The Neuropsychology of Childhood Lead Poisoning

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Lead, documented as toxic for literally millennia, is above all a child's poison. Due to the manner in which it is absorbed and distributed in the body as well as the particulars of its toxic mechanisms, lead is a poison that targets the developing brain of children. The present review discusses the reasons for this exquisite sensitivity as well as the behavioral effects of lead, how these effects are best measured and the long-term outlook for the poisoned child.

Toxic Mechanisms[3]

The toxicokinetics of lead are complex [4,,5,6,7,8.] The primary routes of lead absorption are via respiration and ingestion; cutaneous absorption is negligible. Absorbed lead is cleared by the kidneys in the urine and unabsorbed lead is eliminated in the feces. Absorbed lead travels throughout the body in the blood with the major burden (~95%) carried by erythrocytes and the remainder, that most accessible to other tissues, in the plasma. Lead enters all of the other tissues of the body following the distribution of calcium. The half life of lead in blood approximates that of the erythrocyte (i.e. about 35 days) while in brain its about 2 years and in bone decades. For this reason, blood lead levels[9], the most common method for establishing degree of exposure in childhood lead poisoning, is primarily an indicator of recent exposure. However, it should be noted that due to the complex toxicokinetics of lead, wherein stored lead from soft tissues or

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[3]Lead has such diverse toxic effects that a comprehensive review is beyond the scope of this paper; the next section presents an overview of lead's influences on the brain. The interested reader is referred to more detailed reviews by Bressler and Goldstein, 1991 (4), Silbergeld 1992 (5), and Anderson et al., 1996 (6).

[4]Bressler JP, Goldstein GW. Mechanisms of lead neurotoxicity. *Biochemical Pharmacology*, 1991, 41: 479-484.

[5]Silbergeld EK. Mechanisms of lead neurotoxicity, or looking beyond the lamppost. *The FASEB Journal*, 1992, 6: 3201-3206

[6]Anderson AC, Pueschel SM, Linakis JG. Pathophysiology of lead poisoning. In Pueschel SM, Linakis JG, Anderson AC. *Lead Poisoning in Children.* PH Brookes Publ. Co., Baltimore, MD, 1996, pp. 75-96.

[7]Hartman DE. *Neuropsychological Toxicology, Second Edition*, Plenum Press, New York, 1995, 95-125.

[8]Leggett RW. An age-specific kinetic model of lead metabolism in humans. *Environmental Health Perspectives*, 1993, 101: 598-616.

[9] Blood-lead levels in people are most usually reported in μg/100 ml (i.e. μg/dl) although μg/l and μmol/l have also been used.

bone can re-enter the circulation due to a variety of factors (e.g. bone resorption during pregnancy; *vide infra)*, blood lead levels can also vary due to mobilization of internal lead stores.

At present, the primary source of lead exposure for the majority of children, is through inhalation and ingestion of dust inside the house from deteriorating paint and outside from soil contaminated by deteriorating external paint and, to some extent, the residue of leaded gasoline. Toddlers, because they are closer to the floor where lead dust settles, are most exposed to the sources of lead and are most likely to breathe in lead dust. In addition, because they engage in many hand to mouth activities are also more likely to ingest lead dust. Children absorb a greater proportion of lead than adults, retain more and deposit more of the retained lead in the brain.

Lead has direct toxic effects on neurons including influences on neurotransmitter storage and release processes, mitochondria and second messengers. While there is no single unifying mechanism that explains the multiplicity of lead's actions, interactions with physiological functions involving calcium is a factor common to many of these toxic actions (although there is evidence that lead may also substitute for zinc[10]). For example, lead enters into brain cells, both neurons and glia, by channels that under normal conditions allow the passage of calcium ions[11,12]. Lead accumulates in and damages mitochondria[13], the organelle in brain cells responsible for energy metabolism. Lead enters mitochondria via the cellular mechanism that normally functions to bring calcium into this organelle[14], disrupts normal functioning and cellular energy metabolism decreases. Under conditions of decreased energy metabolism, ordinarily benign synaptic transmission mediated by the neurotransmitter glutamate is transformed into a neuron killing process called excitoxicity[15]. Lead also binds to sites within the mitochondria normally occupied by calcium and initiates a sequence of events that kills the host neuron via programmed cell death[16]. In addition, lead can kill neurons by either directly or indirectly producing oxidative

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[10]Bressler JP, Goldstein GW. Mechanisms of lead neurotoxicity. *Biochemical Pharmacology*, 1991, 41: 479-484.

[11]Kerper LE, Hinkle PM. Cellular uptake of lead is activated by depletion of intracellular calcium stores. *Journal of Biological Chemistry*, 1997, 272: 8346 - 8352.

[12]Legare ME, Barhoumi R, Herbert E, Bratton GR, Burghardt RC, Tiffany-Castiglioni E. Analysis of Pb2+ entry into cultured astroglia. *Toxicological Sciences*, 1998, 46: 90-100

[13]Kerper LE, Hinle PM. Lead uptake in brain capillary endothelial cells: activation by calcium store depletion. *Toxicology and Applied Pharmacology*, 1997, 146: 127-133.

[14]Chavez E, Jay D, Bravo C. The mechanism of lead-induced mitochondrial Ca2+ efflux. *Journal of Bioenergetics and Biomembranes*, 1987, 19: 285-295.

[15]Beal MF, Brouillet E, Jenkins BG, Ferrante RJ, Kowall NW, Miller JM, Storey E, Srivastava R, Rosen BR, Hyman BT.Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. *Journal of Neuroscience*, 1993, 13:4181-92.

[16]He L, Poblenz AT, Medrano CJ, Fox DA. Lead and calcium produce rod photoreceptor cell apoptosis by opening the mitochondrial permeability transition pore. *Journal of Biological Chemistry*, 2000, 275: 12175-12184.

stress[17],[18],[19].

In addition to its potentially lethal effects on neurons, lead also alters cellular regulatory processes and thereby causes abnormal functioning of surviving brain cells. For example, lead substitutes for calcium in affecting the activity of second messengers, a class of intracellular agents (e.g. proteins) that are crucial to orchestrating the myriad of cellular processes that allow normal neuronal functioning. Second messengers are regulated by neurotransmitter actions that result from synaptic transmission between neurons. When the neurotransmitter is released into the synapse, it binds to its receptor thereby triggering a flow of ions (most typically calcium - Ca^{2+}) that bind to the second messenger. As a result, the second messenger becomes functional and initiates the repertoire of biochemical reactions within its purview. The actions of second messengers control a vast array of biological processes including those necessary for cell survival, for the growth and differentiation of developing neurons, and for response plasticity intrinsic to learning and memory.

Lead, at lower (nanomolar) concentrations[20], substitutes for calcium in activating the second messenger calmodulin while, at higher concentrations, appears to reduce activity[21]. Lead's activating effects on calmodulin perturbs intracellular calcium homeostasis[22], an effect with potential disruptive influences on the multiplicity of calcium mediated processes intrinsic to normal cellular activity. Protein kinase C (PKC), another second messenger that is affected by lead, participates 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

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[17]Antonio MT, Copras I, Leret ML. Neurochemical changes in newborn rat's brain after gestational cadmium and lead exposure. *Toxicological Letters*, 1999, 104: 1-9.

[18]Shukla GS, Hussain T, Chandra SV. Possible role of regional superoxide dismutase activity and lipid peroxide levels in cadmium neurotoxicity: in vivo and in vitro studies in growing rats. *Life Sciences*, 1987, 41: 2215 - 2221.

[19]Villeda-Hernandez J, Barroso-Moguel R, Méndez-Armenta M, Nava-Ruíz C, Huerta-Romero R, Ríos C. Enhanced brain regional lipid peroxidation in developing rats exposed to low level lead acetate. *Brain Research Bulletin*, 2001, 55: 247 - 251.

[20]Concentrations are described in different ways in clinical and research work. Lead concentrations, in blood testing of children, is indicated in micrograms (millionths of a gram) of lead per deciliter (tenth of a liter) of blood. Often in research, concentrations are also expressed in molar concentrations corresponding to milecular or formular weight per liter of solvent. Ten micrograms per deciliter corresponds to a 0.48 micromolar (millionths of a molar) solution.

[21]Kern M, Audesirk G. Stimulatory and inhibitory effects of inorganic lead on calcineurin. *Toxicology*, 2000 150: 171-178.

[22]Ferguson C, Kern M, Audesirk G. Nanomolar concentrations of ionorganic lead increase Ca^{2+} efflux and decrease intracellular free Ca^{2+} ion concentrations in cultured rat hippocampal neurons by a calmodulin-dependent mechanism. NeuroToxicology, 2000, 21: 365-378.

may be involved in memory and learning[23,24]. In *in vitro* studies, acute administration of picomolar concentrations of lead activates PKC, an action normally induced by nanomolar concentrations of calcium[25,26]. With chronic administration of lead *in vivo*, there was reduced expression of PKC in the hippocampus[27].

