

# The lead files

A chronicle of ignorance, avarice, and progress

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Some years ago, at a teaching conference in Long Beach, California, Dr. Mellinkoff discussed the case of a middle-aged Cambodian man who presented to the emergency room with severe episodic abdominal pain. Anyone could tell he was in agony from his facial expression and constant shifting motion. However, his physical examination showed no evidence of peritoneal irritation or bowel obstruction, nor did his radiographs or blood tests suggest any gastric, duodenal, pancreatic, or biliary disorder. Even a porphyria test proved negative.

Then, just as mysteriously as it had begun, the man's pain resolved, and he left the hospital, only to return weeks later in the same distressed state. This time, however, some of his red cells contained subtle blue inclusions. A bell rang, and a blood specimen was sent for a lead level. When it returned

unequivocally high, discussions through a translator finally solved the mystery. Before arriving in the United States, while he was still living in a refugee camp, the patient had been charged with procuring alcohol for use in religious ceremonies. Being an enterprising fellow, he built a still from a car radiator and produced what was needed. Periodically, he also drank the spirits.

Cracking a case of recurrent colic—and then deducing that a soft, blue-white metal leaching from radiator solder into homemade brew was its cause—was no doubt exhilarating to the physicians who first spied basophilic stippling in this religious celebrant's blood. What doctor would not delight in such a Sherlock Holmesian coup? There's another moral to the tale, however. The exotic denouement of a clinical-pathologic conference sometimes stands in stark contrast to everyday reality outside hospital lecture halls. Nothing could be truer when considering the ubiquity of lead poisoning from ancient to modern times.



**Lead poisoning—still a global calamity**

Even today, a global burden of lead poisoning persists, especially in developing countries where leaded gas is still in use.<sup>1</sup> And despite anecdotes often shared in medical lectures, many activities other than drinking moonshine, or quaffing juice from

Photo of basophilic stippling courtesy of Steven E. Coutre, MD, associate professor of Medicine (Hematology) at Stanford University School of Medicine.

a lead-glazed jug, or inhaling lead-laced dust from peeling paint, pose danger. Literally hundreds of global occupations place people at risk, from mining, welding, and automotive and battery manufacture, to ship-building, ship-breaking, printing, and toy manufacture.

Another paradox in the annals of lead is the backlash experienced by many would-be reformers throughout history. Consider Sir George Baker, an eighteenth century medical detective bar none. In his "Essay Concerning the Cause of the Endemial Colic of Devonshire," originally presented to the London College of Physicians in 1767, Baker described an epidemic of lead poisoning in his county.<sup>2</sup> Its impact was not trivial: nearly three hundred afflicted persons were admitted over five years to just one hospital in Devonshire. Baker's sleuthing eventually pinpointed apple cider as the source of harm, and reckless lead contamination in equipment used to make and store the "ruddy cup"—from lead-glazed earthenware rollers and jugs, to lead-soldered metal troughs, to lead-lined cisterns in which the drink aged—as the underlying hazard. For these important discoveries, however, he received little thanks or praise back home.



**Solo preventive medicine—  
difficult to impossible**

Instead, when Baker urged local cider-makers to get the lead out of their beverage, they told him in no uncertain terms to get his nose out of their business. As Christian Warren writes in a recent history, they "insisted that the only lead to be found in Devonshire cider came from the shot farmers used when picking birds off the apple piles."<sup>3p23</sup> To add insult to injury, Baker, the son of a minister, was calumniated. In the words of Sir Norman Moore, a president of the Royal College of Physicians in the late nineteenth century: "Great was the storm that arose. He was denounced as a faithless son of Devonshire."<sup>4</sup>

Recalling Baker's ordeal, the relatively recent campaign



**Sir George Baker, Bart., MD and FRS.**

Drawn on stone by G.P. Harding from a miniature by Ozias Humphrey, Esq., RA.  
Courtesy of the National Library of Medicine

to eliminate lead from U.S. gasoline could be viewed as just another, larger struggle between those who would reduce harm and those who would reap gain from the substance once called "the father of all metals." In any event, it's a story worth remembering by those of us who grew up pumping "ethyl," as well as by the younger "unleaded" generation.

Tetraethyl lead (TEL) was first discovered in 1854 in Germany and considered a technical oddity. Then, in 1921, three General Motors engineers found that TEL could dramatically improve fuel performance and reduce engine knock. The results spelled the beginning of the U.S. love affair with

the compound, as well as the seminal event leading to the high-power, high-compression internal combustion engines that would later dominate our nation's automotive industry.

