

# 10 Neurodevelopmental Effects of Childhood Exposure to Heavy Metals: Lessons from Pediatric Lead Poisoning

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Increasing industrialization has led to increased exposure to neurotoxic metals. By far the most heavily studied of these metals is lead, a neurotoxin that is particularly dangerous to the developing nervous system of children. Awareness that lead poisoning poses a special risk for children dates back over 100 years, and there has been increasing research on the developmental effects of this poison over the past 60 years. Despite this research and growing public awareness of the dangers of lead to children, government regulation has lagged scientific knowledge; legislation has been ineffectual in critical areas, and many new cases of poisoning occur each year.

Lead, however, is not the only neurotoxic metal that presents a danger to children. Several other heavy metals, such as mercury and manganese, are also neurotoxic, have adverse effects on the developing brain, and can be encountered by children. Although these other neurotoxic metals have not been as heavily studied as lead, there has been important research describing their effects on the brain. The purpose of the present chapter is to review the neurotoxicology of lead poisoning as well as what is known concerning the neurotoxicology of mercury and manganese. The purpose of this review is to provide information that might be of some help in avoiding repetition of the mistakes that were made in attempting to protect children from the dangers of lead poisoning.

An unfortunate result of industrialization has been the increasing exposure of the population to chemicals with neurotoxic potential. Children, due to a variety of physiological and behavioral factors, represent a particularly vulnerable target for some of these toxins with the developing brain the most significant casualty.<sup>1</sup> Heavy metals, metals with high atomic weight, pose one of the most prominent neurodevelopmental threats. However, despite growing awareness of the dangers of heavy metals, regulation by government agencies charged with protecting public health has been slow to keep up with the information provided by science and even slower to react. Due to shortcomings of regulatory bodies, children continue to be adversely affected by neurotoxins long after research has clearly demonstrated their pernicious effects.

The archetype of such a neurotoxin is lead. Known for millennia to be generally poisonous and for more than a century to be especially poisonous to children, this metal continues to claim hundreds of thousands of young victims in the United States and millions internationally. Recognized by scientists long before public health officials as a danger to development, the effects of lead on the brain and behavior have been the subject of intensive study. Despite its disappointing history in public health, there are a number of insights that can be gained from a review of the research on lead poisoning that are generalizable to other neurotoxins and that might be of some help in avoiding repetition of the mistakes that were made in attempting to protect children from the dangers of lead poisoning.

### **Lead: A Child's Poison**

#### **Unique Vulnerability**

Although the earliest reports of lead poisoning date back at least to the Roman empire, the singular vulnerability of young children to this metal was first noted in 1897 (Pueschel et al., 1996). In the first half of the 20th century, public health policy was primarily concerned with occupational exposures and as a result focused on adults. However, accumulating scientific information about children's exquisite sensitivity to this neurotoxin, especially (though certainly not exclusively) during the latter part of the 20th century, eventually resulted in public health regulation addressed to the specific protection of children.<sup>2</sup>

Children are more susceptible to the neurotoxic effects of lead for several physiological reasons (Leggett, 1993; Hartman, 1995). With similar degrees of exposure, children, in comparison to adults, (a) absorb more lead, (b) retain more lead (i.e., excrete proportionally less of the absorbed lead), and (c) deposit relatively more of the retained lead in the brain.

In addition, the developing brain is more damaged by lead than is the mature brain. Human brain development continues well past birth into the teenage years and, for certain systems, into the 20s (Giedd, 2004).

There are several possible mechanisms for the increased vulnerability of the developing brain to lead; these are not mutually exclusive.<sup>3</sup> Lead, at very low concentrations, affects the activity of second messengers. For example, both protein kinase C (PKC) and calmodulin are activated by lead at concentrations that are well below the equivalent of the toxic threshold in children. Both second messengers participate in many important cellular functions including proliferation and differentiation. In addition, PKC is also involved in long-term potentiation, a form of neuronal plasticity that may be involved in memory and learning. Lead also disrupts synaptic release of the excitatory neurotransmitter glutamate and also alters glutamate receptors. Normal transmission involving glutamate is critical during development for cell mi-

gration, differentiation, and cell survival. Acute lead exposure has been shown to decrease activity of CNPase, an enzyme preferentially located in myelin and shown to be an integral protein for myelin synthesis during development. Lead also can produce anemia, both by interfering with heme synthesis and by decreasing iron absorption from the gut. Severe iron deficiency and iron deficiency anemia are associated with impaired cognitive and neuropsychological development. Lead also disrupts thyroid hormone transport into the brain. Thyroid hormones are critical to the normal development of the brain with severe deficiencies causing mental retardation.

In addition to the biological determinants of a child's vulnerability, there are also behavioral factors that increase risk. The primary source of lead is in dust, either from deteriorating lead-based paint or from soil contaminated by leaded gasoline. Crawling infants are closer to surfaces on which lead dust is likely to be located, a proximity that results in increased exposure both from breathing in the dust and also from ingestion due to hand to mouth activities (Weiss, 2000).

The greater sensitivity of children to lead's effects on the brain is reflected in a lower threshold for poisoning. Exposure levels are typically measured in micrograms of lead per deciliter of blood. In the early 1960s the upper acceptable limit for children was 60  $\mu\text{g}/\text{dl}$ , the level at which lead poisoning could cause such physical symptoms as vomiting, clumsiness and hyperirritability. However, as research led to the recognition that lower blood lead levels that may lack clear physical symptoms were also neurotoxic, the threshold was lowered to 40  $\mu\text{g}/\text{dl}$  in 1970. With further research demonstrating adverse effects at ever lower levels of exposure, what was considered to be an "acceptable" blood lead level has been successively decreased; in 1975 it was dropped to 30  $\mu\text{g}/\text{dl}$ , in 1985 to 25  $\mu\text{g}/\text{dl}$ , and finally, in 1991, to 10  $\mu\text{g}/\text{dl}$  (Pueschel et al., 1996). Most recently, the Centers for Disease Control and Prevention (CDC; 2005) reported that they no longer consider *any* blood lead level to be safe for children. In contrast, 40  $\mu\text{g}/\text{dl}$  is the action threshold established by the Occupational Safety and Health Administration for adults.

Another factor that influences vulnerability is socioeconomic status (SES). Traditionally, SES has been treated simply as a confounding factor because lower SES is associated with increased risk of exposure and also because of SES's effect on certain components of standard intelligence tests, the typical endpoint in the seminal epidemiological studies of lead's effects on neurodevelopment. However, to assume that SES is simply a confound might be incorrect. Rutter (1983) theorized that the neurodevelopmental status of economically disadvantaged children, rendered fragile by environmental influences, might be more susceptible to the neurotoxic effects of lead. Findings in accord with this idea were reported by Winneke and Kraemer (1984). SES *interacted* with lead's effects on visual-motor integration and reaction time; performance deficits were greater in poorer lead exposed children than their more economically fortunate counterparts. Similar results and conclusions were reported by Bellinger (2000) for prenatal lead exposure.

