Environmental Factors Associated With a Spectrum of Neurodevelopmental Deficits

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A number of environmental agents have been shown to demonstrate neurotoxic effects either in human or laboratory animal studies. Critical windows of vulnerability to the effects of these agents occur both pre- and postnatally. The nervous system is relatively unique in that different parts are responsible for different functional domains, and these develop at different times (e.g., motor control, sensory, intelligence and attention). In addition, the many cell types in the brain have different windows of vulnerability with varying sensitivities to environmental agents. This review focuses on two environmental agents, lead and methylmercury, to illustrate the neurobehavioral and cognitive effects that can result from early life exposures. Special attention is paid to distinguishing between the effects detected following episodes of poisoning and those detected following lower dose exposures. Perinatal and childhood exposure to high doses of lead results in encephalopathy and convulsions. Lower-dose lead exposures have been associated with impairment in intellectual function and attention. At high levels of prenatal exposure, methylmercury produces mental retardation, cerebral palsy and visual and auditory deficits in children of exposed mothers. At lower levels of methylmercury exposure, the effects in children have been more subtle. Other environmental neurotoxicants that have been shown to produce developmental neurotoxicity include polychlorinated biphenyls (PCBs), dioxins, pesticides, ionizing radiation, environmental tobacco smoke, and maternal use of alcohol, tobacco, marijuana and cocaine. Exposure to environmental agents with neurotoxic effects can result in a spectrum of adverse outcomes from severe mental retardation and disability to more subtle changes in function depending on the timing and dose of the chemical agent.

Key Words: environment; mental retardation; developmental disabilities; mercury; lead; neurotoxicant
effects observed following developmental exposure may be different both quantitatively and qualitatively from adult exposure because of the potential to affect processes in the developing child that have no parallel process in adults.

Central nervous system development consists of a series of processes that occur in sequence and are dependent upon each other, such that interference with one stage may also affect later stages of development. This makes the timing of a potential environmental neurotoxicant a critical parameter in risk for subsequent neurologic effects. The sequence includes proliferation, migration, differentiation, synaptogenesis, apoptosis, and myelination. Both ethanol [Miller, 1993] and methylmercury affect proliferation [Rodier et al., 1984; Choi, 1989; Ponce et al., 1994] and migration [Choi et al., 1978; Choi, 1986] after gestational exposure. Perturbations that alter neural proliferation and migration often result in altered differentiation, such as exposure to X-ray irradiation [Sager et al., 1984; Norton and Donoso, 1985]. Environmental agents that affect differentiation of the nervous system include ethanol [Valles et al., 1996; 1997; Laev et al., 1995; Lauder and Schambra, 1999], nicotine [Frischer et al., 1988; Slotkin et al., 1993; Pennington et al., 1994; Cutler et al., 1996; Levitt, 1998; Audesirk and Cabell, 1999], methylmercury [Barone et al., 1998], and lead [Petit and LeBoutilier, 1979; Alfano and Petit, 1982; Petit et al., 1983]. The formation of myelin occurs later in development than proliferation and migration of neuronal populations. Malnutrition can affect myelination, particularly during late gestational development, as can maternal thyroid dysfunction. Perinatal exposure to ethanol and postnatal lead exposure produces significant decreases in myelination.

The schedule by which synapses form is carefully controlled within each region of the nervous system, and differs from region to region. Therefore, environmental exposure to a toxic agent that affects synaptogenesis, such as lead, may affect brain areas differentially depending on timing of exposure. In the adult nervous system, neurotransmitters mediate or modulate synaptic transmission. However, during development, neurotransmitters and other factors may interact with their corresponding receptor types to influence the formation of the architecture of brain regions and nuclei. Therefore, agents that act through effects on neurotransmitter systems, such as pesticides, may have quite different effects in the developing fetus or child compared to the adult.

The nervous system continues to remodel and change throughout the entire period of development in response to environmental influences and genetically programmed events. One mechanism for this remodeling is the normal genetically-programmed overproduction and subsequent elimination of neurons and neural processes (apoptosis). This has been extensively documented in the monkey [e.g., Bourgeois and Rakic, 1993], and occurs in humans as well [Rakic et al., 1994].

Since different brain areas develop on different time lines during prenatal and postnatal life, an environmental neurotoxic agent may produce impairment in different functional domains depending on the time of exposure. For example, the same exposure at different points in development could result in an adverse effect on motor systems versus memory or executive functions. Similarly, exposures at different concentrations or for different lengths of time could potentially produce differential effects. Therefore, the constellation of observed effects should not be expected to be the same in different children exposed to the same neurotoxic agent.

