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Toxicological Properties of Lead

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The pathological effects of lead on the renal, nervous, reproductive, endocrine, and immune systems have been reviewed. Emphasis is placed on reported subclinical effects due to chronic, low-level lead exposure. The crucial issue of whether subtle behavioral, intellectual, and developmental impairment occurs in young children, as a result of lead-induced CNS damage is discussed in detail. This issue remains unresolved. Further studies are needed in order to determine the long-term health effects of continuous, low-level lead exposure.

Introduction

Lead has been recognized for centuries as a general metabolic poison. Acute lead poisoning results in a well-characterized syndrome manifested in adults by colic, anemia, headache, fatigue, gum line, and peripheral neuropathy (*1*). In children, the symptoms of acute lead intoxication include vomiting, anorexia, lethargy, convulsions, coma, and encephalopathy (*2*). Such symptoms of lead poisoning usually do not occur until blood lead levels exceed 80 μg/100 ml. Therapeutic intervention at this stage is only partially successful in preventing permanent injury. Although occasional episodes of classical lead poisoning still occur, particularly in young children, acute exposure is becoming a diminishing problem. Of greater concern is the possibility that continuous exposure to lower levels of lead, as a result of widespread environmental contamination may result in adverse health effects. Although other systems may also be affected, it has been well documented that lead impairs the renal, hematopoietic, and nervous system (*3*). Renal effects are seen only in subjects with long-term, high exposure, and in association with other symptoms of lead toxicity (*4*). Adverse subclinical effects such as an excretion of porphyrins and their precursors into the urine have been observed in the hematopoietic system; these effects were discussed in the previous article (*5*). It is presently not known whether subtle CNS impairment can occur at lead levels before effects are observed in the hematopoietic system. Simple neurochemical tests for signaling early metabolic changes in the nervous system, comparable to the tests used to measure changes in the hematopoietic system, are currently unavailable. In general, CNS impairment has been assessed through the use of various functional tests. Since, reports concerning CNS damage due to asymptomatic lead exposure have been conflicting and controversial, this review has emphasized this crucial aspect of lead toxicity.

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Effects of Lead on the Nervous System

Encephalopathy

The neurotoxicity of lead at high levels of exposure has been well documented for both man and animal species. Acute encephalopathy is one of the most serious consequences of plumbism, since permanent impairment of the central nervous system may occur, particularly in young children. Byers and Lord (*6*) showed that lead encephalopathy produced some irreversible neurological and psychological sequelae in 19 out of 20 children. The American Academy of Pediatrics (*7*) estimates that 25% of children affected with lead encephalopathy will suffer permanent damage to the central nervous system. This damage is usually reflected in behavioral and educational abnormalities, with or without accompanying mental retardation. Perlstein and Attala (*8*) observed that 82% of children with a history of lead encephalopathy experienced recurrent seizures and mental retardation. Mellins and Jenkins (*9*) and Bradley and Baumgartner (*10*) found that 60–80% of children treated for

plumbism later had impaired visual-motor coordination. Smith (*11*) found abnormal EEG tracings in six of ten children affected with encephalopathy. Children who have already experienced lead encephalopathy and are subsequently re-exposed to lead, will almost certainly develop permanent CNS damage (*12*). Recently, Albert et al. (*13*) and Rummo (*14*) have reconfirmed the deterimental effects of severe lead poisoning on the subsequent behavior and intellectual functioning of children.

Neurological Diseases

Warren (*15*) has speculated on a link between lead exposure and several chronic neurological diseases. Cone (*16*) reported that the cerebrospinal fluid of multiple sclerosis patients contained elevated lead levels; however, Butler (*17*) and Westerman (*18*), using more sensitive techniques for lead analysis, were unable to show an association between lead absorption and multiple sclerosis. The possibility of an association has been revived by Warren (*15, 19, 20*) by demonstrating that certain geographical areas with high environmental lead levels have a high incidence of multiple sclerosis. A number of studies (*21–23*) have reported an association of exposure to lead with motor neuron disease, but the etiological role of lead is not clear in these studies. Lead insult has also been associated with scrapie and swayback in sheep and kuru and amyotropic lateral sclerosis in humans (*15*). These suggestive associations warrant further investigation, but to date, controlled, positive studies are lacking.

