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Neurol Clin 23 (2005) 321–336

NEUROLOGIC
CLINICS

Neurodevelopmental Toxicology

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> And the angel of the Lord said unto Manoah: Of all that I said unto the woman let her beware. She may not eat of any thing that cometh of the grapevine, neither let her drink wine or strong drink, nor eat any unclean thing...
>
> Judges 13:13–14

Identical twin12-year-olds present to a pediatric neurology clinic with high-functioning autism manifesting as impaired social skills, impaired language, and stereotypic behaviors. The children have had developmental disability since infancy. Twin B has similar (although more severe) manifestations, with marked anxiety, violent outbursts, and Tourette's syndrome. The mother reports that the patients' father died at 37 years of age due to a glioblastoma multiforme. He had spent 19 years in the military working on nuclear weaponry. The father is described as "an odd duck" who had few friends. The mother recalls that he had a large head and hat size (it is common for military members to know their hat size). There is no history of accidental overexposure or a quantification of exposure.

The twins' head circumferences are at the 90% percentile. They make poor eye contact. They have frequent stereotypies with anxiety and have tics. Twin B clears his throat and both children have motor tics. The mother and maternal uncle (both are present) are noted to have poor eye contact, pressured speech, and somewhat bizarre affect.

The mother attributes the brain tumor and the subsequent autistic spectrum disorders on the occupational exposure. She asks for the physician's opinion.

Throughout history, medical practitioners have articulated scientific interest and medical concern about neurodevelopmental toxins. Because of

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The opinions expressed are those of the authors and do not represent those of the United States Air Force or the Department of Defense.

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doi:10.1016/j.ncl.2004.12.010 *neurologic.theclinics.com*

the proliferation of environmental hazards and the concerns for their effects, the contemporary neurologist needs to have a familiarity with neurodevelopment and the agents that disturb its normal processes.

When a child is diagnosed with a neurologic disorder, it is common for parents to consider toxic exposures as a possible explanation. In addition, there is strong interest by educators, policy makers, community activists, lawyers, and scientists about possible associations between neurodevelopmental disorders and environmental exposures.

It is estimated that 3% of neonates have a central nervous system (CNS) or multiorgan malformation. Although it is estimated that only 3.5% of these insults can be attributed to environmental teratogens, new provocative agents are routinely discovered. In 60% of individuals, the cause of the malformation remains unknown. The Centers for Disease Control and Prevention reports that 17% of American children are diagnosed with developmental disabilities (eg, learning disabilities, behavioral/emotional impairments, mental retardation). Attention-deficit hyperactivity disorder affects up to 12% of school-aged children; learning disabilities affect up to 10% of children attending public school; autistic spectrum disorders increased in prevalence from 0.5 cases per thousand to 2 cases per thousand over the past 20 years [1–5].

The hazards of environmental toxins are significant and largely unstudied. The National Research Council estimated in 2000 that 3% of developmental disabilities are direct consequences of neurotoxic exposures and another 25% are due to environmental exposures plus genetic susceptibility [4]. Epidemiologic studies have identified in utero and childhood exposures to lead, mercury, polychlorinated biphenyls (PCBs), and pesticides that are associated with neurobehavioral disabilities.

According to the EPA's Office of Children's Health Protection, there have been over 80,000 commercial chemicals developed and used within the last century, and most have not been tested for hazardous properties [1]. There are 2800 chemicals produced in excess of 1 million pounds per year; fewer than half have been tested for toxicity to adults and children. In 1995, consumption of synthetic pesticides was estimated at 2.6 million metric tons with an expected increase of 1% per year thereafter. Exposure to lead today is 300 times that of the preindustrial era due to the proliferation of leaded products. Over 50 million plantation workers worldwide have direct contact with pesticides and over 500 million agricultural workers are exposed. Mining for precious metals in the Amazon River basin accounts for the release of 130 tons of methylmercury (MeHg) each year. In 1996, 3 to 4 million children living in the United States were within 1 mile of one of the 15,000 hazardous waste sites [1].