Lead directly interferes with the ability of neurons to communicate with each other both by decreasing activity dependent release of neurotransmitters and conversely increasing spontaneous release. This effect is seen with amino acid neurotransmitters (glutamate and GABA) acetylcholine and dopamine[24,25,28,29]. While the mechanism(s) for these effects is not known, lead affects presynaptic Ca^{2+} channels[28,29] involved in transmitter release and has a a variety effects on synaptic mechanisms and structures[30].

In addition to affecting neurotransmitter storage and release, lead also alters neurotransmitter receptors, the site on the neuronal membrane where transmitters bind during synaptic

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[23]Bressler JP, Goldstein GW. Mechanisms of lead neurotoxicity. *Biochemical Pharmacology*, 1991, 41: 479-484.

[24]Silbergeld EK. Mechanisms of lead neurotoxicity, or looking beyond the lamppost. *The FASEB Journal*, 1992, 6: 3201-3206.

[25]Bressler J, Kim KA, Chakraborti T, Goldsten G. Molecular mechanisms of lead neurotoxicity. *Neurochemical Research*, 1999, 24: 595-600.

[26]Goldstein GW. evidence that lead acts as a calcium substitute in second messenger metabolism. *NeuroToxicology*, 1993, 14: 97-101.

[27]Nihei MK, McGlothan CD, Toscano D, Guilarte TR. Low level Pb^{2+} exposure affects hippocampal protein kinase Cδ gene and protein expression in rats. *Neuroscience Letters*, 2001, 298: 212-216.

[28]Devoto P, Flore G, Ibba A, Fratta W, Pani L. Lead intoxication during intrauterine life and lactation but not during adulthood reduces nucleus accumbens dopamine release as studied by brain microdialysis. *Toxicology Letters*, 2001, 121: 199 - 206.

[29]Lasley SM, Green MC, Gilbert ME. Influence of exposure period on *in vivo* hippocampal glutamate and GABA release in rats chronically exposed to lead. *NeuroToxicology*, 1999, 20: 619-630.

[30]Jabłońska L, Walski M, Rafałowska U. Lead as an inductor of some morphological and functional changes in synaptosomes from rat brain. *Cellular and Molecular Neurobiology*, 1994, 14: 701-709. Regunathan S, Sundaresan R. Effects of organic and inorganic lead on synaptosomal uptake, release and receptor binding of glutamate in young rats. *Journal of Neurochemistry*, 1985, 44: 1642-1646.Bettaiya R, Yallapragada PR, Hall E, Rajanna S. *In vitro* effect of lead on Ca^{2+}-ATPase in synaptic plasma membranes and microsomes of rat cerebral cortex and cerebellum. *Ecotoxicology and Environmental Safety*, 1996, 33: 157-162. Bouton CMLS, Frelin LP, Forde LP, Godwin HA, Pevsner J. Synaptotagmin I is a molecular target for lead. *Journal of Neurochemistry*, 2001, 76: 1724-1735. Gillis KD, Mossner R, Neher E. Protein kinase C enhances exocytosis from chromaffin cells by increasing the size of the readiliy releasable pool of secretory granules. *Neuron*, 1996, 16: 1209 - 1220.

transmission. One important target of lead's disruptive influences are glutamate receptors[31]. Hippocampal long-term potentiation and depression, a form of response plasticity dependent on normal glutamatergic functioning, is also disrupted by chronic lead administration[32]. Lead also has disruptive effects on dopamine receptors with the D_2 receptor subtype most vulnerable[33].

Lead also has negative effects on other cells in the brain that are important to normal brain functioning. Lead had cytotoxic effects on both oligodendrocytes, the cells that generate myelin, and astrocytes, cells involved in supportive functions that include clearance of amino acid transmitters. Although both types of glia cells are affected, oligodendrocytes are far more vulnerable[34]. In *in vitro* experiments, oligodendoglia progenitors were more sensitive than cultures of mature oligodendrocytes[35].

Lead exposure delayed the differentiation of progenitors[35] and, *in vivo*, causes hypo- and demyelination[36]. Lead also accumulates in astroglia to produce concentrations that far exceed those found in neurons. Mature astrocytes took up less lead than did immature astrocytes[37]. Lead also affects the cerebrovascular endothelial cells that constitute the blood brain barrier

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[31]McCoy L, Richfield EK, Cory-Slechta DA. Regional decreases in alpha-[^{3}H]amino-3hydroxy-5-methylisooxazole-4-propionic acid ([^{3}H]AMPA) and 6-[^{3}H]cyano-7-nitroquinoxaline-2,3-dione ([^{3}H]CNQX binding in response to chronic low-level lead exposure: reversal versus potentiation by chronic dopamine agonist treatment. *Journal of Neurochemistry*, 1997, 69: 2466-2476. Lasley SM, Green MC, Gilbert ME. Rat hippocampal NMDA receptor binding as a function of chronic lead exposure level. *Neurotoxicology and Teratology*, 2001, 23: 185-189. Guilarte TR. Pb^{2-} inhibits NMDA receptor function at high and low affinity sites: developmental and regional brain expression. *NeuroToxicology*, 1997, 18: 43-52.

[32]Gilbert ME, Mack CM, Lasley SM. Chronic developmental lead exposure increases the threshold for long-term potentiation in rat dentate gyrus in vivo. *Brain Research*, 1996, 736: 118-124. Sui L, Ruan D-Y, Ge S-Y, Meng X-M. Two components of long-term depression are impaired by chronic lead exposure in area CA1 and dentate gyrus of rat hippocampus in vitro. *Neurotoxicology and Teratology*, 2000, 22: 741-749.

[33]Scortegagna M, Hanbauer I. The effect of lead exposure and serum deprivation on mesencephalic primary cultures. *NeuroToxicology*, 1997, 18: 331-340. Widzowski DV, Finkelstein JN, Pokora MJ, Cory-Slechta DA. Time course of postnatal lead-induced changes in dopamine receptors and their relationship to changes in dopamine sensitivity. *NeuroToxicology*, 1994, 15: 853-866.

[34]Tang HW, Yan HL, Hu XH, Shen XY. Lead cytotoxicity in primary cultured rat astrocytes and Schwann cells. *Journal of Applied Toxicology*, 1996, 16: 187-196.

[35]Deng W, McKinnon RD, Poretz RD. Lead exposure delays the differentiation of oligodendroglia progenitors *in vitro*. *Toxiology and Applied Pharmacology*, 2001, 174: 235-244.

[36]Coria F, Berciano MT, LaFarga M. Axon remodeling in the lead-induced demyelinating neuropathy of the rat. *Brain Research*, 1984, 291: 369-372.

[37]Lindahl LS, Bird L, Legare ME, Mikeska G, Bratton GR, Tiffany-Castiglioni E. Differential ability of astroglia and neuronal cells to accumulate lead: dependence on cell type and degree of differentiation. *Toxicological Sciences*, 1999, 50: 236 - 243.

(BBB). The BBB prevents certain substances that are in the general circulation from gaining access to the uniquely sensitive cells of the brain. Lead freely passes through the BBB into the brain due in large part to its unfortunate ability to substitute for calcium ions. Calcium is actively transported into the brain via a biological "pump". Lead uses this same mechanism to gain access to the brain by readily substituting for calcium ions[38]. In addition to passing through the BBB via mechanisms designed to transport calcium, lead also damages this barrier by accumulating in mitochondria in the cellular constituents of the BBB in the same areas as calcium, an effect the authors suggest "...may be associated with lead-induced disruptions in intracellular calcium metabolism and transepithelial transport processes." [39]

In addition to its direct neurotoxic actions, lead also has deleterious influences on brain function that are exerted indirectly. Lead, at levels at least as low as 10 μg/dl, has disruptive effects on the synthesis of heme causing increases in the levels of the precursor δ-aminolevulinic acid (ALA). ALA interferes with neurotransmission mediated by the transmitter GABA[40]. By interfering with heme synthesis and by decreasing iron absorption from the gut[39] , lead also produces anemia. Both iron deficiency and iron deficiency anemia can be associated with impaired cognitive and neuropsychological development[41].

Another indirect effect of lead on the brain is via disruption of thyroid hormone transport into the brain. Thyroid hormones are critical to the normal development of the brain with deficiencies resulting in irreversible morphological, biochemical and electrophysiological dysfunctions that, in the extreme, produce cretinism. Several lines of evidence suggest that transthyretin, synthesized in the choroid plexus, is fundamentally involved in the transport of thyroid hormones into the brain[42]. The choroid plexus "...accumulates lead (Pb) to an extraordinary degree following Pb exposure" resulting in decreases of transthyretin levels[41].