NEUROTOXIC EFFECTS OF LEAD

Sources and Exposure

Lead has been used for millennia. Toxic effects of lead were noted by Hippocrates in ancient Greece, and lead was used to both sweeten wine and as birth additives was initially reduced, and finally eliminated from these consumer products. With these reductions, exposure has declined, but has not been eliminated. Two major sources of lead exposure remain: contaminated soil and paint in older housing. Despite reduction in airborne lead associated with the phasing out of lead-based fuels, soil near roads and freeways is still contaminated with lead dust [ATSDR, 1995]. Houses and commercial buildings built in the United States prior to 1978 are likely to contain lead paint unless removal/remediation has occurred. Cracked, peeling or chalking paint can expose children through contact with dust or pica. Children also absorb a higher dose compared to adults with similar exposures (for example, gastrointestinal absorption is 42–53% in children less than two years of age and 7–15% in adults) [ATSDR, 1995].

The blood lead levels of United States children have decreased over the latter part of the 20th century as a result of efforts to lower lead levels in the environment. In the second National Health and Nutrition Examinations Survey (NHANES II, 1976–1980), the proportion of children with blood lead greater than 10 μg/dL was 88.2% compared to 8.9% during the first phase of NHANES III (1988–1991) and 4.4% during the second phase (1991–1994) [CDC fact-sheet, 2001].

Effects of Poisoning

Acute encephalopathy is one of the most serious clinical manifestations of lead poisoning along with severe mental retardation [Piomelli, 2000]. The first mention of lead poisoning in children in the modern medical literature occurred in 1894. Australian physicians noted acute childhood lead poisoning associated with lead-based paint [described in Needleman, 2000]. Within a decade, cases of acute childhood lead poisoning were recorded in the United States but it was not until the 1940s that the medical community began to recognize long-term consequences associated with frank lead poisoning. Byers and Lord [1943 described in Needleman, 1993] reported that 19 of 20 children who had supposedly recovered from acute lead intoxication, exhibited learning or behavioral disorders (such as distractibility and poor impulse control). A general overview of
types of behavioral deficits observed after developmental exposure to lead is provided in Table 1.

In one study, persistent cognitive effects in adults were evaluated up to 50 years after their initial diagnosis of lead poisoning at age four years or younger [White et al., 1993]. The initial sample of lead poisoned children (n = 192) were treated in Boston Children’s Hospital between 1930–1942. Of these, 72 were traced through public records; 34 participated in the follow-up study. From the symptoms described, blood lead levels at the time of poisoning were probably 60 µg/dL and higher. Adults with a history of childhood lead poisoning had deficits in all the cognitive measures assessed (such as attention, memory, reasoning, motor speed) when compared to a population-based control group matched on age, sex, race and neighborhood. These findings suggest that lifelong cognitive impairments can result from childhood lead poisoning.

**Effects of Exposures Outside of Poisoning Episodes**

Intensive studies to examine children with lead levels in the “normal”
range (that is, without acute lead poisoning) began in the late 1970s. This literature is extensive and reviewed in detail elsewhere [Needleman, 1993; Rice, 1996a; Tong, 1998]. It is now recognized that lead produces a continuum of effects, from death at high doses to subtle impairments in cognitive function or behavior that can occur at or near currently observed body burden levels (Fig. 1).

In a landmark study, Needleman et al. [1979] assessed lead in children at ages 6–7 in 1975–8. They measured lead in shed primary teeth and determined blood lead levels for a subset of the sample. Children with low tooth lead levels (<10 parts per million (ppm)) had blood levels ranging from 12–36 μg/dL (mean 24 μg/dL) compared to children with higher tooth lead levels (> 20 ppm) whose blood levels ranged from 18–54 μg/dL. These children had no classical signs of lead poisoning when initially enrolled but deficits were observed in attention and class performance, intelligence scores, and speech and language processing. Results from a follow-up of these children when they were in 5th grade were consistent with earlier findings; lower IQs and higher rates of academic failure were observed in the group with tooth lead levels > 20 ppm than in the group with tooth lead levels < 10 ppm [Needleman et al., 1990]. Test batteries, along with self-reports of delinquent behavior and a school record review were used to assess neurobehavioral endpoints. The investigators found a range of outcomes, including significantly higher rates of drop-out and reading disabilities, longer reaction times and poorer hand-eye coordination in the group with higher tooth lead levels compared to the group with lower tooth lead levels. The participants in this 11-year follow up were not representative of the earlier group; respondents had higher IQs, lower dentin lead levels and higher teachers’ ratings than found on average in the earlier study. Thus, the results from this subsample may underestimate the effects of lead in the entire group.

