

Full-length review

Low-level lead-induced neurotoxicity in children: an update on central nervous system effects

Yoram Finkelstein ^{a,*}, Morri E. Markowitz ^b, John F. Rosen ^b

^a *Department of Neurology, Shaare Zedek Medical Center, P.O. Box 3235, Jerusalem 91031, Israel*

^b *Division of Environmental Sciences, Department of Pediatrics, Albert Einstein College of Medicine, Montifiore Medical Center, Bronx, NY, USA*

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Abstract

The neurotoxicity of low-level long-term exposure to lead has a special relevance in children. An extensive database has provided a direct link between low-level lead exposure and deficits in the neurobehavioral–cognitive performance evidenced in childhood through adolescence. Electrophysiological studies showed that neurosensory processing may be affected by lead, with consequent decrease in auditory sensitivity and visuomotor performance. Lead disrupts the main structural components of the blood–brain barrier by primary injury to astrocytes with a secondary damage to the endothelial microvasculature. Within the brain, lead-induced damage occurs preferentially in the prefrontal cerebral cortex, hippocampus and cerebellum. Some characteristic clinical features of lead poisoning may be attributed to this specific anatomical pattern. The cellular, intracellular and molecular mechanisms of lead neurotoxicity are numerous, as lead impacts many biological activities at different levels of control: at the voltage-gated channels and on the first, second and third messenger systems. These effects could be related to lead's ability to interfere with the regulatory action of calcium in cell functions. Consequently, it may be assumed that lead acts as a chemical stressor and causes breakdown of the homeostatic cellular mechanisms. This is expressed in both the anatomical site and the neurotransmitter systems which are crucial in modulating emotional response, memory and learning. There is no threshold below which lead remains without effect on the central nervous system; thus, symptoms could simply be a clinical reflection of the brain regions preferentially involved. In integrating these physiological and clinical data, it may be suggested that the different mechanisms of low level lead neurotoxicity have a final common functional pathway. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Lead poisoning; Child; Neurotoxicity; Hippocampus; Prefrontal cortex; Cerebellum

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* Corresponding author. Fax: +972-8-9456586; E-mail: yfinkel@md2.huji.ac.il

1. Introduction

The definition of a minimal toxic lead level in children has been repeatedly reduced over the last three decades [13,50]. The environmental, clinical and toxicological aspects of overexposure to lead were reviewed in the medical literature [4,29,77,99], with special relevance to occupational health problems. Since then, a vast amount of new information has accumulated in this field. The results of different clinical studies were reproducible and corroborated the previous observation that neurotoxicity of lead is organ-specific [93]. This article is an update on the neurotoxicological concepts of low-level exposure to lead and its effects within the central nervous system, with special relevance to children. The critical remarks and comments express the authors' own views and the experience gained (by J.F.R. and M.M.) in the pediatric lead program and the lead poisoning prevention project at the Montefiore Medical Center in Bronx, New York.

1.1. Neuroanatomy

1.1.1. Blood–brain barrier disruption

The blood–brain barrier is highly vulnerable to the toxic action of lead [46]. The earliest lead-induced morphological changes are observed in the endothelium of the microvessels, which form the main structural component of the blood–brain barrier [69]. The endothelial cells are exposed to lead during its passage into the brain [36].

Using autoradiography and direct measurements in isolated brain microvessels, the endothelial cells showed a marked affinity for lead and accumulated it to a much higher concentrations than in other brain structures [92]. The other major structural components of the blood–brain barrier are the astrocytes, the foot processes of which sheathe almost the entire circumference of the microvessels, without forming a sealed physical barrier [35]. Astrocytes in cell cultures were quite sensitive to the toxic effect of lead at low concentrations [43]. Endothelial cell cultures, on the other hand, were relatively resistant to lead at the same low concentrations [34]. It was suggested, therefore, that lead might cause primary injury to astrocytes with a secondary damage to the endothelial cells, thus disrupting the blood–brain barrier [36]. The intracellular mechanisms of the selective toxic damage to the glia will be discussed further.

1.1.2. Cerebral cortex

The prefrontal cortex is a likely site of damage responsible for behavioral impairment induced by lead [76]. Indeed, prefrontal cortical damage results clinically in perseveration, inability to inhibit appropriate behavioral response, and increased distractibility [33], all clinical hallmarks of lead-induced impairment in both monkeys and humans.

