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Lead Poisoning in a Historical Perspective

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Lead poisoning existed and was already known in Antiquity but was forgotten, at least in the literature, until the end of the Middle Ages, where it was mentioned sporadically. In the 19th century this disease, which reached epidemic dimensions during the period of industrialization, was "rediscovered." Several comprehensive clinical articles appeared in the literature. The clinical picture deepened during the beginning of the 20th century, and preventive efforts were started. However, the concept of poisoning remained strictly clinical. During the latter half of the 20th century a new concept emerged: subclinical and early forms became recognized as undesirable effects. This led to a substantial lowering of hygienic standards. Pediatric poisoning has also been a serious problem during the 20th century. After the 1920s, environmental pollution by lead caused by the introduction of tetraethyl lead in gasoline became an alarming public health problem. The use became restricted in the 1980s; its effects on blood lead levels are now evident. Today's research focuses on the effects of low exposure, often with the aim of defining noneffect levels for different types of effects. Am. J. Ind. Med. 38:244–254, 2000.

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INTRODUCTION

Lead has been mined and used by mankind for 6,000 years, and the history of lead poisoning is nearly 2,500 years old. Summarizing such a long story in a few pages in a balanced way is impossible. The older history of lead poisoning has been reviewed many times in articles, book chapters, and textbooks [e.g., Cantarow and Trumper, 1944, Hernberg, 1975, Hamilton and Hardy, 1983, Nriagu, 1983, Hunter, 1988]. This review focuses on recent history, especially prevention, the new concept of poisoning, and on some of the controversies involved in studying, defining, and preventing lead poisoning.

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THE EARLY DAYS

Lead was known to man as early as 4,000 BC. Both the Egyptians and Hebrews used lead and the Phoenicians mined lead ore in Spain around 2,000 BC. The earliest written accounts of lead toxicity have been found in Egyptian papyrus scrolls. According to them, lead compounds were often used for homicidal purposes. Hippocrates, in 370 BC, was probably the first to describe lead colic, without however recognizing the etiology. The first to describe lead palsy was Nicander in the 2nd century BC, but he too was not able to attribute the palsy to lead exposure. But in the 1st century AD Dioscorides saw the connection between lead exposure and toxic manifestations, and Pliny stated that lead poisoning was common in shipbuilding. The Romans produced an average of 60,000 tonnes of lead a year for 400 years. They used lead compounds for glazing pottery, and metallic lead for cooking utensils and piping. They also used to boil and condense grape juice in lead pots for preserving and sweetening of wine. Lead poisoning from all these sources must have been common in ancient Rome. The poisoning was epidemic and is said to have

caused many stillbirths, deformities and cases of brain damage. Considering that lead also reduces fecundity, it has been suggested that widespread lead poisoning, selectively affecting the patricians who drank much wine and had access to plumbing, contributed to the decadence and later the fall of the Roman Empire [Gilfillan, 1965]. Indeed, high lead concentrations have been found in archeological Roman bones; higher in bones retrieved from patrician tombs than in those found in plebeian graves.

THE PREINDUSTRIAL PERIOD

Although both lead poisoning and its connection to lead exposure were known in late Antiquity, this disease was almost completely forgotten in the literature preserved from the Middle Ages. This is astonishing, because lead was widely used both for industrial, domestic, and medicinal purposes. For example, lead acetate (''lead sugar'') was used as a sweetener of wine and ciders, and it caused severe epidemics of poisoning. In some German countries the problem was so severe that death penalty was prescribed, first in 1498 and later in 1577, for those caught mixing lead sugar into wine. Also mixing lead compounds into (so-called) medicinal preparations helped many patients to a better world more quickly than ''normally.'' Industrially lead and its compounds gained more and more use at the beginning of the New Age, for example, in pottery, piping, shipbuilding, window making, the arms industry, pigments, and later book printing. Lead poisoning became a plague in Europe and later in America during the 15th, 16th, 17th, and 18th centuries. However, it was not until in the 16th century that lead poisoning reappeared in the medical literature in Paracelsus' description of what he called ''the miner's disease.'' In the beginning of the 18th century Ramazzini wrote that potters who worked with lead became ''paralytic, splenetic, lethargic, cachectic, and toothless, so that one rarely sees a potter whose face is not cadaverous and has the color of lead'' [Ramazzini, 1713].

Sir George Baker made an important observation in 1767 [Baker, 1772]. He understood that the so-called Devonshire colic, which had plagued the county for a century, was due to contamination of cider with lead. He showed that lead had dissolved from the weights used to crush the apples; hence he could prove that the etiology of the colic was lead poisoning, not stardust or eastern wind, as formerly believed. Severe poisoning was characterized by palsy, encephalopathy, pallor and abdominal cramps, and the case fatality rate was high. Sir George did pioneering work, but it was not until well into the 19th century that significant advances in the understanding of lead poisoning and descriptions of its clinical picture began to appear in the literature.