Although the mechanisms of the effect of SES on lead's neurotoxicity are not known, there are several possible alternatives. Lead absorption from the gut is increased by several dietary conditions (i.e., deficiencies in calcium, iron, zinc, or protein) that are more frequently encountered in economically disadvantaged people (Chisolm, 1996; Cheng et al., 1998). Calcium deficiency also increases lead uptake in an *in vitro* model of the blood-brain barrier (Kerper & Hinkle 1997); it has been hypothesized that increased uptake of lead kills capillary endothelial cells and thereby disrupts the blood-brain barrier (Anderson et al., 1996). However, dietary differences do not completely explain the moderating effects of SES since analogous effects can be observed in laboratory rats. Rat pups were put in either impoverished or enriched environments. Half of the animals in each environment were exposed to lead via drinking water. Although similar levels of lead were observed in the blood and in the brain, lead-exposed rats reared in impoverished environments showed learning deficits. Dietary considerations do not explain the differential sensitivity of the groups of rats since, apart from lead exposure, diet was identical (Schneider et al., 2001).

#### **Neurodevelopmental Effects of Lead**

In laboratory research, lead has been demonstrated to have a variety of adverse effects on brain development and functioning that include disruption of synaptic transmission, disruption of intracellular neurochemical processes, and impaired cellular metabolism that results in abnormal neuronal development, reduced neuronal plasticity, and, in some cases, death of neuronal elements (Lidsky & Schneider, 2003).

Lead's neurotoxic effects are manifest in children in a dose-dependent fashion. At higher blood levels (typically  $\geq 70$   $\mu\text{g}/\text{dl}$  but, in some children, at levels of 50  $\mu\text{g}/\text{dl}$ ), encephalopathy can result. The symptoms include vomiting, clumsiness, and ataxia, ultimately progressing to alternating periods of hyperirritability and stupor and then finally coma and seizures. Children who survive have severe cognitive impairments including mental retardation (Byers & Lord, 1943).

Lower blood lead levels, which can be asymptomatic or associated with nonspecific complaints (e.g., stomachaches, constipation, or loss of appetite), can also be neurotoxic, although the consequences of such poisoning are different in degree and perhaps in type. Except in a developmentally fragile child, lower blood-lead levels do not result in retardation but have adverse consequences for neurocognitive development. Although scanning techniques, only recently used with lead poisoned patients (Trope et al., 2001; Meng et al., 2005), demonstrate a variety of brain abnormalities associated with neuronal loss, behavioral assessments are currently most useful for identifying lead's effects in children.

The pioneering research on the neurocognitive effects of nonencephalopathic lead poisoning on neurocognitive development was performed by Needleman and asso-

ciates (e.g., 1979). These investigations demonstrated that overall level of cognitive functioning as represented by IQ<sup>4</sup> decreased as blood lead level increased. Needleman's findings have been replicated and extended by more than 30 studies by different groups of investigators studying children in various parts of the world. Lead's adverse effects on cognition are observed with blood levels below 10 µg/dl; no safe level has been identified (Canfield et al., 2003; Lanphear et al., 2005).

Lead's effects on IQ have been further investigated by the use of neuropsychological tests, assessment instruments that are designed to target specific cognitive functions that could be affected by brain injury. These studies have shown that lead poisoning can have deleterious effects on a child's fine motor functioning, memory, language functioning, ability to pay attention, and executive functioning (Bellinger et al., 1994; Faust & Brown, 1987; Dietrich et al., 1992; Stiles & Bellinger, 1993; Stokes et al., 1998; Walkowiak et al., 1998; T. F. Campbell et al., 2000; Wasserman et al., 2000; White et al., 1993a; Winneke & Kramer, 1997; Ris et al., 2004; Canfield et al., 2004). As with lead's influences on IQ, many of these functions are affected at blood levels below 10 µg/dl.

When any source of brain injury produces symptoms of great similarity in each patient, it is said to have a behavioral signature: Lead lacks a behavioral signature. Lead poisoning, like the majority of causes of brain injury, affects different neuropsychological processes in different children. For example, while one child might evidence problems in verbal memory, a second child could have deficiencies in executive functioning.

In addition to lead's adverse effects on cognition, children who have had elevated lead levels as infants will subsequently have reduced proficiency in basic academic skills (e.g., reading, arithmetic) and lessened achievement at school (e.g., Needleman et al., 1990; Lanphear et al., 2000; Wang et al., 2002). For every 1 µg/dl increase in blood lead, there was about a 0.7 point decrease in average math scores and about a 1 point decrease in average reading scores (Lanphear et al., 2000). Lead-poisoned children are also at increased risk for antisocial behavior and delinquency (e.g., Dietrich et al., 2001).

The effects of lead poisoning, even at lower blood lead levels, persist through the teenage years into early adulthood and appear to be permanent (e.g., Needleman et al., 1990; Fergusson et al., 1997; Ris et al., 2004). In a recent dose-response study, functional imaging was used evaluate cortical activation patterns during a verb generation task in individuals between the ages of 20 and 23 years who had been poisoned with low lead levels in infancy (Cecil et al., 2005). Activation of the left frontal inferior gyrus (Broca's area) showed an inverse relationship with blood lead level while the right temporal region, the *contralateral* area to the traditional Wernicke's area, showed a strong positive association. These effects were seen in a dose-dependent fashion with blood lead levels ranging from about 5 to about 30 µg/dl.

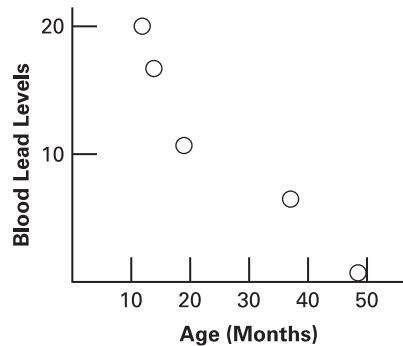
### Diagnostic Considerations

In the majority of cases, lead poisoning is diagnosed by blood test. With severe poisoning, the presence of overt signs of encephalopathy can alert a physician to the possibility of severe lead poisoning, a diagnosis that would be confirmed with a blood test. Lower blood lead levels can also be neurotoxic, but the particulars of the syndrome present diagnostic problems for the clinician. At lower blood lead levels, poisoning does not produce clinical symptoms on physical examination that are informative with respect to etiology. Although some children experience stomachaches, constipation, or loss of appetite during periods of elevated blood lead levels, other children have no such complaints. Similarly, anemia is seen in some but not all children with lower blood lead levels. Even when children do exhibit some of these symptoms, any of a myriad of etiologies are possible; lead poisoning is not the only or most obvious candidate.

Diagnosis of lead poisoning at nonencephalopathic levels is often due to routine screening or surveillance of at-risk populations (see below). Lead has a fairly short half-life in the blood, 35 days with a simple exposure. Therefore, if not performed close in time to the actual exposure, blood tests can result in false negatives or underestimation of the degree of poisoning (Erkkila et al., 1992).

Estimates of total body burden of lead have been attempted by use of chelation with CaEDTA (ethylenediaminetetraacetic acid). Excretion of lead, mobilized from tissue storage, is measured in urine. Body burden is also estimated by examination of bone, wherein more than 90% of lead is stored, via x-ray fluorescence techniques. However, it is unclear which pools of lead (e.g., cortical, trabecular) are being assessed, as well as what the threshold of detection is (Cory-Slechta & Schaumberg, 2000).