It has been suggested that basal forebrain and the primary visual cortex may also be damaged by lead. Morphological changes were observed in areas V1 and V2 of the occipital cortex of monkeys following moderate level exposure [72].

1.1.3. Hippocampus

Morphologic changes were observed in the rat hippocampus following low level exposure to lead during lactation, and at blood lead levels (PbB) of 20 $\mu\text{g}/\text{dl}$. Namely, a significant increase in the size and numerical density of the mossy fibers, the granule cell layer and the commissural–associational area of the dentate molecular layer were reported [88]. This was related to the high zinc content in the hippocampus [30]. The opposite effect (i.e., decreased density of cell layers) was observed at much higher PbB (250 $\mu\text{g}/\text{dl}$), which might be irrelevant to our discussion on low-level exposure. However, this latter finding suggests a bimodal effect of lead on the developing hippocampus [15]; and this type of dose–response curve is consistent with those described for some behavioral outcomes in experimental animals [20].

A recent report has demonstrated long-lasting decrease in the density of cholinergic innervation of the hippocampus as the result of perinatal low-level lead exposure. The loss of septohippocampal cholinergic projection neurons in neonate animals resulted in a deficit in hippocampal cholinergic innervation that persisted into young adulthood. This may account for persistent cognitive impairments associated with early Pb exposure [9].

1.1.4. Cerebellum

Lead-induced inhibition of postnatal structuring of the rat cerebellum was indicated by an impaired developmental time course of desialylation of the D2-CAM-N-CAM protein [71]. N-CAM, the neural cell adhesion molecule, regulates neuronal fiber outgrowth and synapse formation [22]. This phenomenon was observed at PbB of 20–30 $\mu\text{g}/\text{dl}$, and may contribute to impairment in fine motor skills. Its possible clinical correlate in human is postural disequilibrium, as was described in a clinical study of 6-year-old children with PbB of 10–14 $\mu\text{g}/\text{dl}$ measured during their first 5 years of life [6].

1.2. Neurobiology: cellular, intracellular and molecular mechanisms

Lead impacts on a wide variety of biological activities at different intracellular levels: at the voltage-gated channels and on the first, second and third messengers (Fig. 1).

1.2.1. First messenger systems

Lead may cause variable changes in several neurotransmitter systems (Fig. 1 point 2). Earlier studies showed changes in the cholinergic systems which was accompanied by hyperactive behavior in mice. Acetylcholinesterase

