Environmental Influences on Learning Disabilities

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Abstract

Determining environmental contributions to learning disabilities, particularly subtle learning deficits from exposures at low levels, is extremely difficult. The environment seldom operates in isolation; many other factors must be in place for a particular exposure to cause the specific damage needed for learning deficits to develop. Additionally there is no single battery of tests, in either humans or animal models, that can identify the entire universe of potential learning disabilities. Nonetheless we continue to improve our understanding of how environmental exposures influence learning disabilities. This knowledge was instrumental in leading national efforts to reduce exposures to lead, mercury, polychlorinated biphenyls and other toxicants. As the field continues to mature, it is hoped that new insights will be gained in the etiology and prevention of learning disabilities and of those disorders, such as attention deficit/hyperactivity disorder and autism, whose prevalence might be increasing.

Introduction

That environmental agents can damage the nervous system is unquestioned. Metals such as lead and mercury, drugs of abuse such as alcohol, and recently discovered toxins such as that produced by the dinoflagellate *Pfiesteria* have been shown to cause seizures, memory loss and other central nervous system (CNS) deficits in adults exposed at high levels.

Exposures to these same agents can occur in early human development, both *in utero* and during infancy and early childhood. We are now learning that the damage inflicted by neurotoxicants on the developing nervous system can be quite different than that found in mature nervous systems (Weiss & Elsner, 1996). Additionally, the developing nervous system appears to be more vulnerable than the mature system, sustaining damage at low dose levels for which adults show no apparent ill effect. Thus studies in adults do not accurately predict either for a safe level of exposure or for expected health outcomes when these studies are used to predict effects in infants and children. Yet only recently have attempts been made to establish regulatory levels of environmental agents based on an understanding of the enhanced vulnerability of early childhood.

Neurotoxicity itself covers a vast array of endpoints, including locomotor and balance problems, confusion, memory loss and learning disabilities. The focus of this article will be on a specific subset of neurotoxicity — learning disabilities — and the possible role of environmental exposures in the development of learning disabilities.

Traditionally learning disabilities have encompassed difficulties in reading, writing and mathematics, difficulties with language and deficient social skills. Other conditions that impede learning would include hyperactivity/attention deficit disorders and autism. Although these latter conditions have learning problems only as a subset of a larger dysfunction, they are included as disorders of interest in this article.

This article focuses on environmental contaminants and involuntary exposures. Because the developing nervous system is much more vulnerable than that of adults and because deficits early in life have a longer span of effect, this discussion will concentrate predominately on children. It should be noted that in addition to the synthetic chemicals and industrial byproducts discussed in this article, a child's environment includes their diet and nutrition, their social setting and economic status, and the mental stimulation they get from parents, playmates, television and video games. These latter environmental components can also have an effect on mental development, but are outside the scope of this article.

Difficulties Facing Researchers in Determining Environmental Influences on Learning Disabilities

Determining environmental contributions to learning disabilities, particularly subtle learning deficits from exposures at low levels, is extremely difficult. The environment seldom operates in isolation; many other factors must be in place for a particular exposure to cause the specific damage needed for learning deficits to develop. Additionally there is no single battery of tests, in either humans or animal models, that can identify the entire universe of potential learning disabilities. Some of the more notable problems in study design and execution are noted below.

Multifactorial Nature of Learning Disabilities: Diseases and disorders, including learning disabilities, arise from the complex interplay of environment, genetic susceptibilities and time. Thus identical levels of exposure can have dramatic effect, or no effect at all, depending on an individual's underlying susceptibility and the age at which the exposure occurred. This individual variation in responsiveness to exposures generates a very high "background noise" that can mask some of the contributions of environmental agents to disease risk. It is hoped that we can better control for the confounding variable of genetic susceptibilities as our rapidly improving knowledge of genes and the susceptibility genetic variation confers becomes incorporated into study design.