Nonencephalopathic lead levels, because they are neurotoxic, clearly do produce brain injury and, as a consequence, neurocognitive symptoms. However, there are two reasons that the behavioral effects of lead poisoning are not useful in diagnosis. First, lead poisoning, like the majority of causes of brain injury, lacks a behavioral signature. Thus, there is no set of impairments that would identify lead poisoning as the culprit rather than, for example, traumatic brain injury or perinatal asphyxia. Second, lead-poisoning-induced neurocognitive impairments demonstrate a “lag” effect; symptoms are often not evident for a considerable time after the initial intoxication, well after blood lead levels have declined to normal (Bellinger & Rappaport, 2002). Three transition points have been identified at which a child could show the aftereffects of early lead poisoning. The first is at 5 to 7 years of age when a child is learning to read; the second is beginning at 8 to 10 years (and thereafter) when the child begins to use reading as a tool for learning; the third is when a child enters adolescence and is required to make use of mature executive functions (e.g., planning, concept formation, self-monitoring). Some children show problems immediately as infants, while others seem normal until the first transition point, the second, or even the third (Bellinger & Rappaport, 2002).



**Figure 10.1**

Blood lead levels (in micrograms per deciliter) in case 10.1 (Albert) as a function of age.

**Case 10.1: Albert** Albert was delivered by normal spontaneous vaginal delivery following a full-term pregnancy. Although there were variable heart rate decelerations during delivery, resuscitation was not needed and Apgar scores were 9 at 1 minute and at 5 minutes. The pregnancy was significant for group B hemolytic streptococcus infection and also chlamydia, both treated during the intrapartum period.

Developmental milestones in all areas were reached in an age-appropriate fashion through at least 20 months. However, at about 13 months of age, Albert was found to be lead poisoned. His history of blood lead test results is summarized in figure 10.1. At about 5 years of age, Albert was diagnosed with severe expressive and receptive language delays and attention deficit/hyperactivity disorder (ADHD) Combined Type, and, due to persisting acting out behavior, he was also diagnosed with oppositional defiant disorder. His ADHD is being treated with Ritalin.

Albert experienced considerable academic difficulty since he first started formal education. Evaluated for an individualized education program while in kindergarten, it was noted that “Reading, Writing and Math were all areas of concern . . .” as were language delays. The Evaluation Report stated: “The language deficit is not caused by: visual or auditory acuity deficits, emotional disturbance, mental retardation, dialectal differences or second language influence, environmental or economic disadvantage, or cultural difference.” On administration of the Stanford–Binet Intelligence Scale (4th ed.), a composite score of 81 (4th percentile) was attained. To address his deficiencies, Albert is now receiving special educational services that include preferential seating, modified assignments, seating next to a “study buddy,” small group instruction in a separate setting, and extra time to complete schoolwork.

A comprehensive neuropsychological evaluation was conducted when Albert was about 8½ years old. Results showed normal performance in tests of verbal fluency, attention, and aspects of executive functioning (e.g., planning). However, in association with these areas of normalcy, Albert showed impairments of naming, fine motor functioning, verbal memory, visuospatial memory, auditory working memory, verbal concept formation, and cognitive flexibility. These deficiencies observed in association with normal functioning in other neurocognitive domains and interpreted in the context of Albert’s history are indicative of brain injury (Lezak, Howieson, & Loring, 2004; Lidsky & Schneider, 2006). Lead was determined to be the causative factor by the process of differential diagnosis. Thus, in addition to lead poisoning, review of Albert’s available medical history indicated no factors or events capable of producing brain injury. Impairments similar to those seen in Albert have been described as sequelae of early childhood exposure to lead (Lidsky & Schneider, 2006).

### Treatment

Encephalopathic lead levels are treated with chelation, a procedure that rapidly lowers blood lead level and removes some lead stored in soft tissues. Rebound increases in blood lead levels are common as stored lead leaches out from various tissue compartments; repeat chelation is often necessary (Chisolm, 1996). Chelation, by rapidly reducing blood lead albeit sometimes only temporarily, decreases the acute toxic effects of lead on the brain and other organ systems and has dramatically reduced mortality (Dietrich et al., 2004). Chelation, however, does not appreciably reduce lead stored in the brain (Cremin et al., 1999) and does not prevent the well-documented effects of severe poisoning on neurocognitive development. As previously discussed, lead exposures that are well below those that can cause encephalopathy are also neurotoxic and also result in neurocognitive damage. Attempts have been made to treat these lower lead levels ( $\leq 44 \mu\text{g}/\text{dl}$ ) with chelation. Unfortunately chelation also does not mitigate the detrimental effects of lower lead levels on a child's cognitive development (Dietrich et al., 2004; Rogan et al. 2001).

As of yet, no treatment modalities have been identified that can prevent the neurotoxic effects of lead, once a child has been exposed, as evidenced in an elevated blood lead level. The use of calcium supplementation has been advocated as a way to reduce lead absorption and thereby reduce the toxic dose. However, while there is a clear rationale for this procedure based on research using laboratory animals, there is no strong clinical evidence for the efficacy of this treatment in children (Ballew & Bowman, 2001). There appears to be more support for the use of iron supplementation in reducing lead absorption (Hammad et al., 1996).

Since the effects of lead poisoning on a child's brain are permanent and there is no effective treatment to prevent the adverse effects of lead exposure on neurocognitive development once a child has been poisoned, prevention of lead exposure is the only *cure* for this disease; once a child has been poisoned, the most effective actions may mitigate but will not prevent damage. In the United States, government regulations led to the banning of lead in paint in 1978 (*several* decades after Australia and some parts of Europe) and the removal of lead from gasoline in 1985. Unfortunately these regulations have not been effective at prevention; although they reduced the addition of more lead into the child's environment, they did nothing to remove lead that was already present in a child's surroundings. For example, the U.S. Environmental Protection Agency (EPA, 1996a) estimates that about three quarters of housing built in the United States before 1978 still contains lead paint (approximately 64 million houses). As a result, new cases of childhood lead poisoning from old paint continue to occur with an alarming frequency.

Another example of the inadequacy of government regulation is seen in the ineffectiveness of special legislative efforts that have been made in public housing. Because



much public housing was built before 1978 and has lead paint, there are regulations specifically targeted toward preventing lead poisoning of children in these dwellings. However, a recent comparison of children in public housing in New Orleans with other high-risk children in private residences showed no differences in the incidence of lead poisoning. Thus, children living in public housing were no safer from lead poisoning despite the existence of special legislation. The authors concluded “. . . public housing does not appear to protect children from elevated lead levels, calling into question the efficacy of existing regulations” (Rabito, Shorter, & White, 2003).

There are also other sources of lead exposure that can result in poisoning. Leaded solder used in older plumbing can contaminate drinking water, a hazard that affects not only homes but also day care facilities, schools, and restaurants. A variety of other commodities, particularly those imported from outside the United States, are also sources of lead poisoning; certain alternative medicines, confections, glazed pottery and dishes, inexpensive children’s jewelry, some candlewicks, and certain cosmetics have all been implicated in lead poisoning (Jones et al., 1999; CDC, 2003). The CDC Web site (<http://www.cdc.gov/nceh/lead/lead.htm>) provides current information about product recalls and other recently identified sources of lead poisoning.