A CENTURY OF INDUSTRIALIZATION—AN EPIDEMIC OF LEAD POISONING

In 1831 Laennec described the anemia of lead poisoning and in 1832 Thackrah published a clinical description of lead poisoning (''plumbism'') in plumbers and white lead manufacturers. The first ''modern'' clinical description of lead poisoning was Tanquerel des Planches' famous ''*Traité des maladies de plomb ou saturnines*,'' which appeared in 1839 and was based on over 1,200 cases.

Probably no one before him had seen so many cases of plumbism—and probably no one later, either. des Planches gave a detailed and good description of the abdominal, neurological, and arthritic aspects of lead poisoning, but he erroneously believed that they were different entities [Hunter, 1988].

The hematological effects of lead have been known for long. The anemia of lead poisoning is hypo- or normochromic and of a moderate degree. It is accompanied by a yellowish pallor, which is partly due to anemia, partly to vasospasm. Behrend, in 1899, was the first to describe basophilic stippling of erythrocytes. Counting stippled cells became an essential part of the health surveillance of lead workers in the first half of the 20th century. However, this method was neither specific nor sensitive, and its use was abandoned in the 1960s. That lead impairs the heme synthesis has been known for a century. In 1898 Garrod was the first to report increased excretion of porphyrins in the urine and in 1934 Vigliani and Angeleri [cited by Haeger-Aronsen, 1960] demonstrated that the incorporation of iron into heme was impaired, resulting in accumulation of protoporphyrin IX in the erythrocytes. Haeger-Aronsen published her classical thesis on the excretion of delta-aminolevulinic acid (ALA) in the urine of lead workers in 1960, and a few years later Bonsignore and his coworkers demonstrated that lead inhibited the enzyme delta-aminolevulinic acid dehydratase (ALA-D), which explained the increased ALA excretion [Bonsignore et al., 1965]. Apart from inhibiting heme synthesis, lead shortens the life span of the erythrocytes, which contributes to anemia. Sheets and his coworkers [1951] were the first to report this mechanism, which has later been corroborated many times.

Lead palsy and lead encephalopathy belong to the earliest known manifestations of lead toxicity. Less well known are reports from the late 19th century, describing involvement of the nuclei of the cranial nerves. For example, lead blindness struck many patients in the beginning of the 20th century [e.g., Gibson, 1908; Prendergast, 1910; cited by Hamilton and Hardy, 1983]. Lead encephalopathy, together with anemia, was also a prominent manifestation of the severe epidemics of childhood lead poisoning that had probably occurred for long, but were first revealed in the beginning of the 20th century in Australia. Like in medicine

in general, the severe, clinical forms of nervous system involvement were the only ones that counted earlier, but in the 1970s subclinical manifestations of peripheral [Seppäläinen and Hernberg, 1972] and central nervous system involvement in industrial workers [Hänninen et al., 1978] also became documented. Subclinical effects in children have also received much attention during the last three decades.

Lead colic is another typical feature of frank poisoning. It probably was common already in ancient Rome. The Devonshire colic provides another historical example. Kehoe [1972] has described lead colic as characterized by ''sharp onset and recurrent spasms in which the patient writhes in pain, retracts his legs spasmodically to his abdomen, groans, clenches his hands, grits his teeth, with beads of sweat on his brow.''

Joint and muscle pain is another classical manifestation of clinical lead poisoning. Already Tanquerel des Planches reported in 1839 that 755 of his 1,217 patients complained of joint pain and Garrod described ''lead gout'' in 1854 [Hamilton and Hardy, 1983]. Also, later clinical studies confirm that joint pain is common in clinical poisoning [Linenthal, 1924, Mayers, 1927, cited by Hamilton and Hardy].

Early studies from Queensland, Australia, demonstrated that lead has toxic effects upon the kidney. Patients who had suffered from severe lead posoning as children later got chronic interstitial nephritis with a clinical picture resembling the Fanconi syndrome [Nye, 1929; Henderson and Inglis, 1957]. Also, industrial workers, heavily exposed during the first half of the 20th century, have shown renal involvement, characterized by diffuse interstitial fibrosis and renal failure. In addition, heavy users of lead contaminated ''moonshine'' whiskey used to suffer from progressive renal disease, saturnine gout, and moderate hypertension. The condition has probably been aggravated by the concomitant abuse of alcohol.

In the 19th century and in the first half of the 20th century women working in lead industries knew well that lead caused abortions. So did baby-farmers, and lead compounds were widely used to induce illegal abortions. Women industrially exposed to lead were more likely to be sterile, and if they became pregnant, the risk of stillbirth was much higher than for women not so exposed [Oliver, 1911, cited by Hamilton and Hardy, 1983]. Also, the mortality of their children during the first year was higher than normal. Many other studies from the beginning of the 20th century confirm these effects of lead on pregnancy outcome [Hamilton and Hardy, 1983]. Lead also affected male fertility. In the 19th century this was known to be profoundly lower among lead workers [Paul, 1860, cited by Hamilton and Hardy, 1983]. These old studies seem often to have been forgotten when today's researchers ''redetect'' adverse pregnancy outcome in moderately exposed workers—as such no new finding, although lower exposure levels can now be incriminated.