Causative links between putative toxins and neurobehavioral disorders are difficult to substantiate except in some well-studied instances. Most research has focused on the effects of teratogenic toxins in causing anatomic nervous system anomalies, whereas less research has focused on behavior.

Consequently, the clinician will have difficulty gleaning answers from the literature. Certain basic principles can guide the clinician, however, when evaluating patients and counseling families.

In this review, the authors offer basic principles for the clinician faced with a potential developmental neurotoxin. Normal CNS development is described, with particular attention to known vulnerable periods for toxic exposures. Three prevalent nervous system teratogens are discussed in detail. Finally, the controversy regarding mercury exposure and the hypothesized link to autism is addressed.

Neurodevelopmental toxicology—lessons from teratology

When a toxic exposure is a consideration for a pediatric neurologic disorder without a clear anatomic derangement, the problem is further complicated by the passage of time from exposure to presentation and the complexity of behavioral syndromes. Development, growth, medical illness, secondary psychiatric illness, and familial coping mechanisms are always the added dimensions in evaluating neurobehavioral syndromes in children. For instance, one might wonder if a flare of stereotypic behaviors in a teenage child with autism reflects the course of the primary condition, household psychosocial stressors, adolescence, or a manifestation of a coexistent medical problem (eg, sleep deprivation).

The detailed encounter, background scholarship, and clinical time for risk communication are often felt to be beyond the scope of the generalist. Such is not the case for most children with neurobehavioral disorders. Many principles of teratology can be applied to allay the fears of families. For instance, a single agent cannot cause many varied forms of developmental aberration in different individuals. One agent causes a recognized pattern of dysmorphism. As an illustration, nicotine alone has been linked to neurocognitive changes but not to spinal cord anomalies.

Clinicians should stress that agents with known teratogenic potential or adverse neurodevelopmental potential may be innocuous, depending on the scenario. There are several critical questions for assessing possible toxic exposures in the clinic.

1. What was the agent? Are there simultaneous coexposures? MeHg exposures from excessive fish consumption during gestation are more likely to be teratogenic than the ethylmercury in thimerasol-preserved vaccines. Fish with high levels of MeHg may also have high levels of PCBs.
2. At what age did the exposure take place? Some agents have a narrower window of possible effect than others. Although exposure to retinoic acid can cause spinal dysraphism, exposure in the ninth month of gestation could not cause such a malformation. Knowledge of the ontogeny of the nervous system allows a rational assessment of the likelihood of a putative teratogen effect.

3. What was the route of exposure? Oral exposures are more easily quantifiable than vapor exposures (usually a product of concentration and time).
4. What was the dose and duration of exposure? Any potential teratogens follow a dose-response curve, below which its effects are negligible. Several exceptions are discussed later.
5. Can a relevant biologic assay be performed? Although one can measure an instantaneous level of a toxin or its function, it may not be clinically relevant. For example, one can assay red blood cell acetylcholinesterase levels that can be suppressed following exposure to organophosphorus agents; however, there is a great variation in the activity of this enzyme in the population. A single measure in an adult individual is most valuable when it is compared with stable values before or weeks after an exposure. As a result, this assay is most useful for determining occupational exposures compared with a baseline. In addition, specific cholinesterase levels do not necessarily correlate with symptoms.

These considerations do not substitute for a detailed history of gestation, birth, development and a three-generation pedigree. Other significant variables include genetic variance in susceptibility, placental factors, and the pharmacokinetics of the individual agent. Of course, the physiology of pregnancy, the placenta, and the fetus will alter the dose and metabolism of the primary agent. It is difficult to extrapolate from adult or animal data to the prenatal human experience.

