Neurotoxic Effects in Children

An epidemic of neurobehavioral problems is sweeping through children today. According to *In Harm's Way: Toxic Threats to Child Development*, a May 2000 report published by the Greater Boston Physicians for Social Responsibility, 12 million American children suffer from learning, developmental, or behavioral disabilities. Specifically, these disabilities may include attention-deficit/hyperactivity disorder (ADHD), autism, learning disabilities, mental retardation, and other neurobehavioral problems. And the prevalence of some of these disabilities may be increasing.

In the past few years, much research has examined the factors that make children markedly vulnerable to neurotoxic substances. Although science cannot always pinpoint the cause of neurological disabilities, many investigators believe that exposure to environmental contaminants *in utero* or soon after birth could be responsible for at least some of these problems. The list of potentially harmful agents covers a wide range—alcohol, lead, manganese, mercury, organophosphate pesticides, environmental tobacco smoke, and more. Per pound of body weight, children eat more food, drink more fluids, and breathe more air than adults, thereby increasing their potential exposure to harmful toxicants. Moreover, some toxic materials may pose a particularly significant threat to the fetus when crucial systems such as the brain and associated nervous systems are under development.

Although a host of scientists are now exploring neurodevelopmental problems, the causes of many such problems still remain unknown. Philip J. Landrigan, director of the Mount Sinai School of Medicine's Center for Children's Health and the Environment, says, "We know the cause of only a relatively small minority of these conditions. It depends on whom you talk to, but we know the cause of no more than 10–30%, and 30% . . . is being generous."

Long-Lasting Effects of Lead

Researchers are learning that many neurobehavioral problems may arise from exposure to lead. Historically, lead exposure is usually associated with decreasing IQ scores and mental retardation. More recently, lead has also been associated with other problems including aggressive and antisocial behavior in children. In a 7 February 1996 article in the *Journal of the American Medical Association*, Herbert Needleman, a professor in the department of psychiatry and a lead exposure expert at the University of Pittsburgh in Pennsylvania, and colleagues reported that increased bone lead concentrations in 12-year-olds correlated with increased aggression, attention problems, and delinquency.

Many U.S. children are exposed to high levels of lead in a variety of places both outdoors and indoors, through agents including air pollution from vehicle emissions and lead-based paint in homes. In 1990 (the most recent year for which such figures are available), the Centers for Disease Control and Prevention (CDC) reported that 930,000 U.S. children had lead blood concentrations higher than 10 micrograms per deciliter (μg/dL), the concentration considered safe by the U.S. Environmental Protection Agency (EPA). According to Howard W. Mielke, a geographer at Xavier University of Louisiana in New Orleans, the highest concentrations of lead exist around the areas of highest traffic flow in cities. "The inner city population is carrying a big lead burden," he says. In an article in the January–February 1999 issue of *American Scientist*, Mielke wrote, "Over 50 percent (some studies place this figure at around 70 percent) of children living in the inner cities of New Orleans and Philadelphia have blood lead levels above

the current guideline of 10 micrograms per deciliter."

Children are also exposed to lead in older homes through lead-containing pipes, solder, and house paint. Although modern drinking water supply lines in the United States do not contain lead, it is still present in old plumbing systems. Similarly, although lead was banned from U.S. paints for household use in 1978, it still exists in coats applied in older homes before the ban, and is used in paints produced in other countries.

But Mielke says that the current trouble comes mostly from lead dust, not lead paint. In the *American Scientist* article, he wrote, "Research in my laboratory and others shows that in predictable locations of many cities, the soil is a giant reservoir of tiny particles of lead. This means that many children face their greatest risk for exposure in the yards around their houses and, to a lesser extent, in the open spaces such as public playgrounds in which they play."

Lead proves to be especially dangerous during fetal development because it can cross the placenta. Once in the developing brain, lead adversely affects the organ's structure, preventing it from forming properly. Ellen K. Silbergeld of the University of Maryland School of Medicine in Baltimore reported in the 1 October 1992 issue of the *FASEB Journal* that fetal lead exposure can prevent synapse formation and cell differentiation.