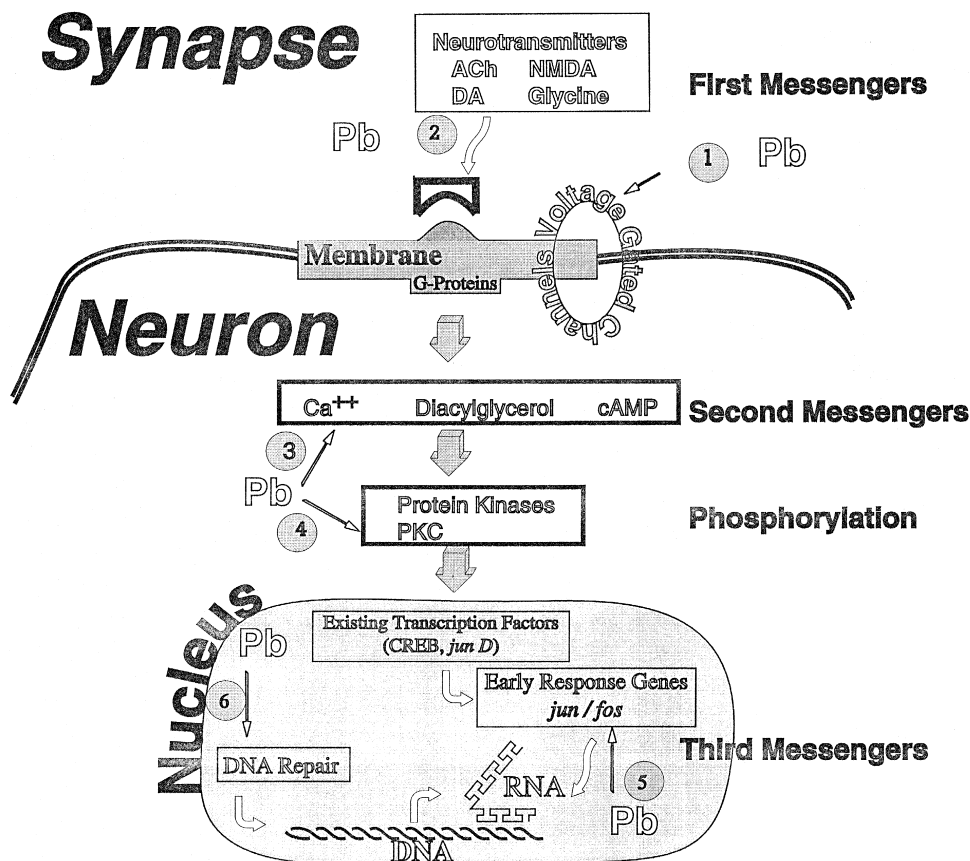


Fig. 1. Possible sites of action of Pb in neurons. Points of lead interaction: (1) voltage-gated channels; (2) neurotransmitters (first messenger systems); (3) second messengers; (4) protein kinases; (5) third messenger systems; (6) DNA repair.

inhibitors (i.e., physostigmine) suppressed the hyperactive state [86]. These observations are compatible with the dynamics of the septohippocampal cholinergic system during lengthy stress periods [27]. It may be assumed that lead acts as a chemical stressor at both an anatomical site (septohippocampus) and on a neurotransmitter system (acetylcholine) which plays a critical role in the modulation of the emotional responses, memory and learning.

The long-term effects of moderate lead exposure during development were examined in the cholinergic visual system of adult rats. These effects were observed only in the visual cortex and not in other sites along the visual pathway, namely in the retina, superior colliculus or lateral geniculate nucleus. The muscarinic receptors in the visual cortex decreased in their density (B_{max} values) but not in the affinity (K_d), while the specific muscarinic binding by quinuclidinyl benzilate (QNB) decreased. Acetylcholinesterase (AChE) activity diminished as well [17]. These region-specific biochemical observations are parallel to the above described morphological alterations in the primate cortex following moderate lead exposure [72].

The dopaminergic and glutamatergic systems, and specifically the *N*-methyl-D-aspartate (NMDA) receptor complex, play a role in learning and memory processes

[28,49]. These systems are affected by chronic lead exposure [48]. Changes in the glutamate synthesis were shown in guinea pigs at PbB of 13 $\mu\text{g}/\text{dl}$ [85], alongside with a reduction in glutamine synthetase activity [84]. Lead may also be acting as a non-competitive antagonist of the glycine site [45]. Animals exposed to lead during development were hypersensitive to systemic administration of NMDA [68].

1.3. Voltage-gated channels, second messenger systems and protein kinases

Many of the neurotoxic effects of lead could be related to the ability of lead to interfere with the action of calcium as a regulator of cell function. Lead characteristically perturbs processes linked to calcium and the calcium messenger systems. Lead activates protein kinase C (PKC), in a process which is calcium-dependent and phospholipid-dependent [53,51]. Lead-induced rise in intracellular free calcium is mediated by PKC [80].

Activation of protein kinases at the nerve endings may enhance spontaneous release of neurotransmitters from presynaptic nerve endings [93]. On the other hand, evoked release of neurotransmitters may be inhibited by the block-

ade of voltage-dependent calcium channels [10] depicted in Fig. 1, point 1. The dual effect of Pb on the voltage-gated calcium channels has been observed by whole cell patch-clamp technique used on cultured bovine adrenal chromaffin cells. In contrast to extracellular blockade, intracellular lead ions promotes calcium ion currents by attenuating the calcium-dependent, steady-state inactivation of calcium channels [89].

At the functional level of the blood–brain barrier, lead may cause a breakdown of the homeostatic mechanisms, as it mimics or mobilizes calcium and activates PKC in endothelial cells [11]. In experimental models of blood–brain barrier (i.e., capillary-like structures or co-cultures of neural and endothelial cells), lead acts as a calcium substitute in second messenger metabolism [37]. Lead may also damage the astrocytes that provide signals for the maintenance of the blood–brain barrier integrity [10]. However, it appears unlikely that the disruptive effects of lead on the astrocytes are mediated via direct changes in intracellular calcium transients [18]. Taken together these studies implicate second messenger metabolism and PKC activation as most vulnerable sites for the disruptive action of lead (Fig. 1 points 3,4).