Especially with neurobehavioral syndromes, *stochastic* phenomena (in which damage to one cell causes a malformation that is an "all-or-nothing" event) are less common than *threshold* phenomena. Threshold phenomena are active at many biological sites over time; consequently, within a population, the severity and the prevalence increase with greater exposure. For instance, although all toxins have a threshold dose below which they are innocuous, the picture is not as clear for lead. The Centers for Disease and Control and Prevention set a maximal allowed blood level of 10 μg/dL, but subsequent studies have found adverse outcomes at levels below the set benchmark. In the case of lead, the threshold phenomenon for adverse neurodevelopmental outcome may be seen at minute amounts.

Finally, the clinician should keep the potential for neurodevelopmental toxins in context and avoid the hubris of certainty. Numerous factors affecting neurodevelopment are still poorly understood. Numerous confounders may be operative in clinical situations and uncontrolled studies. Viruses, physical factors, radiation, diet, and even stress can have untoward effects on prenatal and postnatal development. Underlying genetic susceptibilities may also be interacting with the environmental exposure. Consequently, parental claims and medical literature (especially unproven hypotheses, case reports, and uncontrolled studies) should be viewed with circumspection.

Central nervous system ontogeny

Classic teaching of CNS embryology describes visualized histologic changes divided into arbitrary phases that end at birth. In truth, the phases of CNS development overlap in sequence and continue postnatally. In addition, there is a molecular "new neuroembryology" [6]. Molecular biology and genetics have revolutionized this field, revealing the genes and their products that shape CNS development. Although the present article gives specific illustrative examples, the reader is referred elsewhere for details [6].

Even before the neural tube is seen on gestational day 21, critical events in the formation of the nervous system have taken place. Gastrulation establishes a midline, axes for dorsal–ventral and anterior–posterior orientation, and symmetry. The notochord and somites develop during this phase to induce the ectoderm to form the neural plate and to establish a segmental organization, respectively.

The development of the nervous system, per se, begins at 3 weeks' gestation as the ectoderm forms the neural plate. From the neural plate, the neural tube forms in axial fusion, with closure occurring in a simultaneous caudal and cranial progression. During this process of neurulation, the anterior and posterior neuropores close by gestational day 24 to 26 and gestational day 25 to 28, respectively.

After neurulation, subsequent processes are further divided into proliferation, migration, differentiation, synaptogenesis, apoptosis, and myelination. These processes start after gestational day 28 but continue postnatally. Glial and synapse formation continue to be robust until approximately 3 years of age.

Myelination begins prenatally and continues in the CNS throughout childhood and into adulthood. The vestibular system is primarily myelinated prenatally, whereas association cortices continue to be myelinated in the second decade. This progression is commonly seen on MRI scans of children's brains.

Newer research has focused on the ontogeny of neurotransmitter systems. These neurotransmitters have trophic functions in the developing brain and have function in synaptic neurochemical signaling. One line of inquiry has focused on the effects of stressors (eg, seizures, handling) on receptor development [7,8].

Given this complex progression, it is difficult to ascertain by way of animal and epidemiologic studies the precise cause of developmental aberration. Specific toxins have postulated mechanisms and they exploit certain periods in development. Table 1 illustrates some potential toxins and their corresponding vulnerable periods.

Neural proliferation is vulnerable to ethanol, organophosphates, and MeHg disruption. It follows that if proliferation is altered, migration may also be altered, leading to ectopic tissues [9]. Ethanol and MeHg are culprits in interfering with migration [4,10,11]. Neural cells receive multiple signals

Table 1
Potential neurotoxic agents and their teratogenic windows

Age	Process in development	Potential neurotoxic agents	Altered outcomes
0 to 4 weeks' gestation	Gastrulation—notochord and somite formation	Retinoic acid	Disordered polarity, malformations of the hindbrain and spinal cord
4 weeks' gestation	Neurogenesis in spinal cord and hindbrain	Hot tubs Folic acid antagonists	Anencephaly, hydrocephaly
28–35 weeks' gestation	Migration	Ionizing radiation MeHg	Ectopia Cerebral palsy Learning disorders
Middle-late pregnancy	Neuron proliferation Synaptogenesis	Lead PCBs MeHg	Neurobehavioral deficits
Third trimester	Neurogenesis in cerebellum, hippocampus Cell migration, myelination, synaptogenesis	Pesticides	Multiple: poor motor control, emotional lability, cognitive deficits and delays
Infant to 3 years of age	Development of executive functions in the prefrontal cortex	Lead, postnatal Alcohol, prenatal Cigarettes, prenatal	Behavioral impairments, possible increased criminality
4–17 years of age	Increase in fiber tracts of motor and speech functions	Organophosphates	Poor axonal outgrowth
	Ability to build on previous learning	Lead PCBs	Lowered IQ
	Improved sensory function, specifically auditory	MeHg Lead	Impaired concentration