Despite TEL's pluses, however, its safety worried many. A decade before Detroit's rediscovery of leaded gasoline, white-lead interior paint had already been banned in several European countries. Respiratory fumes of TEL soon proved even more perilous, when eight heavily-exposed refinery workers in New Jersey and Ohio died in straitjackets.<sup>5</sup> Their devastating terminal brain damage gave poignant testimony to organic lead's especially diabolical effects upon the central nervous system.

Soon, tabloid headlines decrying TEL as "loony gas" forced U.S. Surgeon General Hugh Cummings to temporarily suspend the production and sale of leaded gasoline. Cummings then commissioned a hasty report whose panel members complained they had insufficient time to detect lead poisoning in experimental subjects. Nonetheless, their 1926 ruling that there were "no good grounds for prohibiting the use of ethyl gasoline . . . as a motor fuel, provided that its distribution and use are controlled by proper regulations" prevailed. It took another forty-five years before the Environmental Protection Agency's first director, William D. Ruckelshaus, declared that the addition of alkyl lead to gasoline posed a major public health threat. In 1986, lead was finally outlawed as an automotive gasoline additive. Since its disappearance, the mean blood-lead level of the American population has declined more than seventy-five percent.<sup>6</sup>



Close-up of the mouth of an edentulous person suffering from chronic exposure to high levels of lead. Note the gray appearance of the palate.

St. Bartholomew's Hospital, London/Photo Researchers, Inc.



### Saturnine symptoms— neuropathic pain and many more

Connecting the dots between lead exposure and symptoms has never been easy. Before Sir George Baker's landmark investigation, for example, some Devonshire folk blamed their century-long abdominal woes on stardust and eastern wind.<sup>5</sup> Whatever its alleged cause, lead colic could incapacitate even the hardest of them. In a modern article by automotive industry physiologist Robert Kehoe, the one-time TEL defender characterized a typical attack of lead colic as having a sharp onset and recurrent spasms "in which the patient writhes in pain, retracts his legs spasmodically into his abdomen, groans, clinches his hands, [and] grits his teeth, with beads of sweat on his brow."<sup>7p298</sup>

Kehoe's vivid description notwithstanding, "colic" may not be the best term to describe the variable and mystifying abdominal pain—sometimes vague, sometimes nearly unbearable, but almost never linked to classic abdominal findings—experienced by many lead victims. One problem is this: to many physicians, colic implies intermittent cramps—a process akin to a "green apple bellyache," a partial bowel obstruction, or uterine contractions prior to childbirth. Another definition of colic, however, is pain arising in the abdominal viscera (as stated in the three-volume *International Dictionary of Medicine and Biology*: "Any of various conditions characterized by abdominal pain, especially paroxysmal pain occurring in a crescendo-decrescendo pattern dependent upon visceral smooth-muscle peristalsis."<sup>8p59</sup>) When a clinician is trying to decipher a particularly occult distress arising in or near the abdomen, the second definition, encompassing neuropathic causes, should always be kept in mind. Lead "colic," like the similarly featureless abdominal misery of porphyria, is almost

certainly due to a visceral neuralgia.

The first modern description of lead colic belongs to Tanquerel des Planches, a young physician practicing in a Paris city hospital in the early nineteenth century. In his 1839 *tour de force*—a treatise entitled "Traite des maladies de plomb ou saturnines"—Planches summarized 1207 cases, many of whom were painters or workers involved in the manufacture of lead pigments. Among other astute observations, he noted that the most severe poisoning cases followed exposure to lead-laden dust and "emanations," as opposed to solid metal, a finding validated decades later by bodily assays confirming the near-total absorption of inhaled lead. Planches also described neurological and joint manifestations of lead poisoning and theorized that lead colic had neuropathic roots. It is fair to say that no single physician before or since has seen as many cases of human disease due to lead.

Since the time of Planches, lead poisoning has revealed even more clinical faces,<sup>9</sup> which is why it is sometimes called an "aping disease." In addition to colic, its devastation includes diffuse encephalopathy, blindness, peripheral nerve palsies, male sterility, anemia, jaundice, hypertension, gum deposits called "lead lines," and a curious form of gout named after the Roman God Saturn, who in ancient mythology devoured his own young. Due to its citizens' insatiable appetite for lead-laden products—from cosmetics, paints, and vessels, to lead-sweetened wine, to the pipes of its vast arterial water system—historians now believe that the Roman Empire was rife with lead poisoning.<sup>10</sup> "Saturnine gout," a term that arose many centuries later, refers to someone who not only has painful, crystal-laden joints (the result of lead's decreased clearance of uric acid), but lead-induced melancholia as well.