The preceding overview of lead's multiple toxic effects has several implications for understanding the prognosis of the lead poisoned child. Certainly, the effects of lead on second messengers, transmitter release, transport of thyroid hormone, and other actions previously

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[38]Bradbury MW, Deane R. Permeability of the blood-brain barrier to lead. *Journal of Neurotoxicology*, 1993, 14: 131-136. Kerper LE, Hinkle PM. Lead uptake in brain capillary endothelial cells: activation by calcium store depletion. *Journal of Toxicology and Applied Pharmacology*, 1997, 146: 127-133.

[39]Silbergeld EK, Wolinsky JS, Goldstein GW. Electron probe microanalysis in isolated brain capillaries poisoned with lead. *Brain Research*, 1980, 12: 369-376.

[40]Anderson AC, Pueschel SM, Linakis JG. Pathophysiology of lead poisoning. In Pueschel SM, Linakis JG, Anderson AC. *Lead Poisoning in Children.* PH Brookes Publ. Co., Baltimore, MD, 1996, pp. 75-96

[41]Briner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomized study of cognitive effects of iron supplementation in non-anemic iron-deficient adolescent girls. *Lancet*, 1996, 12: 992-996. Grantham-McGregor S, Ani C. A review on the effect of iron deficiency on cognitive development in children. *Journal of Nutrition*, 2001, 131: 649S-666S.

[42]Zheng W, Lu Y-M, Lu G-Y, Zhao Q, Cheung O, Blaner WS. Transthyretin, thyroxine, and retinol-binding protein in human cerebrospinal fluid: Effect of lead exposure. *Toxicological Sciences*, 2001, 61: 107-114.

described alter normal neuronal development, effects manifest in, for example, volumetric changes in the developing hippocampus[43] and morphological changes in the developing cortex[44] of lead exposed rats as well as decreased dendritic branching of cerebellar Purkinje cells in postnatally exposed kittens[45]. These effects on development establish the basis for cognitive impairments in lead exposed children while specific effects on glutamatergic transmission, critically involved in both development and also neuronal plasticity, presage learning and memory impairments. Disruption of dopaminergic functioning, normally involved in not only motor control but also attention, memory and executive functioning[46], can produce a host of behavioral problems including ADHD as well as cognitive impairments. Review of the clinical literature (*vide infra*) amply demonstrates that the unfortunate expectations based on the consideration of lead's toxic mechanisms are fulfilled by the findings from studies of neuropsychological functioning in lead exposed children.

In addition, many of the toxic effects of lead on the brain's regulatory systems occur at concentrations far lower than the CDC's currently acknowledged threshold for poisoning. That level, 10 μg/dl, corresponds to a 0.48 micromolar concentration. However, lead affects calmodulin[47] and synaptotagmin I[48], a protein intimately involved in neurotransmitter release, at nanomolar concentrations and PKC at picomolar concentrations (51)[49]. In addition, effects taking place at higher concentrations, in the micromolar range, are not ruled out with blood-lead levels <10 μg/dl since active transport mechanisms regularly increase central concentrations of various ions, including Ca^{2+} and presumably Pb^{2-}, to levels that far exceed that in the systemic circulation.

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[43]Slomianka L, Rungby J, West MJ, Danscher G, Andersen AH. Dose-dependent bimodal effect of low-level lead exposure on the developing hippocampal region of the rat: a volumetric study. *NeuroToxicology*, 1989, 10: 177-190.

[44]Wilson MA, Johnston MV, Goldstein GW, Blue ME. Neonatal lead exposure impaired development of rodent barrel field cortex. *Proceedings of the National Academy of Sciences*, 2000, 97: 5540-5545.

[45]Patrick GW, Anderson WJ. Dendritic alterations of cerebellar Purkinje neurons in postnatally lead-exposed kittens. *Developmental Neuroscience*, 2000, 22: 320-328.

[46]Brown, L., Schneider, J.S., Lidsky, T.I. Sensory and cognitive functions of the basal ganglia. *Current Opinions in Neurobiology*, 1997, 7: 157-163.

[47]Kern M, Audesirk G. Stimulatory and inhibitory effects of inorganic lead on calcineurin. *Toxicology*, 2000 150: 171-178.

[48]Bouton CMLS, Frelin LP, Forde LP, Godwin HA, Pevsner J. Synaptotagmin I is a molecular target for lead. *Journal of Neurochemistry*, 2001, 76: 1724-1735.

[49]A nanomole is a thousandth of a micromole and a picomole is a millionth of a micromole.

The studies of lead's effects on the developing brain also identify the immature neurons and glial cells as the cellular elements most vulnerable to toxic effects. Human brain development continues far into the postnatal period continuing at least into the teenage years and perhaps beyond. The basic toxicology of lead indicates that lead poisoning anytime during this period will have negative consequences on brain functioning. In addition, since different parts of the brain mature at different ages, lead will damage different systems as a function of when poisoning begins and how long toxicity lasts. Thus, lead poisoning can produce a different pattern of behavioral effects in children poisoned at different ages or for different durations.

Lead and Pregnancy

Lead is a neurotoxin that can carry a lethal legacy. Young women who live in lead contaminated housing or who were lead poisoned themselves as youngsters can pass lead on to their unborn fetuses. There is a strong correlation between maternal and umbilical cord blood lead levels indicating the transfer of lead from mother to fetus[50]. Lead accumulates and is stored in bone for decades and these bone lead stores may pose a threat to women of reproductive age long after their exposure to lead has ended. Lead in maternal plasma appears to derive in large part from maternal bone lead stores. In some studies, the contributions from endogenous (bone) and exogenous (environmental) sources on maternal blood lead levels were about equal[51], while others suggest that skeletal lead stores are the dominant contributor to blood lead during pregnancy and the postpartum period[52]. When cumulative lead release (lead flux in micrograms) mobilized from the skeleton during pregnancy and the postpartum period was measured, results implied a high skeletal turnover of greater than 10% and possibly greater than 30% in some subjects during pregnancy and the postpartum period[52]. In addition to transfer of lead prenatally, lead levels in breast milk also increase with lead level in maternal blood, posing an additional risk to the neonate[53]. In pregnant women with low exposure to lead, high intakes of calcium (>2,000 mg/day) decreased serum lead concentration, potentially minimizing the fetal exposure. High calcium intake may attenuate pregnancy-induced increases in maternal blood lead concentrations by decreasing maternal bone resorption or demineralization during pregnancy and the subsequent release of lead from the bone[53].

The mobilization of bone lead stores in pregnant and postpartum women is particularly

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[50]Gardella, C. Lead exposure in pregnancy: a review of the literature and argument for routine prenatal screening. Obstetrical and Gynecological Survey, 2001, 56: 231-238.

[51]Chuang, H.Y., Schwartz, J., Gonzales-Cossio, T., Lugo, M.C., Palazuelos, E., Aro, A., Hu, H. and Hernandez-Avila, M Interrelations of lead levels in bone, venous blood, and umbilical cord blood with exogenous lead exposure through maternal plasma lead in peripartum women. Environmental Health Perspectives, 2001, 109: 527-532.

[52]Gulson, B.L., Pounds, J.G., Mushak, P., Thomas, B.J., Gray, B., and Korsch, M.J. Estimation of cumulative lead release (lead flux) from the maternal skeleton during pregnancy and lactation. J. laboratory & Clin. Med., 1999, 134: 631-640.

[53]Johnson, M.A. High Calcium intake blunts pregnancy-induced increases in maternal blood lead. Nutrition Reviews, 2001, 59: 152-156.

troublesome in view of the experimental literature demonstrating that exposure to lead during pregnancy and lactation (approximately 40 μg/dl in blood of pregnant dams) induced hyperactivity, decreased exploratory behavior, and impairment in learning and memory in weaned rats, and anxiety in adult rats[54]. Behavioral alterations were observed in weaned rats at blood levels comparable to those that may be attained in lead-exposed children (approximately 20 μg/dl) and in adult rats with no detectable blood lead levels. These data demonstrate that lead transferred from mother to offspring may have serious and long-lasting effects on behavior. Work in children indicates that deleterious effects on cognitive development occur with placental blood-lead levels below 10μg/dl[55].

The Behavioral Effects of Lead Poisoning

The symptoms of severe lead poisoning in children initially include lethargy, abdominal cramps, anorexia and irritability. Over a period of weeks, or days in children younger than 2 years of age, there is progression to vomiting, clumsiness, ataxia ultimately to alternating periods of hyperirritability and stupor and then finally coma and seizures. This syndrome is typically associated with blood-lead levels of ≥70 μg/dl although it can occur in some children at levels of 50 μg/dl[56].

