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Lead Poisoning: the Evolving Definition

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Lead poisoning has been recognized for thousands of years but remains an occupational and environmental hazard worldwide. While some have attributed its first recognition to Hippocrates around 500 BC, the first description that approximates modern understanding of the disease is found in a poem by Nikander of Colophon in 200 BC.[1] The major symptoms of lead poisoning can be identified in Nikander's poem including lead colic (abdominal pain), peripheral neuropathy (wrist drop), encephalitis (mental confusion), and anemia (pallor). But early physicians had difficulty in separating lead colic from the far more common infectious gastroenteritis. Modern recognition of the symptom complex of acute lead poisoning dates to a series of essays by Sir George Baker in 1767 who unraveled the cause of the Devonshire Colic. Baker recognized that lead introduced into the local apple cider by soldered repairs to the cider presses was the cause. He was aided in this seminal insight by Benjamin Franklin who reported to Baker that New Englanders suffered from the "dry gripes," (abdominal pain without diarrhea) from West Indian rum contaminated by lead from the "lead worms" (condensation coils) used in the stills.

Saturnine gout was added to this description by Alfred Barring Garrod in 1859 who devised a method for measuring uric acid in blood and recognized that many of his hyperuricemic gout patients in 19th century Britain were lead workers.[2] Current investigations indicate that uric acid itself contributes to the development of hypertension and renal failure.[3, 4]

Baker's classical description remained the clinical standard for recognition of acute lead poisoning until the 20th century when blood lead measurement became available. The exponential increase in the use of lead during the industrial revolution exploded further with the introduction of tetraethyl lead as an anti-knock agent in gasoline in 1923. Under the influence of Robert Kehoe, research on the health effects was largely limited to studies in children. Kehoe, an industrial hygienist, who was simultaneously the Medical Director of the Ethyl Gasoline Corporation and the Kettering Laboratory of Applied Physiology at the University of Cincinnati declared blood lead levels of 80 µg/dL as acceptable for lead workers.[5] At this level of exposure, symptomatic lead poisoning was usually present. Seizures, sometimes fatal, occurred in children who consumed lead-paint chips in deteriorating lead-painted housing, a practice called "pica." These children had blood lead levels of 80 µg/dL or higher. While studies of childhood lead poisoning in the 20th century established the long-term impairment of cognitive development induced at even low levels of lead absorption, few studies of the effect of lead on adults were performed until the 1970s.

On the basis of epidemiologic data, the acceptable blood lead level for children promulgated by the Center for Disease Control and Prevention (CDC) was progressively reduced from 60 µg/dL

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to 10 µg/dL from 1960 to 2000.[6] However, the acceptable level for adults, established by the Occupational Safety and Health Agency (OSHA) in 1978, remains unchanged—50 µg/dL. The occupational standard for lead exposure remained unchanged despite a substantial body of evidence obtained in Europe, Australia and the United States that low-level lead exposure in adults contributes to the development of hypertension and kidney disease.[1] Nevertheless, in 1973, the President of the American Petroleum Institute, representing the lead industry and echoing Kehoe, declared that lead poisoning does not occur at blood lead levels below 80 µg/dL and that 10 to 40 µg/dL is "normal" for children and adults.[6]

While examination of symptomatic lead workers followed the definition of lead poisoning described by George Baker, epidemiologic studies of normal populations not heavily-exposed to lead, give a very different picture of the adverse effects of lead on both children and adults.[7] Such studies typically exclude individuals with identified disease. Epidemiologic studies identified subtle adverse effects in cognition, blood pressure, renal function, in populations with exposure defined by lead measurements in body tissues (*e.g.*, blood, bone, teeth) that could not be attributed to lead in a single individual. Many of these investigations examined the cumulative impact of lead absorption through analysis of lead stores in bone or teeth using x-ray-induced x-ray fluorescent techniques. Thus, the reduction in cognitive development in children exposed to low levels of environmental lead that cannot be confidently attributed to lead at the bedside, can be statistically significant when large numbers of individuals are evaluated. Similarly, epidemiologic studies of normal adults have established adverse effects of lead on blood pressure and renal function at ever lower levels of exposure sometimes including blood lead concentrations less than 10 µg/dL. These studies show no threshold for the adverse effects of lead on blood pressure and renal function.[7]

The incidence and prevalence of chronic lead nephropathy in adults are not known because the hypertension and interstitial nephritis induced by lead are rare even among lead workers. Rare events, occurring, for example, in less than 1% of those exposed, cannot be reliably detected in the relatively small groups of lead workers available for study. There is, however, good evidence that lead contributes to renal disease of non-lead etiology. Hypertension and reduced renal function unrelated to lead exposure are very common among middle-aged males making it difficult to dissect out the contribution of lead. Searching for sustained lead-induced hypertension and renal dysfunction among worker cohorts is therefore, usually futile. The low-molecular weight proteinuria and enzymuria which predict the development of renal failure in cadmium workers, do not predict renal failure in lead workers. In addition, the *healthy worker effect* tends to remove lead workers with kidney disease from the workplace. The contribution of lead to kidney failure can, however, sometimes be identified by excessive body burdens of lead identified in the adult kidney clinic.[8] In contrast, the transient proximal tubule reabsorptive defect, known as the Fanconi syndrome, induced by acute lead poisoning, occurs in virtually all individuals (experimental animals and humans) when blood lead levels exceed 80 µg/dL.[1]

The geometric mean blood lead levels in the United States diminished from 12.8 µg/dL in 1984 to 1.48 µg/dL in 2005 through both voluntary and legally required reductions in lead exposure in the United States. During this period, numerous epidemiologic studies at blood levels below 10 µg/dL showed adverse effects

on cognitive development in children and blood pressure and renal function in adults. Studies published up to 2007 showing low-level lead exposure effects have been summarized in *Recommendations for the Management of Adult Lead Exposure* by Kosnett, *et al.*[7] Some of these studies showed adverse effects at levels below 5 µg/dL. As the diminishingly small adverse effects are examined at ever lower blood lead concentrations, the variability in the measurements, often expressed as the standard deviation, increases relative to the means and it becomes increasingly difficult to find statistical significance unless the populations studied are extremely large.

No threshold below which there are no adverse effects of lead has been found; no amount of lead absorption is without hazard. Practical compromise for policy development has lead to the selection of 10 µg/dL as the arbitrary upper acceptable blood lead level for the general population for the time being. For pregnant women, and women who may become pregnant, the maximum safe level has been designated at 5 µg/dL.[7] The definition of lead poisoning has thus shifted from symptomatic disease at blood lead levels above 80 µg/dL to adverse effects in asymptomatic individuals at blood lead levels below 10 µg/dL. The concept that adverse effects could be detected by epidemiologic studies in large groups but not in the individual worker has been unacceptable to the lead industry concerned more with the cost of clean-up.[6] While blood lead levels fell markedly in the United States over the last 50 years, exposure in the developing world remained high, around 40 µg/dL.[9] The source of the heavy exposure to lead is often unclear.

Recent studies have reinforced the principle that prevention is the treatment of choice for lead poisoning at blood lead levels below 45 µg/dL.[10] Although chelation therapy is frequently recommended at blood leads over 80 µg/dL, it is reasonable to remove asymptomatic individuals from exposure rather than chelating them. Chelation hastens the rate of lead removal from the body but the same negative balance occurs naturally over weeks rather than days by urinary excretion when exposure is stopped. While the definition of lead poisoning has evolved over time, the public health imperative remains unchanged—prevention.

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