For learning disabilities, the timing or age of exposures is particularly critical — fetal development and early infancy represent the stage of life during which neurological systems

undergo major growth and change. The carefully orchestrated series of events by which a fertilized cell develops into a sentient being offers many opportunities for environmental interference or disruption. Each event, though, controls for different aspects of brain development. Thus, identical exposures could be expressed as very different outcomes, depending upon what particular part of the neurological system is being laid — be it during cell migration, cell proliferation, selection of neurotransmitters or other critical events in brain system development.

Rodent studies have aptly demonstrated the effect of timing of exposures in neurobehavioral development. In one series of studies, five different drugs were administered at different stages of development (Vorhess, 1986). These studies showed that differences of as little as one day in exposure regimes could produce dramatic differences in the behavioral dysfunction produced.

Delay in Detection: Damage by an environmental agent can occur in early fetal development or postnatal life, or might even be the result of an exposure to the mother or the father. The subsequent learning disability, however, is unlikely to be detected until much later in life. Some learning disabilities might be apparent by the age of two years, but the majority will not be diagnosed until around school age. Thus the time between the original exposure and the final diagnosis can be six or more years. This time lag greatly complicates our ability to determine what the critical exposure was. Studies that rely on memory recall or on current exposure levels can miss the actual causative agent.

Complex Mixtures: Further complicating the picture is that real world exposures are generally to multiple agents rather than single agents. Despite this fact, most chemical studies are on single agents rather than complex mixtures. Yet some studies have demonstrated that exposures to two different environmental agents can potentiate the action compared to either one alone. As environmental health matures as a science, it is hoped that this deficit in our understanding will be improved.

Multiplicity and Variability of Learning Disabilities: Learning disabilities cover a broad array of endpoints, including difficulties in reading, writing and mathematics, difficulties with language, deficient social skills, and may be outcomes of hyperactivity/attention deficit disorders and autism. Additionally diagnosis is based on symptoms rather than a fundamental underlying condition. Language, for example, requires an integration of cognitive, perceptual and motor functions; two individuals experiencing language difficulties do not necessarily have the same biological or neurological deficits.

Inadequate Diagnostic Vehicles: There is no single test or battery of tests that can adequately detect or quantify learning disabilities. Of necessity, studies must use multiple measures of learning ability, each with its own strengths and weaknesses. Diagnosis for many learning disabilities is highly subjective and, even where tests exists, the skill of the test giver can influence the outcome as much as the test taker. Further complicating study in this field is the fact that definitions of particular disorders such as autism and attention deficit/hyperactivity disorder (ADHD) are variable, subjective, and in a state of flux.

No Definitive Animal Models: Animal models, upon which much of the environmental health sciences rely, can not adequately address the full complexity of human learning disabilities. Although there are a number of standard measures that, given as a battery, can help screen for a particular chemical's ability to impair learning, none can capture every possible aspect of learning. Thus routine screening via rodent models can not be expected to detect all potential impairments on the array of neurological functions that comprise the learning process.

A Sampling of Environmental Agents Known or Suspected to Cause Learning Disabilities

Alcohol: Probably the most ancient of neurotoxicants, ingestion of alcohol during pregnancy can result in severe mental retardation in a woman's offspring. The resulting fetal alcohol syndrome (FAS) in these children is accompanied by distinct facial characteristics, including epicanthal folds, flat midface, thin upper lip and ear anomalies. At lower dose exposures, though, children do not have the facial features or severe mental retardation (IQ less than 70) of the classic FAS. They do, however, suffer from a number of neurobehavioral effects that persist into adulthood, including learning disabilities, particularly with arithmatic concepts and behavior problems. Studies in animals verify the ability of alcohol, when the exposure is early in life, to cause persistent neurobehavioral problems. These studies suggest that there is no dose, or at best only a very low dose, at which no effect would be expected when exposure occurs during critical periods of brain development (Sampson, et al., 2000).