Peripheral Neuropathy

Animal studies have shown that lead produces segmental demyelination (*24–26*), and interferes with myelin metabolism in tissue culture (*27*). Such damage to the myelin sheath has been shown to impair nerve function. Catton, et al. (*28*) and Seppäläinen and Hernberg (*29*), using sensitive electrophysiological techniques, observed impaired motor nerve conduction velocities in neurologically symptom-free lead workers, whose blood lead levels exceeded 70 μg/100 ml. The recent studies by Sepäläinen et al. (*30*) also revealed a slowing of motor conduction velocity of the median and ulnar nerves of asymptomatic workers whose blood lead values had never exceeded 70 μg/100 ml. Abnormal measurements began to occur at blood lead levels of 50–60 μg/100 ml. Although a dose–reponse relationship between a slowing of motor nerve conduction velocity and blood lead values has not yet been adequately documented, these preliminary findings suggest that the acceptable level of blood lead (70 μg/100 ml) for occupationally exposed workers may need to be reevaluated.

Peripheral neuropathy has been considered to be a rare occurrence in children with lead intoxication (*31*). However, Feldman et al. (*32*) suggested that childhood neuropathy may be overlooked and overshadowed by the clinical symptoms of encephalopathy. These authors observed slightly reduced motor nerve conduction velocities in children with a known history of plumbism. Whether peripheral neuropathy occurs in asymptomatic children with no history of lead poisoning remains a matter of conjecture and is discussed in the following section.

Neurological and Behavioral Toxicity of Chronic Lead Exposure in Children

A growing concern, which has received a great deal of publicity recently, is the possibility that chronic, asymptomatic lead exposure may cause "minimal brain dysfunction," behavior problems, and neurological impairment in children exposed to lead *in utero* and/or during early childhood. Wiener (*33*) reviewed the literature up until 1968. He concluded that methodological shortcomings in all of the studies made it impossible to draw definitive conclusions. Weiner notes that:

> "Those reports which claimed positive findings had either used too few cases from which to generalize or had not provided for controls for relevant variables such as social class, pica; or premorbid status. A rigorous statistical and experimental approach has been conspicuously absent. Further, the variations in diagnostic procedures and definitions lead to unclear conclusions regarding the degree of lead ingestion which may or may not be important for later development."

A brief critique of some representative, frequently-cited studies will indicate that such criticism continues to apply, in varying degrees, to all subsequent studies. For exmaple, David et al. (*34*) suggested an association between lead exposure and hyperactivity in children. Children, whose hyperactivity had no known cause, had higher blood lead levels and body burdens of lead than normal children or children whose hyperactivity had a "known cause." However, since the numbers in the "known cause" group were very small, it cannot be ruled out that lead absorption was secondary to hyperactivity, particularly since it has been shown that disturbed children tend to exhibit an increased incidence of pica (*35–37*). The statistical treatment of this study by David et al. (*34*) has also been criticized (*38*).

Pueschel et al. (*39*) and de la Burde and Choate (*40, 41*) compared children with a history of pica and elevated blood lead levels (40 μg/100 ml and above), to control children with no history of pica. The lead exposed children showed mental impairment, irritability, and poor fine motor control. In most cases, lead blood concentration was high (> 50 μg/100 ml). Although the groups were matched for race, age, sex, and several socioeconomic variables, no lead assessments were made for the control group. Again it can be argued that children with some history of psychological disturbance (i.e., pica) may have other signs of disturbance which are not directly related to lead exposure. Kotok (*42*) included pica in addition to age, sex, race, and environmental factors in matching his controls. He failed to find significant differences in mental development between lead-exposed (blood lead > 40 μg/100 ml) and control groups and concluded that the differences observed were related to home environment rather than lead exposure. However, his controls (many of them were siblings of the exposed group) had a mean blood lead of 38 μg/100 ml. Thus, as many of the controls may have been at high risk for lead, and Kotok's data must be considered inconclusive (*43*). Other studies suggesting a causative association of lead exposure with mental impairment have been equally inconclusive (*14, 44–47*).

