LEAVING THE HOUSE OF BUTTERFLIES

Subclinical Lead Toxicity and Blood Lead Screening for Asymptomatic Populations

by

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Introduction:

Screening questionaires, family history and Public Health Priority Area listings should be used to identify asymptomatic low risk persons.

Asymptomatic children aged 9 to 72 months should be screened yearly for lead exposure until a child has documented subclinical (<10 mcg/dl) blood lead levels on two occasions that are consistant with an environmental risk comparable to that of a priority three community. It is important to recall that children are statistically at highest risk from one to three years old, at which time much crawling and hand to mouth activity occurs. Any change in the child's environment including a new job for parents, a new day care center or nursery school, the renovation of a previously "safe" house or movement to a safe house in a locality where local industry, incinerators or local water supplies may be a point source for lead contamination may require an increase from this level of screening.

Unfortunately, children at highest risk include those of Afro-American descent, those receiving Medicaid, and those from low socioeconomic backgrounds. These are precisely the people who have the least access to health care. Senator Patrick Moynihan's office has estimated that approximately one third of the children born in 1980 spent at least one year on Medicaid. It is unlikely that this figure will have improved for 1990.

It is important that primary care physicians be educated as to the importance of large scale screening of asymptomatic populations for blood lead (PbB) levels.

Because of the financial burden and the practical difficulties of large scale screening, initial efforts need to be prioritized in accordance with Center for Disease Control (CDC) guidelines and N.J. State Department of Health guidelines.

Although the states of New Jersey and Massachusetts have passed regulations stipulating the screening of high risk populations, the broader implementation of blood lead monitoring will only occur as the public and physicians become aware of the magnitude and the pervasiveness of the problem. As this process unfolds, screening recommendations will undoubtedly change.

Historically, environmental lead pollution peaked during the period 1976-80. Global emissions from lead alkyls used primarily for gasoline additives accounted for 200,000 tons of lead per year prior to 1976. In comparison, lead smelting and natural sources accounted for 20,000 and 2,000 tons/year respectively.[1]

The average estimated daily absorbtion of lead into the blood of a prehistoric human was 210 ng; a contemporary adult absorbs 29,000 ng/day.[2] The lead content of fresh tuna albacore, which is used as a benchmark for estimating prehistoric levels, is 0.3 ng/gm. Albacore muscle from a lead soldered can contains an average of 700-1400 ng/gm. Whereas a U.S. citizen has a typical intake of 0.29×10^{-4} gm/day, acute toxicity occurs at 1.5×10^{-4} gm/day.[3] Because of world wind patterns, airborne lead pollution effects in remote parts of the southern hemisphere are estimated to be one tenth of those in the northern hemisphere.[4]

Treatises on classical lead poisoning were published as early as 1839[5], but the terms "plumbism" and "saturnalia" reflect a knowledge of the toxic effects of lead as early as the time of Pliny.[6] Although some members of the public health community made staunch but short lived objections to the introduction of lead additives to gasoline by Standard Oil in the 1920's[7], the heightened institutional concern for lead toxicity at this time is due in large measure to the staged withdrawal of the economic risk to the chemical and automotive industries that are now protected by statute of limitations.

It is no coincedence that the final phase of the reduction in the allowable amount of lead in interior home paint occurred in 1978 during the four year phase down of leaded gasoline. In 1978, Federal legislation set an upper limit of 0.06% lead in interior home paint.[8] Use of lead solder in plumbing was banned by federal law in 1986.[9] However, in 1991 the average amount of lead in pigments of bread wrappers taken from store shelves was 23 mg.[10]

On 2/21/91 the Assistant Secretary of Health James Mason announced a plan to eradicate childhood lead poisoning.[11]

Children:

The primary factor in the association between children from low socio-economic groups and led toxicity is the complex of older, less well maintained housing, proximity to heavy vehicular traffic and/or proximity to industrial complexes and incinerators. Because anemia facilitates lead absorbtion, children who are malnourished are at further risk.[12] Afro-American children incur additional risk because their bone density is higher than age, sex and weight comparable Caucasian children.[13,14] Approximately 17% of Caucasian children above the poverty level have PbB levels above the EPA defined level for neuropsychological impairment; for poor Black children the rate is 55%.[15]

Schwartz et.al.[16] used NHANES II audiometry data on 4,519 children aged 4-19 years old to confirm earlier work showing a direct correlation between elevated hearing thresholds from 500-4000 hz and blood lead(PbB) levels. This correlation remained constant throughout the entire range of PbB levels indicating that there was no lower threshold for the effect of lead ($P < 0.001$). PbB levels were also significantly inversely associated with age that a child first sat up, walked and spoke. Again, no threshold for effect was found for the association between PbB and the age that a child first walked. A threshold for effect was found for the age at which a child first sat up and first spoke, corresponding to the 28th percentile of lead rank. PbB was not associated with a later diagnosis of speech difficulty, but it was associated with the probability of a child being diagnosed as hyperactive.

This should not be construed to mean that Attention Deficit Hyperactivity Disorder (ADHD) is caused soley by elevated PbB levels. It does add further weight to the conclusions of an increasing number of animal and human studies that link elevated PbB levels with a predispositon to a variety of behavioral problems.[15,17-23,28,29]

In 1980 in a Supplement to Developmental Medicine and Child Neurology, Michael Rutter made a closely reasoned and encyclopedic review of studies looking at PbB and impaired cognitive/behavioral functioning. This has historical significance only in that it is probably the last serious attempt to minimize the effects of elevated PbB levels, which he defined as above 40 mcg/dl.[24]

Oliver David, et.al., in a series of studies spanning the ten years from 1976-85 evaluated the association between PbB and hyperactivity. They took a group of ADHD children with elevated PbB levels and treated them with chelation. Using a random double blind treatment regimen, they found statistically significant and obvious behavioral improvement based on the Conners Rating Scales for Hyperactivity.[25-27]

But perhaps the most chilling effect of low level PbB toxicity is its effect on cognition in general and I.Q. in particular.

In a cohort study of 249 Boston children the PbB level of umbilical cord blood was inversely related, after adjustment for 26 covariates, to cognitive development assessed every six months up to the age of two years. The effect was most evident in the children in the upper and middle tertiles of PbB (6-21 mcg/dl).[30]

The following year another study evaluated a cohort of 537 children born between 1979-82 to women living in and around the Australian lead smelting town of Port Pirie. Within this cohort the mean concentration at ages 15 and 24 months exceeded 21 mcg/dl. PbB levels were obtained at birth, 6,15,24,36 and 48 months. Mental development was assessed at the age of two years by the Bayley Scales of Infant Development. At four years of age the children's abilities were evaluated with the McCarthy Scales of Children's Abilities (MSCA), which yields a General Cognitive Index (GCI) scale based on a median score of 107.1. After multiple regression analyses with adjustment for 16 covariables that could act as confounders, they found that a child with an average PbB level of 31 mcg/dl during the first four years of life would have a GCI score 7.2 points lower than a similar child with a PbB level of 10 mcg/dl. The downward shift of distribution of GCI scores represents 1/2 a standard deviation (one S.D. is 15 GCI points). No threshold for effect of lead was evident. The authors concluded that because the observed effect was stronger after four years than after two years, that "... any adverse effect of lead is cumulative and may result in long term impairment in development rather than a delay in development."[31]

Other epidemiological studies in Scotland, Denmark and Greece have shown that PbB levels as low as 10-14 mcg/dl can result in a decrease of mean I.Q. scores of 4-7 points.[32-34] Herbert Needleman's commentary is worth repeating in toto:

> This 4-7 point difference in means has been taken by some as a small effect. This is deceptive. The cumulative frequency distribution for IQ, typical for many distributions, is sigmoid. When cumulative distributions between groups are plotted and compaired, a shift in the curve resulting in a difference in medians of six points results in a four-fold increase in the rate of severe deficit (IQ < 80). In addition, the same shift in distribution truncates the upper end of the curve, where superior function is displayed, by 16 points. This means that five per cent of lead exposed children are prevented from achieving truly superior function (IQ > 125). The costs of this effect at the high end of the distribution have received no attention; they may be extraordinarily important to our society.[15]

In conclusion, a large number of studies of low level lead exposure have found that lead is associated with disturbances in cognition, behavior and attention at levels previously considered to be benign. A meta-analysis of 24 recent studies found a combined P value of < 0.0001 in support of this association. To undermine that joint possibility there would have to be 93 unpublished negative studies.[35]

Under the 1991 CDC guidelines, as many as four million children are at risk for health problems associated with lead poisoning.[36] Seventy-four per cent of all private housing built before 1980 contains some lead paint. Three million tons of lead line the walls and fixtures of 57 million homes. One out of nine children under age six has enough lead in their blood to place them at risk. Children with elevated PbB levels are 6 times more likely to have reading disabilities.[37]

The socio-economic impact of endemic elevated PbB levels has been estimated by CDC econometricians in a variety of ways. Avoided medical costs from preventing a child PbB level of 25 mcg/dl are $ 1,300. Avoided special education costs for that child are $ 3,331. Based on a 0.25 point I.Q. decrement per mcg/dl PbB increase, and a 0.5% decrease in wage rate for each I.Q. point decrease, they estimated a decrease in wage rate of 0.125% for each one mcg/dl in PbB level.[35]

At the far end of the childhood rearing and educational process we collect our failures in the prison system. The U.S.A. has held the dubious honor of one of the highest rates of violent death, of incarceration, and of gasoline use per capita in the developed world. Is there an association?

Dr. Herbert Needleman, one of the deans of American PbB research comments on this association.

> "' There are a number of parallels between risk factors for criminality and lead. Wilson and Herrnstein, in Crime and Human Nature[38], argue that criminality has constitutional roots. They ground their position on seven findings:
> 1) criminal behavior shows itself early in life;
> 2) criminality is commoner in males;
> 3) the rate of criminal behavior is higher in Blacks;
> 4) the rate is higher in urban areas;
> 5) criminals have lower IQs, with particular impairment on verbal scores;
> 6) criminals have a high incidence of hyperactivity in early childhood; and
> 7) the families of criminals are disorganized and aggressive, and their homes are ill kept.'
>
> All of the above associations also exist either as effects of lead or risk factors for lead exposure. Lead exposure occurs early in life; it is commoner in males, in Blacks, and in city dwellers; it lowers IQ, particularly verbal IQ scores; and dirty disorganized households have children with higher lead levels."[15]

No one is claiming that lead is the sole cause for crime or delinquency or ADHD or developmental delay or miscarriage. What is clear is that the cumulative experience of the last 150 years behooves us to evaluate and reduce the lead factor in our population. Because of the accumulation of effects physiologically, developmentally and economically, the place to start is with the children.

Adults:

> "Between 1976 and 1980, mean blood [lead] levels in the general population dropped from 14.6 to 9.2 mcg/dl, corresponding with decreased sales of leaded gasoline." [39]

While it is heartening that the spigot could be closed so easily, unfortunately for most adults, their tanks were already full.