This sketchy history pinpoints some milestones in our understanding of the clinical picture of lead poisoning and gives some hints of how dramatic its manifestations were. Moreover, this disease was often fatal; at least it left irreversible neurological sequelae. Exactly how widespread lead poisoning was is not clear, but its incidence must have been very high for centuries, even without taking subclinical effects into account. Some figures from the late 19th and early 20th century can serve as examples.

During the 25-year period, 1875–1900, about 30,000 cases of lead poisoning were reported from the lead mines of Utah alone; more than 1,000 cases a year. The annual incidence in Great Britain at the beginning of the 20th century was about 1000 cases and of them about 50 were fatal [Hernberg, 1975]. There is no reason to believe that the situation on the European continent was better; the system of reporting was weaker, however. Dangerous trades were especially primary and secondary smelting, scrapping, the printing industry, the pottery industry and, later, the manufacture of storage batteries. However, lead was used for so many purposes that a comprehensive list of exposed jobs would be too extensive in this presentation.

PREVENTION IN THE 20TH CENTURY

The epidemic occurrence of lead poisoning in the industrializing world led to a slow realization of the need for preventive action, and a number of legislative and other preventive measures were introduced in many countries. In the UK, Sir Thomas Morrison Legge became the first Medical Inspector of Factories in 1898. A centralized system of factory inspection had been created under the Factories and Workshop Act of 1878, and Legge did pioneering work to implement the Act. He wrote together with Goadby the classic treatise ''*Lead Poisoning and Lead Absorption*'' [Legge and Goadby, 1912]. Thanks to Legge's and the Inspectorate's activities, the number of notified cases of lead poisoning dropped from 1058 in 1900 (58 fatal) to 41 in 1944 (5 fatal) [Lloyd Davies, 1957]. However, although improved, the situation was far from satisfactory in the middle of the 20th century. For example, in 1970, 70 cases were still being notified in the UK, 443 cases were reported in West Germany and 61 in Sweden in 1969, while in Finland the number was 58 in 1971 [Hernberg, 1975]. Probably these cases were milder than 50 years earlier, but on the other hand there is reason to assume underreporting.

In the US occupational medicine plainly did not exist at the beginning of the 20th century. Much credit for the awakening goes to Alice Hamilton. In her autobiography she lamented that although European medical journals were full of articles on industrial poisoning, the number published

in American medical journals up to 1910 could be ''counted on one's fingers'' [Hamilton, 1943]. She was the first American physician to devote her life to the practice of industrial medicine and her impact was great. The lack of a reporting system comparable to the British one makes it impossible to evaluate the magnitude of the lead problem and its improvement over the years, but anecdotal reports from the first half of the 20th century indicate that the problem was at least as severe as in Europe, if not worse.

In particular, painting with white lead paint and rubbing down old paint caused many severe cases of lead poisoning worldwide in the beginning of the 20th century. In 1921 the International Labour Conference organized a meeting in Geneva to adopt the White Lead Convention. Sir Thomas Legge was strongly in favor of it. The convention led to the prohibition of the use of white lead in indoor painting in several countries, for example, in Sweden and Czechoslovakia in 1923, in Austria, Poland and Spain in 1924, and in Finland and Norway in 1929 [Silbergeld, 1997]. However, when the British Government refused to ratify the convention in 1926, Legge in protest resigned from the labor inspectorate [Lloyd Davies, 1957]. The U.S. did even worse, much because the Lead Industries Association succeeded in blocking the U.S. government from signing the ILO convention [Silbergeld, 1997]. In 1970 only four U.S. states and 10 municipalities had laws or ordinances prohibiting indoor use of lead paint [NRC, 1972]. A federal law came into force as late as 1972. The consequences of this delay have been disastrous.

In industry, prevention relied first on medical surveillance, such as clinical examinations, measuring the hemoglobin level, and counting stippled erythrocytes (which in a strict sense was early diagnosis rather than prevention), together with attempts to improve housekeeping, enhance the personal hygiene of the workers, and teaching them safer working habits. It is true that a number of technical preventive measures were introduced as well, such as, if possible, abolition of the use of lead (e.g., the development of a leadless or low-lead glaze in the pottery industry), exhaust ventilation, wettening dusty processes, and personal protective equipment, but they were based more on common sense than on scientific and technological theory. Occupational hygiene, as we understand it today, emerged much later. Here the United States took the lead. In Europe the medical emphasis prevailed into the 1960s, perhaps reflecting the fact that occupational medicine (not ''health''!) was in the hands of clinicians, not public health officers, and also the lack of trained occupational hygienists.

Some rather strange ''preventive'' measures were applied. One was the practice of feeding 1 l of milk daily to the workers, often free and sometimes as a part of the wage agreement. This was based on the undocumented belief that calcium in the milk retarded the absorption of lead, and that this foodstuff, perhaps, through better nourishment, alleviated the toxic effects. Chelating agents, such as British Anti-Lewisite (BAL), $CaNa_2EDTA$ and d-penicillamine came into use in the 1950s as therapeutic agents against lead poisoning. Their efficacy soon tempted Eastern European researchers (especially) and plant physicians, but also others, to use them as prophylactic agents even for symptomless exposed workers. However, while the therapeutic use was generally approved for treatment of severe poisoning, many experts, especially in the U.S. and the Nordic countries, considered the prophylactic use of chelating agents as malpractice. The argument was that the only acceptable method of prevention was the reduction of dangerous exposure levels and better hygiene. Anything else gave the employer too easy a way of neglecting workplace hygiene. In the 1970s and even in the early 1980s, hot disputes were commonplace at occupational health congresses.