The studies described up to this point have dealt primarily with urban children whose exposure to lead may come from many sources. Recently, attention has also focused on the effects of chronic lead exposure in children living in the vicinity of ore smelters (*48–50*). McNeil and Ptasnik (*51*) evaluated 138 children (21 months–18 years old) living near a large ore smelter in operation for about eight years in El Paso, Texas. Serial blood lead determinations indicated that these children had prolonged, asymptomatic elevations in blood lead levels (40–80 μg/100 ml). They had no neurological symptoms, and nerve conduction tests were normal. The authors found no differences in the activity measurements, and psychometric evaluations of exposed children and matched controls, living outside Smeltertown. They concluded that sustained blood lead levels of 40–80 μg/100 ml had not resulted in any apparent deleterious effects. Landrigan et al. (*52*) also evaluated the neuropsychological function of a group of children living in the vicinity of the same ore smelter. They concluded that at blood lead levels of 40–80 μg/100 ml subtle impairment of nonverbal cognitive and perceptual-motor skills occurred. However, since their controls were poorly matched with respect to age, history of pica, etc., the etiological role of lead cannot be clearly established. Another study by Landsdown et al. (*53*) found no association between blood lead and intelligence and activity levels of school children living near a smelter. These authors concluded that social factors were more important than physical exposure to lead in determining mental development. However, their social factors were not quantified and very subjective assessments of behavior were used (*54*), thus rendering their conclusions dubious.

Neurological and psychological evaluations have also been made on a large, random sample of children living near a primary smelter in Shoshone County, Idaho (*55*). Landrigan et al. (*56*) evaluating matched pairs of children (with 40 μg/100 ml as the criterion to divide the children into low and high blood levels) reported a significant correlation between lead intake and slowing of motor nerve conduction velocity. However, Gregory et al. (*57*) independently forming their own set of matched pairs (also using 40 μg/100 ml as the standard delineating point), found no differences in nerve conduction velocities or intellectual measures between the lead exposed and control children. Gartside and Panke (*58*) reviewed the matched pairing techniques and statistical analyses used in the Landrigan and Gregory studies. They also noted that in the Landrigan study only six children (out of 202) had nerve conduction velocities below the lower limit of normal children of similar ages (*59*). When other matched pairing and statistical analyses were performed on the same two groups of children, no significant differences were observed. It should be noted that the use of 40 μg/100 ml blood lead level to divide the pairs in arbitrary. Sets of matchings using different dividing points might produce different statistical results. Since conflicting results are produced using different ways to analyze the same data, a significant relationship between blood lead level and nerve conduction velocity in children cannot be regarded as established.

The crux of the problem, applicable to all the studies cited, is that many of the traditional methodologies, approaches, and data analyses used to assess the behavioral and neuropsychological consequences of lead exposure in young children are open to subjective interpretations. For example, the assessment of "hyperkinesis," a syndrome not well defined operationally, often relies primarily on the "impressions" of parents and teachers. Baloh et al. (*46*) found that many mothers reported overactivity in children with elevated lead levels, but this was not observed in objective behavior ratings by a neurologist or psychologist. On the other hand, it is difficult to make a valid assessment of children's behavior for purposes of statistical com-

parison. Matched controls cannot accommodate all the significant, concomitant variables which may affect activity levels and mental functioning. A persistent reliance upon such traditional approaches will only succeed in stimulating controversy. Another general criticism of these studies is that testing is performed primarily on school age children. These studies were unable to document whether excessive lead absorption, encephalopathy, etc. occurred in infancy and early childhood, i.e., during the time that suspected brain damage is most likely to occur. Ideally young children's intelligence and behavior should be assessed before exposure to lead to determine whether an elevated lead burden causes or was caused by defects in mental abilities. Even then, other causative factors must also be considered. Thus the data presently available are inadequate to conclude that subtle psychological, emotional, and neurological sequelae occur in children as a result of lead exposure at levels below those causing clinical symptoms.