Leviton et al. [1993] examined children born more recently (in 1979–80), which provided an opportunity to examine the effects of lower environmental lead levels. Of 3,814 children screened, 2,657 were enrolled as infants, and follow-up data were collected at eight years of age for between 1923 and 2275 children, depending on the component of the study. Elevated lead levels (≥ 10 μg/dL cord blood or ≥ 5 μg/g den- tin lead) were associated with reading and spelling difficulties as well as inappropriate approaches to problems among girls and difficulties with following directions among boys.

A recent study investigated the association between antisocial behavior [Needleman et al., 1996] and bone lead levels. From a population of 850 boys in the first grade at public schools, 503 were selected on the basis of a risk scale for antisocial behavior. Antisocial behavior was measured using ratings from teachers, parents and directly from the boys. Those scoring in the top 30% on the risk scale, using these three measures, and a sample of the remaining 70%, were invited to participate in the study. Of the 503 invited, 301 students participated. A number of measurements were repeated: antisocial behavior questionnaires were administered at mean ages of 7.4 and 10.9; psychological measures were collected at two times: at mean ages of 10.2 and 12.0. Only borderline differences were observed for teachers’ assessment of delinquent and aggressive behavior at age seven (using bone lead levels measured at age 12); however, statistically significant differences were observed for most endpoints at 11 years of age including differences for social, thought, and attention problems; somatic complaints; and anxious/depressed state. Higher bone lead levels were also associated with increased self-reports of delinquent behavior.

These examples show consistency in general findings in a number of different study groups. A threshold for neurobehavioral effects has not been identi-
fied [Schwartz, 1994]. A recent examination of NHANES III data observed cognitive effects (arithmetic, reading, block design, and digit span) in children 6–16 years old associated with blood lead levels lower than 5 μg/dL [Lanphear et al., 2000]. As the data on effects of lead levels evolved, CDC’s action level for children’s blood lead levels declined, from 60 μg/dL in the 1960s, to 30 μg/dL for 1970–85, 25 μg/dL from 1985–1991, and now to 10 μg/dL, with an emphasis on primary prevention by removing lead from the environment.

NEUROTOXIC EFFECTS OF METHYLMERCURY

Sources and Exposure

Mercury is found in three states: elemental mercury, inorganic mercury salts and organic mercury. Elemental mercury can be found in small amounts in dental amalgams, thermometers, sphygmomanometers, batteries and some latex paint formulated prior to 1991. Inorganic mercury salts are present in some pesticides and disinfectants and have been used as preservatives in medications. Elemental and inorganic mercury can be transformed in the environment by microorganisms in water or soil into organic mercury. Most organic mercury in the environment is methylmercury (MeHg).

MeHg bioaccumulates in the aquatic food chain. Consumption of contaminated predator fish and fish-eating animals can result in significant body burden levels as well as short-term high blood levels, particularly among subsistence eaters. The major source of MeHg exposure to the general population is typically through consumption of contaminated fish and other food products [NRC, 2000]. Approximately 90 percent of MeHg is absorbed from the gastrointestinal tract. MeHg is lipophilic and easily transported across the blood-brain barrier and placenta [ATSDR, 1999].

MeHg has demonstrated neurotoxic effects and is preferentially stored in the brain and central nervous system [Philbert et al., 2000]. Over time, brain levels may exceed blood levels by three to six times [Berlin, 1979]. Once it is demethylated in the brain, elemental mercury (Hg) bioaccumulates in the brain tissue [Cavanagh, 1988] although whether this inorganic mercury represents an ongoing source of toxic exposure is unknown. In experimental animals, dymorphogenesis of the cerebellum is a classic feature of exposure to MeHg during development with additional effects observed in the visual cortex and sensory paraspinal ganglia [Philbert et al., 2000]. Oxidative stress may be a mechanism of mercury toxicity and antioxidants, such as Vitamin E [Ganther, 1980] and possibly selenium, may be protective against MeHg toxicity. Calcium ion channel disturbances and inhibition of protein synthesis have also been observed in various animal studies [Philbert et al., 2000].

Effects of Poisoning

Methylmercury poisoning has been clearly associated with severe neurotoxic effects in both animal studies and human poisoning episodes, whereas the evidence for developmental impairments associated with lower level exposures is less clear [Myers and Davidson, 2000].