New methods for measuring lead in biological media were developed in the late 1960s. First, the dithizone method and later atomic absorption spectrophotometry, gradually made blood lead determinations the cornerstone of the medical surveillance of lead- exposed workers. The term ''biological monitoring'' was introduced. Several studies began addressing the relation between blood lead values and different toxic manifestations in the first crude attempts to find dose–effect and dose–response relationships [Nordberg, 1976; WHO, 1980]. Unfortunately, laboratories did not do well in the beginning and therefore many of the results were highly unreliable. Even worse, many lead researchers failed to realize how severely such confusion hampered our understanding of the dose dependence of toxic effects. Also, the definition of limits for ''safe'' exposure became cloudy. Fruitless debates in the literature and at conferences led to further confusion, because 50 μg/100 ml for one researcher could be the same as 90 for another, and so forth. At last the need for method control and good laboratory practice became evident. Interlaboratory comparisons both in the U.S. and in Europe gave dreadful results when the first systematic attempts to improve the situation were made in the early 1970s. Four-to-sixfold variation in the results of different laboratories measuring lead from the same blood samples was not uncommon. It was understandable that, under such circumstances, experts could not agree on what blood lead values were ''safe'' and ''unsafe.'' Gradually the situation improved. Today articles without documented method control are rarely accepted for publication in the ''better'' journals and should not be accepted in any.

The strong (and usually unfounded) belief that their own laboratories could analyze blood lead concentrations accurately and better than others, made some experts believe in ''true'' values and categorically stated that one could not develop poisoning as long as the blood lead concentration remained below 80 μg/100 ml (approx. 4 μM/l). Robert

Kehoe especially was a strong advocate of this black-or-white viewpoint, and he used to state vigorously that he had never seen a case of lead poisoning with a blood lead level below 80 μg/100 ml before chelation, with the ''modest'' addition that he had personally seen more lead poisoning than anyone else in the world. This was circular reasoning, because according to his definition poisoning *could not* occur at lower levels. But he was not alone in believing in this categorical limit. In 1968 a group of European experts chaired by Ronald Lane recommended that the following criteria should be used as border values for ''safe'' exposure: blood lead, 80 μg/100 ml; urinary lead, 150 μg/l; urinary coproporphyrin, 500 μg/l; and urinary ALA, 20 mg/l [Lane et al., 1968].

Apart from being unacceptable from today's viewpoint, this European recommendation illustrates two important principles. First, effect parameters were recommended for the surveillance of lead workers, an old tradition arising from relying on clinical examinations in periodic surveillance, and second, substantial deviations from ''normal'' were accepted. Kehoe and his followers in the US, on the other hand, recommended that only exposure parameters (preferably blood lead) should be used for preventing toxic effects. In principle this is correct, even according to the present view. Action should be taken before effects occur. The crux was that Kehoe (and later OSHA) agreed on the same unacceptably high (as of today) biological lead standard as did Lane's committee, a level that definitely does not rule out toxic effects. However, in those days the European standpoint, although logically wrong, was probably better founded than the U.S. approach, considering the analytical inaccuracy of blood lead determinations and the scarcity of laboratories capable of doing any lead analyses at all. But both schools, like most of the world, were fixated on the old clinical concept of lead poisoning, according to which subclinical states did not count and whose existence was even questioned by many experts. For example, Lloyd Davies wrote in 1957 in his textbook ''*The Practice of Industrial Medicine*'': ''A fall in the haemoglobin and red cell count if accompanied by punctate basophilia, is probably the earliest sign of exposure to lead. These changes do not necessarily indicate poisoning (p. 170).'' However, although we view matters differently today, these pioneers' impact on the prevention of poisoning should not be underestimated. They were children of their own time. It is not decent to criticize them too severely in the light of what we know and what we think 30–40 years later.

The important thing was that periodical examinations became integrated in occupational health care, that they were based on biochemical and not only clinical examinations, and that they became mandatory in several countries in the latter half of the 20th century. An action level based on a correctly determined blood lead value of 80 μg/100 ml (approx. 4 μM/l) probably would have prevented frank, classical lead poisoning, although definitely not subclinical manifestations. However, a very strange assumption was that industrial workers were a special race or species, because one postulated that they could withstand much higher lead levels—up to 80 μg/100 ml—than the general population. The argument went that they were ''subject to periodical health examinations.'' But how such examinations could protect anyone is highly questionable, based as they were on insensitive toxicity indicators—history of early symptoms, testing of the extensor strength of the hand, looking for a lead line in the gums, measuring the hemoglobin concentration, and counting of stippled cells. These examinations were, except for the lead line, all based on early manifestations of toxicity. The correct philosophy would have been to take action before the appearance of toxic effects, based on exposure measurements and a standard of ''safe'' levels of exposure.