In large part, environmental health efforts to address the problem of lead focus on decreasing exposures. In the 1970s, 60 µg/dL was considered the limit of safe exposure. In the early 1990s, experts revised that to today's level of 10 µg/dL. In essence, what scientists consider to be a safe exposure level for lead decreased with increasing knowledge. Says Needleman, "As we bring better [assessment] methods to bear, the toxicity appears at lower and lower levels."

The Good and Bad in Manganese

Humans need trace amounts of manganese for some enzymatic reactions, but too much manganese in adults leads to tremors and psychological symptoms including violent behavior and hallucinations. Some studies suggest that manganese exposure causes hyperactivity and learning disabilities in children, but in the June 2000 issue of *EHP Supplements*, neurotoxicologist Michael Aschner of the Wake Forest University School of Medicine in Winston-Salem, North Carolina, wrote that there are a limited number of studies that address the neurological deficits of manganese exposure in children, and that some of the studies must be considered cautiously because of the possibility of researcher bias.

Everyone is exposed to a certain amount of manganese, which is found in many foods including avocados, blueberries, nuts, seeds, seaweed, egg yolks, whole grains, legumes, dried peas, green leafy vegetables, and tea. Infant formula, including soy-based formulas, also contains manganese (up to 300 µg/L), but the National Research Council considers 2–5 mg of manganese per day to be safe, so a child would need to consumer more than 16 L of formula each day to surpass the current

INITIATIVES TOWARD BETTER BEHAVIOR

PCBs

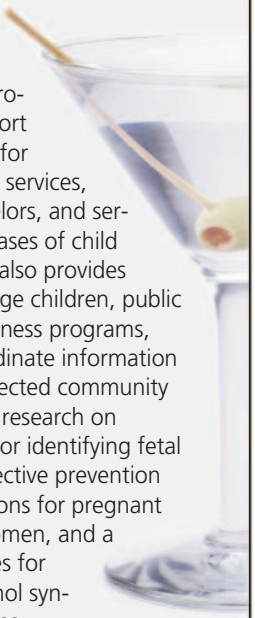
In 1998, the EPA amended the Toxic Substances Control Act to streamline procedures for disposing of PCB wastes. The change was intended to protect human health and the environment against unreasonable risks from PCBs by providing cost-effective and environmentally protective disposal options that will reduce exposure to PCBs by encouraging their removal from the environment. The change also authorizes certain continued uses of PCBs and materials contaminated with PCBs where exposures can be controlled and where removal and disposal of the material would be costly or impractical.

Environmental Tobacco Smoke

The Children's Health Act of 2000 was introduced in May as an amendment to the Public Health Service Act with respect to children's health. The Children's Health Act contains provisions for the Centers for Disease Control and Prevention to collect, analyze, and disseminate data on prenatal smoking; conduct applied epidemiological research on the prevention of prenatal and postnatal smoking; support, conduct, and evaluate the effectiveness of educational and cessation programs; and provide information and education to the public on the prevention and implications of prenatal and postnatal smoking.

Alcohol

The Health Professions Education Partnerships Act of 1998 includes a fetal alcohol syndrome prevention and services program that would support educational programs for medical schools, social services, and educators, counselors, and service providers in all phases of child development. The act also provides education for school-age children, public and community awareness programs, and strategies to coordinate information and services across affected community agencies, and calls for research on appropriate methods for identifying fetal alcohol syndrome, effective prevention services and interventions for pregnant alcohol-dependent women, and a host of support services for people with fetal alcohol syndrome and their families.