Frank human poisoning, both prenatal and postnatal, have been associated with severe mental retardation. In Japan, in the 1950s and 1960s, MeHg was discharged into Minamata Bay. Fish eaten by the local community became contaminated with high levels of MeHg. Severe neurodevelopmental effects were observed in children exposed in utero even when mothers were asymptomatic or had very mild symptoms [Study Group of Minamata Disease, 1968]. Congenital Minamata disease has been characterized by low birthweight, microcephaly, profound developmental delay, cerebral palsy, deafness, blindness and seizures [Goto, 2000]. Following a similar episode of individual contamination of fishing stock in Niigata, Japan, physicians recommended abortion to pregnant women with hair mercury levels of > 50 ppm. Of thirteen infants whose mothers had levels > 50 ppm in hair, one case of Minamata disease was described [Tsubaki and Irukayama, 1977]. In these poisoning episodes, exposure assessment and techniques for developmental testing were limited. Although it is impossible to confidently characterize the relationship between a specific level of MeHg exposure and neurodevelopmental outcomes on the basis of these studies, it is clear that severe disability can result from MeHg exposure.

In another poisoning episode, MeHg-treated seed grain that was meant for planting was accidently consumed during the winter of 1971–1972 in Iraq. More than 6,500 persons were admitted to hospitals for treatment during the outbreak and 459 deaths were reported. Groups of children exposed in utero were examined. Exposure assessment was based on maternal hair samples during pregnancy. Mental retardation and seizures were observed with greater frequency among the more highly exposed children [Marsh et al., 1987]. The most severely affected children were blind and one was reported to have a hearing impairment [Bakir et al., 1980]. Age at first independent walking and an index of neurologic signs were correlated with maternal hair mercury levels. Exposed males appeared to exhibit more abnormal neurologic signs than females [Marsh et al., 1987]. It is impossible to determine the incidence of developmental disorders associated with various exposure levels since there was no systematic enumeration of the exposed population. It is likely that not all of the affected individuals sought medical attention. Children with severe sequelae may be more likely to appear in study populations because they would be identified as needing special care. Additionally, only an estimate was available for birth dates and age when the children reached certain milestones, such as walking. However, despite the limitations, the Iraqi population studies identified some dose-related effects of MeHg and raised concern that lower levels of MeHg might be associated with developmental delays.

Effects of Exposure Outside of Poisoning Episodes

A number of studies have addressed the consequences of environmental exposure to MeHg through consumption of contaminated fish. None of the studies has identified an increase in severe mental retardation or other serious developmental outcome in association with maternal fish or marine mammal consumption during pregnancy. However, the limited sample size of these studies generally would not be expected to detect even a modest increase in the risk for relatively rare severe outcomes, such as mental retardation, in association with dietary (non-poisoning) exposure levels. Rather, these studies have focused on identifying more subtle developmental delays and neurologic signs as the anticipated outcomes of lower level MeHg exposures.

The National Research Council of the National Academy of Sciences (NAS [NRC, 2000] reviewed three longitudinal cohort studies assessing neurodevelop-
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<td>PCBs</td>
<td>poorer cognitive development, developmental delays persistent over time</td>
<td>in utero exposure to contaminated rice oil in Taiwan and Japan</td>
<td>Yu et al., 1991</td>
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<td>Urabe et al., 1979</td>
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<td>alterations in “motor maturity”; weak reflexes; lower scores on numerous measures of cognitive development; poorer short term memory function</td>
<td>in utero exposure though maternal consumption of contaminated fish (Lake Michigan, Oswego cohorts)</td>
<td>Lai et al., 2001</td>
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<td>suboptimal neurological development during infancy; poorer cognitive functioning during early childhood</td>
<td>in utero exposure to “background” levels through general food supply</td>
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<td>Pesticides</td>
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<td>no effects based on Bayley Scales and FTII</td>
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<td>decreases in stamina, gross and fine hand-eye coordination, 30 minute memory, and the ability to draw a person</td>
<td>in utero exposure</td>
<td>Guillette et al., 1998</td>
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<td>Ionizing radiation</td>
<td>lowered mean IQ; speech-language disorders; emotional disorders; small head circumference; decline in average school performance; severe mental retardation**</td>
<td>in utero thyroid exposure from Chernobyl accident</td>
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<td>Other metals (As, Mn, Al)</td>
<td>AsU concentration inversely associated with verbal IQ</td>
<td>post-natal exposure to Pb and As from smelter</td>
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<td>Tobacco use</td>
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<td>in utero exposure</td>
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<td>Alcohol use</td>
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<td>Marijuana use</td>
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*A review article or commentary.