The attitude is somewhat but not entirely different today. Research during the last 30 years has greatly enhanced our knowledge on subclinical and nonspecific manifestations of lead toxicity and caused a fundamental revision of our concept of lead poisoning. Based on this knowledge, action levels have dropped much in most countries, even to 30 μg/100 ml, as recommended by ACGIH and OSHA in 1995. This is a right direction, but apparently workers are still thought to be a different, hardy species, who can withstand toxic effects better than the general population, whose blood lead levels should be and indeed are well below 10 μg/100 ml.

Today's recommendations were considered totally unrealistic by industry as recently as 20–30 years ago. In addition to technological and economical arguments, research to disprove the significance of subclinical effects was sponsored by industry [e.g., Ramirez-Cervantes et al., 1978], and hence, medical arguments were used to make a case for not lowering the action level from 80 μg/100 ml. In Europe industry was also against revising exposure limits. In 1978 WHO convened an expert meeting to scrutinize the present knowledge on dose–effect and dose–response relationships for three heavy metals: lead, mercury, and cadmium. A booklet called ''*Recommended Health-Based Limits in Occupational Exposure to Heavy Metals*'' was finally published [WHO, 1980]. The group recommended a health-based exposure limit of 40 μg/100 ml for lead in the blood. Those WHO officers who were involved in editing the document have privately stated that industry representatives lobbied heavily, both in the WHO and in the then CEC Health Protectorate, to prevent the publication. Various ''experts'' tried to discredit the research that was the foundation of the WHO recommendation. These activities delayed the publication of the report and degraded it to a ''technical report.'' When 2 years later the Finnish labor protection authorities convened a group to oversee the Finnish hygienic standard, the Employers' Federation

strongly opposed the proposed reduction from 70 to 50 μg/100 ml, claiming that the limit of 50 μg/100 ml was totally unfeasible, and calling in ''international expertise'' to ''prove'' that WHO and the Finnish Institute of Occupational Health, represented by me, were wrong. In spite of this, the limit finally was set at 50 μg/100 ml. Both the decrease in compensated cases of lead poisoning, from about 20 annual cases in the 1980s to 2-5 in the 1990s—here very ''subclinical'' criteria have been adapted—and the results of the Finnish Institute's biomonitoring program clearly show how wrong the industry representatives were. Blood lead values in excess of 50 μg/100 ml (approx. 2.4 μM/l) have been very rare—less than 4%—for years. (And, the higher the blood lead value, the more frequent the monitoring!) However, a limit of 50 μg/100 ml is still far too high. In 1997 the Finnish Institute of Occupational Health proposed to the Ministry of Social Affairs and Health that the limit be lowered to 30 μg/100 ml (approx. 1.5 μM/l), but so far no action has been taken.

Now clinical lead poisoning is rather uncommon in the developed world and the cases that are notified are much milder than before. What must be heavily stressed, however, is that clinical lead poisoning—as well as other clinical occupational morbidity—is still common in developing countries and in several former socialist countries. How common is hard to tell because of poor or lacking health statistics. This regrettable situation not only concerns occupational lead poisoning, but also poisoning from domestic sources, such as primitive ceramics and earthenware, family exposure in cottage industries, ingestion of contaminated alcoholic beverages and flaking lead paint, and sometimes heavy environmental pollution, for example, in the vicinity of primary and secondary smelters. Unfortunately, part of the improved situation in the developed countries is due to the fact that dangerous industries, such as ship breaking, secondary lead smelting, and manufacturing of storage batteries, have been relocated to developing countries.

CHILDHOOD POISONING

Childhood lead poisoning must have occurred already in the 19th century, but it was first brought to attention in New South Wales at the turn of the century. Turner and Gibson [also cited by Needleman, 1993] were the first to describe lead poisoning in children and they were able to ascribe it to ingestion of flaking lead paint from decaying homes. However, first the very existence of pediatric lead poisoning was disputed, and later it was believed that once the child recovered from the acute phase, no lasting late effects would occur [Needleman, 1998b]. In spite of the attempts to play down the problem, Turner and Gibson's observations made Australia pass a lead paint prevention act in 1920. Many other countries passed such acts in the 1920s. In the U.S., where no such act was in force, pediatric lead poisoning became an epidemic, whose shocking magnitude was not understood until the late 1960s or early 1970s. The epidemic had two main causes: Flaking lead paint in old houses and the environmental pollution with lead resulting from the use of tetraethyl lead in gasoline.