Neurochemical and Behavioral Toxicity of Chronic Lead Exposure in Animal Species

In order to obtain more reliable information on the neurologic and behavioral effects of lead exposure during early development, various experimental animal models have been employed. Pentschew and Garro (*60*) showed that nervous system lesions similar to those observed in children with lead encephalopathy could be produced in suckling rats by adding lead to the maternal diet. Rosenblum and Johnson (*61*) developed a similar model of lead encephalopathy in suckling mice. In these animal models extremely high doses of lead were necessary in order to produce symptoms of toxicity, and severe growth retardation occurred in the exposed neonates. Various modifications of these models have been used in studies on the neurochemical effects of lead in young rodents. Krigman et al. (*62*) observed a delay in myelination accompanied by decreased concentrations of brain phospholipids, cholesterol, cerebrosides, and gangliosides in lead-intoxicated suckling rats. Michaelson and Sauerhoff (*63*) observed a 10–20% reduction in the DNA content of the cerebellum of lead-exposed rats. No changes in RNA or protein content were observed.

Observations on the effects of lead-induced changes in neurotransmitter metabolism have been conflicting. Modak et al. (*64*) observed a decrease in acetylcholine content in lead-exposed suckling mice, but Silbergeld and Goldberg (*65*) did not observe such changes in mouse brain. In 1973, Sauerhoff and Michaelson (*66*) reported no changes in norepinephrine, but a 20% decrease in dopamine levels was observed in lead-exposed neonates. However, in later reports, Golter and Michaelson (*67*) were unable to detect changes in dopamine levels, but found increases in norepinephrine levels and an enhanced turnover of whole brain norepinephrine (*68*). Increases in norepinephrine but not dopamine levels have also been reported by Silbergeld et al. (*69*). Sobotka et al. (*70*) and Grant et al. (*71*) found no changes in monoamine levels following lead exposure. Many of these studies were confounded by growth retardation, which may also affect neurotransmitter metabolism (*72*), and thus their significance remains unclear. Studies on the attenuated behavioral responsiveness of lead-treated animals to adrenergic pharmacological agents, such as amphetamine, are consistent and suggest that the monoamine system may be affected by neonatal lead exposure (*73–75*).

Table 1 summarizes some of the pertinent literature on the effects of prenatal and neonatal lead exposure on the subsequent development and behavior of several animal species. Delayed nervous system development, deficits in visuomotor function, impaired learning behavior, abnormal social and aggressive behavior, hyperactivity, hypoactivity, and no changes in activity have been variously reported. Many of these studies employed toxic lead exposure levels. Several recent studies, however, have examined learning behavior after exposure to relatively low levels of lead (*70, 76–78*). These studies suggest that early low-level lead exposure may result in alterations of some subtle and specific aspects of behavior. The nature and significance of these alterations have not been determined, and it is not known whether they were the result of a direct effect of lead or reflect secondary changes. The most frequent and most controversial behavioral measure examined in the studies cited in Table 1 has been locomotor activity. A brief analysis of some of these studies indicates that the investigations on animal models may have confused rather than clarified the human data.

Sibergeld and Goldberg (*79*) exposed suckling mice to 1090–5500 ppm lead acetate through their mother's milk and at weaning directly through the drinking water. They reported a threefold increase in their spontaneous locomotor activity as compared to control mice. Although lead toxicity symptoms were not apparent, the growth of the lead exposed offspring was significantly retarded, as indicated by reduced body weights and developmental delays. Thus the nutritional status of the animals was not adequately considered. Malnutrition confounded the early studies of Sauerhoff and Michael-

Table 1. Behavioral effects of low-level lead exposure in animals.