Only a small variable fraction of ingested lead is actually absorbed, but once absorbed the lead is distributed through the common pathway of blood into three physiologically distinct compartments. Rabinowitz et.al.[40,41] developed the three compartment model based on radioactive lead tracer and balance data. His figure from the 1990 EPA Toxicological Profile for Lead gives the lead content, the mean half life of each pool and the rates of lead movement between pools.[48]

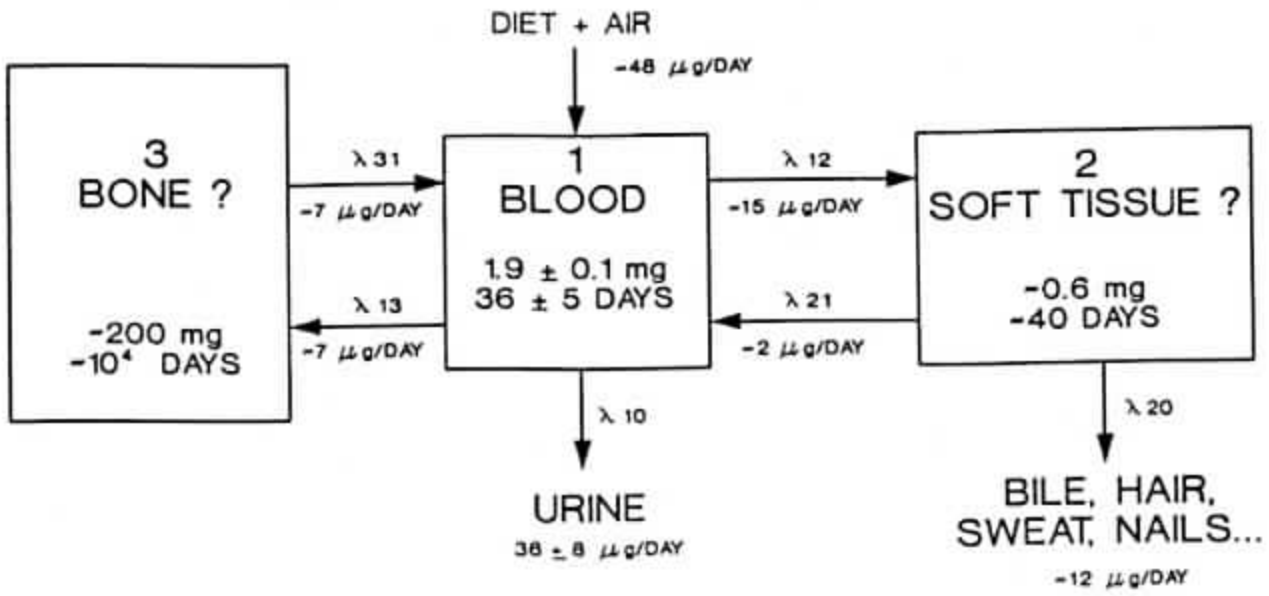

Fig. 4.1. Lead metabolism model. *Source:* Rabinowitz et al. 1976.

Because of similarities to calcium, lead collects in the bony compartment. An estimate of cumulative total lead released into the atmosphere could be generated by an integral function:

$$\int_{'24}^{'76} Fx\left\{\left(\text{Vol gasoline sold/yr} \times \text{mg/gal}\right) \times \text{country}\right\} \times 1.4\ dt + \int_{'76}^{'80} Fx\,dt + \int_{'80}^{'92} Fx\,dt$$

If we take the U.S. as an example, the period from 1924-30 saw the introduction of tetra-ethyl lead into essentially all gasoline formulas. Grace Burnham, then Director of Workers Health Bureau wrote to the editor of the New York Times on 7/6/25:

> If the expectation of Standard Oil officials that 15 billion gallons would be sold in the next year proves true, it would mean that 50,000 tons of lead would be distributed over the streets of the country.[7]

From 1930-76 the amount of lead per gallon was that sufficient to optimize engine compression ratios in the anti-knock formulas. Ethyl gasoline production peaked in 1976 during which some 200,000 tons of lead were added to the atmosphere.[7] From 1976-80 the allowable amount of lead per gallon was phased down in the U.S. From 1980 to present the allowable amount of lead/gallon has been reduced by a factor of 100.