Lead: Lead is widely distributed in the environment. Outside of occupational settings, the major exposures are through lead-based paints (now banned, but exposures still occur via chipping paint in older homes), lead deposited in dusts and soils from automobile exhausts of leaded gasoline, and water distributed in lead or lead-soldered pipes. Neurological effects in adults are usually manifested as peripheral neuropathy; in children the effects are quite different. Children exposed to very high levels of lead (80 µg/dL and above found in the blood) exhibit encephalopathy and, if the child survives, epilepsy, mental retardation and blindness are possible outcomes (Goyer, 1996). Such high exposure levels are now rare in this country. Children successfully treated for more moderate levels of lead poisoning seem to sustain permanent neurological damage that manifests itself as poor school performance, short attention span, restlessness and impulsive behavior (Byers & Lord, 1943).

Before the 1960s a blood lead level of 60 µg/dL and above was considered toxic; by 1978 that level was dropped to 30 µgdL. The past two decades, though, have provided new evidence that for every 10 µg/dL increase of blood lead in the range of 5-35 µg/dL, a child experiences a 2- to 4-point IQ deficit (Goyer, 1996; Robert A. Goyer, personal communication). Furthermore, these deficits translate into later problems in school, particularly decreased attention spans, reading disabilities, increased aggression as juveniles and failure to graduate from high school (Needleman et al., 1990; Needleman et al., 1996). Although these studies have the confounding factor that much of the lead exposure occurs in inner-city and impoverished neighborhoods, where low socioeconomic status and low

parental education can also negatively affect IQ, they nonetheless have led to a reassessment of what constitutes an "acceptable" blood lead level in children. A clinical trial funded by National Institute of Environmental Health Sciences (NIEHS) is currently underway to assess if these lower blood lead levels can be treated by oral chelation therapy and if expected decrements in IQ can thereby be reversed (Rogan et al., 1998).

In animals, prenatal lead exposure results in impairment of a wide variety of tasks designed to assess learning and memory (Rice, 1996). One particular set of experiments offered the intriguing possibility that lead exposure could play a role in some cases of attention deficit hyperactivity disorder (ADHD). Groups of monkeys were dosed at a steady state of 20 µg/dl blood lead levels from birth, from infancy, or during infancy only. In all three groups deficits were found in discrimination reversal tasks and nonspatial discrimination tasks. The researchers maintain that these tests correlate with behavior in children diagnosed with ADHD, specifically the inability to organize behavior within a time dimension and the inability to learn from past mistakes (Rice, 2000).

Mercury: Inorganic mercury is released into the air and water through a variety of industrial processes. Once in the environment, it is usually converted to its organic form, methylmercury. This compound has the ability to bioconcentrate in the environment, i.e., become concentrated as it moves up the food chain. For this reason, mercury in the water can become concentrated in tissues of fish that occupy the higher levels of the food chain.

The greater sensitivity of the fetus to methylmercury was aptly demonstrated during the episode of inadvertent exposure in Minamata Bay, Japan during the late 1950s (Watanbe & Satoh, 1996). Industrial effluent had contaminated the Minamata Bay with methylmercury, which was subsequently concentrated in the local fish supply. The resulting "Minamata Disease" was characterized by abnormal gait, ataxia, deafness and constriction of the visual field. The most dramatic effects where in newborns who had been exposed to methylmercury *in utero*. These individuals often suffered from cerebral palsy-like symptoms, mental retardation and psychomotor retardation. The Minamata episode, coupled with other inadvertent human poisoning experiences and confirming tests in animals has led to advisories that pregnant women limit their intake of fish.

Since methylmercury exists at some level in almost all vertebrates, the question arises as to what levels are safe in children. Several prospective epidemiologic studies have been instituted in methylmercury-exposed, fish-eating populations with results that, to date, are somewhat conflicting. One of these is in a group of Faroe Islanders whose main protein source is seal and whale meat. These sources are rich in two neurotoxicants --- methylmercury and polychlorinated biphenyls (PCBs). Mercury levels in this population were assessed both by levels in maternal hair and by levels found in cord blood. A second study in a fish-eating population in the Seychelles Islands have exposures to only methylmercury. Methylmercury in this cohort was assessed only by levels in hair samples of women and, after birth, their children. Children were followed through early infancy and childhood. Both studies are continuing and interim results have been published.