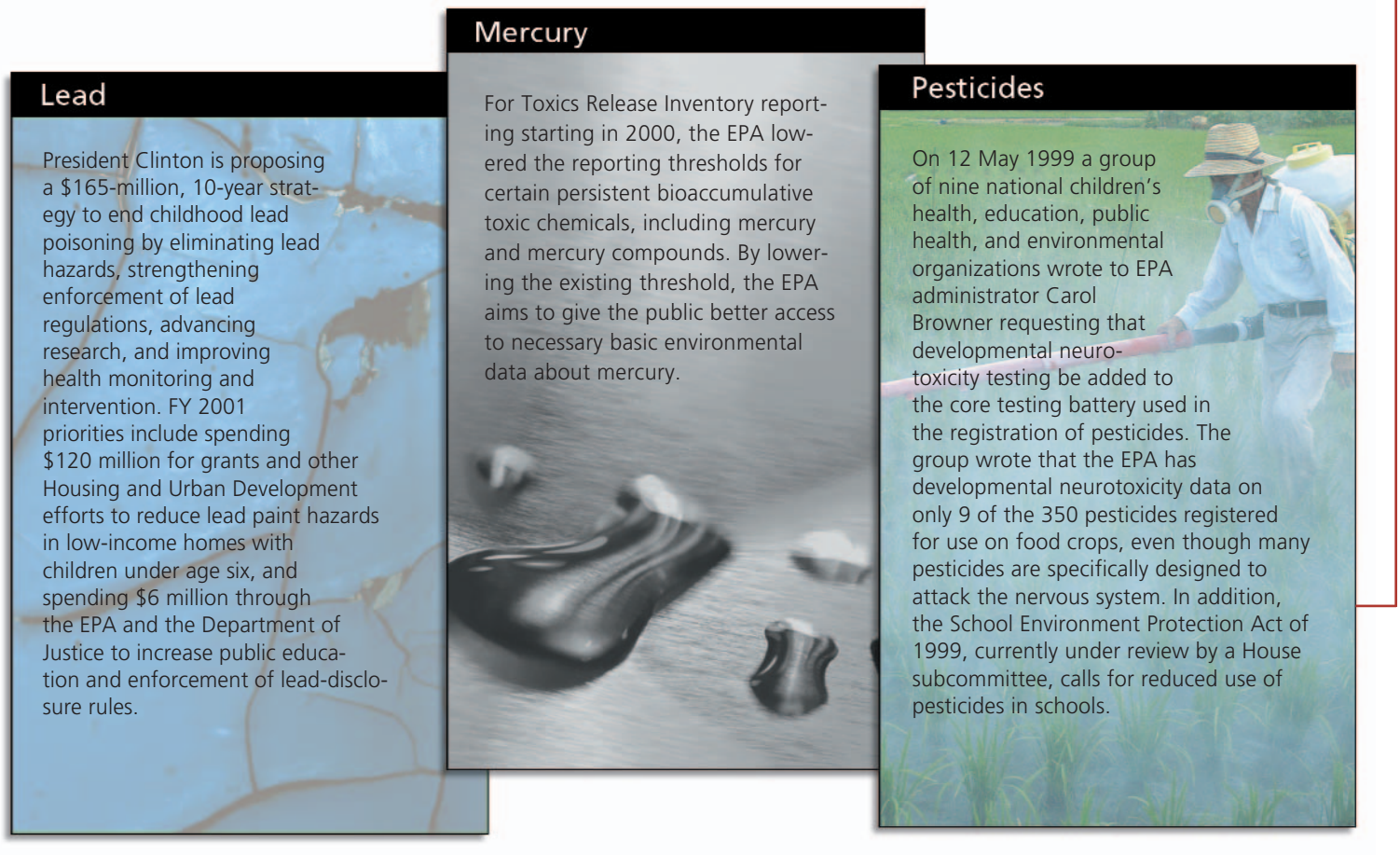
safety level. It's also possible to inhale manganese because one of its organic forms is sometimes used in gasoline and releases inorganic manganese when it combusts.

Aschner writes that, once manganese gets in the circulatory system, it "readily crosses the blood–brain barrier in the developing fetus, neonate, and the mature mammal." He also states that manganese concentrates in a variety of brain structures, including the hypothalamus and the cortex. Still, much more work remains to be done on manganese; as the authors of *In Harm's Way* wrote, "The susceptibility of the developing brain to manganese toxicity deserves further attention."

Rising Concerns over Mercury

Increasing scientific evidence shows that exposure to another heavy metal, mercury, during fetal and neonatal periods leads to a variety of developmental problems affecting motor skills such as walking and speech, and may cause mental retardation. Children may be exposed to several forms of mercury. Metallic mercury is the silvery liquid in a thermometer. The gaseous form, called mercury vapor, can combine with carbon to make other compounds, including methylmercury. Elemental mercury in the earth's crust is released into the oceans, where bacteria can convert it, too, to methylmercury. Some industries release mercury-contaminated waste into bodies of water.