**Severe mental retardation diagnosed if a child was “unable to make simple conversation, to perform simple calculations, to care for himself or herself or if he or she was completely unmanageable or had been institutionalized” [Orake and Schull, 1998]. Generally, mental retardation is diagnosed by IQ score.
Fetal outcomes [NRC, 2000]. A series of longitudinal cohort studies have also documented impaired neurological status during infancy, and poorer cognitive performance during early childhood [Patandin et al., 1999; Koopman-Esseboom et al., 1996; Jacobson and Jacobson, 1997].

In a study of the effects of pesticide exposure in Mexico, children living in a high use area for a number of pesticides were compared to children from the same cultural group living in an area not sprayed with pesticides [Guillette et al., 1998]. Those exposed to pesticides both pre- and postnatally were found to have functional deficiencies in stamina, gross and fine eye-hand coordination, 30-minute memory, and the ability to draw a person compared to unexposed children.

The unique susceptibility of the central nervous system to ionizing radiation exposure has been demonstrated through studies of survivors of the atomic bombing of Hiroshima and Nagasaki and the meltdown of the Chernobyl nuclear power plant in 1986 [Yamazaki and Schull, 1990; Schull et al., 1990; Otake and Schull, 1998; Kolominsky, 1999]. Brain injury resulting in microcephaly and mental retardation occurred in infants born to mothers who were within 2000 meters of the site of the detonation of the bomb. Uncertainty remains as to the dose response function and the possibility of a threshold level of exposure [Yamazaki and Schull, 1990].

There is strong evidence for a causal relationship between maternal alcohol use and a spectrum of effects ranging in severity from fetal alcohol syndrome (FAS), fetal alcohol effects (FAE) and alcohol related neurodevelopmental disorder (ARND) [AAP, 2000; Sampson et al., 2000]. The teratogenicity of alcohol has been established in the experimental animal literature and demonstrates that the outcome of exposure is determined by the timing and conditions of exposure, as well as individual sensitivity of both the mother and fetus. [Sampson et al., 2000] Milder effects including a decrease in spoken-language and verbal comprehension scores in infants have been associated with maternal social drinking [Gusella and Fried, 1984]. Maternal alcohol use during breast-feeding was associated with a slight detrimental effect on motor development, although not with deficiencies in mental development, at one year of age [Little et al., 1989].

Maternal cigarette smoking is associated with lower global intelligence, impaired visuospatial functioning, and lower language and reading scores after control of covariates in a low-risk population [Fried et al., 1997; 1998; Fried and Watkinson, 2000]. Maternal smoking has also been implicated as a risk factor for idiopathic mental retardation [Drews et al., 1996; Fried, 1989]. Prenatal cocaine exposure is associated with deficits in fine and gross motor development [Arendt et al., 1999]. Maternal cocaine ingestion is associated with impaired fetal growth, including small head size [Holzman and Paneth, 1994], although results may be confounded by other exposures related to maternal lifestyle and behaviors. There is an emerging consistency of evidence that in utero exposure to marijuana produces deficits in executive functions including attention and visuospatial analysis in children, in the absence of effects on IQ [Fried and Watkinson, 1988; Fried et al., 1998; Fried and Smith, 2001].

CONCLUSION

High-level exposure to certain environmental contaminants can cause mental retardation and developmental disabilities. This is clearly the case for lead and methylmercury. At lower doses, lead is associated with a constellation of effects that includes decreases in IQ, poor school performance, problems with impulse control and attention deficits. There is evidence that prenatal exposure to lower levels of methylmercury may produce effects on attention, sensory and motor function and other aspects of neurodevelopmental function. Exposure to high doses of PCBs and ionizing radiation are also associated with mental retardation and other clinical syndromes, whereas in utero exposure at lower levels is associated with more subtle neurobehavioral and cognitive effects. In utero exposure to high levels of ethanol produces a wide spectrum of developmental disabilities, and negative long-term cognitive and behavioral effects of in utero tobacco exposure are consistently observed. The findings regarding recreational drugs such as cocaine and marijuana are less
definitive, although deficits in executive functioning appear to be a consistent result of marijuana exposure. Many other environmental neurotoxicants have not been adequately evaluated to determine their potential to produce developmental impairment. Exposure to a number of environmental agents with neurotoxic effects can result in a spectrum of adverse outcomes from severe mental retardation and disability, to more subtle changes in function depending on the agent, timing and target tissue dose.

REFERENCES


MRDD RESEARCH REVIEWS • ENVIRONMENTAL FACTORS AND NEURODEVELOPMENTAL DEFICITS • MENDOLLA ET AL.