Methylmercury exposure in both cohorts was roughly comparable. Interestingly the children of the Faroe Islander women were found to exhibit deficits in language, attention and memory, as well as some visual-spatial and motor functions at seven years of age (Grandjean, et al., 1997). With the exception of the Finger-Tapping measure, cord blood mercury was a better predictor of effect than hair mercury levels. In contrast, the Seychelles Islanders' children showed no adverse effects at 66 months of age (Davidson, et al., 1998). It has been postulated that the difference in effect could be because the Faroe Islander study used tests better able to discern subtle cognitive and neuromotor performance disturbances, whereas the Seychelles Islander study relied on more traditional indices of child development that might have missed these deficits (Mahaffey, 1998). Also the mercury levels in Seychelles Islanders were assessed using hair samples, which in the Faroe Islander study was not as good a predictor as cord blood. The fact that the Faroe Islanders had co-exposure to PCBs might also provide a confounding factor, although statistically controlling for PCB exposure yielded the same results. These studies will continue and attempts will be made to include more readily comparable test instruments. Certainly these two studies illustrate the difficulties in assessing neurobehavioral effects of low-level contaminant exposures.

Recently, concern has been expressed about mercury exposures via vaccination. Many, though not all, vaccines contain a preservative, thimerosal, that contains ethylmercury, a compound structurally similar to methylmercury. Thimerosal has been used since the 1930s, but exposures to it are increasing since vaccination schedules can now start at birth and continue intermittently throughout childhood, creating scheduled exposures to a known neurotoxicant. In fact, if all of a child's immunizations contain thimerosal, then the body burden of mercury could exceed existing federal limits (AAP & USPHS, 1999). Although "there is no evidence of any harm caused by low levels of thimerosal in vaccines" (American Academy of Family Physicians, 1999), there is an admitted paucity of information in the literature on the effects of ethylmercury, particularly for exposures in the young. One rat study comparing ethylmercury and methylmercury indicates that there are slight differences in uptake and distribution (Magos et al, 1985), suggesting that although methylmercury studies might be generally predictive of ethylmercury effects, there could still be subtle differences. The National Institute of Environmental Health Sciences (NIEHS) and the National Institute of Allergy and Infectious Diseases (NIAID) are now funding a study in non-human primates to compare the uptake and distribution of methylmercury and ethylmercury when given early in life.

The fact that ethylmercury exposure occurs simultaneously with an immune challenge represents an exposure scenario that merits further exploration. Anecdotally, a number of parents have described onset of autistic behavior in their children following routine vaccination. Strikingly, in many of these reported cases, the autism assumes a regressive form in which a child appears to be developing normally in speech and social interaction, but then begins to regress and loses these skills.

There is currently no evidence proving a vaccine-autism connection, or a mercury-autism connection. Intense study of a possible association between the measles, mumps and rubella (MMR) vaccine and autism has so far proven negative (Taylor et al., 1999), but no work has been done examining the consequence of the full spectrum of today's vaccination schedule. Certainly it seems prudent to limit mercury exposure where it is not necessary and is preventable.

Autism itself might well be a learning disability with a gene-environment interaction. Twin and family studies have indicated a genetic component in autism (Rodier & Hyman, 1998; Risch et al., 1999). Given, however, that its prevalence might be increasing as much as 3.8% each year (Gillberg & Wing, 1999), genes clearly are not the entire answer. Improved reporting and broader definitions of autism doubtless account for some of the increase, but an underlying susceptibility to environmental influences must also be considered. Polymorphisms, or variants, of *Hox* genes, which are important during early development, have been postulated to confer increased susceptibility to autism when environmental pertubations occur *in utero* (London & Etzel, 2000).

Polychlorinated Biphenyls: Polychlorinated biphenyls (PCBs) are a class of chemicals once used in hydraulic fluids, plasticizers, adhesives, electric transformers and capacitors. Although they have now been banned in this country, their extreme stability, widespread use and ability to biomagnify in the environment impose an exposure that will remain for some time. Native populations in the Arctic regions can get significant PCB exposure from consumption of fish, seal and whale meat. PCBs can also concentrate in the lipids of breast milk, so breast feeding infants can get a significant exposure early in life if their mothers are exposed to PCBs.