Because mercury in water bioaccumulates in the fish that live there, fish-eating populations generally receive the highest exposures to the metal; when people eat mercury-laden fish, the metal can bioaccumulate in their bodies, as well. Bioaccumulated mercury can pass through the placenta to the fetus during pregnancy, where it can cross the blood–brain barrier to impact the developing central nervous system. A study by Philippe Grandjean and colleagues at Denmark's Odense University, published in the November–December 1997 issue of *Neurotoxicology and Teratology*, involved 917 children in the Faroe Islands, where pregnant mothers consume considerable methylmercury through seafood. Grandjean's group tested the children with a battery of tests at age seven and found that children with higher prenatal exposures to mercury showed deficits in attention, language, and memory. (These results may have been confounded by exposure to polychlorinated biphenyls.) And in the June 2000 *EHP Supplements*, neurologist Gary J. Myers and psychologist Philip W. Davidson, both of the University of Rochester in New York, note several neurotoxic effects of mercury including inhibition of microtubule formation and protein synthesis in neurons and effects on neurons' membrane activity. They state that methylmercury "appears to be most neurotoxic prenatally when the brain is developing rapidly." Myers says that some animal studies suggest that exposure to methylmercury can produce delayed effects that do not appear until long after the exposure. He suggests that studies of mercury-exposed children might reveal whether such delayed effects apply to humans as well.



As with lead, supposedly safe levels for mercury keep changing downward as researchers learn more about toxicity at low concentrations. In 1972, the World Health Organization indicated that people could consume 0.47 µg per kilogram of body weight per day (µg/kg/day). By 1997, the EPA lowered that figure to 0.1 µg/kg/day. Then, in 1999, the Agency for Toxic Substances and Disease Registry set their limit at 0.3 µg/kg/day. But as with many toxicants, no one can be sure what level of exposure may actually prove safe to a developing child.

Persistent PCBs

Polychlorinated biphenyls (PCBs) are a family of about 200 industrial chemicals used as lubricants and coatings. Although PCBs were banned in the United States in the 1970s, these persistent compounds remain scattered throughout the environment. Like mercury, PCBs can contaminate fish, but PCBs also end up in many other foods, including beef, dairy products, pork, and human breast milk.

Early exposure to PCBs is frequently associated with decreases in IQ. For example, in the 12 September 1996 issue of *New England Journal of Medicine*, Joseph and Sandra Jacobson of Wayne State University in Detroit, Michigan, reported on an 11-year study of children who were exposed to PCBs *in utero*. The investigators collected blood samples from the mother and the umbilical cord shortly after each child's birth, plus milk samples from the mothers. They also collected blood samples from the children at ages 4 and 11. All samples were tested for PCBs. A variety of neuropsychological tests on the children later revealed that PCB exposure *in utero* correlated with decreased IQ in the children. In fact, the children exposed to the highest amounts of PCBs had an average IQ that was 6.2 points lower than that of the other children in the study. This work also showed that exposure to PCBs correlated with decreases in children's ability to comprehend words as well as whole bodies of reading material. Specifically, the children with the highest exposures to PCBs lagged more than seven months behind the norm for children of the same age in word comprehension. The Jacobsons concluded, "The most highly exposed children were more than three times as likely to perform poorly in terms of the scores for full-scale IQ, verbal comprehension, and freedom from distractibility and more than twice as likely to be at least two years behind in comprehension in reading."

Although PCBs in breast milk may pose a risk, the work by the Jacobsons showed that PCB exposure proves more damaging to the fetus than to the infant. They found that breast-feeding could expose infants to higher concentrations of PCBs than their experience *in utero*, but that the PCBs in breast milk did not adversely affect a child's intellectual capabilities. Various animal studies suggest that PCBs might be more damaging to the fetus by affecting the thyroid hormones, which regulate proliferation, migration, and differentiation of neurons. Specifically, these hormones are needed for assembly of the cytoskeleton, and they regulate brain systems. As a result, these hormones play a crucial role in the timing of many neurodevelopmental events. In most cases, exposure to PCBs leads to reduced brain levels of the thyroid hormone thyroxine. Some evidence suggests that thyroxine is transported to brain cells via a binding protein, and some PCBs might bind that protein more readily than thyroxine does. Consequently, some PCBs might outcompete thyroxine for transport.