directing the differentiation of the cells. The offenders of changing or interrupting the differentiation process include ethanol, nicotine, MeHg, and lead. Some of the same agents—ethanol, lead, MeHg, parathion, permethrin, di-isopropyl fluorophosphates, and PCB compounds—are involved in altering synaptogenesis [2,5,10,12–21].

The support network for neural elements is vulnerable to insults because its formation continues for several years. The genesis of the supporting cells (glia) begins at the time of neuron genesis (early gestation). The glia continue to differentiate and proliferate long after the migration of neural cells is complete. Myelination peaks during the third trimester in humans; however, it continues into the teenage and young adult years, accounting for

its longer period of vulnerability. Myelination disturbances have been linked to malnutrition, iron deficiency, alcohol, and lead exposures [2,5,10,12–21].

Another important process for the developing nervous system is apoptosis (programmed cell death). Abnormal patterns of apoptosis are noted after toxic exposures. The hypothesis is that exposure leads to a shift in the balance of neurotrophic signals, resulting in an increase or decrease in the number of cells. Ethanol, lead, MeHg, and PCBs have been implicated in altered cell numbers [2,5,10,12–21].

Lead

Lead is a pervasive neurotoxin related to human industrial and chemical endeavors. Exposure was first recognized as a toxin among adults with occupations requiring use of lead-containing products (brass and bronze foundry workers, jewelry makers, painters, glassmakers, and potters). Today, humans are exposed despite increased regulation of its use in industrial products, leaded gasoline, and household interior paints. The major domestic sources of lead are dust and soil contaminated by lead-containing paint and industrial and vehicle emissions. Although there has been a dramatic decrease in lead levels, populations at risk have shifted from adult workers to pregnant mothers to toddlers and school-aged children.

In adults, the nervous system effects can be reversible, but in children, the outcome of lead encephalopathy is not good. Severe encephalopathy (seizures and coma) can be seen at high ($\geq$70 μg/dL) blood lead levels (BLLs). At low levels, lead is a significant neurodevelopmental toxin. In Europe, it is estimated that mild mental retardation resulting from lead exposure accounted for 4.4% of disability-adjusted life years [22]. Despite regulations and overall reduction in youth BLLs, significant concern exists regarding the loss of IQ points with chronic exposure, even at defined acceptable blood levels ($<$10 μg/dL) [5,11,23,43].

Children are vulnerable to exposures at various times of development due to their behaviors, socioeconomic factors, exposure to parental activities using lead (occupation or hobbies), use of folk remedies, malnutrition, neglect, or pre-existing developmental disorder. Fetuses may be exposed due to lead from maternal bone accumulation that is utilized during pregnancy. Toddlers are at risk due to hand-to-mouth activity. School-aged children may live and play in contaminated environments or use imported toys that contain lead. Children at high risk who should be tested for lead exposure are listed in Box 1.

When ingested, 40% of lead is absorbed, whereas 90% of inhaled lead is absorbed. This differential has implications for lead abatement programs that leave high levels of lead-containing dust.

Lead's mechanism of action is unknown. It affects multiple organ systems in the human body, including the bone marrow (specifically heme synthesis), the kidneys (specifically tubules), and the nervous system. It accumulates in

Box 1. Populations who should be tested for elevated blood lead level

After initial screening of children at risk (9–12 months old), assessment of BLLs should be repeated at 24 months when levels peak.