Reference	Species	Parameters of lead administration	Parameters measured	Effects observed
Xintaras et al. (*85*)	Rat (Albino)	1.5 mg lead acetate/kg drinking H_2O for several days at 6–7 wks	EEG	Disturbance in REM sleep
Brown (*86*)	Rat (Sprague-Dawley)	Nursing mothers gavaged (17–35 mg lead acetate/kg) for 20 days after parturition	T-maze learning	Decreased learning
Brown (*76*)	Rat (Sprague-Dawley)	Lead acetate, either by gavage to the dam or IP to the pup	T-maze (visual discrimination) Spontaneous motor activity	Impaired learning no changes in activity
Goode et al. (*87*)	Rhesus monkey	Fed 0.05 mg–5.0 mg lead acetate in coconut milk for 30 months	Conditioned and delayed response learning	No effect
Allen et al. (*88*)	Rhesus monkey	Infants: 0.5 mg/kg lead acetate in formula for 4 wks Adults: 20 mg/kg in drinking H_2O for 4 wks	"Systematic" observation of behavior	Infants: Hyperactivity, insomnia, abnormal social behavior Adults: No effect
Carson et al. (*89*)	Sheep	4.2 mg lead/kg body weight in diet 4 wks before and throughout gestation and lactation	Visual discrimination learning	Performance deficit
Sobotka et al. (*70*)	Rat	Orally; 5, 15, and 44 mg of lead acetate/kg body weight for 3 wk after birth	General locomotor activity Exploratory activity Passive avoidance Learning behavior Habit-reversal Operant task	 No effects Impaired performance
Silbergeld and Goldberg (*79*)	Mouse (CD-1)	Nursing mothers receiving 2–10 mg lead acetate/ml drinking water; at weaning directly through water	Locomotor activity	3-fold increase in activity
Sauerhoff and Michaelson (*66*)	Rat (Sprague-Dawley)	27,300 ppm lead acetate to nursing mothers; 25 ppm Pb in diet for 3 wk	Locomotor activity	40–93% increase in activity
Reiter et al. (*75*)	Rat (Sprague-Dawley)	5 or 50 ppm lead in drinking H_2O 40 days prior and throughout gestation and lactation to adulthood	Reflex development Locomotor activity in residential maze	Hypoactivity delay in righting reflex
Reiter and Ash (*82*)	Rat	Nursing mothers receiving 5% lead carbonate in diet, at 16 days 50 ppm through drinking water	Locomotor activity in residential maze	Hypoactivity
Grant et al. (*84*)	Rat (Long-Evans)	Stomach intubation 0.01–200 μg lead acetate/g body weight 1–30 days	Aggression towards mice T-maze learning operant conditioning Locomotor activity	No persistent effects
Hastings et al. (*78*)		Nursing mothers receiving 0.2–1.0 mg lead acetate/ml drinking water for 21 days	Spontaneous activity Shock-induced aggressive behavior	No changes in activity reduced aggression
Brady et al. (*77*)	Rat (CFE)	Daily oral intubation (500 mg of lead acetate) to both males and females 60 days prior to mating; females throughout gestation and lactation.	Acquisition and performance of a visual discrimination task (water T-maze)	Performance deficit

son (*66*) who also observed an increased spontaneous activity in the offspring of nursing rats exposed to 27,300 ppm lead acetate in the diet. In a subsequent study, Golter and Michaelson (*67*) found that oral administration of lead acetate to suckling rats did not affect their growth rate, but that these rats continued to exhibit periods of increased motor activity. However, spurious activity measurements could have occurred in either their control or experimental groups; since these investigators tested the activity of six siblings simultaneously without specifying the sexual composition of each litter. The more crucial issue, however, is that the doses of lead administered, resulted in malnourished offspring. Michaelson et al. (*80*) recently reported that early undernutrition, comparable to that frequently reported in lead-exposed mice, resulted in enhanced spontaneous locomotor activity. Castellano and Oliverio (*81*) also reported that malnourishment caused increased exploratory activity and impaired avoidance behavior in mice. Sobotka et al. (*74*) found that malnourished weanling rats displayed a state of heightened "emotionality" and impaired learning behavior. Thus some of the behavioral reponses seen in these lead exposed rodents may be due to early undernutrition.