On the cellular and molecular level, lead's assaults are just as diverse as its clinical expressions. As a divalent cation, the element often displaces other cations such as calcium—this accounts for its long-term reservoir in bone and teeth. In brain tissue, lead injures immature astrocytes and interferes with myelin formation and the integrity of the blood-brain barrier. In kidneys, it produces tubular damage. But perhaps the best cellular laboratory in which to study the element's treacherous handiwork is the human erythrocyte, in which ninety-nine percent of circulating lead is concentrated. Which brings us back to a telltale clue in a patient in Long Beach and a little-known chapter in the annals of research pertaining to red cell biochemistry, inherited enzyme deficiencies, and lead.



### Basophilic stippling of RBC— important but insufficient for diagnosis

In the early nineteenth century, the great pathologist and inventor René-Théophile-Hyacinthe Laënnec first described anemia in lead poisoning.<sup>9</sup> Of course he had no sophisticated



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Woman carrying basins filled with washed white lead from vat to stoves. Courtesy of the National Library of Medicine.

tools with which to unravel its mechanisms, which are nothing if not complex. Lead shortens the lifespan of red cells. It also impairs heme synthesis by perturbing a variety of red cell enzyme systems including delta-aminolevulinic acid dehydratase and ferrochelatase (the former is needed to conjugate levulinic acid to form porphobilinogen while the latter aids in integrating iron into protoporphyrin IX).

On the other hand, basophilic stippling—the key to the diagnosis of the Cambodian man with colic—would later reveal another of lead's attacks on the inner workings of red cells. The useful clue eluded lead detectives until the close of the nineteenth century, when the English occupational physician Henry Behrend first noted the abnormality.<sup>9</sup>

Within a few decades, monitoring workers' blood for basophilic stippling had become a routine health surveillance activity in many U.S. factories. Some diligent company doctors also tested for stippled red cell precursors and urine lead, hoping to identify victims before they suffered irreversible harm.<sup>11</sup> But clinical correlations were poor: some workers whose blood and urine tests suggested only traces of lead exposure still suffered colic and other toxic complications. As a result, by the 1960s, the practice of counting stippled cells was abandoned.<sup>5</sup> Meanwhile, the process leading to basophilic inclusions remained unknown.

Enter a domino-sequence of discoveries aided by new technology and research into inborn errors of metabolism—as

well as serendipity. Starting in 1960 in a Quonset hut on the West Los Angeles Veterans' Administration campus, a UCLA research laboratory led by William Valentine began independent investigations into inherited enzyme disorders of red cell energy pathways. The group first described pyruvate kinase (PK) deficiency in a family with congenital nonspherocytic hemolytic anemia. As additional cases of PK deficiency surfaced around the world over the next decade, the Valentine lab characterized multiple variants of this and other red cell enzymopathies.

Then new kindreds with hereditary hemolytic anemia and pronounced basophilic stippling came to light. Electron microscopy studies from the mid-1960s had already shown that intra-erythrocytic "stipples" were aggregates of whole and partially degraded ribosomes.<sup>12</sup> Working backward, Valentine, fellow researcher Donald Paglia, and colleagues demonstrated that affected red cells in one patient had markedly increased nucleotide content (three- to six-fold higher than normal), of which eighty per cent was pyrimidine. The researchers theorized that in the setting of genetically reduced pyrimidine-5'-nucleotidase, prominent basophilic stippling resulted because the enzyme-deficient red cells could not dephosphorylate and extrude the pyrimidine-rich deposits. Additional families with basophilic stippling and a genetic shortage of pyrimidine-5'-nucleotidase were subsequently studied.<sup>13</sup>

The next piece of the puzzle fell into place when Valentine, Paglia, and coworkers found that pyrimidine-5'-nucleotidase in normal erythrocytes was exquisitely sensitive *in vitro* to lead. The story came full circle when they documented acquired 5'-nucleotidase deficiency in multiple workers from a nearby battery factory (all had varying degrees of lead overload), as well as an acutely lead-poisoned spray painter with several days of sharp epigastric and back pain, gray-blue gingival "lead lines," anemia, and many stippled red cells.<sup>14,15</sup> Although the battery workers had not yet progressed to obvious stippling, the poisoned spray painter with colic had numerous inclusions within his erythrocytes—and his initial nucleotidase level

was a scant twenty-five percent of the normal mean (fifteen percent or less than what would have been expected in comparably reticulocyte-rich blood). As the painter recovered, his stippling disappeared first. Then, over several more months, his blood lead level fell as his pyrimidine-5'-nucleotidase activity slowly rose, ultimately tripling its nadir value.