For those cases of childhood lead poisoning that have already occurred, and those that inevitably will occur absent a tightening of public health regulations, modalities of treatment are those that are applied to mitigate the effects of brain injury from virtually any etiology. Thus, cognitive remediation, with the goal of teaching an injured patient to use remaining functioning to attempt to compensate for deficits, pharmacotherapy when appropriate (e.g., for some attentional disorders), and counseling are all possible approaches to try to lessen the aftereffects of childhood lead poisoning.

### Summary

Lead poisoning causes brain damage that can impair a child’s fine motor functioning, memory, language functioning, ability to pay attention, and executive functioning, as well as social and behavioral development. These effects are irreversible and permanent (Lidsky & Schneider, 2003). Often there is a lag in the emergence of symptoms; cognitive impairments may not be observable until a child, poisoned during early infancy, is an adolescent.

Since the negative effects of lead on child development are mediated by brain damage, evaluations must employ techniques suited to assessing this type of injury. Thus, neuropsychological testing, rather than administration of IQ test batteries, is the methodology of choice. Although IQ will often decrease with brain injury, this is not always the case (e.g., Dlugos et al., 1999). Further, even when IQ does decrease with brain injury, the magnitude of the decrease underestimates the severity of the injury (Lezak et al., 2004, Lidsky & Schneider, 2006).

Given the ubiquity of sources of lead exposure and the ineffectual nature of governmental regulation, new cases of lead poisoning will continue to occur. For this reason, efforts at early detection are crucial to minimize exposure as much as possible. Unfortunately, there are two formidable obstacles to early detection. First, blood lead testing, the most accurate way to determine exposure, if not performed close in time to the actual exposure, can result in false negatives. Second, since nonencephalopathic levels of lead exposure lack overt clinical findings on physical examination that would suggest the possibility that a child has been poisoned, one must depend on serendipity for a child to be brought to a physician at a time that would be optimal to detect an elevated blood lead level. For these reasons, the only sure treatment for childhood lead poisoning is prevention, a goal that can only be reached by removal of existing leaded paint and contaminated soils and strict regulation of other sources of lead exposure (*vide supra*).

### Mercury

The use and misuse of mercury, like that of lead, dates back to antiquity. As reviewed by Hartman (1995),

In the second and third centuries A.D. the Chinese philosopher Pao Pu Tzu recommended mixing pills of three parts cinnabar (red mercuric sulfide) and one part honey to induce immortality . . . Hippocrates was said to have employed mercuric compounds in his pharmacopeia around 400 B.C. . . and Indian physicians of the Brahm period (800 B.C.–A.D. 1000) employed mercury to treat smallpox and syphilis . . .

Mercury has also been used to “treat” children for worms and sore throat (Hartman, 1995).

Because mercury is not curative for any of the diseases for which it was used as a treatment and is, in fact, toxic, a fact that has been recognized for centuries, this metal is no longer employed in conventional medicine. In contrast, its use lingers on in folk medicine:

For example, various Chinese patent medicines have been found to be the source of several cases of severe mercury poisoning, including in a New York City four year old whose mother systematically fed him a Chinese medicine called Tse Koo Choy, which contains mercurous chloride. The child developed progressive neurological deterioration, with drooling, dysphagia, and irregular movements . . . recovery was incomplete (Hartman, 1995)

with evidence of both neurological and neurocognitive damage (Hartman, 1995).

There are three principal forms of mercury—elemental mercury, inorganic mercury salts, and organic forms (methylmercury and ethylmercury). Although each compound is toxic, they differ in potency and bioavailability (Verity & Sarafian, 2000).

### Elemental Mercury and Inorganic Salts

**Toxicology** The primary sources of elemental mercury are emissions from coal-burning electric power generators. Much of this mercury, however, eventually is converted to organic forms via biotransformation (see below; Trasande, Landrigan, & Schechter, 2005). The primary sources of elemental mercury and its inorganic salts that are involved cases of in human exposure are occupational (e.g., miners, photo engravers, and dental technicians) and from home accidents (broken thermometer), alternative/ethnic medicines, and some cultural/religious practices. In addition, dental fillings are also a source of elemental mercury and also organic mercury compounds. Fillings made of amalgam, an alloy that is up to 54% mercury, give rise to levels that “continue to be detectable for 1 year after amalgam implant” (Hartman, 1995) although at low levels. Whether or not these levels are neurotoxic or have adverse neuropsychological effects is not known (Hartman, 1995).

Because elemental mercury is liquid at room temperature and, because it is easily aerosolized or vaporized, one of the principal routes of exposure is via respiration. Mercury then enters the circulation, wherein it is transported to the brain and other organs; elemental mercury readily crosses the blood–brain barrier (e.g., Warfvinge et al., 1992; Pamphlett & Waley, 1996). Although inorganic mercury apparently does not easily cross the blood–brain barrier, it does enter the brain in adults in regions lacking the barrier (e.g., area postrema; Verity & Sarafian, 2000) and in infants due to an incompletely developed barrier (Trasande et al., 2005).

There is also efficient placental to fetal transfer of mercury (Yoshida, 2002), and the fetal brain accumulates more mercury than does the brain of the mother (Feng et al., 2004). Respirated mercury, in addition to entering the brain via the circulation, also may do so by a more direct route; mercury is absorbed through the olfactory mucosa, taken up by olfactory nerves and transported to the olfactory bulbs (Henriksson & Tjalve, 1998). Mercury is also absorbed transdermally (Verity & Sarafian, 2000) and can enter the brain either via the circulation or, potentially, by uptake at the neuromuscular junction, and perhaps other nerve endings, followed by axonal transport (Arvidson, 1992).

Once in the brain, inorganic mercury disrupts the normal functioning of a variety of neurotransmitters including aminergic, cholinergic, and glutamatergic systems (Oudar, Caillard, & Fillion, 1989; Hare et al., 1990; Castoldi et al., 1996; Allen, Mutkus, & Aschner, 2001; Moretto et al., 2004). Cellular activity is impaired by disruption of calcium currents (Szucs et al., 1997) and by generation of reactive oxygen species with resulting oxidative stress (Hussain et al., 1997). Inorganic mercury also has an indirect effect on brain development by affecting thyroid status of the mother during pregnancy (Takser et al., 2005).

**Clinical Effects** In the adult brain, elemental mercury is deposited both cortically and subcortically as well as in the brainstem and cerebellum (Pamphlett & Waley, 1996). There was a preferential deposition in motor cortical neurons, though glial cells were affected throughout the brain (Pamphlett & Waley, 1996). In experimental animals, the hippocampus and cerebellum were particularly vulnerable to mercury deposition (Feng et al., 2004).