Universal screening
- In communities with inadequate data on the prevalence of elevated BLLs
- In communities with >27% of the housing built before 1950

Targeted screening
(Based on the assumption that universal screening is cost-effective in communities in which the prevalence of elevated BLL is at least 11%–14%)
- In communities in which <12% of children have BLLs of 10 μg/dL, or
- In communities with <27% of the housing built before 1950

Symptomatic screening/diagnostic testing
- Any child with an unexplained illness such as severe anemia, seizures, lethargy, or abdominal pain

Other groups to consider testing blood lead level
- Children 1 to 2 years of age living in housing built before 1950 situated in an area not designated for universal screening (especially if the housing is not well maintained)
- Children of ethnic or racial minority groups who may be exposed to lead-containing folk remedies
- Children who have emigrated (or been adopted) from countries where lead poisoning is prevalent
- Children with iron deficiency
- Children exposed to contaminated dust or soil
- Children with developmental delay whose oral behaviors place them at significant risk for lead exposure
- Victims of abuse or neglect
- Children whose parents are exposed to lead (vocationally, avocationally, or during home renovation)
- Children of low-income families who are defined as receiving government assistance (Supplemental Feeding Program for Women, Infants, and Children; Supplemental Security Income; welfare; Medicaid; or subsidized child care)

(*Data from* Screening for elevated blood lead levels. Pediatrics 1998; 101(6):1072. Available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b101/6/1072.) Accessed October 1, 2004.

the bone and is released with high turnover (eg, during pregnancy). There are significant differences between the toxicity of lead in adults versus the fetus and child. Adults tend to have reversible toxicity, whereas the developing child is permanently affected [5,11,23]. One hypothesis for the mechanism of action in the developing nervous system is that lead substitutes calcium, leading to neuronal apoptosis, abnormal neurotransmitter release, and damage to endothelial and glial cells [5,11,23].

Animal studies provide the data for possible mechanisms. Animal nervous systems have shown changes in the N-methyl-D-aspartate glutamate receptors. These changes may account for the cognitive deficits observed in the exposed animals (eg, learning and memory). Further delineation of this mechanism of action and demonstration in vitro in human cell lines may provide another significant route of long-term damage [5,11,23].

BLL is the most frequent assay performed to assess lead exposure. A value greater than 10 μg/dL should be confirmed. In all cases of elevated BLL, a detailed environmental history should be performed. At mildly elevated levels, however, a source is often difficult to identify. Typically, treatment with chelation is not offered until levels are greater than 45 μg/dL. The American Academy of Pediatrics offers a detailed policy on screening and follow-up procedures [24].

When a lead exposure is identified, the emotional valence may be high for the family and the clinician. Before launching on a potential treatment (eg, chelation or environmental mitigation), risks and benefits should be considered.

Manmade substances: polychlorinated biphenyls and polybrominated diphenylethers and relatives

In the 1970s, the United States and European governments banned PCBs due to recognized dermal, fetal, and neurologic abnormalities. Nevertheless, they continue as toxic hazards due to environmental build-up. Widespread use of PCBs and their relatives—polychlorinated dibenzofurans and polychlorinated dibenzodioxins or dioxins—in insulators and industrial electronic equipment led to release into the environment. These chemicals were first noted to affect the environment in 1968 when birds tested positive for PCBs. Due to its ubiquitous presence in the environment and the resiliency of the chemical structures after disposal, PCB exposure is common, with the most common route occurring by ingestion of contaminated foods.