Susan Porterfield of the Medical College of Georgia in Augusta explains in an article in the June 2000 *EHP Supplements* that children who suffer from thyroid dysfunction can end up with reduced IQ scores if the condition is not treated during the first year of life. Even if such a deficiency is treated, various problems including language, motor, and cognitive impairment, ADHD, and reduced fine motor control often persist. Still, no one knows precisely what risks children face from exposure to PCBs. And, says Jacobson, "We don't know a lot about contemporary levels of exposure."

We know the cause of only a relatively small minority of these conditions.

–Philip J. Landrigan

Uncertainties in Organophosphates

Organophosphate pesticides, which are used in gardens, homes, and schools, pose still another threat to developing brains. Landrigan says, "We have become very suspicious . . . that [organophosphate] pesticides also have the power to cross the placenta [and] cause subtle but very real brain injury in children resulting in learning disabilities."

No one knows the extent to which organophosphates may adversely impact children. These pesticides are generally thought of as inhibitors of cholinesterases, which break down neurotransmitters including acetylcholine, but organophosphates do more than just that. Research published in the 17 April 1995 issue of *Brain Research* by toxicologist Jonas Ahlbom and colleagues at Uppsala University in Sweden showed that the effects of certain organophosphates depend on the developmental stage at the time of exposure. Ahlbom and colleagues exposed neonatal mice to a single oral dose of the organophosphate diisopropylfluorophosphate on either postnatal day 3, 10, or 19. Exposure on days 3 and 10 stimulated what the authors called "hyperactive behavior" at the age of four months. Treatments on postnatal day 19 showed no effects. It's not clear exactly what the implications of this research are for humans.

Another organophosphate under investigation is chlorpyrifos, a chemical used to kill insects that is often put in pet collars. According to the Environmental Working Group, chlorpyrifos is linked to health risks including blurred vision and memory loss. In the 15 June 1998 issue of *Developmental Brain Research*, toxicologist Theodore Slotkin of Duke University Medical Center in Durham, North Carolina, and colleagues reported that chronic low doses of chlorpyrifos selectively inhibited DNA synthesis in the brain stem and forebrain of neonatal rats, although the implications of this for humans are unclear. In the 5 August 1999 issue of *Developmental Brain Research*, Slotkin's group revealed that exposing rats to chlorpyrifos during the creation of synapses disrupts a wide variety of neuronal pathways in the brain, including ones controlled by the neurotransmitters acetylcholine, norepinephrine, and dopamine. Now researchers must determine if these compounds affect the developing human brain in similar ways.

Meanwhile, the EPA is expected to announce in early June a decision to remove chlorpyrifos from all over-the-counter products and eventually phase out all home uses of the chemical. Todd Hettenbach, an analyst with the Environmental Working Group, said in a 2 June 2000 Reuters press release that "this will be one of the most significant consumer product decisions the EPA will make this decade."

Drinking and Smoking

In the early 1970s, investigators realized that babies born to chronic alcohol drinkers often possess a suite of abnormal characteristics

including deficiencies in growth, abnormal morphology (especially in the face), and central nervous system problems including microcephaly, mental retardation, and behavioral hyperactivity. This suite of characteristics became known as fetal alcohol syndrome. Fetal alcohol exposure also causes more subtle problems. In the November–December 1997 issue of the *Journal of Learning Disabilities*, researchers from the University of Victoria in Canada reported that young adults with fetal alcohol syndrome scored lower for ability to pay attention and verbal learning than control subjects. More recently, this same group reported in the May 1999 issue of *Psychological Science* that children from mothers who consumed alcohol during their pregnancy but who were not considered to have an alcohol problem—averaging less than one drink per day while pregnant—still developed attention, memory, and information processing problems, and the severity of these problems increased with increasing alcohol exposure.

Fetal exposure to alcohol reduces brain mass, and investigators are beginning to unravel the microscopic causes behind this. For example, Chrysanthy Ikonomidou, a pediatric neurologist at Humboldt University in Berlin, Germany, and colleagues reported in the 11 February 2000 issue of *Science* that rats exposed to ethanol during synaptogenesis (the period when neurons form synapses) may lose millions of neurons. The study, which was modeled on the human period of synaptogenesis (the last three months of gestation), may have implications for humans. According to the authors, if a pregnant mother imbibes ethanolic beverages for several hours in a single drinking episode [200 mg/dL lasting 4 hours or more], she could expose her third-trimester fetus to blood ethanol concentrations equivalent to those high enough to trigger the death of neurons in the immature rat brain.

