly increased the odds ratios (ORs), 1.6 and 1.7, respectively. A stronger OR of 2.2 was found in children who were diagnosed after 1 year of age. They believe that the stronger effect in older children may arise from either greater cumulative exposures or differential effects of pesticides in an etiologic pathway marked by an older age at diagnosis (*1*). Interestingly, there was no evidence that *MYCN* gene status modified the risk of pesticides for neuroblastoma. Daniels et al. (*1*) speculated that some widely used pesticides, such as chlorpyrifos, chlordane, and lindane, affected the immune system by decreasing regulation of cell proliferation or surveillance for dysfunctional or undifferentiated neural crest cells. This finding is even more remarkable because recent monitoring information indicates that these materials are ubiquitous in the United States. Because of this widespread exposure, any epidemiologic study will be biased toward the null hypothesis (*2*,*3*). This study on neuroblastoma parallels findings in farm families in Norway, where children residing on farms around the time of birth had an OR of 2.5 for the same type of tumor (*4*). Paternal exposures of interest include those acting on the father's maturing germ cells in the 3 months before conception. In addition, central nervous system defects, such as spina bifida and hydrocephaly, and cancer were also associated with paternal use of pesticide spraying equipment.

There is growing evidence that some cases of testicular cancer in younger men and breast cancer in younger women may arise from prenatal or early childhood exposures. Some studies have found that both maternal and paternal exposures can affect the risk of testicular cancer. For instance, ORs of testicular cancer were increased more than 4-fold for young men with mothers working in health-related occupations and fathers working in automobile service stations (*5*).

With respect to paternal exposures alone, several studies have provided evidence that male-mediated exposures can critically affect the risk of childhood cancer. Thus, in a cohort study based on a population of 235,635 children in Sweden, Feychting et al. (*6*) followed children from birth to 14 years of age and found increased risk of nervous system tumors related to paternal occupational exposure to pesticides [relative risk (RR) = 2.36; 95% confidence interval (CI), 1.27–4.39] and work as a painter (RR = 3.65; 95% CI, 1.71–7.80), and an increased risk of leukemia related to wood working by fathers (RR = 2.18; 95% CI, 1.26–3.78). In other studies, paternal exposure to solvents, cutting oils, paints, dusts, and fumes has been found to be associated with an increased risk of testicular cancer and leukemia in these men's children. For example, in one study of rare childhood malignant germ-cell tumors, fathers of cases were more likely than fathers of controls to have been exposed to solvents, plastic or resin fumes, metals, and cleaning compounds (*5*,*7*).

Animal studies of the sensitivity of the developing organism have repeatedly confirmed that susceptibility depends on the rate of ongoing cell division at the time of exposure. The synthetic estrogen diethylstilbestrol (DES) produces structural defects in the seminiferous tubule of male offspring after maternal exposures during critical phases of organogenesis (*8*). A single dose of 17β-estradiol early in gestation can create defects that do not occur with exposure later in pregnancy or with neonatal exposure (*9*). Moreover, early gestational exposure to 17α-estradiol, normally considered a very weak estrogen, induces defects in offspring, whereas exposure to the same

compound later in life induces no effect (*10*). Tween-80, a chemical widely used in industry, has been shown to have similar effects; that is, exposure during a critical period of development results in abnormalities, whereas adult exposure results in no effects (*11*).

The question has arisen regarding the relevance of animal studies to humans. However, one only has to look at the published history of early exposure to estrogens to realize the potential information to be gained from treating experimental studies of animals as serious indicators of human hazard. Numerous experimental studies showed that the early hormonal environment plays a pivotal role in later differentiation and growth of reproductive organs and functions. Subsequently, boys and girls born to mothers who received DES in the first trimester of pregnancy, when sexual differentiation occurs, have been found to be at increased risk of functional and structural reproductive abnormalities, paralleling earlier findings in animals (*12*). Girls and boys who are premature and those who are fraternal twins also show increased rates of breast and testicular cancer in young adult life (*13*).