The disposed chemicals remain as oils that pollute the water supplies. Aquatic organisms consume them and the concentration is magnified up the food chain as they are subsequently consumed. Eating fish exposes most humans. Mass poisonings occurred in Japan in 1968 and in Taiwan in 1979 after contaminated cooking oil was used. The Japanese poisonings, approximately 2000 cases, were discovered when the population developed a skin disease named Yusho. The manifestations included severe acne in

adults; however, the offspring of exposed women suffered diffuse damage. The most severe poisonings occurred in fetuses, and these children were born with subsequent ectodermal abnormalities including hyperpigmented skin, dilatation of eyelid sebaceous glands, neonatal teeth, discolored dentition, and growth retardation [25–27]. Infants continued to be exposed if breastfed; however, the significance of this exposure is unknown. In follow-up studies, children exposed in utero to maternal fat stores of PCBs demonstrated measurable behavioral and cognitive disabilities such as motor delays, lowered IQ, cognitive delays, lethargy, and apathy [16,25–27].

Similarly, polybrominated diphenylethers (PBDEs) have recently been more closely examined due to the structural relationship to PCBs and to the increasing concentrations in animal and human tissues. PBDEs are used as flame retardants and are still produced worldwide. Products containing PBDEs include electrical appliances, computer circuit boards, building materials, foam, carpet, upholstery, and vehicles. There is approximately 67,000 metric tons (148 million pounds) produced each year. They are slowly released as the plastics break down, and evidence suggests that exposure occurs by way of air dispersion and unintentional ingestion. Although no mass poisonings have identified teratogenic effects in humans, animal studies indicate that exposed newborn mice have permanent neurologic sequelae including abnormal motor behavior and reduced learning and memory capacity [25]. Due to the large environmental presence, the structural similarities to PCBs, and the animal data, there is concern for potential increases in human neurobehavioral disturbances due to exposure in utero and during childhood.

The proposed mechanism of action is endocrine disruption. Current focus includes evaluating thyroid hormone level and its function in relationship to these toxic exposures. Zoeller et al [28] report on the status of research and further delineate the proposed mechanism. Again, available data come from animal models. The interactions proposed to occur in utero include disruption of thyroid hormone–responsive genes, reduced circulating thyroid hormones, reduced thyroid responsiveness to thyroid-stimulating hormone, and increased clearance of T4 through enhanced liver metabolism [28,29]. The widespread exposures to PCB and PBDE contaminants, the negative impact of abnormal thyroid hormone action on the developing brain (ie, congenital hypothyroidism with severe mental retardation, motor abnormalities, and deafness), and the relationship between thyroid hormone and these contaminants lead to concern for neurodevelopmental hazards imposed on the vulnerable developing human.

Although many laboratories offer measurements of PCBs in breast milk or other samples, such assays have no clinical relevance. There are numerous differences in methods, quality assurance, and reference values. Outside of research studies, measurement of polychlorinated toxins is not recommended.

There is no effective treatment for PCB exposure. Hypothetically, lactating women may be counseled not to lose weight because the metabolism of fat stores liberates the toxin.

Pesticides: organophosphates and carbamates

As noted earlier, the potential exposure to pesticides is profound. Even humans not exposed by way of occupations are often exposed by way of household applications, residues on produce, and commercial applications, leading to dermal, gastrointestinal, or inhalational exposures. Whyatt and Barr reported in 2001 that 20 of 20 infants tested in New York City had positive organophosphate metabolites in their meconium. In addition, the Environmental Protection Agency surveyed American households and found that over 70% of respondents used at least one pesticide in or around the home [29a].

There is such concern for exposure, particularly with the developing child, that the United States Congress passed the Food Quality Protection Act of 1996. This law requires several actions on the part of governmental agencies to research and protect infants and children from toxic levels of exposure.

Much of the known consequences of human exposure to pesticides came about with acute poisonings in agricultural workers. Organophosphorus agents cause irreversible and reversible inhibition of acetylcholinesterase and other esterase enzymes. Excess acetylcholine causes a well-known cholinergic syndrome marked by nausea, vomiting, hypersecretion, bronchoconstriction, and CNS effects (ie, seizures, headache, vision changes, anxiety, ataxia). Miosis is often described as a hallmark sign of exposure but it can frequently be absent.

Acute exposures to organophosphorus agents can lead to chronic neurologic deficits including frequent headaches, difficulty with memory and concentration, mood alterations, and polyneuropathy. These effects can persist for months and even after acetylcholinesterase function has normalized.