Reiter et al. (*75, 82*) investigated possible effects of the nutritional status of lead-exposed rats, as well as some of the parameters used to assay locomotor activity. When Reiter and Ash (*82*) exposed male rat pups to high doses of lead via their mother's milk (nursing mothers received 5% lead carbonate in the diet), and after 16 days directly through the drinking water (50 ppm), they observed that food consumption was reduced in the lead treated dams with a corresponding reduction in the growth of the pups. Delays in the development of the startle response, eye opening, and righting reflex were observed in both lead-treated and pair-fed animals; thus indicating that these developmental delays may be due to malnutrition. Lead-treated animals showed an initial hyperactivity at two weeks, which returned to control levels by 6 weeks. When locomotor activity in a residential maze was measured in adults, no treatment differences were observed. When Reiter et al. (*75*) exposed rats (40 days prior to and throughout gestation and lactation to adulthood) to low levels of lead acetate in the drinking water (5 or 50 ppm), delays in the development of the righting reflex and in eye opening were observed, but body weights were not affected. Locomotor activity of adult males was monitored day and night for five consecutive days in a residential maze. On the first test day, hypoactivity was observed in adult lead-treated animals during all periods of the activity cycle. On subsequent days, no changes in diurnal activity were observed, but nocturnal activity was depressed. These authors suggested that lead treatment may result in a temporary increase in locomotor activity in response to a novel environment in young animals, followed by hypoactivity in adult organisms. The recent observation by Reiter (*83*), that lead treatment may disrupt the normal activity cycles of rats, may also explain some of the conflicting results, since most studies have monitored activity levels for only brief periods of time (hours), rather than for consecutive days. Studies (*70, 78, 84*) using lead exposures not resulting in reduced body weights have not found any persistent changes in the activity levels of the exposed rats.

Thus, all possible variations in locomotor activity (hypoactivity, hyperactivity, no change in activity) as a result of lead treatment have been observed. Some of the confusion is probably due to the wide differences in the doses of lead administered; the chemical form, route, and timing of lead administration; the concomitant nutritional state of the animals; and the technology used to assess locomotor activity. In most studies no attempts were made to assess the internal dose of lead by measuring tissue or blood lead levels during the critical periods of brain development. Unwarranted generalizations and extrapolations from limited behavioral measures have frequently been made. Thus, unfortunately, at the present time the animal data remain inconclusive.

Effects of Lead on the Renal System

Goyer and Rhyne (*4*) reviewed the pathological effects of lead exposure on the renal systems of man and animals. Clinically demonstrable effects in man occur only in association with other symptoms of lead toxicity. Studies in man and experimental animals indicate that chronic kidney effects are also the result of a high renal lead content for a prolonged period of time. There are no reports suggesting that kidney damage occurs in asymptomatic cases. The duration and degree of lead exposure necessary to produce irreversible kidney damage is not known. Malignant renal tumors have been produced in mice and rats fed 0.1% or 1% lead acetate (*90–92*). Benign and malignant kidney tumors were observed in rats fed lead acetate (3 mg/day for 2 months and 4 mg/day for 16 months); besides the kidney tumors, neoplasms of the testes, adrenals, thyroid, pituitary, and prostate were also observed (*93*). In male Sprague-Dawley rats on a diet containing 1% lead subacetate, two gliomas were observed besides 13 kidney tumors in 17 animals (*94*).

Subcutaneous injection of lead phosphate, repeated over a 16-month period, produced adenomas, papillomas, and cystadenomas of the renal cortex in albino rats. The total dose of lead administered varied between 120 and 680 mg Pb in the animals getting tumors (*95*). No positive findings have been reported on humans exposed to high levels of lead. Dingwall-Fordyce and Lane (*96*) followed 425 retirees and others with long exposure to lead in a battery factor. They found no increase in cancer incidence but saw an excess in cerebrovascular accidents. There are sufficient publications on ill effects of lead exposure of humans that cases of cancer in these people, even if anecdotal, would have been reported in the literature over the years. When the experimental data on rodents are used for extrapolation to human exposure, the equivalent dose for renal tumor development in man would be 550 mg lead per day which appears to exceed the maximum tolerated dose of lead for man (*97*). Lead is thus not considered a human carcinogen.