Other recent experimental studies indicate that prenatal exposures to some common plastics and vehicle exhausts can increase development of reproductive defects in male offspring (*14*,*15*). Moore et al. (*15*) assessed effects of *in utero* and lactational exposure to di(2-ethylhexyl) phthalate (DEHP) on reproductive system development and sexual behavior in male Sprague-Dawley rats. Dose-related effects, including reduced anogenital distance, areola and nipple retention, undescended testes, and permanently incomplete preputial separation were observed in male rats treated with corn oil or DEHP (0, 375, 750, or 1,500 mg/kg/day) from day 3 of gestation through postnatal day 21 (PND 21). At PNDs 21, 63, and 105–112, testis, epididymis, glans penis, ventral prostate, dorsolateral prostate, anterior prostate, and seminal vesicle weights were reduced. Other dose-related effects included a high incidence of anterior prostate agenesis and a lower incidence of partial or complete ventral prostate agenesis. Aracadi et al. (*16*) reported that DEHP produces testicular damage in male offspring of female rats exposed to an estimated 3.0–3.5 mg/kg body weight daily in drinking water.

Watanabe et al. (*17*) reported that rats exposed to diesel exhaust during days 7–20 of pregnancy showed a number of profound alterations in sexual function and development. These authors studied three groups of exposures: one group exposed to total diesel engine exhaust containing 5.63 mg/m^3 particulate matter, 4.10 ppm nitrogen dioxide, and 8.10 ppm nitrogen oxide; a group exposed to filtered exhaust without particulate matter; and a group exposed to clean air. The exposure period was from day 7 until day 20 of pregnancy. Differentiation of the testis, ovary, and thymus was delayed and disturbed. Thymus weight was significantly reduced, whereas testis differentiation was delayed. Testosterone levels increased and estradiol decreased, resulting in masculinization of the fetus after exposure during critical phases of organogenesis of reproductive organs and functions.

Although routine monitoring of diesel exhaust is not conducted, exposure to traffic-based pollution appears to be especially common in densely populated urban areas. One study conducted on school children who lived in Harlem (New York, NY) and had no known unusual exposure conditions found that 75% of the children had urinary metabolites of hydroxypyrene, indicating exposure to diesel exhaust. Under some proposed energy scenarios, diesel transportation can be expected to expand, as can the potential for increased exposures to children and young adults who can become parents.

Death rates and hospital admissions for asthma are much higher in poor populations living in areas with elevated exposures to diesel exhausts, with African Americans having 2–4 times higher rates than whites. In 1993, among children and young adults, African Americans were 3 to 4 times more likely than whites to be hospitalized for asthma, and were 4 to 6 times more likely to die from asthma (*19*). Lack of access to primary health care, poverty, and exposure to elevated levels of indoor and ambient pollution, including diesel exhaust, have been implicated as contributing to this racial disparity (*19*). One recent panel study found that fine particulates significantly increased shortness of breath and cough in young African Americans to a greater extent than was previously reported in young whites (*20*).

The reproductive health consequences of these persisting early life exposures to agents that disturb lung health have never been fully assessed but may well be considerable. One analysis has reported that low birth weight is associated with current levels of carbon monoxide and sulfur dioxide in the United States (*21*). The risk of low birth weight increased by a unit increase in the CO third-trimester average concentration [adjusted odds ratio (AOR) 1.31; 95% CI, 1.06–1.62]. Compared to infants in the reference category (< 25th percentile), infants with SO_2 second-trimester exposures were also at increased risk for low birth weight: within the 25th and < 50th percentiles (AOR 1.21; CI, 1.07–1.37), 50th to < 75th percentiles (AOR 1.20; CI, 1.08–1.35), and the 75th to < 95th percentiles (AOR 1.21; CI, 1.03–1.43) (*21*).

A newly reported study of biomarkers and sexual development in adolescents living near waste incinerators in Belgium and Holland provides important evidence linking currently accepted levels of airborne exposures to several major classes of toxicants to a wide range of adverse reproductive, genetic, and functional outcomes (*22*). Urban children with higher levels of exposure to lead—and some chlorinated, polycyclic aromatic, or volatile organic compounds—reached sexual maturity later than children living in more rural areas of the country. The children were from socioeconomically comparable groups with similar proportions of tobacco smokers. Testicular volume in boys near the facilities was significantly smaller than in the more rural, control group boys, and breast development was impeded in more exposed girls. Inter-rater reliability of evaluating school physicians was high. Because follicle-stimulating hormone (FSH) governs the growth of Sertoli cells during fetal, neonatal, and prepubertal life, testicular volume during adolescence effectively reflects early life exposures controlled by FSH (*22*).