**Case 10.2: The B. Family** The consequences of elemental mercury exposure to the brain were demonstrated in a case of exposure involving a family of seven (Cherry et al., 2002). The B. family was exposed via elemental mercury that had been spilled on a carpet prior to their moving into the home. The mercury had been observed only in the youngest of the family, Claudia who is now a 3-year-old girl. Prior to hospital admission and detection of elevated blood mercury levels, Claudia exhibited “progressive weight loss, limping, ataxia, irritability, ‘screaming,’ and regression in speech capability.” When admitted to the hospital, she was drooling, hypotonic, ataxic, and mute with a tremor that disappeared during sleep. The toxic threshold in adults, measured in micrograms of mercury per liter of blood, is 50, while less than 10 is expected in unexposed individuals. Such exposure guidelines for infants and young children have not been developed. The young child in this case had a blood mercury level of 295 µg/l. The child underwent 3 rounds of chelation therapy with dimercaptosuccinic acid (DMSA), and her symptoms gradually resolved over a 4-month period. Unfortunately, this child has not undergone neuropsychological testing, and review of the literature indicates no case reports of the cognitive aftereffects of elemental mercury poisoning in young children. In adults, persisting neurocognitive deficits have been reported including “specific problems with cognitive flexibility, cognitive tracking, inhibiting perseveration, fine manual motor coordination, visuospatial analysis and organization, memory for visuospatial information, affect and personality.” (White et al., 1993b). [all names are pseudonyms]

The nature of the symptoms of poisoning from elemental and inorganic mercury results in diagnostic difficulties: “The non-specific psychosomatic symptoms of mercury poisoning would likely be misdiagnosed as psychiatric illness unless special inquiry and blood screen were conducted on symptomatic patients from high risk populations” (Hartman, 1995).

#### **Organic Compounds—Methylmercury**

Mercury is generated primarily from the combustion of coal but also from volcanic sources, burning of waste, manufacturing processes that use mercury (e.g., fabrication of paper), and chemical production (EPA, 1996; Verity & Sarafian, 2000; Trandsa et al., 2005). This mercury, typically in elemental form, travels some distance in the atmosphere and is eventually deposited in water and soil, where it is converted to methylmercury by bacteria, a process that takes place particularly in water. It thereby enters and bioaccumulates up the food chain, reaching very high concentrations in some fish. Consumption of fish is the primary route by which humans are exposed to methylmercury (California Office of Health Hazard Assessment, 2001).

**Toxicology** Because it is more easily and efficiently absorbed (EPA, 1996) and also because it readily crosses the blood–brain barrier (Aschner & Clarkson, 1989; Verity & Sarafian, 2000), methylmercury is far more toxic than elemental or inorganic mercury. Once deposited in the brain, methylmercury is slowly demethylated to form inorganic mercury (Friberg & Mottet, 1989).

Methylmercury disrupts normal neuronal electrophysiological activity by affecting both  $\text{Ca}^{2+}$  and  $\text{K}^{+}$  channels. Methylmercury's neurotoxic effects include influences on a variety of neurotransmitter systems (Oudar et al., 1989; Castoldi et al., 1996). Notable is its influence on astroglia that results in reduced uptake of extracellular glutamate (Fitsanakis & Aschner, 2005). Increasing concentrations of glutamate resulting from decreased clearance are excitotoxic and cause neuronal cell death (Olney, 1994). Methylmercury also causes damage by generation of reactive oxygen species (Shanker et al., 2005).

**Clinical Effects: High Mercury Levels** At high concentrations methylmercury causes severe toxic encephalopathy. The symptoms of severe poisoning were illustrated by the victims of large outbreaks of mercury poisoning in Iraq, Pakistan, and Guatemala from ingestion of flour and wheat seeds contaminated with organic mercury agents (Bakir et al., 1973) and in Japan (Minimata Bay and Niigata) from the consumption of mercury-laden fish (D. Campbell et al., 1992). Each of these exposures resulted in widespread poisoning. It is estimated that about 50,000 people consumed bread made with the contaminated flour; 459 died, and 6,530 were hospitalized. It is not known how many suffered adverse effects due to lower doses. In the Japanese exposures, the government officially recognizes 2,265 victims, including 1,435 who have died. Another 15,000 people have registered with the government as poisoning victims (Grimel, 2001). D. Campbell et al. describe several types of symptoms:

(a) psychologic—difficult concentrating, short- and long-term memory loss, emotional volatility, depression, decreased intellectual abilities, and ultimately coma; (b) cerebellar-generalized ataxia with stumbling gait, dysdiadochokinesia, and uncoordination; (c) sensory numbness and stocking-glove paresthesias of distal extremities and mouth, deafness, tunnel vision, visual field constriction, scanning speech with slurring, dysphagia; (d) motor-spasticity, tremors of hands, face, or legs, and weakness proceeding to paralysis. The initial symptoms are fatigue and perioral/extremity paresthesias, followed by difficulty with hand movements. Sensation and visual disturbances occur next. Electrocardiographic abnormalities (changes in S–T segment waves) were noted in about one third of cases from the last Iraqi poisoning. Important aspects of methylmercury toxicity include its predisposition for the CNS, its insidious onset, and its poor prognosis for improvement.

When mercury poisoning occurs during pregnancy, the congenital effects in the neonate are particularly severe. In some cases infants are born with CNS mercury toxicity to mothers whose symptoms were so mild that they were unaware of their

own poisoning. Signs and symptoms in the neonate include severe mental retardation, cerebral palsy-like movement problems, both cerebellar and basal ganglia associated dyskinesias, and seizure disorders (D. Campbell et al., 1992). The more severe outcome associated with the congenital form of organic mercury poisoning is probably due to a variety of factors including the undeveloped nature of the fetal blood–brain barrier, the increased susceptibility of the developing nervous system to neurotoxins, and the greater affinity of fetal hemoglobin for mercury that results in higher fetal brain concentrations of mercury (D. Campbell et al., 1992; Trasande et al., 2005).

The National Research Council reviewed the extensive literature on the mass poisoning in Minimata Bay and concluded that there was evidence for both delayed emergence of symptoms, sometimes decades after the initial exposure, and symptom progression. While acknowledging that continued exposure to mercury cannot be ruled out in these cases, the National Research Council pointed out that delayed emergence and progression of effects was also observed in laboratory research employing animals.

Two biomarkers have been used to quantify mercury dose—mercury concentrations in hair and in blood. Many of the studies of encephalopathy have relied on hair measurements, which reflect average exposure over time. Severe symptoms are seen in children whose mother’s hair had 165–320 parts per million (ppm) of mercury, while more mild effects were observed when maternal hair mercury content was in the range of 68–180 ppm (California Office of Health Hazard Assessment, 2001). Although hair and blood mercury concentrations are correlated, there are some suggestions that the former is more imprecise than the latter and blood measurements may be preferred (Budtz-Jørgensen et al., 2004).

**Case 10.3: The Doe Family** Over a 3-month period, a family consumed pork from a hog that had been fed seed grain that was treated with a methylmercury-containing fungicide. Following this period, 3 children in the family became ill and exhibited signs of a central nervous system disorder. Following are the details of the case of Eli, a boy who was 13 years old at the time of the poisoning. During the acute phase of intoxication, Eli was somnolent or agitated and showed choreoathetosis. He also exhibited cortical blindness, right hemiparesis, and loss of proprioception, as well as hyperactive reflexes and Babinski signs. Eli’s mercury levels were 0.21 ppm in urine, 2.91 ppm in serum and 3.33 ppm in cerebral spinal fluid. Although he was treated with chelation, his neurological signs were not reversed. Upon reevaluation 22 years after the initial poisoning, Eli was found to have a Verbal IQ of 99. However, he remained cortically blind with mild ataxia and hyperactive reflexes; there were no Babinski signs. His speech was dysarthric and dysfluent, and he exhibited a mild attentional deficit, a moderate learning deficit and, problems with word retrieval and response inhibition. Magnetic resonance imaging (MRI) of the brain showed tissue loss in visual cortex, parietal cortex, and cerebellar folia. Notably, although both of Eli’s parents were also exposed to methylmercury, neither developed symptoms, though his mother had showed cerebellar atrophy on MRI examination. The mother was pregnant at the time of the poisoning, and the congenitally exposed child Fiama was most severely affected, being both blind and mute and showing severe mental retardation, quadriplegia, choreoathetosis, and seizures (Davis et al., 1994).