An additional factor for contributions from coal mines, Lead, Iron, Zinc and Copper smelting, and natural sources could be added. Each of those sources alone is an order of magnitude lower than that provided by gasoline combustion. Their combined effect could add a factor of 0.4 to each yearly total if the correlation of mining to gasoline production remained constant.[7]

The purpose of this exercise is to point out that although children in 1992 remain at risk, people living during the period 1924-80 have been exposed to a far higher cumulative exposure to lead than their children or their grandchildren. Even in adults whose current PbB level is below the current CDC guideline level of 10 mcg/dl, who have already adjusted to an average estimated I.Q. loss of 2-5 points, and to the effect of lead on developmental disabilities of their childhood, there remains a total body lead burden that is 100 to 1000x their total body blood lead content.

While the half-life of lead in blood and soft tissue ranges from 36-40 days, the half-life of lead in the bone compartment is 27 years.[40] This rate of transfer from bone to blood and soft tissue compartments may accelerate with osteoporosis and immobilization for periods as short as a week, as calcium efflux increases.[42-45] This in turn would mean that geriatric patients may well come under the effect of a reverse lead toxicity at a time when they have less physiological and mental reserve.

As early as 1970, Prerovska et.al.[46] in Prague found elevated PbB levels and decreased ALA-D activity in persons with prior occupational exposure who had had no exposure for the previous 3 to 17 years.

Appendix V provides a spectrum of Lowest Observed Effect Levels (LOEL's) for adults and children.[47] The EPA lists three populations at risk: preschool age children, fetuses and white males aged 40-59 years old.[48]

Elevated blood pressure is associated with PbB levels possibly as low as 7 mcg/dl. A possible mechanism for this effect is the assertion that endothelial cell prostaglandin synthetase responsible for the production of prostacyclin, is sensitive to inhibition by lead.[49]

Given the pervasiveness of lead in the biosphere one can appreciate the difficulty of finding suitable control groups (i.e. adults in developed countries with hypertension and zero PbB levels) to evaluate the effects of PbB levels on hypertension. Comparison of age, sex and weight matched groups of hypertensive adults with PbB levels of above and below 25 mcg/dl may show no difference if the threshold for effect is much lower (or variable). This association could be further masked by our success with a variety of antihypertensive medications.

Using the New Jersey State Department of Health cutoff of PbB levels < 15 mcg/dl for "subtle" or "subclinical" lead toxicity in children,[50] the only clear risk factor for asymptomatic adults at this time is hypertension.

Adult patients with chronic anemia, decreased hearing acuity, renal insufficiency,[47] acute intermittant porphyria,[51] and gout[9] may benifit from PbB screening even when no occupational or environmental exposure is evident.

Epilogue:

In October of 1924, 39 of 49 workers at the Standard Oil tetraethyl lead processing plant in Elizabeth, N.J. died or were severely poisoned by exposure to organic Lead alkyls. A supervisor at a nearby facility remarked that "These men probably went insane because they worked too hard."7

In a similar Du Pont facility in Deepwater, N.J., workers called the plant "'The House of Butterflies' because so many of their colleagues had hallucinations of insects during their bouts of lead poisoning. 'The victim pauses, perhaps while at work or in rational conversation, gazes intently at space and snatches at something not there.'"7 So now the butterflies have flown, and we are left with the intriguing question of whether, and how, we too may leave the House of Butterflies.

GLOSSARY

Screening- refers to testing of large numbers of asymptomatic persons in order to identify those in need of further evaluation.

Diagnosis- refers here to categorizing a child's condition according to severity of lead burden and toxicity. Then on the basis of the category management is selected.

Asymptomatic- deliberately the most poorly defined term, since any one of a wide range of physical or psychological signs or symptoms may be an indicator of lead toxicity.

Lead poisoning- a general term used to describe episodes of acute symptomatic illness.