In the CNS, pesticides affect more than the richly cholinergic areas of the brainstem and forebrain. The limbic system, hippocampus, basal ganglia, and cerebellum are also affected. In animal models, organophosphate exposure affects multiple neurotransmitters systems, second messengers, and neuronal proliferation. Additional evidence is accumulating in humans that chronic exposure during neurodevelopment may cause hyperactivity, poor attention span, and cognitive deficits [19–21,30–33,42]. Given the widespread use of these chemicals, however, there are relatively little data to further delineate the timing during development and amount of exposure needed for significant disabilities.

Treatment for acute organophosphate and carbamate poisoning should be instituted based on a clinical diagnosis of the cholinergic syndrome. In

the United States, this treatment combines atropine and pralidoxime chloride. Seizures are treated with benzodiazepines because other anticonvulsants are ineffective. Organochlorine and pyrethroid exposures are treated with supportive measures.

Blood cholinesterase levels are useful for confirmation of acute exposure or for occupational monitoring, as discussed earlier.

Mercury

Human endeavors (eg, coal-fired power generation, waste incineration, mining, medical/dental uses) allow for exposures to inorganic mercury. Known for its occupational hazards, mercury has long been respected as a neurotoxin. There are three forms of mercury: (1) elemental—used in thermometers, dental amalgams, fluorescent light bulbs, and button batteries; (2) inorganic salts such as mercuric bichloride, also known as corrosive sublimate; and (3) organic compounds—MeHg, ethylmercury, and phenylmercury. Bacteria in the water produce organic mercury compounds.

Although the most commonly known form is elemental, the greater public health concern is for the organic form, as it is biomagnified by consumption along the food chain. Examples of fish with high levels of organic mercury are shark, tuna, and swordfish.

Toxic "epidemics" have occurred due to mercury contamination of waters supplying the fish for human consumption. In the 1950s and 1960s, the first large exposures were reported in Minamata and Niigata, Japan. The clinical syndrome, named Minamata disease, was recognized in adults with neurologic impairments including paresthesias, visual field constriction, ataxia, impaired hearing, and speech impairment. In offspring of the exposed Japanese women, who had minimal symptoms, there were 22 reports of congenital Minamata disease consisting of severe developmental disabilities (eg, cerebral palsy, mental retardation, and seizures). Another large exposure occurred in an Iraqi population who consumed grains treated with a fungicide containing MeHg. The exposures continued from 1959 to 1972, affecting over 6500 individuals including 83 pregnant women. Similar neurodevelopmental disabilities resulted [4,12,34–36].

Due to these disasters, scientists have studied multiple populations who depend on fish consumption for primary nutrition. In comparison to acute exposures, as in Japan and Iraq, these population studies usually involve significantly lower doses of chronic MeHg exposure, as measured in maternal peak hair mercury values. The population studies have been inconsistent; however, organic mercury easily crosses the blood-brain barrier and accumulates in the CNS. The threshold level established by the Environmental Protection Agency is 0.1 μg/kg/d, which is often exceeded in populations regularly consuming seafood (average hair mercury is often >10 μg/g in fishing communities). The long-term sequelae of exposure to organic mercury in the developing nervous system include

abnormal results on the Denver Developmental Screening Test, worse performance on the Wechsler Intelligence Scale for Children-Revised compared with controls, and neuropsychologic deficits (eg, language delays and attention and memory deficits) [34–36].

At the molecular level, MeHg has a high affinity for binding thiol groups such as found on proteins with cysteines. In vitro data from animal models demonstrate that high levels of MeHg (5–10 μmol) impair mitochondrial activity, leading to decreased energy sources and plasma membrane lysis and cell necrosis. Lower exposures (<1 μmol) cause apoptosis by way of activation of calpain and caspase-3 [34,35].