Lower blood-lead levels, while not usually associated with potentially fatal encephalopathy, are also, neurotoxic in children and have lasting effects on neurobehavioral functioning as described below. Lead poisoning from these lower levels of exposure is far more common and is particularly insidious due to its lack of diagnostically definitive physical signs. Some children complain of stomach pains and loss of appetite and may or may not have anemia. However such symptoms are not present in all poisoned children, or even the majority, and in any case, do not unequivocally point to lead as the culprit. Indeed, such poisoning is often termed "asymptomatic" due to the lack of clear physical symptoms. Unfortunately such poisoning is not "asymptomatic" with respect to its effects on brain functioning.

The unique involvement of the brain in lead's toxic effects in children was recognized in the earliest studies of pediatric poisoning. In 1897, Chvostek (described in McKann & Vogt[57]), in reporting the post-mortem examination of a young girl who had died of lead poisoning, described swelling of the brain with effacement of the gyri and reduction in the size of the ventricles. That children were more likely than adults to be severely poisoned by lead and to develop

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[54]Moreira, E.G., Vassilieff, I., and Vasilieff, V.S. Developmental lead exposure: behavioral alterations in the short and long term. Neurotoxicol. And Teratol., 2001, 23: 489-495.

[55]Bellinger DC. Effect modification in epidemiological studies of low-level neurotoxicant exposures and health outcomes. *Neurotoxicology and Teratology*, 2000, 22: 133-140.

[56]Adams AD, Victor M. *Principles of Neurology, 5th Edition*, McGraw-Hill, NY, 1993.

[57]McKann CF, Vogt EC. Lead poisoning in children. *Journal of the American Medical Association*, 1933, 101: 1131-1135.

encephalopathy was also recognized early on as was the fact that those children who survived lead encephalopathy were highly likely to suffer permanent cognitive sequelae most commonly in the form of mental retardation. In 1943, a paper by Byers and Lord[58] drew attention to the neurotoxicity and lasting cognitive aftereffects seen in children who survived lead poisoning without persisting overt neurological signs.

In the years following publication of the Byers and Lord study, considerable efforts have been directed at measuring the cognitive effects of lead exposure at levels below those that produce overt signs of encephalopathy. The major goal of much of this work has been to describe the nature of lead's effects on cognition and also to determine what levels of lead exposure are presumptively safe.

Lead exposed children have been evaluated in both cross sectional and longitudinal studies with the results of traditional intelligence testing, that is IQ, the typical behavioral endpoint[59]. IQ was chosen for studies of lead's effects in children because of its strong psychometric properties and also because it "...is sufficiently well standardized to be comparable across studies, and exhibits attractive simplicity for the regulator in a public health context."[60] The generally agreed upon finding from this research is that with post-natal exposure, there is an inverse relationship between IQ and blood-lead level. The magnitude of this effect has been the subject of some dispute (e.g. [60,61]) though a 1 to 3 IQ point decrement in Full Scale IQ with an increase in blood lead from 10 to 20 μg/dl has been found with some regularity and decrements of 5 to 10 IQ points with moderate levels of exposure (up to 30 μg/dl)[62].

Although at first blush, the size of the lead-induced decrement does not appear impressive, the limitations of the studies of lead's effects on IQ must be considered. The children studied have

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[58]Byers R, Lord E. Late effects of lead poisoning on mental development. *American Journal of Diseases of Children*, 1943, 66: 471-494.

[59]This contentious and, in part, contradictory literature is only briefly summarized; the interested reader is addressed to several recent reviews (e.g.[60]) for more detailed information concerning lead and IQ.

[60]Winneke G, Krämer U. Neurobehavioral aspects of lead neurotoxicity in children. *Centr. Eur. J. Publ. Health*, 1997, 2: 65-69.

[61]Tong S, Baghurst P, McMichael A, Sawyer M, Mudge J. Lifetime exposure to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort study. *British Medical Journal* 1996, 312: 1569-1575. Dietrich KN, Berger OG, Succop PA, Hammond PB, Bornschein RL. The developmental consequences of low to moderate prenatal and post natal lead exposure: intellectual attainment in the Cincinnati lead study cohort following school entry. *Neurotoxicology and Teratology*, 1993, 15: 37-44.

[62]Wasserman GA, Musabegovic A, Liu X, Kline J, Factor-Litvak P, Graziano JH. Lead exposure and motor functioning in 4½-year-old children: The Yugoslavia prospective study. *The Journal of Pediatrics*, 2000, 137: 555-561.

differed in a variety of characteristics including nationality and socieoeconomic status[63] and the methods of measuring exposure have also differed, yet the qualitative outcome has been generally consistent. In addition, these studies only report group averages "...which applies to the individual child only in a probabilistic sense ...even small average effects, due to the normal variability of individual susceptibility, will be associated with larger IQ deficits in individual cases of particular susceptibility."[60]

Most impressive, however, is the relative consistency of the lead/IQ findings despite the fact that intelligence tests, under many conditions, are not particularly sensitive to the effects of brain injury.

IQ is most typically determined by use of one of the Wechsler tests[64] although other tests, such as the McCarthy Scales or Stanford-Binet have also been used. Each however suffers from the same disadvantages with respect to assessing brain injury. In each of these tests, IQ or its equivalent is determined based on the child's overall performance on a battery of subtests that assess multiple and often unrelated functions. For example, the Wechsler Intelligence Scale for Children, Third Edition (WISC-III) is made up of 5 subtests (Information, Similarities, Arithmetic Vocabulary and Comprehension) that contribute to a Verbal IQ (VIQ) and 5 subtests (Picture Completion, Coding, Picture Arrangement, Block Design, and Object Assembly) that contribute to a Performance IQ (PIQ); Full Scale IQ (FSIQ) is determined based on a combination of Verbal and Performance subtest scores.

Brain injury, whether from trauma, hypoxia or from toxic exposures, frequently affects functioning in a limited number of neurobehavioral systems. For example it is not unusual when evaluations of brain injured patients reveal deficits affecting only circumscribed aspects of language (e.g. object naming) or specific memory functions (e.g. working memory only) leaving other aspects of memory (procedural, semantic, episodic) as well as other cognitive functions intact. Intelligence test batteries, wherein global outcome measures reflect the aggregate performance of multiple functions, are unlikely to be sensitive to such injuries. The effect of poor performance on one subtest will have little impact on the composite IQ.

In addition, there is no guarantee that brain injury can always be detected by examining

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[63]Rabin R. Warnings unheeded: a history of child lead poisoning. *American Journal of Public Health*, 1989, 79: 1668-1674. Byers R, Lord E. Late effects of lead poisoning on mental development. *American Journal of Diseases of Children*, 1943, 66: 471-494. Dietrich KN, Berger OG, Succop PA, Hammond PB, Bornschein RL. The developmental consequences of low to moderate prenatal and post natal lead exposure: intellectual attainment in the Cincinnati lead study cohort following school entry. *Neurotoxicology and Teratology*, 1993, 15: 37-44. Wasserman GA, Musabegovic A, Liu X, Kline J, Factor-Litvak P, Graziano JH. Lead exposure and motor functioning in 4½-year-old children: The Yugoslavia prospective study. *The Journal of Pediatrics*, 2000, 137: 555-561.

[64]The Wechsler Intelligence Scale for Children, Revised (WISC-R) or Wechsler Intelligence Scale for Children, Third Edition (WISC-III) for the ages of 6 years to 16 years, 11 months and the Wechsler Primary and Preschool Scale of Intelligence - Revised for children aged 3 years to 7 years 3 months.

individual subtest scores. Not only do each of the IQ scores represent the average outcome of subtests that assess multiple and often unrelated functions, some of the subtests themselves measure multiple and unrelated functions. For example, the Coding subtest requires the child, if 6 to 7 years of age, to fill in a series of geometric figures (i.e. star, circle, triangle, cross and square) as quickly as possible with specific marks (a circle or 1 or 2 vertical or horizontal lines) according to a key that is on the top of the answer page; *viz.* stars are marked with a single vertical line, circles with 2 horizontal lines, etc. Older children are required to mark each of the numbers 1 through 9 with a unique symbol as quickly as possible again according to a key that is on the top of the answer page. The numeral 1 is marked with a dot above a horizontal line, 2 is marked by a parentheses opening to the left, and so on. For children 6 to 7 and also for older children, the score on Coding is the total number of correct responses made in 2 minutes. Performance of Coding requires motor speed, dexterity, the ability to pay attention, and either rapid scanning, to enable the child to glance up to the answer key to identify the appropriate symbol for each figure, and/or working memory, to enable the child to remember the appropriate symbols from the answer key for each figure. Brain injury affecting working memory might not produce deficient performance on the Coding subtest if the patient either scans efficiently or has good motor speed. Conversely, damage that produces motor slowing can be compensated either by intact memory functioning and/or efficient scanning.