Effects of Lead on Other Organ Systems

Effects on Chromosomes

Contradictory results have been published in the last few years with respect to a suggested increased occurrence of chromosome aberrations in workers occupationally exposed to lead. Schmid et al. (*98*) found no evidence of increased chromosome aberrations in lead manufacturing workers; in policemen with increased blood lead levels (*99*); or in male workers exposed to lead oxide fumes in a shipbreaking yard (*100*). However, an increase in chromosome aberrations in people occupationally exposed to lead has been reported by Forni and Secchi (*101*); Schwanitz et al. (102), and DeKnudt et al. (*103*). Unfortunately, most of these studies are based on very few (*10–20*) subjects. A study by Forni and Secchi (*104*) showed that the rates of chromatid changes were higher in 65 workers with preclinical and clinical signs of lead poisoning but were not significantly raised in workers with past poisoning. Forni et al. (*105*) also examined 11 subjects before and during initial exposure to lead. The increase in rate of abnormal chromatid metaphases was doubled after one month of exposure, was further increased after 2 months, remained in this stage up to 7 months, and then decreased. The fact that most alterations were of the chromatid type (i.e., occurring in cell culture after DNA synthesis) indicates that these may be culture-produced aberrations, not repaired in the presence of lead, and may not reflect a real *in vivo* situation. Thus the biological significance is unknown.

Effects on Reproduction

It has been reported since antiquity that lead compounds can be used as abortifacients, and that lead poisoning is associated with reduced fertility, miscarriages, and stillbirths (*106*). Little evidence is available as to whether subtoxic levels of lead affect fertility or cause fetal injuries in man. Lancranjan et al. (*107*) reported that moderate absorption of lead (blood Pb 50–80 μg/100 ml) in male workers resulted in hypospermia and teratospermia. A slightly increased absorption of lead had no such effects. A recent study by Fahim et al. (*108*) suggests that subtoxic lead absorption during pregnancy may be associated with an increased incidence of preterm delivery and early membrane rupture. A high correlation was found between lead concentration in maternal and fetal blood; both were significantly higher in the preterm pregnancies and early membrane ruptures than in term pregnancies. However, these authors offer no explanation for the large differences they observed between maternal and fetal blood lead levels. Other studies have shown that the quantities of lead present in newborn infants generally reflect that of their mother (*109–112*). An analysis of human fetal tissues (*113*) demonstrated that placental transfer of lead begins as early as the 12th week of gestation and that total lead content increases throughout pregnancy, with the highest concentrations occurring in bone, kidney, and liver; but significant amounts are also present in blood, brain, and heart. However, as Barltrop (*113*) has pointed out, the distribution of lead within the fetus at different stages of development is probably more important than the total amount present at birth.

Several animal studies indicate that lead exposure may impair the reproductive ability of both males and females. Schroeder and Mitchener (*114*) observed that lead-exposed mice produced fewer litters, and that many of the offspring had reduced body weights and experienced early death. Stowe and Goyer (*115*) studied the paternal and maternal effects of lead on the reproductive performance of normal and lead-exposed F_1 offspring. Reduced birth weight, growth, retardation, and decreased postnatal survival were observed in the lead-intoxicated rats. The authors made no assessment of lead body burden. Hilderbrand et al. (*116*) observed that sexually mature male rats exposed to lead acetate for 30 days exhibited impotence and prostatic hyperplasia at blood lead levels of 14–26 μg/100 ml, and testicular damage at blood lead levels of 50–100 μg/100 ml. Similarly exposed

female rats exhibited irregularities of the estrous cycle at blood lead levels of 14–30 μg/100 ml and ovarian cysts at blood lead levels of 50–100 μg/100 ml. Der et al. (*117*) exposed 21-day old female rats daily to subcutaneous injections of lead acetate for 40 days. A delay in vaginal opening and onset of estrous was observed in lead-treated females (blood lead, 60 μg/100 ml) fed a normal protein diet. Vaginal opening and estrous cycles never occurred in females treated with lead (blood lead, 108 μg/100 ml) and fed a low protein diet.

Although malformations have not been observed in most experimental investigations, a few studies have demonstrated a teratogenic effect of lead. Urorectocaudal malformations were produced in rats (*118*), and tail abnormalities in hamsters (*119*) as a result of intravenous lead administration during early gestation. Cardiac abnormalities have also been reported after treating chick embryos with lead (*120*). All these studies employed acute dosages of lead. There are no convincing reports that lead in teratogenic in humans.