In addition to altering cell death mechanisms, MeHg affects the developing nervous system in other crucial mechanisms including the cytoskeleton, leading to errors in migration (eg, brain reduction, heterotopias in white matter, and abnormal neuronal arrangements); calcium homeostasis, leading to elevated intracellular calcium, which may lead to cell death; excitatory amino acid uptake inhibition, leading to extracellular accumulation of glutamate, which leads to neurodegeneration; and muscarinic cholinergic and dopaminergic systems with unknown long-term consequences. The reader is encouraged to read the in-depth review of the molecular consequences of MeHg exposure by Castoldi et al [34] and Davidson et al [35].

Mercury exposure can be diagnosed by a history and physical examination and confirmed with elevated blood mercury levels. A normal level does not rule out mercury exposure. For inorganic mercury, a 24-hour urine collection can be assayed. For inorganic mercury, whole blood mercury levels are recommended. For cumulative burden of mercury exposure, hair can be assayed, with a normal concentration being less than 1 part per million.

The most effective treatment is to curtail exposure. Although chelation regimens exist for inorganic mercury toxicity, no treatment exists for organic mercury exposure.

Area of controversy—autism

The apparent increase in autistic spectrum disorder, whether due to heightened awareness or an actual increase in prevalence, has attracted widespread public attention. The personal and social impact of this long-term disability has provoked much interest in determining its etiology and what, if anything, neurotoxins might contribute to this disorder. Autistic spectrum disorders commonly present at approximately 1 year of age, when verbal and social skills should be established.

In 1999, the Environmental Protection Agency published safe limits of mercury exposures. Although a level was specified, several other aspects of this policy should be noted. The primary exposures of concern were oral consumption of MeHG over time. Policy makers hypothesized that the

ethylmercury in childhood vaccines might be as harmful as MeHG and contribute to autism. The measles-mumps-rubella vaccine contained thimerosal (approximately 50% ethylmercury) at the time. The doses of ethylmercury in the vaccines ranged from 12.5 to 25 μg/dose. In smaller infants, this could have exceeded the 0.1 μg/kg/d guideline. There were no data for a developmental impact of a single day's dose exceeding the guideline.

The hypothesis of the effects of ethylmercury had meager scientific evidence to validate it. Most pathologic studies of autism point to prenatal genetic factors causing changes in minicolumn organization or other anatomic findings. No postnatal exposures have been etiologically linked to autism.

Still, concern for a potential for developmental toxicity drove changes in immunization practices and vaccine production. The Food and Drug Administration requested that thimerosal, a preservative allowing for multidose vials, be removed from vaccines [37]. No vaccine in the United States currently contains thimerosal, but worldwide, many still do.

Since the initial hypothesis, research has concluded that the preponderance of the evidence negates this hypothesis. Further studies evaluating retrospective and prospective cohorts determined that there is no association between these vaccines and autism. In fact, two recent British epidemiologic studies with a combined number of over 120,000 participants not only found no adverse effects but also found protective effects on development with the thimerosal vaccines [38,39]. An excellent review of the epidemiologic studies has recently been published [40,41].

Summary

The fields of neurotoxicology and developmental toxicology are exploding in research and interest. Much of the data currently known are from epidemiologic human studies or studies of animal models. Each of these modes is difficult to translate to individual clinical encounters. It is often difficult to state with certainty which of the numerous chemical or physical agents in our environment are neurotoxic. Basic scientists will help with advances in molecular biology and toxicology. Improved clinical understanding of these issues may help patients to understand the medical issues; allay feelings of anxiety, guilt, or fear; and avoid unnecessary testing.

For exposures that manifest as threshold phenomena, such as lead, the risk to society is even greater than to an individual. Individual risk may be less of a concern than the population's risk because small elevations in the average BLL can cause profound shifts in the normative curve of intelligence, increasing the burden on our institutions and bankrupting the brain trust.

Good scholarship and interpersonal judgment are vital when counseling patients on the potential consequences of chemical exposures and are no less

important when making policy. The challenge for the clinician reading the research is to remain aware of the limitations and biases of our science.

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