1.3.1. Third messenger systems

Lead elevates the mRNA levels of the early response genes *fos* and *jun*. Lead may alter gene expression, by perturbation of biochemical pathways or second messenger systems. Maternal exposure to lead acetate resulted in an approximately 30% reduction of expression of vesicular acetylcholine transporter mRNA in septum of 7 and 21-day-old rat pups without affecting its levels in the dams [91]. In a related work, it was demonstrated that the expression of choline acetyltransferase mRNA was attenuated by the exposure to lead [90].

Lead may also alter specific metal-dependent transcription factors including zinc-finger proteins [15] (Fig. 1 point 5).

Ions of lead may inhibit DNA repair and exert indirect genotoxic effect, acting as a co-mutagenic agent with ultraviolet (UV) irradiation or alkylating agents [5]. The DNA repair inhibition is caused by the interference of lead with the polymerization or ligation step in excision repair [41] (Fig. 1 point 6).

The expression of lead-induced perturbation of molecular, biochemical or physiological events may vary among different tissues, according to the importance of each molecular event in each cell type. Thus, the lead effect on the voltage-gated channels is much more crucial in neurons than in bone cells. In a like manner, the toxic effects of lead on neurotransmission may change during the different phases of neuronal activity: under physiological resting conditions, lead enhances the spontaneous release of neurotransmitters, via PKC mechanisms or through interaction with the putative calcium receptor of exocytosis

[93,94]. Under activated conditions lead inhibits the evoked neurotransmitter release (via voltage-gated channels) [10]. This may explain the variability of experimental results.

1.3.2. Experimental animal studies

The reported changes in cognitive and behavioral functions, observed in experimental animal studies at PbB of 10–15 $\mu\text{g}/\text{dl}$, directly paralleled those of concern as defined by human studies. These levels do not represent thresholds for neurotoxicity, but simply the lowest levels of exposure at which neurotoxicity has yet been studied in animals [15]. Research in primates has clearly shown memory and learning deficits as a consequence of lead exposure. Experiments implicated the same behavioral problems as those observed in lead-exposed children: increased distractibility, inability to inhibit inappropriate behavioral response and perseveration in behaviors which are no longer appropriate [76]. The first two manifestations are symptomatic of the clinical Attention Deficit Disorder. Deficits were more severe in the presence of distracting irrelevant stimuli. The methods which were applied in primates were the intermittent fixed-interval schedules of reinforcement. The unusual behavioral pattern of response observed by this method was demonstrated in monkeys with steady-state PbB of 11–13 $\mu\text{g}/\text{dl}$, following long-term exposure. This behavioral pattern was also shown at higher PbB, in a dose-dependent manner [73].

This same behavioral response has also been observed in rats with PbB comparable to those in monkeys [16]. However, most of the experimental data in rodents were obtained after relatively short-term exposure to lead (weeks, in most of the studies). Consequently, it is difficult to interpret these biological data or to establish their clinical relevance to the natural history of low-level long-term exposure (for years) in children.

Monkeys exposed to lead only during infancy were impaired on spatial but not on non-spatial tasks, while monkeys dosed continuously from birth or beginning after infancy were impaired on both spatial and non-spatial tasks of learning and memory [75,74]. It is extremely difficult to establish whether these deficits might be the same in children.

It has also been suggested that all animal studies dealt entirely with unnatural mechanisms in lead biodynamics, as non-leaded controls were actually exposed to the unnatural conditions of massive air pollution nowadays [66]. The extent of atmosphere pollution is reflected in the 200-fold increase of lead content in the snow strata of northern Greenland, over the past 3000 years [24].

The risk for PbB exceeding 15 $\mu\text{g}/\text{dl}$ has been recently assessed in 1583 schoolchildren in Mexico City. The strongest association was with the area of residence, followed by education level of parents, cooking of meals in glazed pottery and chewing or sucking of yellow or other colored pencils [62].