Another child from this family, Gustav, was poisoned at the age of 8 years. He developed severe mental retardation, quadriplegia, and blindness. Gustav died at the age of 30 years and on post-mortem showed cortical atrophy, particularly in paracentral and parieto-occipital areas, loss of neurons, and gliosis. Notably, although the mercury content of his internal organs did not differ from that of an adult without known mercury exposure, Gustav's brain mercury levels were about 51 times control levels (Davis et al., 1994). Thus, after severe poisoning, mercury appears to remain in the brain indefinitely.

**Clinical Effects: Moderate to Low Mercury Levels** There have been several prospective studies of the effects of low to moderate levels of methylmercury on adults. The participants for several of these studies were drawn from populations with a large daily consumption of fish caught in waters polluted with mercury (Amazon Basin, and St. John's Bay, Quebec); mercury dose was typically based on hair samples. In reviewing these studies, the National Research Council (2000) concluded that hair mercury concentrations less than "50 ppm are significantly associated with disturbances of the visual system (chromatic discrimination, contrast sensitivity, and peripheral fields) and with neuromotor deficits (tremor, dexterity, grip strength, complex movement sequences, hand-eye coordination, and rapid alternating movement)." A recent study also reported neuropsychological sequelae: problems of attention, verbal learning, and memory (Yokoo et al., 2003). In an older adult population (50–70 years of age) with median blood mercury levels of 2.1  $\mu\text{g/l}$  (range = 0–16  $\mu\text{g/l}$ ), no adverse effects on neurocognitive performance were identified (Weil et al., 2005). Unlike those studies reporting sensory, motor, and cognitive aftereffects of mercury poisoning, the adults in this latter study were drawn from the United States and were exposed to mercury through a diet with fish consumption typical of the U.S. population; their exposure levels were low.

In view of the greater sensitivity to methylmercury's adverse effects shown by the fetuses of exposed mothers in the Minimata and Iraqi mass poisonings, a number of investigations have assessed the influences of lower levels of exposure during pregnancy on infant development. As in the research on low to moderate methylmercury exposure in adults, the infants for several of the investigations of fetal effects were drawn from populations with a large daily consumption of fish caught in waters polluted with mercury. The National Research Council reviewed the findings of those studies published up to the year 2000 and concluded that there was an increased occurrence of abnormal findings on neurological examinations in congenitally exposed children.

Several large prospective studies have evaluated effects of prenatal methylmercury on neurocognitive development. Mother–infant pairs from the Faroe Islands were studied longitudinally for more than a decade (Grandjean et al., 1997; Grandjean

et al., 1999). The Faroe Islands are in the North Atlantic northwest of Scotland and halfway between Iceland and Norway. Mercury exposure in this cohort is from dietary consumption of whale meat and blubber. Prenatal exposure resulted in decreased functioning in several neuropsychological domains (language, attention, memory, visuospatial, and fine motor functioning). The associations of decreased neuropsychological functioning with organic mercury exposure remained after adjustment for covariates and were seen with hair concentrations of less than 10 ppm. Mean maternal hair mercury levels were 4.3 ppm (Grandjean et al., 1997).

A second large cohort came from the Republic of Seychelles in the middle of the Indian Ocean (Myers et al., 2003; Huang et al., 2005). Unlike the diet from the Faroe Islands, wherein exposure was primarily from whale meat and blubber, the mercury exposure of the pregnant mothers from Seychelles was from ocean fish. The mothers' consumption of fish (12 meals per week that included fish) far exceeded that of a typical diet in the United States. Average maternal hair mercury concentrations were 6.8 ppm. Extensive analysis of the effects of prenatal exposure on IQ, academic skills, executive functioning, learning and memory, attention, language, and fine motor functioning failed to show any adverse effect.

There are several important differences between the studies of the Faroes cohort and the Seychelles cohort. First, although the average exposure of the Seychelles group was higher than in the Faroes studies (average maternal mercury hair concentration 6.8 vs. 4.3 ppm), the average concentration of organic mercury in whale meat (1.6  $\mu\text{g/g}$ ) is much greater than in ocean fish (0.3  $\mu\text{g/g}$ ). Thus, the Faroes Islands cohort received a much bigger bolus of mercury than the mothers in the Seychelles group.

A second difference is that whale meat and blubber, in addition to being contaminated with organic mercury, also have a high content of a number of organic pollutants including PCBs, known neurotoxins. Although attempts were made to control for possible confounding due to PCBs (Grandjean et al., 1997), there were effects on language that were difficult to attribute solely to mercury exposure. In addition, possible interactions between mercury and PCB neurotoxicities could not be ruled out (Grandjean et al., 2001).

A third difference between the two studies is that fish, unlike whale blubber, also contains a number of compounds that are important for brain development and may also be neuroprotective. Long chain polyunsaturated fatty acids, iron, iodine, and choline are each found in fish and are each important for brain development. There is also some evidence that choline mitigates excitotoxicity. It is plausible that the negative influences of lower levels of mercury are offset by the positive effects of these nutrients (Clarkson & Strain, 2003).

In view of the controversy about the effects of exposure of the developing fetus to lower levels of mercury, concerns have been raised about whether or not fish should



be consumed during pregnancy. A recent study (Oken et al., 2005) addressed this issue, weighing the risk of mercury's possible toxicity at low doses against the benefits of a fish diet, rich in nutrients that facilitate brain development. Associations between maternal fish intake during pregnancy and maternal hair mercury at delivery with infant cognition at 6 months of age were evaluated in 135 mother–infant pairs. Infant cognition was assessed via a test of visual recognition memory, a measure that is weakly correlated with Full Scale IQ at 6 years of age. The findings were that as fish consumption increased, hair mercury concentrations increased and cognitive scores decreased. However fish consumption per se was associated with *higher* cognitive scores. The most beneficial effects were observed in infants whose mothers consumed more fish but had lower mercury levels. The authors recommended that “women should continue to eat fish during pregnancy but choose varieties with lower mercury contamination.”

**Clinical Effects: Mercury and Autism** In 2001, Bernard et al. proposed that thimerosal, a preservative containing organic mercury that is used in many vaccines given to infants, induced “many cases of idiopathic autism.” Thimerosal is about 49% ethylmercury; Bernard et al. attributed the hypothesized thimerosal-induced autism to mercury exposure. This hypothesis was based in part on the increasing use of thimerosal, the increasing incidence of autism, the known neurotoxicity of ethylmercury, and that mercury exposure “can cause immune, sensory, neurological, motor and behavioral dysfunctions similar to traits defining or associated with autism” (Bernard et al., 2001). In infants who receive several vaccinations, as a function of body weight and vaccination type, certain patients receive substantial exposure to organic mercury that may exceed governmental guidelines.