A recent case series graphically illustrates the insensitivity of IQ testing to the cognitive effects of brain injury[65]. Five children (mean age at surgery was 14 years, 1 month) underwent left temporal lobectomy for temporal lobe epilepsy. Each patient exhibited "...significant language-related cognitive declines after surgery...although VIQ dropped significantly in only one patient." Indeed, VIQ showed non-significant increases in 4 of 5 children. "Visual memory also declined in two left temporal lobectomy patients."

Lezak[66], in arguing against the use of IQ tests to assess cognitive functioning in brain injury, cites Teuber's[67] insightful remarks on the subject:

> "One must never misconstrue a normal intelligence test result as an indication of normal intellectual status after head trauma, or worse, as indicative of a normal brain: to do so would be to commit the cardinal sin of confusing absence of evidence with evidence of absence."

In contrast to intelligence test batteries, neuropsychological tests, designed to target more limited cognitive domains, are, in general, much more sensitive to the effects of brain damage and, in the case of lead's neurotoxicity, demonstrably so. The European Multicenter Study was a cross-sectional evaluation of the cognitive effects of lead exposure combining the results from

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[65]Dlugos DJ, Moss EM, Duhaime A-C, Brooks-Kayal AR. Language-related cognitive declines after left temporal lobectomy in children. *Pediatric Neurology,* 1999, 21: 444-449.

[66]Lezak, M. *Neuropsychological Assessment*, Oxford University Press, New York, 1995.

[67]Teuber, H-L. Neglected aspects of the post-traumatic syndrome. In Walker A, Caveness F, Critchley M (Eds.) The Late Effects of Head Injury. Springfield Il, CC Thomas, 1969.

individual study groups in Bulgaria, Denmark, Greece, Germany, Hungary, Italy, Roumania and Yugoslavia. In addition to IQ testing, neuropsychological tests were administered that assess visuomotor integration, information processing and reaction time. Although the usual 1 to 3 point decrease in IQ with an increase in blood lead from 10 to 20 μg/dl was found, more robust decreases were reported for the neuropsychological measures[68].

There have been a number of studies of lead's cognitive effects in which neuropsychological testing either was used in association with an IQ battery or as the primary behavioral endpoint. Unfortunately, unlike many of the recent IQ/lead exposure studies, there is little uniformity in the basic methods of different groups of investigators. Neuropsychological studies of lead's effects differ in such basics as the characteristics of the study group (e.g. socioeconomic status [SES], levels of exposure, age at testing), the methods for measuring lead exposure and also the choice of tests administered to the study groups. Following is a brief review of the major findings primarily focusing on those studies in which lead exposure was determined from blood samples. Although it is clear that elevated lead concentration in shed deciduous teeth indicates childhood exposure to lead, the quantitative relation between exposure levels based on tooth concentration and those on blood tests are uncertain[69].

Winneke and co-workers[70] investigated the effects of low-level lead exposure (mean 4.3 μg/dl, upper *95%* value 8.9 μg/dl) on cognitive functioning in a cohort of 6 to 7 year old children in Germany. The primary finding, at this low level of exposure, were deficits in a test of attention; tests of other aspects of cognition (visual perception, visual memory, finger tapping and reaction time) were unaffected. Stiles and Bellinger[71] investigated the effects of similar low levels of exposure (mean <8 μg/dl) in a group high SES children (mean age 9 years, 9 months) from the Boston area. A neuropsychological test battery was administered and performance correlated with blood-lead levels previously assessed at 6, 12, 18, 24 and 57 months as well as the time of neuropsychological testing. Although many aspects of performance were marginally correlated ($0.05 < p < 0.1$) with one or more previous blood-lead levels, a more limited set was significantly correlated. The latter group included the tendency to perseverate (repeat previous incorrect responses) seen in tests of rote verbal learning and also cognitive flexibility. In addition, there was an inverse relation between blood-lead level at 24 months and visuospatial constructional

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[68]Winneke G, Krämer U. Neurobehavioral aspects of lead neurotoxicity in children. *Centr. Eur. J. Publ. Health*, 1997, 2: 65-69. Winneke G, Brockhaus A, Collet W, Krämer U, Results from the European Multicenter Study on lead neurotoxicity in children: implications for risk assessment. *Neurotoxicology and Teratology*, 1990, 12: 553-559.

[69]Grobler SR, Theunissen FS, Kotze TJvW. The relation between lead concentrations in human dental tissues and in blood. *Archives of Oral Biology*, 2000, 45: 607-609.

[70]Walkowiak J, Altmann L, Krämer U, Sveinsson K, Turfeld M, Weishoff-Houben M, Winneke G. Cognitive and sensorimotor functions in 6 year old children in relation to lead and mercury levels: adjustment for intelligence and contrast sensitivity in computerized testing. *Neurotoxicology and Teratology*, 1998, 20: 511-521.

[71]Stiles KM, Bellinger DC. Neuropsychological correlates of low-level lead exposure in school-age children: a prospective study. *Neurotoxicology and Teratology*,1993, 15: 27-35.

ability. There were inverse relations between finger tapping performance, a measure of fine motor functioning, and prior lead exposure that were significant at some ages and marginal at others. Unfortunately this study did not include neuropsychological tests of attention.

Dietrich and co-workers[72] studied the effects of low to moderate lead exposure in the neonatal and postnatal period on motor development postulating that tests of movement "...are probably less confounded with social factors than cognitive and academic outcomes." The cohort, 6 year old children from the inner city in Cincinnati, was divided into quartiles based on exposure level with the mean of the first quartile 7.28 μg/dl (range 4.7-9), the second 10.59 μg/dl (range 9.13-12.3), the third 14.48 (range 12.39-16.7) and the fourth 22.00 μg/dl (range 16.72-38.15). Fine motor functioning was more affected than gross motor functioning at levels as low as 9 μg/dl. After adjustment for covariates, neonatal blood lead levels were inversely correlated with upper limb speed and dexterity while postnatal exposure was inversely correlated with bilateral coordination, upper limb speed, dexterity and visuomotor functioning.

Not surprisingly, higher levels of lead exposure are correlated with more severe neuropsychological impairments. Faust and Brown[73] administered a comprehensive battery of neuropsychological tests to a group of 5 to 12 year old children with previous blood lead levels in the range of 30 to 60 μg/dl. In comparison to unexposed matched controls, lead exposed children performed significantly worse on measures of fine motor functioning, language, verbal memory, higher order visuospatial functions and concentration.

Long-term follow-up studies of children who had been exposed to lead indicate that neuropsychological deficits, like changes in IQ, persist into adulthood. Stokes and colleagues[74] evaluated young adults (mean age 24.3 years) 20 years after their exposure to lead as children (9 months to 9 years of age). The exposed cohort grew up in a town with a lead smelter that was operating without emission reducing devices. The mean blood lead level for children in this locale was 50 μg/dl in 1974 and 39.6 μg/dl in 1975. Although blood-lead levels were only known for about 25 percent of the exposed cohort, it was 49.3 μg/dl. K x ray fluorescence of tibia lead content, a recognized measure of cumulative lead exposure, showed that the exposed group had significantly greater body burdens of lead than the matched controls. At the time of the current evaluation, blood-lead levels of both groups were low (exposed- 2.9 μg/dl, controls-1.6 μg/dl). The exposed group performed significantly worse on each test of cognitive functioning including assessments of reaction time, scanning and executive functioning (cognitive flexibility and abstract reasoning). With regard to motor functioning, although grip strength was unaffected, the lead-exposed group also performed poorly on tests fine motor

[72]Dietrich KN, Berger OG, Succop PA. Lead exposure and the motor developmental status of urban six-year-old children in the Cincinnati prospective study. *Pediatrics*, 1993, 91: 301-307.

[73]Faust D, Brown J. Moderately elevated blood lead levels: effects on neuropsychologic functioning in children. *Pediatrics*, 1987, 80: 623-629.

[74]Stokes L, Letz R, Gerr F, Kolczak M, McNeil FE, Chettle DR, Kaye WE. Neurotoxicity in young adults 20 years after childhood exposure to lead: the Bunker Hill experience. *Occupational and Environmental Medicine*, 1998, 55: 507-516.

functioning including eye-hand coordination, manual dexterity and finger tapping and, in addition, displayed postural instability. In addition to the cognitive and fine motor deficiencies reported by Stokes at al, also described were abnormalities of the peripheral nervous system including elevation of the vibrotactile thresholds of the fingers, but not the toes.