Although not generally neurotoxic to adults, very high exposures to PCBs can cause slowed nerve conduction, lassitude and other CNS symptoms (Rogan & Gladen, 1992). It is in the developing brain, though, where PCBs are most toxic. *In utero* exposure to PCBs is associated with delayed motor development, defects in visual memory and impaired short-term memory (Jacobson et al. 1985 and Jacobson et al., 1990). A series of studies tracking children born to PCB-exposed women in Taiwan reported poorer performance on psychomotor tests early in life, poorer cognitive development, and increased activity levels that persisted into ages 6 - 7 years (Chen et al., 1992; Chen et al., 1994). Studies in a North Carolina cohort, where levels of exposures were much lower than in the Taiwan study, found small developmental delays from transplacental PCB exposures by age 2 years, but problems did not appear to persist; by age 5 years there was no difference in the McCarthy Scales of Children's Abilities between high-exposed and low-exposed children (Rogan & Gladen, 1991; Gladen & Rogan, 1991).

Developmental exposures to PCBs in animals support the observations in humans. Both primates and rodents display persistent neurobehavioral deficits following early exposure to PCBs. Results reported include hyperactivity and alterations in higher cognitive processes (de Duffard & Duffard, 1996).

Pesticides: Modern agriculture depends heavily upon the use of pesticides (insecticides, fungicides, rodenticides, herbicides) to feed the earth's burgeoning population. Additionally, public health practices dictate the use of pesticides to reduce insect vectors of disease such as mosquitoes, and insecticides are used extensively to control roaches and termites. In the aggregate, this extensive use has led to widespread exposures in some populations in the U.S. and elsewhere.

Overexposure to pesticides can lead to a variety of cognitive problems, most often in the areas of memory, concentration, and timed psychomotor performance (Keifer & Mahurin, 1997). In children, early exposure to pesticides led to decreased gross and fine eye-hand coordination, 30-minute memory, and the ability to draw a person at ages 4-5 years among a Mexico cohort of children compared to children living in an area without pesticide use (Guilette et al., 1998). It should be noted, though, that in a cohort of children in North Carolina who had early exposures to low levels of DDT and PCBs, small developmental delays found at age 2 years did not persist into ages 4 and 5 years (Rogan & Gladen, 1991; Gladen & Rogan, 1991).

Animal studies indicate a potential for persistent neurobehavioral effects from pesticide exposure early in life. A study in mice showed that a single low oral dose of the organochlorine pesticide, DDT, to the neonate led to permanent hyperactivity in adulthood (Eriksson et al., 1990). A review of organophosphate pesticide studies found a number of animal studies on this broad pesticide class in which exposure early in life resulted in persistent neurobehavioral problems including impaired maze performance (Eskenazi et al., 1999). There is, however, a lack of data on pesticide toxicity in developing organisms, particularly at the low levels to which many children are exposed (NRC, 1993). Much work needs to be done to define how early exposures can translate into later problems in learning and attention.

Ongoing and Proposed Projects to Help Define the Importance of Environment in Learning Disabilities

Greater effort has been focused over the past decade on identifying environmental components of learning disabilities. There are also some proposed projects at the federal level that offer the potential for large-scale prospective studies that could help in defining important neurodevelopmental toxicants. Some of these projects are discussed below.

ADHD Study in Johnston County, NC: The NIEHS is establishing a cohort of children in grades 1 - 5 in Johnston County, North Carolina. These children are being studied in an attempt to assess environmental influences on Attention Deficit/Hyperactivity Disorder. The study will focus on validation of the diagnosis, the course of this condition (does it persist, ameliorate, worsen?), and what environmental components, if any, have an association with ADHD in this group. The main hypothesis of the study is that events during pregnancy, particularly preterm delivery, are risk factors for ADHD. Lead exposure is also of interest as a risk factor and the researchers will attempt to get the data needed for this determination.