In 1970 it was estimated that the annual incidence of symptomatic and asymptomatic lead poisoning in the U.S. was as high as 250,000 cases [Moore, 1970]. In 1988 the Agency for Toxic Substances and Disease Registry estimated that there were six million dangerous houses in the US with a number of 1.7 million children living in them [ATSDR, 1988, cited by Needleman, 1994]. The problem was first tackled by case finding campaigns in some large cities. For example, one campaign in New York City yielded 2,500 cases of poisoning during its first 11 months [Guinee, 1971]. In other cities the results were similar. It was not until 1991 that the authorities realized that screening was not enough and a more comprehensive strategy was proposed: in addition to universal screening, there should be reduction of all sources of lead and abatement of leaded housing stock before the children become exposed. Cost–benefit calculations showed this to be highly profitable, yielding a net benefit of over $ 17 billion over the next 20 years [Needleman, 1994]. Primary prevention of childhood lead poisoning thus seemed to be straightforward and cost-efficient, although expensive in the beginning. However, the progress has not been successful [Needleman, 1998b]. There has been much political, economic and even medical opposition against a nationwide program to eliminate pediatric lead poisoning by means of primary prevention. The debate regarding goals and strategies is still ongoing and belongs rather to the current issues than the history of lead poisoning. While some hold that far too little has been done, others defend a less radical prevention policy. The reader is referred to Needleman's recent review [Needleman, 1998b] and to the violent debate following its publication [e.g., Ryan, 1999, Jacobs, 1999, Vernon, 1999]. The discussion shows that the matter is far from settled and that pediatric lead poisoning continues to be a problem in the slums of the United States. Here it must be emphasized that ''poisoning'' has another meaning than before. Now it is held that the highest nontoxic concentration is as low as 10 μg/l00 ml (0.5 μM/l)—something very different from the 60 μg/100 ml (2.9 μM/l) that was the norm only three decades ago [Silbergeld, 1997].

It is true that blood lead levels among children have fallen clearly during the last decade. For example, one survey has shown that the mean blood lead concentration in children has dropped from 13.7 μg/l in 1976 to 3.2 μg/l in 1994 [Pirkle et al., 1994, cited by Needleman, 1998b]. However, this decrease is directly proportional to the decreasing amount of tetraethyl lead produced and has apparently little to do with prevention of exposure to flaking

lead paint. In fact, the distribution of blood lead values is bimodal, with African-American slum children exhibiting much higher values than children living in more affluent areas [Needleman, 1998b].

Concern over the effects of slightly increased blood lead values stems from the several studies showing that such levels can also cause central nervous system impairment, and that the causative lead levels are much lower than expected [Needleman, 1993, 1994]. Needleman was and still is one of the key persons in this research. Already the fact that industry has attacked him heavily underscores the importance of his message [Silbergeld, 1995]. In his classical studies he used tooth lead (reflecting past exposure better than blood lead) concentrations as the exposure parameter and sensitive psychological tests as the effect parameters. Together with valid and sensitive study designs he could show that clinical poisoning was only the tip of the iceberg. Low exposure was also harmful. He divided children without poisoning into two categories. Those with higher exposure did worse than children with lower exposure, especially in intelligence testing, reaction time measurements, and EEG findings. The decrement in IQ scores was about six points, meaning that the rate of severe deficit was increased fourfold. Other studies have shown that children with high (but far below ''toxic'') blood lead levels performed worse in schools and that their risk of nongraduation increased by seven times [Needleman et al., 1990]. Needleman has suggested that the slipping school performance, which is a general concern in the US today, to a large extent can be attributed to past subclinical childhood lead poisoning. Not only the health consequences, but also the social and economical consequences of such loss of mental capacity are great, considering the large number of children so affected.

THE NEW CONCEPT OF LEAD POISONING

In the realm of occupational exposure, the development of stricter criteria presented earlier in this review got its substance from advances in dose–response lead research and the development of a more modern concept of poisoning in general. During the second half of the 20th century the philosophy of occupational medicine changed. It is not a coincidence that the term ''occupational health'' has begun to substitute the term ''occupational medicine'' more and more, and that an epidemiologic approach in research has substituted conventional clinical thinking. Even mild, subclinical effects have become recognized as unacceptable and occupational hygiene has developed as a discipline. This concerns the whole field of occupational health. In the case of lead, nonspecific long-term effects, such as cancer and adverse pregnancy outcome, have been defined as critical effects, and preventing them has become a goal in a standard setting. The study of early, subclinical effects has at the same time become more feasible thanks to developments in clinical chemistry and other techniques, such as psychological testing and neurophysiological measurements, combined with an epidemiologic approach. These advances in thinking and measurement have been the backbone of the lowering of the hygienic standards, such as TLVs and MACs, described in the previous subchapter.

The study of subclinical lead effects has relied much on measurements of early disturbances of the porphyrin synthesis. These have been mentioned earlier and much of the dose–response research on which our present view of subclinical poisoning is based, has utilized these indicators. After Bonsignore and his coworkers had shown that the enzyme ALA-dehydratase was inhibited by lead [Bonsignore et al., 1965], my group was the first to show that such inhibition was detectable already at blood lead levels occurring in the general population and that they were proportional to the blood lead level [Hernberg and Nikkanen, 1970]. These findings, in combination with another study also including lead workers, suggested the absence of a threshold level [Hernberg et al., 1970]. Accumulation of protoporphyrin in the erythrocytes, due to inhibition of the enzyme ferrochelatase, is another physiological disturbance with a very low threshold, if any [Piomelli et al., 1982; WHO, 1995]. Several studies in the late 1960s and early 1970s established and confirmed dose–effect and dose–response relationships for these hematological effects [Nordberg, 1976; WHO, 1980, 1995]. The question was, and still is, whether slight abnormalities of these parameters have real health significance or not. Perhaps we should learn from history. Only 30 years ago slight anemia and basophilic stippling were not considered harmful [Lloyd Davies, 1957; Lane et al., 1968]. Today they are.