1.3.3. Effects of developmental lead exposure

Exposure of developing rats to lead via administration of 0.2% lead acetate in drinking water to dams from 1 week before birth through the fourth week postpartum, caused a marked, 20–40% reduction in developmental expression of cholinacetyltransferase (ChAT) activity in the septum and the hippocampus [7]. Long-term lead exposure of SPD rats from embryonic day 16 through 21 days of age, resulted in a persistent 30–40% reduction of hemicholinium-3 (HC-3) binding [8]. HC-3 is the specific ligand for the sodium dependent high affinity choline uptake system which is selectively localized in cholinergic nerve endings in the hippocampus. This effect of prenatal exposure resembles in several respects those seen following surgical disruption of the septohippocampal pathways in adult animals. These denervation-like effects may play an important role in learning and cognitive impairments following low-level developmental exposure to lead. Thus, the cholinergic hippocampal pathway may be an important neural target in developmental neurotoxicity.

Developmental lead exposure resulted in a long-term 50–90% increase of tyrosine hydroxylase (TH) activity in the hippocampus [7]. Abnormal sympathetic ingrowth and the associated long-term increase in norepinephrine (NE) levels resulting in ACh/NE imbalance in the hippocampus has been implicated in hyperactivity and impaired performance on learning and memory tasks [40].

In support of this concept, change in hippocampal N-CAM sialylation has been shown to occur in the synapse-specific isoform during the acquisition and consolidation of a passive avoidance response in the adult rat [71]. Lead-induced inhibition of postnatal structuring of the rat cerebellum, in a similar mechanism, has been described elsewhere in this review.

Chronic exposure of rats to low level lead ingestion starting prenatally reduces the number of inositol phosphate IP3 receptors and thus reduces the capacity of IP3 to mobilize Ca^{2+} from intracellular sources in neurons. However, chronic exposure to a comparable dose of lead ingestion starting at an adult age did not cause these changes [87]. This suggests that IP3 receptors may be sensitive to chronic low level lead exposure in the CNS of embryonic rats but not in the CNS of adult rats. Chronic lead exposure may impair neuronal processes underlying synaptic plasticity via a direct interaction with NMDA glutamate receptor subtype. In vitro and in vivo neurochemical studies in the developing brain have shown that Pb^{2+} has a marked inhibitory effect on the activation of the NMDA receptor–ion channel complex, which regulates calcium influx and is involved in the initiation of changes in synaptic plasticity. This inhibitory effect may be mediated by its interaction with a zinc regulatory site on the receptor complex. The ability of Pb^{2+} to inhibit NMDA receptor–ion channel functions was shown to be age-dependent and brain region-specific [38]. Furthermore, the NMDA receptor has also been shown to participate in the

induction of long-term potentiation in the CA1 area of the hippocampus, a cellular phenomenon thought to be involved in some forms of learning and memory [52]. These age-dependent effects may help explain the selective toxicity of lead in the developing brain.

1.3.4. Cognitive neurotoxic effects in children

In children, lead exposure results in deficits in such global measures as IQ, as well as more specific deficits that are suggestive of Attention Deficit Disorder. In reviewing the literature, the US Environmental Protection Agency (EPA) concluded that PbB exceeding 50 $\mu\text{g}/\text{dl}$ are associated with a five-point decline in IQ, PbB of 30–50 $\mu\text{g}/\text{dl}$ with a four-point decline, and PbB of 15–30 $\mu\text{g}/\text{dl}$ with one to two-point decline [25].

An extensive database has provided a direct link between low-level lead exposure during early development and deficits in neurobehavioral–cognitive performance evident later in childhood through adolescence [78]. Furthermore, according to the CDC [13], no threshold for the lead–IQ relationship has been established. Almost a dozen cross-sectional and retrospective cohort studies converge on the unequivocal conclusion that there is a negative association between lead measured in blood or other indexes of exposure and deficits in intellectual performance [78]. In one cross-sectional study, intelligence test scores were found to be 4.5 points lower for school-aged children with high dentine lead levels [59]. These findings were later confirmed by reanalysis, accounting for an array of appropriate covariates [81]. In another cross-sectional study, a difference of 5.8 points was noticed in scores on British Ability Scales, between the lowest and the highest PbB groups [32]. The IQ deficits were considered irreversible [13,60].