As Bernard et al. (2001) suggest, the reported incidence of autism has increased from about 2 to 4 cases per 10,000 when Kanner first described the disorder in 1943 to the present rate of 30 to 60 cases per 10,000. However, it is unclear to what extent the increased incidence reflects an actual increment in cases as opposed to broadening of diagnostic criteria and greater public awareness, resulting in enhanced identification (Rutter, 2005).

In evaluating thimerosal's possible role in autism, attention has been directed to the Danish childhood vaccination program. Since 1970, only pertussis vaccine contained thimerosal and, in March of 1992, that inoculation was replaced with a thimerosal-free vaccine. Although the incidence of autism has increased in Denmark as in other countries, the incidence continued to rise after thimerosal was eliminated and there was no increased risk of autism for children inoculated with or without thimerosal-containing vaccine (Hviid et al., 2003; Madsen et al., 2003). In contrast, Geier and Geier (2005) reported increased risk of autism as well as other developmental disorders (e.g., mental retardation) based on reporting to the U.S.'s Vaccine

Adverse Event Reporting System comparing diphtheria–tetanus–acellular pertussis vaccine with and without thimerisol.

Review of the epidemiological literature offers little support for the thimerosal–autism link. In 2000, the Institute of Medicine (IOM) of the National Academies of Science, at the request of the CDC and the National Institutes of Health, evaluated the evidence that use of thimerosal-containing vaccines was associated with increased risk of autism. The first report was issued in 2001 and then was updated in 2004 due to the publication of several new studies. According to both IOM evaluations, there was no evidence of an association between thimerosal use and autism (IOM, 2004).

Parker et al. (2004) reviewed the original data from 10 epidemiological studies and concluded that “the preponderance of epidemiological evidence does not support an association between thimerosal-containing vaccines and ASD [autistic spectrum disorders],” further noting that those “studies that support an association are of poor quality and cannot be interpreted.” In addition, while ethylmercury and methylmercury are assumed to have similar neurotoxic mechanisms, there are toxicokinetic differences between the two compounds that render ethylmercury less damaging to the brain. Ethylmercury does not pass through the blood–brain barrier as easily as methylmercury and has a shorter half-life (Parker et al., 2004).

### **Manganese**

Unlike lead and mercury, manganese is an essential metal that is found in all tissues and is required for normal amino acid, lipid, protein, and carbohydrate metabolism (Erikson et al., 2005). Manganese plays an essential role in a variety of physiological functions and systems, including but not limited to immune system functioning, regulation of cellular energy, bone growth, and blood clotting (Erikson et al., 2005). In the brain, manganese functions as a cofactor for important enzymes including superoxide dismutase (a critical antioxidant enzyme) and glutamine synthetase (important for brain ammonia metabolism; Hurley & Keen, 1987). Manganese also has effects on metabolism of the neurotransmitters dopamine and serotonin by playing a role in the activities of monoamine oxidase and catechol-o-methyltransferase enzymes (Golub et al., 2005).

Even though manganese is viewed as an essential element, there is no consensus regarding optimal intake of manganese. The National Academy of Sciences (NAS) has recommended an adequate intake (AI) for adult men at 2.3 mg/day and for adult women at 1.8 mg/day (NAS, 2001), taking into account decreased gastrointestinal absorption in men versus women (Finley et al., 1994). AIs for infants (0.003 to 0.6 mg/day) and children (1.2 to 1.5 mg/day) have also been recommended (NAS, 2001).

Manganese deficiency in a variety of animal species can lead to multiple problems including stunted growth, skeletal defects, abnormal glucose tolerance, and altered lipid and carbohydrate metabolism (Erikson et al., 2005). However, “frank manganese deficiency has not been clinically recognized in humans” (Erikson et al., 2005). In contrast, manganese toxicity from exposure to elevated levels of manganese has serious negative implications for human health and has particularly damaging effects on the central nervous system.

### Toxicology

Sources of excess intake of manganese are excess dietary intake, occupational exposures, and environmental exposures. Excess dietary intake of manganese is most typical in infants fed soy-based formulas, which contain higher levels of manganese than breast milk or cow’s-milk-based formulas (Lonnerdal, 1994). Occupational exposures occur in workers in certain industries such as alloy production, mining, battery manufacturing, and welding. Recently, the possible relationship between manganese, welding, and Parkinson’s disease has received considerable attention (Racette et al., 2001; Racette et al., 2005), although a causal relationship between these factors is still considered by some to be speculative and tentative (Jankovic, 2005). Environmental exposures can occur via drinking contaminated water, from environmental deposition of methylcyclopentadienyl manganese tricarbonyl (MMT) used as an antiknock additive to gasoline, and from organo-manganese agricultural fungicides (Vezer, 2005). Even though the environmental level of manganese from MMT may be quite low, the neurotoxic effects of chronic low-level manganese exposure are unknown.

The main routes of exposure are inhalation and ingestion. Following ingestion, inorganic manganese, in trivalent form, is absorbed in the intestine (Cotzias et al., 1971). Once absorbed, manganese is bound to plasma proteins and is readily taken up in the brain as a free ion or in a transferrin-bound form (Aschner & Gannon, 1994). Manganese is deposited preferentially in mitochondria-rich tissues such as liver, pancreas, and brain. The brain is a primary target in chronic manganese exposure (Roels et al., 1987), and the turnover of manganese in the brain is slower than in other parts of the body (Feldman, 1992). Among cell types in the brain, manganese has been shown to accumulate in astrocytes and neurons. Respiratory symptoms of cough, bronchitis, and impaired pulmonary function are associated with inhaled manganese particulate and may reflect direct pulmonary toxicity induced by manganese (Erikson et al., 2005). Although respiratory effects are important, again, the most sensitive organ for manganese toxicity is the brain (Erikson et al., 2005). The basal ganglia are a particular target for manganese deposition (Josephs et al., 2005).

The transport of manganese into the brain may be aided by iron deficiency. Both manganese and iron are transported into the brain via transferrin-mediated endocytosis (Crowe & Morgan, 1992). Iron deficiency causes increased brain regional transferrin and transferrin receptor levels, particularly in basal ganglia regions (Erikson et al., 1997). Iron deficiency may also cause an increase in divalent metal transporter-1 levels, which may also foster manganese accumulation in brain (Erikson et al., 2004).

### **Clinical Effects**

A number of reports in the literature describe outbreaks of manganism (a syndrome characterized by a movement disorder including tremor, dystonia, and/or rigidity and psychiatric disorders) following ingestion of contaminated well water (Erikson et al., 2005). However, many of these studies are difficult to interpret due to the suspected presence of other metals and toxins in the water. Thus, an indisputable link between chronic manganese consumption in drinking water and heightened risk of neurological disorders has not yet been established.