Early neurologic, psychological, and renal effects from lead began to catch attention 30 years ago. Slowing of the conduction velocities in the peripheral nerves could be demonstrated among workers whose blood lead had never exceeded 70 μg/100 ml, and a dose–response relationship was shown starting at 40 μ100 ml [Seppaläinen et al., 1975]. Also the central nervous system became involved at lead levels of 40–50 μg/100 ml, manifested as psychological functional impairment [Hänninen et al., 1978]. Inclusion bodies in the renal tubular lining cells were also described as being a subclinical effect of lead toxicity [Goyer et al., 1970].

Together with improved methods for analyzing lead in the blood, these findings provided a basis for computing dose–effect and dose–response relationships. A task group under the auspices of the then Permanent Commission and International Association of Occupational Health, which convened in Tokyo in 1974, evaluated these relationships and concluded that the critical effects on heme synthesis

began to appear in the range of 30–50 μg/100 ml of Pb in the blood. (Inhibition of ALA dehydratase was then defined as a subcritical effect.) Although the data were scarce, the group agreed that a nerve conduction deficit detectable by electromyography might have been the critical effect for lead on the nervous system. The group had insufficient data on subclinical effects of lead on the adult brain, but pointed out that the central nervous system may be the critical organ in young children [Nordberg, 1976]. When the WHO expert group, referred to earlier, convened in 1978, more data were available and it was concluded that 40 μg/100 ml was the noneffect level for effects on the nervous system [WHO, 1980]. Later research has revealed toxic effects on the central nervous system in children at much lower concentrations (see above). It also appears that exposure levels of the order of 30 or even 15 μg/100 ml (1.44 and 0.72 μM/l, respectively) may cause spontaneous abortion, reduced birth weight and shortened gestation time [WHO, 1995]. Suggestive evidence for the carcinogenicity of lead has also been published in the last two decades, but this matter is not yet settled [WHO, 1995].

These extracts from a very extensive literature illustrate that the concept of poisoning has been broadened to also encompass subclinical effects and that ''poisoning'' today is regarded differently from what it was in the first half of this century. They also show that dose–effect and dose–response relationships are fairly well known—in fact, probably better than for any other xenobiotic. Finally, they show that subclinical effects are not considered acceptable anymore, which is evident from the substantially lowered hygienic standards in most countries.

LEAD AND THE GENERAL ENVIRONMENT

Lead has been used so widely for centuries that it occurs almost everywhere. Throughout history many epidemics of lead poisoning from nonoccupational exposure have occurred. The possible share of lead in the fall of the Roman Empire, the Devonshire colic, poisoning from the addition of lead acetate into wine, and pediatric lead poisoning have already been mentioned. Not only the manufacture, but also the use of leaded pottery and earthenware, has for centuries caused poisoning among the public. When a lead glazed piece of ceramics is not heated enough, as is still the case in many developing countries, acid food and liquids, such as salad dressings, citrus fruit juice, and wine, make lead dissolve from the glaze. Central America and the Mediterranean region have been notorious for this source of poisoning. Discarded car radiators have gained use, especially in some U.S. states, for distilling illicit whiskey, resulting in a leaded drink, which has poisoned many users. Plumbing with lead pipes was earlier common in Europe, the U.S. and many other places. Many old European cities still have water pipes made of lead. When artificial softening of the drinking water began in the 1960s, lead began to dissolve from the pipes. Use of lead arsenate as a pesticide in vineyards contaminated wine earlier in this century. There are many reports of heavy pollution from lead smelters, for example, in New Mexico and former Yugoslavia (the Meza valley), according to which the surrounding population exhibited toxic effects comparable to those prevalent in poorly managed industries. Such conditions still prevail in many countries: in the less developed countries the problem may not even be recognized. Still today dismantling of lead batteries in cottage industries in many developing countries causes poisoning in whole families, especially in children. Lead paints and cosmetics earlier poisoned artists and actors. The sources have been almost innumerable.

However, few single actions of man have had such extensive effects on the environment as the introduction of tetraethyl lead (TEL) as an additive of gasoline in the late 1920s.