Smoking is a frequent companion to drinking. *In Harm's Way* states, "Children born to women who smoke during pregnancy are at risk for IQ deficits, learning disorders, and attention deficits." The report adds that even passive smoke during pregnancy can lead to impaired speech and deficiencies in language and intelligence. But in general the neurodevelopmental effects of smoking remain as mysterious as those of so many other neurotoxicants; neuropsychologist Brenda Eskenazi and environmental health scientist Rosemary Castorina of the University of California at Berkeley reported in the December 1999 issue of *EHP*, "Although some evidence suggests that maternal smoking during pregnancy may be associated with deficits in intellectual ability and behavioral problems in children, the impact of prenatal or postnatal [environmental tobacco smoke] exposure remains less clear."

ADHD and Autism

Although many neurobehavioral and developmental disorders are linked to exposure to a specific substance, the cause of certain disorders including ADHD and autism may be linked more indirectly to environmental factors. Children diagnosed with ADHD generally exhibit impulsivity, inattention, and hyperactivity. In an abstract for a CDC meeting titled Attention-Deficit/Hyperactivity Disorder: A Public Perspective Conference (available online at http://www.cdc.gov/nceh/cddh/ADHD/dadabepi.htm), child psychiatrist Peter S. Jensen of the New York State Psychiatric Institute wrote that estimates of ADHD's prevalence worldwide range from 3% to 18%. Autism, on the other hand, consists of a spectrum of disorders with related symptoms, including trouble interacting socially and communicating, plus repetitive behaviors. The number of children affected remains uncertain. Potential environmental links have been suggested for both of these disorders but not confirmed.

In the 1995 *Annual Review of Pharmacology and Toxicology*, neurobiologist Deborah Cory-Slechta of the University of Rochester wrote, "Increased distractibility has also been cited as the basis of [lead]-associated cognitive impairments." Consequently, some investigators, including epidemiologist Andy Rowland at the NIEHS, have proposed large studies of a potential relationship between exposure to lead and ADHD, but that work remains to be done. Although the cause of most cases of ADHD appears to be primarily genetic, Russell A. Barkley, a clinical psychologist at the University of Massachusetts at Worcester, wrote in an article in the September 1998 issue of *Scientific American* that nongenetic factors may account for 20–30% of ADHD cases among boys and a smaller, unspecified percentage among girls.

The potential for an environmental link to autism is also uncertain. An October 1999 CDC fact sheet states, "Little is known about the causes of autism, although genetic and early prenatal exposures have been suggested." The sheet adds that even the number of children with autism in the United States remains uncertain, but might be as high as 2 in every 1,000 (other groups place the number as high as 5 in every 1,000).

Uncharted Challenges Ahead

The challenges for unraveling the effects of exposure to environmental toxicants on the developing brains of children are huge. In the June 2000 *EHP Supplements*, Lynn Goldman, an adjunct professor in the Department of Health Policy and Management, and Sudha Koduru, a research assistant with the Pew Environmental Health Commission, both at The Johns Hopkins University in Baltimore, Maryland, note that more than 85,000 chemicals are produced in the United States and that many of them go untested for their effects on children. They add that of the nearly 3,000 chemicals that are produced in volumes of more than a million pounds a year, close to half have not undergone basic toxicity testing and more than three-quarters have not been put through developmental toxicology screening. They conclude that current knowledge offers little information about the prevalence of and trends in most developmental disorders. To address these issues, Goldman and Koduru recommend new research on children's developmental issues, including long-term follow-ups, improved surveillance of disabilities, and linking the epidemiological and clinical research findings for a more complete picture.

Many investigators also agree that future research must examine the effects on children of exposure to mixtures of more than one toxic substance at a time. Given the number of possible combinations, the breadth of this challenge is daunting. Says Stephen Schroeder, director of the Schiefelbusch Institute for Life Span Studies at the University of Kansas in Lawrence, "Our technology for dealing with multiple exposures is pretty limited." Still, to decipher the neurobehavioral problems afflicting today's children, scientists now know that they must examine the entire developmental picture, from fetus through adulthood. Says Needleman, "It's incumbent on us to paint a total picture of child development."

It's incumbent on us to paint a total picture of child development.

–Herbert Needleman

Mike May