White et al[75] evaluated the neuropsychological functioning of a group of adults 50 years after they were hospitalized for lead poisoning at the age of 4 years or younger. Since accurate blood-lead analysis was not available between 1930 and 1942 when the study group was poisoned, indirect evidence was used to identify exposed individuals. Each person included in the exposure group had a history that provided evidence of exposure to lead (typically pica for leaded paint), a record of symptoms indicative of lead poisoning and also dense metaphyseal bands (lead lines) on x ray of at least one long bone. The type of physical symptoms seen during hospitalization for poisoning (e.g. vomiting, anorexia, hyper-irritability) are associated with blood-lead levels equal to or exceeding 60 μg/dl. When tested as adults, the lead exposed group had poorer performance on tasks of abstract reasoning, cognitive flexibility, verbal memory, verbal fluency and fine motor speed.

In addition to evaluation of effects on cognition, there has been increasing interest in the influences of early lead poisoning on subsequent social/emotional development. Studies of trends in population exposure to leaded paint and gasoline showed strong correlations with rates of violent crime and unwed pregnancy[76]. However, unlike studies of cognitive functioning in which standardized tests are available, investigations in this area are hampered by the lack of objective means of measuring social/emotional behavior. Mendelsohn et al[77] attempted to overcome this difficulty by using a standardized test battery, the Bayley Scales of Infant Development, to measure factors related to social/emotional functioning. Children, aged 12 to 36 months with lead levels $\leq$25 μg/dl were evaluated. In this age group, the Bayley Scales yields scores that are thought to measure an "Emotional Regulation Factor", associated with "hyperactive/distractible/easy frustration behaviors" an "Orientation-Engagement Factor", associated with "fear/withdrawal/disinterest behaviors and a "Motor Quality Factor" that measures "the appropriateness of movement and tone."[78] Children who had been exposed to lead scored significantly worse than non-exposed children in both the Emotional Regulation and also the Orientation-Engagement Factor. The authors suggested that these behavioral traits might be

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[75]White RF, Diamond R, Proctor S, Morey C, Hu H. Residual cognitive deficits 50 years after lead poisoning during childhood. *British Journal of Industrial Medicine*, 1993 50: 613-622.

[76]Nevin R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. *Environmental Research, Section A*, 2000, 83: 1-22.

[77]Mendelsohn AL, Dreyer BP, Fierman AH, Rosen CM, Legano LA, Kruger HA, Lim SW, Courtlandt CD. Low-level lead exposure and behavior in early childhood. *Pediatrics*, 1998, 101: E10

[78]Mendelsohn AL, Dreyer BP, Fierman AH, Rosen CM, legano LA, Kruger HA, Lim SW, Courtlandt CD. Low-level lead exposure and behavior in early childhood. *Pediatrics*, 1998, 101: E10

of particular significance "...in poor children, whose behavior might be adversely affected on the basis of other environmental factors."

Other studies have used behavioral check lists, completed on the basis of information provided by parents, teachers and the children themselves, to assess social/emotional effects of lead. In each of these studies, lead exposure is associated with increased reports of problems of conduct and behavioral adjustment[79]. Wasserman et al[80] suggest that while lead exposure is associated with increases in behavior problems, it's contribution is outweighed by the influences of other social factors. However, as also suggested by Mendelsohn et al[78] (*vide supra*), the effects of social factors and lead might be interactive rather than additive. Indeed, there is evidence that social factors affect the nature of the biological response to lead (see below - **Selective Vulnerability**).

Increases in problematic behaviors associated with lead exposure are caused by lead-induced brain damage together with secondary handicaps imposed by cognitive impairments. Brain injured children frequently experience a loss of confidence in response to the academic difficulties they experience due to cognitive deficiencies. Repeated reminders of one's inadequacies in comparison to peers, and nowhere is this more likely than in a classroom where testing allows letter grade ranking of abilities, ultimately often causes loss of self-esteem and poor social development.

Selective Vulnerability

A general principle of toxicology is that a variety of factors can either increase or decrease an individual's sensitivity to a toxin. As already discussed, several variables associated with normal development increase the vulnerability of young children to the neurotoxic effects of lead. However, in addition to changes accompanying maturation, there are other factors that more selectively affect the response of subgroups of children to lead exposure.

SES: One influence on vulnerability that has been attracting increasing attention is SES. A child's SES clearly affects the likelihood of exposure to lead. The Third National Health and Nutrition Examination Survey[81], that studied blood-lead levels in the U.S. population between 1988 and 1991, showed that 21% of children in the inner city had blood-lead levels equal to or greater than the CDC's maximal allowable level of 10μg/dl as compared to 5.8% of children in

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[79]Sciarillo WG, Alexander G, Farrell KP. Lead exposure and child behavior. *American Journal of Public Health*, 1992, 82: 1356-1360. Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB. Bone lead levels and delinquent behavior. *Journal of the American Medical Association*, 1996, 275: 363-369.

[80]Wasserman GA, Staghezza-Jaramillo B, Shrout P, Popovac D, Graziano J. The effect of lead exposure on behavior problems in preschool children. *American Journal of Public Health*, 1998, 88: 481-486.

[81]Brody, D.J., Pirkle, J.L., Kramer, R.A., Flegal, K.M., Matte, T.D., Gunter, E.W., Paschal, D.C. Blood levels in the U.S. population: Phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1991), *Journal of the American Medical Association*, 1994, 272: 277-283.

other areas. When stratified by income level, 16.3% of children from low income families had blood-lead levels ≥ 10μg/dl as compared to 5.4 and 4.0 percent of children from middle and high income families. However, in addition to the role of lower SES in increasing the probability of lead exposure, there is increasing recognition that the concomitants of poverty also enhance lead's neurotoxicity (e.g. Needleman et al[82]).

Since SES has an effect on certain components of standard intelligence tests and IQ was the behavioral endpoint in the first investigations of lead's effects on cognitive development, care has been taken, typically in the form of multiple regression or covariate analysis, to control for confounding influences. However, to consider SES simply as a confound might be underestimating its influence. Rutter hypothesized that economically disadvantaged children, because of a neuropsychological status rendered fragile by environmental influences, might be more vulnerable to the neurotoxic effects of lead[83]. Confirmatory evidence was found by Winneke and Kraemer[84]. 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. The authors concluded that, in the light of their data, "...the common practice of merely removing the effects of confounding factors, such as socioeconomic status, appears doubtful... In addition, some of the inconsistencies in this area of research might be due to differential sampling of subgroups of lead-exposed children characterized by different levels of psychosocial adversity."

More recently, similar findings were reported by Bellinger for prenatal lead exposure and similar conclusions drawn[85]. Three groups of infants, with umbilical cord blood-lead levels of either 3 μg/dl (low), 6-7 μg/dl (medium) and ≥10 μg/dl (high), were studied. Development was assessed at 6, 12, 18 and 24 months using the Bayley Scales of Infant Development, at 57 months using the McCarthy Scales of Children's Abilities and, at 10 years, using the Wechsler Intelligence Scale for Children, Revised. Through the first 24 months, children with high cord lead levels had lower scores on cognitive tests than the children in the medium and low exposure level groups. In addition, however, SES played a modulating role. At 24 months, children with lower SES seemed to be more affected by lead exposure performing more poorly on cognitive tasks than children with similar high cord lead levels but with higher SES. At younger ages, there was no effect of SES on the cognitive effects of lead exposure. Moreover, at medium levels of cord

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[82]Needleman HL, Schell A, Bellinger D, Leviton A, Allred EN. The long-term effects of exposure to low doses of lead in childhood: an 11 year follow-up report. *The New England Journal of Medicine*, 1990, 322: 83-88

[83]Rutter M. Low level lead exposure: sources effects and implications. In Rutter M, Russell-Jones (eds.) Lead Versus Health. Chichester, UK: John Wiley, 1983, pp 333-70.

[84]Winneke G, Kraemer U. Neuropsychological effects of lead in children: interactions with social background variables. *Biological Psychology/Pharmacopsychology*, 1984, 11: 195-202.

[85]Bellinger DC. Effect modification in epidemiological studies of low-level neurotoxicant exposures and health outcomes. *Neurotoxicology and Teratology*, 2000, 22: 133-140.

lead, only those children with lower SES were adversely affected by lead; children with medium cord lead but with higher SES were protected against the adverse effects of lead on cognition.

Although the mechanisms of the effect of SES on lead's neurotoxicity are not known, there are several concomitants of poverty that not only increase the likelihood of a child being exposed to lead, but also that, once exposed, more lead will be absorbed. Several poverty-related factors converge to increase the risk of lead poisoning for inner city children. While the use of lead paint in residential housing was banned by Consumer Product Safety Commission regulations in 1978, no provision was made to remove existing lead-based paint from houses constructed before this edict went into effect. Thus older houses have increased probability of having been painted with lead paint and a substantial number (estimated at 42-47 million) of such dwellings still exist[86]. Older houses tend to be concentrated in older urban centers where many economically disadvantaged families live. Leaded paint is particularly hazardous to children when it is deteriorating and producing lead-containing dust that is absorbed as a result of hand-mouth activities. The dangers of lead exposure are also increased by several dietary conditions that are more frequently present in economically disadvantaged children[87]. "...they are also more likely than children from wealthier homes to have a diet deficient in calcium, iron, protein, and/or zinc, deficiencies that increase the absorption of lead and may increase vulnerability to its adverse effects..."[88].