Effect of Early Pesticide Exposure in Rodents: The NIEHS has completed a series of studies in rats to assess the impact on the neurological, reproductive and immune systems following early exposure to pesticides. Currently heptachlor, tebuconazole, methoxychlor, carbaryl and chlorpyrifos have

been studied. Of these, tebuconazole (Moser et al., 1999) and heptachlor (manuscript in preparation) gave evidence of affecting neurological development in rats.

Children's Environmental Health and Disease Prevention Centers: The NIEHS teamed with the Environmental Protection Agency (EPA) and the Centers for Disease Control and Prevention (CDC) to create a network of eight Children's Environmental Health and Disease Prevention Research Centers throughout the country. These centers focus on identifying the environmental underpinnings of common childhood disabilities such as asthma and developmental disorders. Several of these Centers focus on neurobehavioral aspects of common pollutants such as lead and pesticides. Currently four more Centers are being recruited to specifically address environmental aspects of developmental problems. The Request for Applications (RFA) for these centers encouraged researchers in the fields of behavioral and learning disabilities, including ADHD and autism, to apply. Applications are due January, 2001 and awards might be made as early as July, 2001.

Norwegian Birth Registry: Studying the adverse effects of low-dose exposures during fetal development is significantly complicated by the fact that many of these effects do not appear until much later in life. The best way to detect these effects in humans is through long-term epidemiologic studies that follow a child through its mother's pregnancy and into the later years of a child's life. Such studies are expensive and can be difficult to monitor. One cost-effective approach is in collaborating on existing studies in countries where this type of monitoring is done. The NIEHS is investigating the possibility of such a collaboration with Norway, which has an excellent infrastructure for human health studies. The Norwegian government plans, beginning in 2000, to establish a cohort of 100,000 pregnant women and their children to be followed for the rest of their lives. Questionnaires will be administered periodically throughout the mothers' pregnancy and the babies' childhood. Study participants will also be followed through the various Norwegian national medical registries. NIEHS is exploring the feasibility of collecting blood and urine of all mothers during pregnancy. If such a collaboration is feasible, then NIEHS would store these biological samples and use them later to determine maternal and fetal exposure to environmental agents such as pesticides, plasticizers and heavy metals. Although not aimed specifically at determining learning disabilities, this study could yield important clues if enough of the children are discovered to develop learning disorders.

National Longitudinal Study of Environmental Influences on Child Health: The Norwegian Birth Registry offers an excellent opportunity to gain insight into genetic and environmental components of children's health with a relatively modest investment. This study, though, will be unable to fully capture the exposures and genetic diversity of the U.S. population. There is a great deal of federal interest in creating a U.S. Birth Cohort — the National Longitudinal Study of Environmental Influences on Child Health — that could be tracked over an entire lifespan and assessed for genetic and environmental contributors of disease. The sample size, as well as monitoring expenses, might well prevent such a cohort from being developed in this country. Nevertheless, the possibility of such a study is being actively discussed by the agencies participating in the President's Task Force on Environmental Health Risks and Safety Risks in Children and a public hearing on the concept is planned for December 2000.

Conclusion

There is compelling evidence that environmental agents can cause life-long learning disabilities. How these environmental influences are expressed, however, is highly dependent on the stage of brain development at the time of exposure and the underlying genetic susceptibilities. The fetus, infant and young child are generally more vulnerable than adults to neurotoxicants. For this reason environmental protection of children cannot be based on studies done in adults.

Identifying important environmental influences on learning behavior is complicated by the broad array of different disabilities, the importance that the timing of exposure plays, the variability in responsiveness among individuals, and the lack of definitive evaluation instruments. Nonetheless, we continue to improve our understanding of how environmental exposures can lead to learning disabilities. This knowledge has been instrumental in leading national efforts to reduce exposures to lead, mercury, polychlorinated biphenyls, pesticides and other toxicants. As the field continues to mature, it is hoped that new insights will be gained in the etiology and prevention of learning disabilities and of those disorders, such as attention deficit/hyperactivity disorder and autism, whose prevalence might be increasing.

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