Lead toxicity- a broader term defined by PbB and erythrocyte protoporphyrin (EP) levels that includes persons with elevated PbB levels who are asymptomatic. The following guidelines were related by Dr. Roxanne Kendall of the St. Peters Medical Center Lead Clinic. They must be correlated with the classification protocol in Appendix II.

PbB	
< 10 mcg/dl	SUBCLINICAL; probably not toxic.
10-15 mcg/dl	SUBTLE: increase monitoring
15-20 mcg/dl	SYMPTOMATIC; environmental evaluation
> 20 mcg/dl	must report to NJS Department of Health

EPA- Environmental Protection Agency

CDC- Center for Disease Control

ALA-D- Delta-amino levulinic acid Dehydrase; an enzyme poisoned by lead resulting in anemia.

EP- a hemoglobin precursor that builds up when ALA-D is inhibited.

Recommendations for Blood Lead screening of Asymptomatic Populations

Recommendations are written from the point of view of an office manager or primary physician in charge.

a) Copy Appendix's I-V.
b) Confirm that your laboratory will accept and process 500 microliter capilllary blood samples for EP and PbB. Also request quality control reports on lead content of their microliter containers and needles.
c) Identify referral sources for elevated (> 20 mcg/dl) PbB levels, which may include the Public Health Department, local Child Lead Clinics, and pediatric ICU units capable of handling acute lead poisoning. (St Peters Medical Center Lead Clinic (908) 745-6663.
d) Go over Appendix I "Capillary Sampling Protocol" with nursing staff or phlebotomists, and decide on protocol particulars, e.g. simple hand washing vs silicone spray.
e) Place information in the waiting room to alert patients to risk factors for lead toxicity.

1) Have front desk persons use Appendix III to identify geographic priority levels for each parent and provide them with a "Childhood Lead Poisoning Risk Assessment Questionaire" (Appendix IV). A smaller questionaire should be provided at each subsequent visit. c.f. Appendix II.

2) The initial PbB screening should occur between 6 and 12 months of age. Sufficient capillary blood should be drawn from a heel stick into a 500 microliter heparin or EDTA tube (green or lavender top) for a PbB and EP level.
LOGIC:
EP blood levels are not sensitive enough to identify PbB levels below 25 mcg/dl. They are however still a good screen for anemia, which may enhance concommitant lead absorbtion, or occur alone as a result of iron deficiency. While venous blood is more reliable in terms of PbB accuracy, it is physically difficult for many office personnel to perform on infants, and may increase noncompliance of parents who perceive their child as being used for a pin cushion.

3) Any screening capillary PbB level > 15 mcg/dl should nonetheless be confirmed with a venous sample.
COMMENT:
Improvement in the accuracy of capillary PbB levels and minimization of contamination from containers, finger wipes and external sources is paramount.

4) The screening schedule from Appendix II may be used for follow up screening, classification and management for children.

5) If average PbB levels continue to drop, and as preliminary results of universal screening become available, we may be able to reduce our vigilance. Physicians should be aware that they are susceptable to a bias towards ordering screening tests and procedures that are not always benign.[52-54] However, now is not a time for reduced vigilance.

6) Venous PbB levels should probably be included as part of a prenatal workup for pregnant women.[30,31,55]
LOGIC:
This would provide an opportunity to introduce the expectant mother to environemtal lead risks to the foetus and infant. Elevated maternal PbB levels could be followed up with environmental investigation and umbilical cord blood samples as necessary.

7) A verbal or written questionaire similar to Appendix IV can be used for adults.

8) Adults with hypertension should be screened with a venous PbB level.

9) Inertia, lack of resources and lack of access to health care will act against what amounts to a period of universal child PbB screening. Where triage is necessary, a coherent system of questionaires, community intervention PbB level screening will identify those most at risk.

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FIGURE 1.—Advertisement featuring the Dutch Boy trademark on a can of white-lead paint which emphasized the durability of the product. SOURCE: *Oil, Paint and Drug Reporter* magazine, December 6, 1937.