Little is known about the effects of lead on reproductive performance and postnatal development following chronic, low-level exposure. Kimmel et al. (*121*) exposed female rats chronically to lead acetate via the drinking water (0.5, 5, 50, 250 ppm) from weaning through mating, gestation, and lactation. Vaginal opening was delayed 1–2 weeks, in females exposed to 50 and 250 ppm lead, but estrous cycles and pregnancy rates were normal. No teratogenic effects were observed, although exposure to 250 ppm lead acetate caused a slight, but nonsignificant increase in fetal resorptions. The lead-treated animals produced litters of normal numbers, but the offspring from the 50 and 250 ppm groups weighed less at weaning and showed delays in physical development. Reiter et al. (*75*) also observed developmental delays in rat offspring exposed to 50 ppm lead throughout gestation and lactation. Whether these delays in development were the result of a direct effect of lead on the nervous system of the pups or reflect secondary changes (malnutrition, hormonal imbalance, etc.) is not clear. Whatever the mechanisms involved, these studies do suggest that low-level chronic exposure to lead might induce postnatal developmental delays.

Effects on the Immune System

Several studies in animal models have suggested that lead may interfere with various aspects of the immune response. Lead has been reported to result in an increased susceptibility to infection in mice and rats. Selye et al. (*122*) found that rats injected with lead acetate (minimal) effective dose 1 mg/100 g body weight) were susceptible to a variety of bacterial endotoxins to which this species is usually resistant. This susceptibility occurred only when lead and the endotoxin were administered either simultaneously or within several hours of each other. Hemphill et al. (*123*) found that mice injected with subclinical doses of lead nitrate for 30 days showed a reduced resistance to *Salmonella typhimurium*. Gainer (*124*) observed that administration of lead aggravated the response of mice to viruses. Various factors may be involved in producing this enhanced susceptibility to infection. Lead can bind to antibodies (*125*) and when administered orally it diminished the level of circulating antibodies in mice (*126*). Trejo et al. (*127*) observed that an intravenous injection of lead had no effect on antibody production in rats, but impaired their phagocytotic activity. Vengris and Mare (*128*) found no immunosuppression in chickens fed lead acetate and challenged with Newcastle disease virus, but toxic levels of lead suppressed the interferon response. Bingham et al. (*129*) found that the inhalation by rats of lead sesquioxide aerosol (10 $\mu g/m^3$) significantly reduced the number of alveolar macrophages. Bruch et al. (*130*) found that rats inhaling particulate lead oxide (200 $\mu g/m^3$) showed mitochondrial and endoplasmic reticular damage of alveolar macrophages and pneumocytes, and exhibited a considerable loss in the activity of the benzopyrene hydroxylating enzyme. Further studies are needed in order to determine and understand the effects of lead on immune mechanisms in animal models. A difficulty in determining the effects of lead on the immune system of children, is that urban, lead-exposed children are also likely to be at high risk for contracting infectious diseases. Reigart and Graber (*131*) found that 12 children with blood lead levels of 41–51 μg/100 ml did not differ from 7 children with blood lead levels of 7–13 μg/100 ml with respect to complement levels, immunoglobulins, or anamnestic response to tetanus toxoid antigen. There do not appear to be any systematic epidemiological investigations on the effects of elevated lead levels on the incidence of infectious diseases in man (*132*).

Effects on the Endocrine System

Excessive exposure to lead has been associated with an impairment of endocrine function in both man and experimental animals. The uptake of iodine and its conversion to protein-bound iodine was retarded in lead-intoxicated rats (*133*). Iodine uptake was also decreased in lead-poisoned patients, but this effect could be overcome by ex-

ogenous administration of thyroid-stimulating hormone (*134*). High lead levels resulted in a decreased secretion of pituitary hormones (*135*) and an impairment of adrenal gland functioning (*136*) in lead-poisoned patients. Whether low-level chronic lead exposure can affect pituitary, adrenal, and thyroid to be determined.

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