These findings were corroborated by several large prospective longitudinal studies, in which children were examined and followed up for lengthy periods. In these studies, chronic exposure to lead occurred in utero or in early infancy. The Cincinnati study [21] found effect of prenatal lead exposure on Mental Development Index of the Bayley Development Test that amounted to an eight-point deficit for each increase of 10 $\mu\text{g}/\text{dl}$ in PbB. In the Australian study in Port Pirie [56], infant and childhood PbB were inversely related to cognitive scores at 4 years of age; children with PbB of 30 $\mu\text{g}/\text{dl}$ had cognitive scores 7.2 points less than children with PbB equal to or less than 10 $\mu\text{g}/\text{dl}$. In the Boston study, the cohort was composed of advantaged middle- and upper-class children living in optimal conditions. The General Cognitive Index of the McCarty test administered at the age of 57 months in these children showed a decrease by three points for each natural log unit increase in PbB measured at 24 months of age [3]. When retested at 10 years of age, an increase of PbB at age 2 years of 10–20 $\mu\text{g}/\text{dl}$ was associated with a six-point decline in full-scale IQ on the Wechsler Intelligence Scale for Children—Revised and

nine points approximately on the Kaufman Test for Educational Achievement [1,3]. Preliminary findings from a prospective study conducted in Yugoslavia also indicate a significant inverse association between PbB at 2 years of age and concurrent Mental Development Intelligence scores, corresponding to a decrease of 2.9 points as PbB increased from 10 to 30 $\mu\text{g}/\text{dl}$ [95].

High lead body burden is associated with increased risk of antisocial and delinquent behavior. A recent retrospective study was carried out in 301 students at 7 years of age, who scored in the upper 30th percentile of distribution on a self-reported antisocial behavior scale. Their bone lead concentrations were measured by *in vivo* X-ray fluorescence (K XRF), a measure of cumulative exposure. The relationship of bone lead burden to reports on antisocial behavior was examined, using three separate sources of information: parents, teachers and the subjects themselves, with a follow-up period of 4 years until 11 years of age. Attention, function, neurological and academic performance were also evaluated in relation to bone lead [61].

As the length of follow-up has increased to include assessment at school-age, striking consistencies are emerging, reporting significant inverse associations between PbB measured in the first few postnatal years and the intellectual performance at ages 4 to 10 years. This may reflect the natural history of neurotoxicological deficits, simply because long latencies are so characteristic of neurological diseases.

The link between early lead exposure and later deficits in intellectual and school performance is remarkably consistent, with three exceptions: the Cleveland study [26] and the Multicenter European study [98], failed to find an association between lead levels and cognitive scores. In the Sydney study, the association was positive rather than negative, *i.e.*, children with greater exposures achieved higher scores [14]. However, a meta-analysis statistical method was employed to combine the results of the different studies. In this approach, individual studies served as data points in a larger study. The combined results of seven studies [81] indicated an average decrease of 0.25 IQ points for each 1 $\mu\text{g}/\text{dl}$ increase in PbB. An additional meta-analysis of 13 studies strongly supported the conclusion that low-level lead exposure is related directly to neurobehavioral and cognitive deficits [58].

Collectively, the results of the prospective and cross-sectional studies and the meta-analyses implicate a causal link between remarkably low levels of lead exposure and neurobehavioral–cognitive–IQ deficiencies in children [78].

A global measure like IQ serves as a standardized marker of the basic cognitive competence. However, as the higher cognitive functions are extremely complex, the use of a single global measure might be insensitive. Therefore, a battery of tests was applied in several studies, in order to identify the cognitive skills which might be most vulnerable to chronic low-level exposure to lead. A consistent

finding in these studies is the inverse association between lead exposure of children and their attention span. Lead-exposed children perform worse on simple reaction time [44], serial choice tasks [97] and the Continuous Performance Test [39]. Dose-dependent impairment of attention-related behavior was described as manifested distractibility, impulsiveness, low frustration tolerance, inability of organization and inability to follow directions. This was shown in longitudinal studies using Rutter B2 Scale and the Connors Teacher Rating Scale [2,70].

In some studies, the verbal and auditory skills seem to be most affected [54,64]. In other studies, visuo-spatial and visuo-motor integration skills (like eye–hand coordination) were shown to be impaired [39].

The weight of evidence support the basic hypothesis that low-level exposure is associated with neuropsychological dysfunction, while there is insufficient data to arrive the minimal threshold and the maximum acceptable blood level [82,81]. An interesting observation on the remote effects of lead poisoning has been recently described in 454 pediatric hospital patients who were diagnosed with lead poisoning between 1923 and 1966. These patients were traced through 1991. Mortality from all cardiovascular diseases was elevated and cerebrovascular deaths were particularly common among women [55]. Despite limitations in these data, the pattern of mortality suggests persistent effects of lead poisoning throughout life and may be experienced differently by men and women.