Manganism is typically associated with elevated brain levels of manganese, particularly in basal ganglia regions. A biologic marker for manganese accumulation in the brain is an increased T1 MRI signal, particularly within the globus pallidus but also in the striatum (Josephs et al., 2005). Patients (career welders) with manganese evidenced on MRI had a variety of neurological symptoms (many of which are Parkinson-like in nature) including tremor, ataxia, rigidity, bradykinesia, headaches, memory loss, reduced learning capacity, decreased flexibility, and cognitive slowing. Symptoms persisted even after removal from exposure (Josephs et al., 2005). Manganese accumulation in specific basal ganglia structures appears to be related to diverse neurological outcomes and may be causative, but currently this remains speculative.

The developing nervous system appears to be a target for manganese neurotoxicity, as it is for mercury and lead neurotoxicity. Most of the studies relating brain manganese accumulation to brain damage or dysfunction have been performed in animals. The increased susceptibility of young animals to manganese neurotoxicity is likely related to several factors including increased absorption from the gastrointestinal tract, an incompletely formed blood-brain barrier, and immature biliary excretory mechanisms (Erikson et al., 2005).

In contrast to an extensive literature describing manganese effects on brain and behavior in developing animals, there are scant reports concerning the effects of developmental manganese toxicity in children. Excess manganese has been suggested to cause hyperactivity (Barlow, 1983), psychosis and motor dysfunction (above 7.5 µg/l blood; Mergler et al., 1999). Impaired psychomotor development and a variety of cognitive deficits (e.g., in verbal learning, visual recognition, and digit span) have been noted (Takser et al., 2003). Takser et al. prospectively investigated developmen-

tal effects of low-level manganese exposures in humans in 247 pregnant Canadian women and their babies to determine effects of in utero manganese exposure on psychomotor development. After controlling for several potentially confounding factors such as maternal educational level and child's gender, negative relationships were observed between cord blood manganese levels and several factors including attention, nonverbal memory, and manual dexterity measured at 3 years of age.

Other reports demonstrate the ill effects of higher level manganese exposures on children. A child developed severe epilepsy after exposure to welding fumes that resulted in blood manganese levels of 15–20 µg/l (Herrero Hernandez et al., 2003). Chelating treatment reduced blood manganese levels, and seizures abated. Tremor and seizures have been reported in a child receiving parenteral nutrition (Komaki et al., 1999). Blood manganese levels were elevated, and T1-weighted MRI images showed hyperintensities in basal ganglia, brainstem, and cerebellum. Symptoms and MRI abnormalities disappeared after withdrawal of manganese-containing formula. Neurobehavioral deficits have been described in Chinese children who drank water containing high levels of manganese (from an area with high-level manganese sewage irrigation). Children with elevated manganese levels scored lower on tests of digit span, manual dexterity, digit symbol, and visual memory than did children from a control area (He, Liu, & Zhang, 1994).

**Case 10.4: Helen** Helen is an 8-year-old girl with end-stage cholestatic liver disease due to Aligille's syndrome. She presented with episodes of dystonia and cramping of her hands and arms (Devenyi, Barron, & Mamourian, 1994). These episodes had been occurring over a period of 2 months. Each instance lasted several minutes with a gradual return to normal motor functioning; consciousness was not altered. Helen's history was also significant for vitamin E deficiency and a stable peripheral neuropathy. On neurological examination cognitive screening was within normal limits as was speech. Helen exhibited a low-amplitude resting tremor that intensified with intention; strength was normal. There was decreased muscle bulk, but tone was normal. "sensory testing revealed decreased thermal, vibratory, and pinprick sensation in a fiber-length distribution. Romberg's sign was markedly positive. Tests of coordination revealed mild dysmetria bilaterally. No truncal titubation was noted. Helen had marked propulsion, retropulsion, and a poor check response bilaterally. Reflexes were 1+ in the upper extremities and absent in the lower; plantar responses were flexor. Her gait was narrow based, but she was unable to tandem-gait."

Helen's whole blood manganese levels were elevated at 27 µg/L (normal range = 1–14 µg/L). Her head MRI showed symmetrical hyperintense globus pallidi and subthalamic nucleus with T1 weighting but not with T2 weighting. The morphology of her basal ganglia as well as the rest of her brain was otherwise normal. Helen had a liver transplant 1 year after the onset of her symptoms, and 2 months later, whole blood manganese level had dropped to 8.6 µg/L, all symptoms except peripheral neuropathy had disappeared, and the abnormalities noted previously on the brain MRI were gone.

The case of Helen illustrates several features common to manganese poisoning. Individuals with liver problems are at increased risk for manganese intoxication.

Extrapyramidal motor abnormalities are typically observed, and reversibility of neurological signs and symptoms (e.g., motor symptoms, seizures; Herrero Hernandez et al., 2003, *vide supra*) often occurs with reduction of manganese levels. However, irreversibility of symptoms can occur, particularly with prolonged exposure. In addition, cognitive impairments are also frequently observed in manganese neurotoxicity (Devenyi et al., 1994).

### Summary

Manganese is essential for the normal functioning of a variety of physiological processes. Excess levels of manganese can be dangerous to children as well as adults and can result in a variety of motor and cognitive/psychiatric disturbances. In some instances, the effects of acute manganese toxicity may be reversible. It is unclear at this time whether the effects of chronic manganese poisoning can be reversed. Additionally, while much is known about the manifestations of chronic occupational exposures, virtually nothing is known about the effects of chronic low-level environmental exposures on neurodevelopment and behavior.

### Summary—Lessons to be Learned from Lead Poisoning

Lead, known to be a potent developmental neurotoxin for more than a century, continues to cause brain damage in large numbers of children. Extensive research on the diagnosis, treatment, and prognosis of pediatric lead poisoning has indicated that the detrimental effects of lead poisoning are permanent, irreversible, and largely untreatable. Ongoing research is addressed toward determining the toxic threshold as well as genetic and other factors that influence vulnerability.

Prevention of exposure is the only “cure” for this disease, while early detection is critical to limiting exposure in those children who have already been poisoned. Unfortunately, there are a number of unique features of childhood lead poisoning that pose serious obstacles to early detection. These include the short half-life of lead in blood and the lack of specific symptoms of neurotoxic levels of exposure that could alert a clinician to elevated blood lead levels. Another problem is that the neurocognitive effects of lead poisoning may not be observable until years after the poisoning, when the patient’s blood lead levels have dropped below regulatory agencies’ threshold of concern.

Mercury and manganese, heavy metals that are developmentally neurotoxic, have only recently been the subject of increasing investigation. Inasmuch as the neurotoxic effects of mercury on the child’s brain also appear to be permanent, early detection is crucial to minimizing harm. Research directed toward this goal should be guided by knowledge of the factors identified in studies of lead poisoning to be important for diagnosis.

## Notes

1. Lead also has toxic effects on other organ systems including the kidneys, lungs, heart, hematopoietic system, and reproductive system. The present chapter only addresses effects of lead on the brain.
2. For a comprehensive history of lead and public health, the reader is referred to *Brush with Death: A Social History of Lead Poisoning*, by C. Warren, The Johns Hopkins University Press, Baltimore, 2000.
3. These are reviewed in Lidsky and Schneider (2003), wherein detailed references are provided.
4. General Cognitive Index from the McCarthy Scales of Children's Abilities; Full Scale IQ from the Wechsler intelligence batteries and Test Composite from the Stanford Binet Test of Intelligence.

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