Those more highly exposed to toluene, benzene, and polycyclic aromatic hydrocarbons also had significantly greater amounts of DNA damage, measured through the Comet assay, while those exposed to higher levels of lead exhibited evidence of renal dysfunction, expressed by cystatin-C in serum. Of those exposed, 40% had not reached adult sexual maturity, whereas almost all of the control group had. Urban children consistently had higher concentrations of biomarkers of all pollutants tested, including urinary hydroxypyrene as well as dioxins, and PCBs, two endocrine disruptors that retard development when tested experimentally. Children's smaller, less mature, and developing bodies are more vulnerable to pollutants (*23*).

Although general population time trends in these subtle developmental end points remain in dispute, a provocative finding derived from autopsy reports in France and Finland demonstrated an 11% reduction in testes weight and a 27–51% reduction in spermatogenesis (*24*).

Several studies have consistently found that paternal and maternal genomes both make important contributions to health problems of offspring, including germ cell cancers in infants. For example, with respect to paternal exposures before conception, Garry et al. (*25*) found that children of male pesticide applicators were at increased risk of birth defects and that the risks varied with the amount of reported spraying, lagged for gestation. They also found that male infants were at greater risk than female infants for a number of birth defects (*25*). Thus, the importance of timing of exposure extends to the period of spermatogenesis, some 62 days before conception.

These studies make clear that the study of hormonal cancers, such as testicular and breast cancer, requires careful consideration of timing of exposure along with dose. Studies of persistent organic pollutants such as DDE and polychlorinated biphenyls (PCBs) present in adults at the time of diagnosis cannot shed light on their role in causing cancer when exposure occurs at earlier stages of development (*26*). In addition, studies of these persistent compounds cannot assess the role of agents known to cause breast and testicular cancer (e.g., methylene chloride, benzene, some phthalates, and chlorinated organic solvents), nor can they clarify the impacts of those prescription pharmaceuticals that have been identified as tumor promoters.

All of these compounds leave no residues that can be detected months or years after exposures have occurred. For many reproductive outcomes, no direct measures of prenatal exposure are readily available. In one innovative investigation in 10 California counties, Bell et al. (*27*) estimated daily maternal exposure by linking a statewide information system regarding commercial applications of restricted pesticides to maternal address. They found that the risk of fetal death after 20 weeks, infant deaths within 24 hr of birth, and congenital anomalies was highest when the pesticide application occurred within the same square mile of maternal residence (*27*).

Several recent air pollution studies also reveal the exquisite sensitivity to the fetus and newly born. In São Paulo, Brazil, late fetal loss increased nearly 20% in areas with the highest combined index of air pollution, in contrast to zones with the cleanest air (*28*). Maternal cord blood analysis showed that carboxyhemoglobin levels were also elevated in mothers living in these more polluted areas, providing a biological marker of air pollutant exposure.

Epidemiologic studies of reproductive and developmental defects and childhood, testicular, and breast cancer in persons under 30 years of age have been hampered by the failure to achieve statistical significance. This is chiefly due to the relatively rare nature of these events when considered within their separate groupings. For analyses of clusters of relatively rare events in small areas, this problem is especially difficult to resolve. Thus, in the first 5 years of life, all childhood cancer occurs in < 5 per 100,000 children; breast cancer in women under 35 years of age occurs in approximately 4 per 100,000 white women and in 8 per 100,000 African-American women (*29*). The power to detect an effect depends on the expected probability of that event and on the size of the population surveyed. Because environmental exposures are so widespread and common and because these end points are relatively rare, it has been very difficult to design studies to detect whether environmental factors play any role.

When it comes to assessing the connections between environmental or workplace exposures and health problems, studies of clusters in small areas pose especially difficult problems. Traditionally two-tailed tests of significance have been applied to estimate the 0.05 probability that a given OR or RR falls within specified upper and lower bounds, commonly called a confidence interval. These tests ask whether the results are significantly greater or significantly lower than would occur by chance alone. Because the real question at hand for any suspect environmental or occupational risk is whether the observed results are greater than expected, it is actually appropriate to apply the one-tailed test in these circumstances. Thus, there is a need to rethink the application of statistical guidelines in such situations, along with re-evaluating information on timing of exposure and the rarity of outcomes.