In addition to increasing lead absorption, dietary factors leading to calcium deficiency may also have the potential to increase the effect of lead on the brain. As described (see above), the endothelial cells of brain capillaries form tight junctions that contribute to the blood-brain barrier. Kerper and Hinkle[89] showed that in primary cultures of bovine brain capillary endothelial cells, lead uptake was activated by depletion of intracellular calcium stores. It has been hypothesized that increased uptake of lead kills capillary endothelial cells and thereby disrupts the blood-brain barrier[90].

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[86]Lin-Fu, J. Modern history of lead poisoning: a century of discovery and rediscovery. In *Human Lead Exposure*, (edited by H.L. Needleman), Boca Raton, FL, CRC Press, 1991, 23-43.

[87]Chisolm, JJ Jr. Medical Management. In Pueschel SM, Linakis JG, Anderson AC. *Lead Poisoning in Children.* PH Brookes Publ. Co., Baltimore, MD, 1996, pp. 141-162. Berney, B. Epidemiology of childhood lead poisoning. In *Lead Poisoning in Childhood.* (edited by S.M. Pueschel, J.G. Linakis, A.C. Anderson), Baltimore, MD, P.H. Brooks Publishing, 1996, 15-35.

[88]Berney, B. Epidemiology of childhood lead poisoning. In *Lead Poisoning in Childhood*, (edited by S.M. Pueschel, J.G. Linakis, A.C. Anderson), Baltimore, MD, P.H. Brooks Publishing, 1996, 15-35.

[89]Kerper LE, Hinkle PM. Cellular uptake of lead is activated by depletion of intracellular calcium stores. *Journal of Biological Chemistry*, 1997, 272: 8346 - 8352.

[90]Anderson AC, Pueschel SM, Linakis JG. Pathophysiology of lead poisoning. In Pueschel SM, Linakis JG, Anderson AC. *Lead Poisoning in Children.* PH Brookes Publ. Co., Baltimore, MD, 1996, pp. 75-96.

However, apart from enhancing the ease with which lead gains access to the brain, there is evidence that SES can increase the neurotoxic effects of a given level of lead once it is in the brain. Immediately post-weaning, 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. Conversely, lead-exposed rats raised in enriched environments performed similarly to their unexposed counterparts. Dietary considerations do not explain the differential sensitivity of the groups of rats since, apart from lead exposure, diet was identical[91].

There are a number of environmentally modulated factors that could affect the response of the brain to a neurotoxin such as lead. In the previously described study[91], lead-exposed rats in the impoverished environment had significantly decreased neurotrophic factor gene expression in the hippocampus while neurotrophic factor gene expression in rats raised in the enriched environment was relatively spared. Altered neurotrophic factor gene expression during development can lead to a number of aberrations in cell function, survival and connectivity. While impaired neurotrophic factor gene expression was found in the hippocampus, an area critical for learning and memory, it is likely that lead exposure affected neurotrophic factor gene in other areas as well.

Genetics: In addition to SES, another factor influencing the vulnerability of the brain to lead's neurotoxic effects is genetics. At least 3 genes have been identified that can influence the accumulation and toxicokinetics of lead in humans[92].

The ALAD gene, that codes for delta-aminolevulinic acid dehydratase, has been most heavily studied but, as yet, the consequences of the different alleles for vulnerability to lead poisoning are unclear. ALAD protein is an enzyme that catalyzes the condensation of 2 molecules of 5-aminolevulinic acid (ALA) to form porphobilinogen, the precursor of heme. Lead binds to ALAD, inhibiting its activity and leading to increased levels of non-condensed ALA, with neurotoxic properties in its own right.

ALAD2 has higher affinity for lead than does ALAD1 so that individuals with the ALAD 1-2 or ALAD 2-2 tend to have higher blood-lead levels than those with ALAD1-1[92]. However, whether ALAD2 increases vulnerability, by raising blood-lead levels, or decreases it, by keeping lead sequestered in the blood, is not known. Evidence suggestive of the latter was reported by Bellinger et al[93]. Attention and executive functioning was assessed in adolescents who had been exposed to lead as measured by tooth dentin levels. The subjects expressing the ALAD2

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[91]Schneider JS, Lee MH, Anderson DW, Zuck L, Lidsky TI. Enriched environment is protective against lead-induced neurotoxicity. *Brain Research*, 2001, 896: 48-55.

[92]Onalaja AO, Claudio L. Genetic Susceptibility to Lead Poisoning. *Environ. Health Perspectives* Vol 108. Suppl 1. March 2000

[93]Bellinger D, Hu H, Titlebaum L, Needleman HL. Attentional correlates of dentin and bone levels in adolescents. *Archives of Environmental Health*, 1994, 49: 98-105.

phenotype tended to have lower dentin lead levels than those with ALAD1 consistent with the idea that the increased affinity of the ALAD2 phenotype decreases the entry of lead from the blood into other tissues. Moreover, after correcting for exposure level, adolescents with the ALAD2 phenotype performed better in virtually all areas than those with ALAD1. Unfortunately, since there were only 5 individuals with the ALAD2 phenotype, the sample size precluded evaluation of statistical significance and these findings, while certainly indicating the need for additional research, are inconclusive.

The second gene, the Vitamin D receptor gene (VDR), is involved in Ca^{2+} absorption through the gut and into calcium rich tissues such as bone, particularly under conditions when Pb^{2+} levels are high enough to compete with the available Ca^{2+}. The blood borne variant of vitamin D binds to VDR's in the nuclei of intestinal cells, kidney and bone thereby activating genes that encode calcium binding proteins including calbindin-D. These proteins, involved in calcium transport, result in increased absorption of calcium and, if present, lead[94]. There are at least 2 alleles (b and B) and 3 variants of the VDR geneotype denoted as bb, BB and Bb. In occupationally exposed adults, individuals with the B allele had higher chelatable lead levels as well as higher lead levels in blood and bone (tibia)[95]. There have been no studies that indicate which if any of the VDR phenotypes are associated with increased vulnerability to the neurotoxic effects of lead.

The third gene, the Hemochromatosis gene, coding for the HFE protein, might also influence lead absorption. Mutated HFE protein causes hemochromatosis in homozygotic individuals wherein large quantities of iron are deposited in many internal organs; polymorphisms in HFE might influence the absorption of lead especially since Pb^{2+} can be mistaken for Fe^{2+}, and incorporated into processes requiring Fe^{2+}.

The Threshold for Behavioral Toxicity

As described in elsewhere in this paper (**Toxic Mechanisms** - *vide supra*), lead has negative effects on neuronal regulatory mechanisms at concentrations at least several orders of magnitude lower than 10 μg/dl. Are there behavioral correlates in humans consistent with toxic effects at levels below the CDC's threshold for poisoning?

Electrophysiological studies in children have described effects of lead on sensory functioning at exposure levels below 10 μg/dl. Otto and Fox[96] reported changes in cortical visual evoked potentials in children from 3 to 12 years of age with blood lead levels from 6 to 59 μg/dl.

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[94]Onalaja AO, Claudio L. Genetic Susceptibility to Lead Poisoning. *Environ. Health Perspectives* Vol 108. Suppl 1. March 2000

[95]Schwartz BS, Lee B-K, Lee G-S, Stewart WF, Simon D, Kelsey K, Todd AC. Associations of blood lead, dimercaptosuccinic acid-chelatable lead and tibia lead with polymorphisms in the vitamin D receptor and γ-aminolevulinic acid dehyratase genes. *Environmental Health Perspectives,* 2000, 108: 949-954.

[96]Otto DA, Fox DA. Auditory and visual dysfunction following lead exposure. *Neurotoxicology*, 1993, 14: 191-208.

Rothenberg et al[97] recorded the brainstem auditory evoked response (BAER) in children 5 to 7 years of age, that had been exposed prenatally to lead. The mean maternal blood lead level at 20 weeks of pregnancy was 7.7 μg/dl and was significantly associated with changes in the BAER; blood lead levels at other prenatal times was not correlated with responses changes. The data were best described by a non-linear second order polynomial model wherein BAER interpeak intervals decreased as blood lead levels rose from 1 to 8 μg/dl. With further increases, from 8 to 30.5 μg/dl, interpeak intervals increased.. Although the functional significance of these changes is not clear, it may be relevant that increases in auditory threshold have been reported with blood-lead levels ranging from 6 to 18 μg/dl[98].