1.3.5. Physiological studies in children

Neurosensory processing may be affected by lead: altered auditory processing in young children [82], decreased auditory sensitivity in children and youth [83] and decreased performance in tests requiring appropriately timed reactions [96].

Visuomotor performance was decreased in preschool children, as a function of their PbB [64]. Proprioceptive mechanisms of posture and balance have also been reported during lead exposure in children [6].

An American national health survey found increased hearing thresholds in children aged 6–19 years at PbB of 6–18 $\mu\text{g}/\text{dl}$ [83]. A pattern of ‘inversed tea cup’ was described in audiograms [42].

Electrophysiological studies have also been performed in children, in spite of the objective methodological difficulties. An Israeli study in asymptomatic lead-exposed children (age 8–17 years) showed increased latencies in brainstem auditory evoked potentials (BAER), namely in the peaks III and V and in the interpeaks I–III and I–V as PbB increased [42].

Lead-induced changes were also measured in pattern reversed evoked cortical potentials in children: in 6–12 year-old children with PbB 6–59 $\mu\text{g}/\text{dl}$, the amplitude of N1P1 increased with increasing PbB; and in children 3–7 year-old with PbB 6–47 $\mu\text{g}/\text{dl}$ the latency of P2 decreased with increasing PbB [64]. Lead also appeared to

alter the inhibitory–excitatory interaction between the rods and the cones in the retina, which is dependent upon the level of dark or light adaptation [31]. Other studies reported lead-induced changes in sensory evoked potentials (SEP) [63] but not in EEG power spectra [12].

An important question, from both biological and clinical points of view, is whether lead accumulates irreversibly in the neurons. The reversibility of the cognitive deficits attributable to lead poisoning was examined in a study of moderately lead-poisoned children, some of whom were treated with the chelating agent EDTA. Decreases in PbB were associated with cognitive improvements, as measured by Bayley Mental Development Scale or Stanford–Binet Intelligence Scale [79]. The reversibility of the behavioral deficits was examined in hyperactive school-age children whose PbB were elevated around 25 $\mu\text{g}/\text{dl}$. These children showed behavioral improvement following chelation with penicillamine [19]. The results of these two clinical studies indicate that lead-induced neurotoxicological deficits may be reversible and potentially treatable. The degree of reversibility and the contribution of chelation therapy remain to be investigated [47].

1.3.6. High-risk populations

Body burdens of lead in humans in the modern era are 1000-fold higher than during preindustrial era [66,65]. When lead concentrations are normalized to the levels of calcium, Ca/Pb ratios in human brain tissue are 30 times higher than in bone [67]. Lead is integrated into critical target tissues within the central nervous system.

Under these circumstances, the margin of safety to lead overexposure is most probably narrow. Therefore, the insidious impact of increased body burden represents a potential epidemic of acquired disease.

Leaded gasoline is still a major source of air pollution in Israel, although its use is being tapered gradually [77]. Massive air pollution in the urban areas might cause high lead concentrations in the soil. High lead amounts in the inner-city soil play a significant role in the incidence of lead poisoning in children, as has been recently shown in the city of Washington, DC [23]. Most of the lead is taken up from the soil by oral route, by finger–mouth contact (including pica behavior), during play at sandboxes in urban areas and from additional sources like leafy vegetables grown alongside highways.

The neurodevelopmental studies, discussed above, have led to the identification of infants, children and pregnant women (as surrogates for fetuses) at greatest risk of toxicity from low-level exposure [57].

2. Conclusions

Apparently, there is no threshold below which lead remained without effect. This suggests that any exposure to lead is harmful to the central nervous system. This has

special relevance to infants and children. However, exposure to lead is preventable and its neurotoxicological effects potentially treatable. The environmental conditions in many countries still enable overexposure of children to lead. National attention and public health effort are required to minimize the problem.

There is insufficient data regarding the full extent of the global problem. Few studies have been carried out in non-Western countries [77]. A large-scale epidemiological study is warranted, comparable to the American and European studies, in order to learn the prevalence of lead exposure in the general population of Third World countries. This will enable to carry out programs designed to eliminate lead exposure and its neurotoxicity, an entirely preventable disease.

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