Further complicating the assessment of risks to children are recent studies that have identified synergistic effects between some commonly encountered organochlorine pollutants (*30*). Efforts to understand the vulnerability of the young must take into account early life exposures and the potential importance of combined effects. A recent survey from the U.S. Centers for Disease Control and Prevention (*31*) found elevated exposures to some phthalate metabolites in young adults of reproductive age and fairly widespread general population exposures.

These recent experimental studies indicate the rationale for devising epidemiologic studies that combine childhood cancer, early adult cancer, and major developmental and structural defects as combined indications of terminal cell differentiation that reflect potential prenatal and early childhood exposures. In conducting assessments of potential environmental factors in a given region, we need to create standardized incidence ratios that integrate these cancer and developmental end points in order to maximize opportunities for finding evidence of linked patterns. The biological rationale for creating such analyses has been previously described (*32*). Statistical principles should also be modified with one-tailed tests, as appropriate.

It is clear that children are at enhanced risk from pollution for a number of important reasons. Physiologically, their organ systems continue to develop through their first few years of life. A child's lung, for example, grows most rapidly in the first 2 years of life and continues to grow until the late teen years (*33*). Developing organs can be extremely sensitive to the toxic effects of pollutants. Children also tend to absorb pollutants more readily than adults and retain them in the body for longer periods of time. While the average active adult inhales about 10,000–20,000 L of air per day, a 3-year-old child takes in twice the amount of an adult per unit body weight (*34*). That child therefore absorbs double the amount of pollutants for its weight than an adult. In a study of infant deaths in the first month of life and particulate air pollution in the United States, those living in areas with greater PM_{10} (particulate matter < 10 μm in aerodynamic diameter) exposure encounter a 45% higher risk of dying from respiratory illness than those living in less polluted areas (*35*).

Today, most of the world's children live in the rapidly developing world. Children living in urban environments are in double jeopardy from poverty and degraded environments. Many do not have access to basic health care and therefore are not immunized (*34*). Moreover, a significant number of these children suffer from malnutrition and infectious diseases. Environmental pollution only adds to the burden of food deprivation, microbial diseases, and lack of preventive care or medical treatment that many children face in the developing world. It has long been known that air pollution can aggravate illnesses such as bronchitis, asthma, and chronic obstructive pulmonary disease (*36*). Children with diets deficient in vitamins, minerals, and protein are especially vulnerable to toxic effects of chemicals. When their immunity is reduced, they cannot transform pollutants easily to more benign substances in their bodies and tend to retain toxic materials for longer periods. Also, nutritional, workplace, and other exposures of young parents affect their ability to have children as well as their long-term health.

Seen in the context of globalization now under way, the vulnerability of children becomes one of the central public health problems for our time. Some have argued that increased economic development will axiomatically result in improved living conditions. Efforts to induce environmental protection in rapidly growing societies are sometimes opposed on the basis of limited understandings of the short-term costs of acquiring more efficient technologies without consideration of the health damages associated with continuing business as usual. These recent studies on diesel exhaust, plastics, and pesticides make clear that the full costs of continuing with old technologies and rates of use of toxic materials may well include permanent damage to the gene pool and brains of the youngest generation. Problems of neurologic development and reproduction that stem from early life exposures will not be reparable later, no matter how much money is available.

Unfortunately, over the years in some areas of research, we have decided to fund studies that we see as "a sure thing." A number of these sure things fall into what can be described as "street light science." This involves looking for your wallet under the brightest street light, even though you lost it in the dark. This is a good way to

describe some of the recent studies on the effects of environmental estrogens (*37*). These studies have often tried to equate body burden at the time of diagnosis with the burden at the time of initial exposure, and have failed to take into account exposures to potentially harmful volatile materials that cannot be measured years after they have occurred.

Those who argue that societies cannot afford to make immediate investments in reducing environmental pollution fail to appreciate that there are some forms of harm that cannot be repaired. The best way to prevent children from incurring irrevocable damage to their reproductive systems and to lower their risk of cancer and other chronic diseases is to reduce their exposures to damaging materials in the first place.

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