Unfortunately, outside of research studies, pyrimidine-5'-nucleotidase is not a practical tool with which to directly measure lead overload, in part because immature red cells released from the bone marrow following hemolysis contain disproportionately higher quantities of the enzyme. Because delta-aminolevulinic acid dehydratase may be altered by a variety of conditions, including porphyria, it is also an imperfect gauge. Thus, pediatricians and public health and occupational physicians are left with an age-old problem: the lack of simple, accurate screening tests for lead. Lead's unpredictable sequestration in different body compartments (from five to six weeks in blood to two years in brain to decades in cortical bone) is the principal stumbling block. Although blood-lead levels can certainly detect acute poisoning, many other exposures are slow and cumulative. The final, silent repository of lead in bone—unquantifiable except by special scans—may be harmless to some, but can also leak lead during childhood growth spurts, immobilization, and other stress



Poster by the U.S. Department of Health, Education, and Welfare Health Services and Mental Health Administration Bureau of Community Environmental Management.

Courtesy of the National Library of Medicine.

states such as pregnancy, lactation, and chronic disease. In such cases, toxic symptoms can recur long after primary exposure.



### A societal legacy: The bad effects of lead on intelligence and behavior

Simply put, our earliest encounters with lead haunt us for the rest of our lives.

School dropouts, violent youth offenders, hardened criminals—is this the twenty-first century legacy of lead that medical historians will someday record? It's no secret that lead's most overt as well as its most insidious damage targets the nervous system.

Now that many societies have moved beyond acute and deadly lead poisoning, preventing lead's chronic neurocognitive effects is the next big hurdle—especially among children. Not only are youngsters' minds and personalities more vulnerable to lead-induced damage, their universal hand-to-mouth activity and highly absorptive guts (which siphon up to fifty percent of ingested lead, five- to tenfold more than the gastrointestinal tracts of adults) compound the potential for harm.

The recent focus on the occult devilry of lead in brain has been fueled by several decades of clinical and epidemiological evidence. Key supporting data include the irreversible loss of intelligence seen in lead-intoxicated infants, as well as the significant fall in IQ points suffered by children with even modestly elevated blood lead levels. Lead exposure can also trigger behavioral disorders. One of the earliest clues was the correlation of high lead levels in schoolchildren's teeth with poor classroom conduct and attention spans.<sup>16</sup> A major ecological study later linked leaded gasoline sales and ambient lead levels to deadly crime.<sup>17</sup> As these and other disturbing patterns emerged, the Centers for Disease Control lowered its threshold for childhood lead poisoning three times over two decades, from a blood-lead level of 60 µg/dL in the 1970s to ≤10 µg/dL in 1991.

Despite the new set-point for alarm, expanded screening

efforts, and overall declines in U.S. blood-lead levels, poverty still puts many U.S. youngsters at risk. Low-income urban minority children are especially vulnerable, since they often occupy the nation's oldest and most dilapidated housing stock. According to current estimates, eighty percent of American houses built before 1950—more than twenty million units—still contain leaded paint.

From a global perspective, on the other hand, the foremost goal is the wholesale phase-out of leaded gasoline. As Planches first observed, lead-laden fumes are far more dangerous than direct contact with the metal. How would he view, one wonders, our current era of spiraling automobile use, traffic, and human density? These modern conditions around the world have now rendered gasoline the most efficient means ever known of dispersing lead, especially among urban dwellers. Today, in many global cities, lead accounts for more than ninety percent of all atmospheric emissions.<sup>18</sup>

No one claims the solution is easy. Converting refineries to produce gasoline components with relatively high octane (a prerequisite to eliminating leaded fuel), poses special challenges for low- and middle-income countries. Despite this, governments are taking action. During the last decade, Brazil, Colombia, Nicaragua, the Slovak Republic, and Thailand all eliminated leaded gas. Even now, however, China has been exporting lead-painted toys.

In the meantime, physicians, public health authorities, and citizens must remain savvy and vigilant regarding the hazards of lead. After all, the clock will never tick backwards: in North America, background concentrations have already increased several hundred-fold since European settlement. Plus, lead never biodegrades. Of all the lead ever mined (an estimated three hundred million metric tons), most of it still lingers in modern-day soil and dust.

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