Blood-lead levels below 10 μg/dl have also been shown to be associated with changes in neurochemistry and behavior. Tang et al[99] investigated the effects of prenatal lead exposure on the behavior of 9 month old infants. In addition to measuring cord blood lead levels at delivery, plasma from these samples was used to evaluate the concentrations of the dopamine metabolite homovanillic acid, and the serotonergic metabolite 5-hydroxyindoleacetic acid. The mean cord blood lead level was 3.9 μg/dl with the 5th and 95th percentiles of the range 2.5 and 7.0 μg/dl respectively. The Brunet-Lézine Scales, used to evaluate behavior, have subscales that measure posture, coordination, language and sociability as well as a composite score reflecting the overall level of functioning. Correlational analysis showed that both 5-hydroxyindoleacetic acid levels and sociability subscale scores were negatively associated with cord blood lead levels. When the effect of 5-hydroxyindoleacetic acid levels was factored in, there was an inverse correlation between cord lead levels and all behavioral indices except language. The authors interpreted their results as suggesting that low-level prenatal lead exposure "...could produce a neurotoxic effect on the developing serotonergic system ...." and "...may affect the sociability of infants."

With regard to the threshold for cognitive effects of lead exposure, Schwartz[100] performed a meta-analysis of studies of IQ in children with varying blood lead levels. The principle findings were that there was an inverse relation between IQ and blood lead level and that the slope increased with blood leads $\leq$15 μg/dl "...suggesting that a threshold of 10 μg/dl is implausible." Recent work by Lanphear and his colleagues[101] is in accord with Schwartz's conclusion. They

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[97]Rothenberg SJ, Poblano A, Schnaas L. Brainstem auditory evoked response at five years and prenatal and postnatal blood lead. *Neurotoxicology and Teratology*, 2000, 22: 503-510.

[98]Holdstein Y, Pratt H, Goldsher M, Rosen G, Shenav R, Linn S, Mor A, Barkai A. Auditory brainstem evoked potentials in asymptomatic lead-exposed subjects. *Larnygology and Otology*, 1986, 100: 1031-1046.

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reported an inverse relationship between blood lead concentration and achievement test scores of arithmetic and reading skills in children with blood lead concentrations lower than 5 μg/dl.

Schwartz's results are particularly important since IQ tests, in contrast to neuropsychological tests, are not especially sensitive to the effects of brain injury. Moreover, the results of neuropsychological testing support Schwartz's conclusion. Winneke and co-workers[102] found, with low-level lead exposure (mean 4.3 μg/dl, upper *95%* value 8.9 μg/dl), attentional deficits. Stiles and Bellinger[103] investigating the effects of similar low levels of exposure (mean <8 μg/dl) reported impaired performance in tests of rote verbal learning and also cognitive flexibility. Dietrich and co-workers[104] found that fine motor functioning was negatively affected at blood-lead levels as low as 9 μg/dl. In children with low SES, prenatal blood-leads <10 μg/dl were associated with cognitive impairments when assessed at 24 months of age.

Long-Term Effects of Lead Exposure

As previously discussed, long-term follow-up studies of patients initially assessed as young children established that cognitive impairments persist unchanged into adulthood. However, about 15-25% of children who were initially assessed were lost to follow-up. Since there were indications that the patients who were not retested were among those most affected by lead, it is possible that some lead poisoned children, instead of exhibiting stable symptoms, show a different outcome.

There are indications that the neuronal effects of childhood lead poisoning are, in some individuals, progressive. In Stokes et al's[105] long-term follow-up of adults who had been lead poisoned as children (*vide supra*), in addition to cognitive impairments, abnormalities of the peripheral nervous system were described that are typically associated with lead exposure of adults rather than children. Clinical neurology texts stress that central nervous system effects are characteristic of childhood lead poisoning while peripheral nervous system effects are more prevalent with adult poisoning (e.g. Adams & Victor[106]). However, the symptoms of pediatric lead poisoning are typically described when the patient is still a child. It is possible that the somatosensory impairments seen in adults who were poisoned as children reflects an aging-related emergence of neurological signs and/or the exacerbation of pre-existing signs that were

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too subtle to be detected by clinical neurological examination.

In a recent paper presented to the Society for Neuroscience[107], 7 case histories were described of subjects, presently 16 to 21 years of age, who had been poisoned before 3 years of age (mean blood lead .18 to 29 μ/dl). Each subject received a comprehensive evaluation of neuropsychological functioning. General level of cognitive functioning before the age of 9 years was determined from school records and from previous evaluations. Each subject was impaired in visual memory, attention and fine motor functioning. Individual subjects also had additional impairments in other cognitive domains. However, 3 subjects were distinctive in showing very severe deficits in virtually all of the tested neuropsychological domains and in exhibiting clear evidence that their cognitive functioning had significantly deteriorated since they were tested as children.

The proportion of lead poisoned children that show such deterioration and the determinants of their poor outcome remains to be determined. However, the literature on pediatric brain injury is replete with examples of symptom progression in certain cases and lead-induced brain damage appears to be no different in this regard. The development of the brain continues well into the teenage years and perhaps beyond (e.g.[108]). As a result, behavioral capacities that are not present in a young child emerge over time with normal development. In addition, some complex behaviors are dependent on the integration of earlier developing primary skills and are also only seen as a child grows older. The problem of assessing the long-term effects of any acquired brain injury in children is complicated by the fact that the insult not only disrupts established functions but also affects those functions that are in the process of developing as well as those that have yet to develop[109]. Higher order cognitive functions that depend on the integrity of primary functions and normal brain activity, may develop late, incorrectly, incompletely or perhaps not at all. Cognitive and behavioral deterioration may also occur over time as greater academic and social demands are placed on a child's already compromised learning abilities or when cognitive abilities dependent on damaged brain regions fail to develop[109, 110] Thus, brain injury sustained early in development often results in a slowly emerging continuum of deficits. "This process is sometimes referred to as 'growing into a deficit.' Problems may appear ...even years after the initial injury, as greater academic and social demands are placed on the child's already compromised learning abilities, or when abilities dependent on damaged brain regions fail to develop ..."[109]

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[107]Lidsky, T.I., Schneider, J.S. Cognitive deterioration after childhood lead poisoning. *Society for Neuroscience*, 2001. 27

[108]Chugani HT. A critical period of brain development: studies of cerebral glucose utilization with PET. *Prev Med.* 1998 27: 184-188. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *Journal of Comparative Neurology*, 1997, 387: 167-178. Spreen O, Risser AH, Edgell D. *Developmental Neuropsychology*, Oxford University Press, New York, 1995

[109]Mateer CA, Kerns KA, Eso KL. Management of attention and memory disorders following traumatic brain injury. *Journal of Learning Disabilities*, 1996, 29: 618-632.

[110]Barth, JT, Gideon, DA, Sciara, AD, Hulsey, PH, Anchor, KN. Forensic aspects of mild head trauma. *J. Head Trauma Rehab.*, 1986, 1: 62-70.

This problem is particularly important with regard to executive functioning. The neural systems that mediate executive functioning are among the last to mature in the brain. For this reason, behavioral impairments due to damage in these neural systems only become fully evident as a child grows older and the demands for higher level functioning increase with age. Significantly, one of the primary mediators of executive functioning, the frontal lobes, are particularly sensitive to the effects of lead poisoning[111].

The possibility that the nature of neuropsychological impairments caused by brain injury in children will change as a child develops has implications for treatment. Identification of a child's neuropsychological impairments is a necessary prerequisite to developing a program of rehabilitation to help the patient achieve the highest level of functioning possible based upon surviving cognitive abilities. However in some cases problems that are not detectable in a young child will emerge over time while those already present will become exacerbated. For this reason, periodic re-evaluation of neuropsychological functioning is needed so that treatment goals can be modified based upon the child's evolving pattern of impairments.

Conclusions

Childhood lead poisoning continues to be a world wide public health problem. Although there has been progress in decreasing lead exposure, sources of contamination abound and many children continue to have elevated blood lead levels. The information reviewed in the present paper has several implications for understanding the neuropsychological concomitants of elevated blood lead levels in children.

1. The existing literature indicates that there is no safe level of blood-lead; there is solid evidence for detrimental effects on behavioral and cognitive development with blood lead levels below 10 μg/dl.

2. In some children, the nature of neuropsychological impairment caused by early brain injury changes with age. Accordingly, periodic re-evaluation of neuropsychological functioning is needed so that treatment goals can be modified based upon the child's evolving pattern of impairments.

3. Both genetic factors and some as yet unidentified variables associated with SES affect the vulnerability of a particular individual to lead's neurotoxic effects. Additional research is needed to further characterize the genetic influences and the concomitants of SES that influence a child's biological response to lead.

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