In the early 1920s it was found that addition of what was called ''ethyl'' (lead was not mentioned!) to gasoline had a strong antiknocking effect and improved the performance of the engine. Soon production began on an industrial scale. However, the U.S. Public Health Service began to receive warnings about the dangers of TEL, because several serious episodes of poisoning occurred among the production workers. When eight workers had died in straitjackets from dramatic central nervous system involvement, and the press had made an issue of it, the Surgeon General convened a meeting in 1925 [Needleman, 1997]. At the meeting two of this century's pioneers, Dr. Robert Kehoe and Dr. Alice Hamilton, debated the dangers connected to the use of TEL. Kehoe, who represented industry, tried to play down the risks while Hamilton was worried and pointed out that the risk, if there was one, would spread to the whole population. Other public health scientists supported her, but in spite of these concerns, the hearing could not reach any conclusion and finished in disarray. Industry, especially the Ethyl Gasoline Corporation, put very strong pressure on the health authorities, and its representative, Frank Howard, stated that ''Our continued development of motor fuels is essential to our civilization'' and called the discovery of tetraethyl lead ''an apparent gift of God'' [Rosner and Markowitz, 1985]. To save face, the Surgeon General set up a committee to further study the problem. Later the committee reported to the Surgeon General that there was no evidence that TEL presented a hazard to the community. We all know the result: TEL went into general production and all over the world the public had to live for over 60 years with the enormous lead pollution released through exhaust gases [Rosner and Markowitz, 1985; Needleman, 1997].

The use of TEL increased exponentially. In 1933, only 10,000 tonnes of lead alkyls were burned as compared to 350,000 tonnes worldwide in the 1970s. The use of TEL

peaked in the mid-1970s, when the introduction of first low-lead and later unleaded gasoline has lowered the consumption substantially. In the US practically no leaded gasoline was sold after 1990 and the development has been similar in most European countries. When TEL was used, this source alone contributed 98% to environmental lead pollution. It took a long and violent fight before health authorities realized that lead in gasoline had to be abandoned. Industry tried to find errors in the research revealing that low lead doses were also toxic and did not accept the conclusions. It supported all the time research to disprove the claims of danger and of the existence of subclinical toxicity. In 1924 Charles Kettering had hired Robert Kehoe on behalf of General Motors to investigate the health hazards in the TEL manufacturing plants. The industry-paid Kettering Institute was soon set up and Kehoe was appointed its director, a post that he held for half a century. The lead industry not only paid Kehoe's salary, it also financed most of his research. In return Kehoe, through his central position in lead research, could stifle environmental pollution control programs in the U.S. for several decades [Nriagu, 1998]. When the risks of TEL use were debated, Kehoe always used to claim ''Show me the data.'' Considering the complexity of the problem, this was not easy. Kehoe did not believe in subclinical lead poisoning. He defined poisoning rigidly in clinical terms: either you had poisoning or you were healthy. As already mentioned, Kehoe held strongly that poisoning could not occur as long as the blood lead level was less than 80 μg/l. Since such levels were not reached from environmental pollution alone, his conclusion was that this source had no health consequences. Kehoe also claimed that a certain concentration of lead in the blood, of the order of 20 μg/100 ml (approx. 1 μM/l) on the average, was ''natural'' and ''normal.'' Such was the paradigm until a geologist by the name of Clair Patterson entered the picture in 1965 [Nriagu, 1998].

Patterson could show that technological activities had raised the lead body burdens of modern humans by 100 times compared to pretechnological man. He could also show how substantial air pollution had been by sampling cores of the Greenland ice pack and relating the layers to different time periods. The concentrations had risen fourfold during the century of the industrial revolution, and again by three times after the introduction of TEL in the late 1920s to the mid-1960s. The icecaps of the Antarctic showed no such increase. Patterson's laboratory was kept scrutinously uncontaminated by lead, which was a prerequisite for his conclusions. By contrast, Kehoe's laboratory was contaminated, and in addition many of his ''normal'' referents had, in fact, been exposed. All his lead values were therefore probably too high, even the sacred 80 μg/100 ml border. Although heavily opposed in the beginning, especially by Kehoe and other industry-funded scientists, Patterson began to get support from the academic scientific community, and finally the health authorities accepted that TEL was an unacceptable source of pollution [Needleman, 1998a].

The new concept of subclinical lead poisoning and the idea that even slight effects were unacceptable certainly also contributed to the scientific community's realization that environmental pollution caused by the burning of TEL could not continue. The abandoning of TEL has indeed had an impact: The ''normal'' average values of lead in the blood of adults and children have declined from 15–10 μg/100 ml (0.72–0.5 μM/l) to much less than half during the last two decades [WHO, 1995; Silbergeld, 1997; Needleman, 1998b]. Getting rid of TEL has been a great achievement for preventive public health. However, because lead has no known beneficial effect on living organisms, because there are still subpopulations with all too high blood lead levels, and because refined research methods push the no-detectable-effect level lower and lower, the goal must be to achieve even lower exposure levels and lower blood lead concentrations in all subsets of the population than those occurring today.

THE HISTORICAL PERSPECTIVE

In a qualitative sense the clinical manifestations of most toxic effects of lead have been established more than a century ago. These include effects on the central and peripheral nervous system, the kidneys, hematological effects, adverse pregnancy outcome and many others. There is probably no biological function and no enzyme activity that is not affected by lead in sufficiently high concentrations. Today we are looking for the same qualitative types of effects as historically, but quantitatively at the subclinical level and the group level. Our scientific interest now focuses on the low to very low exposure range. The goal is to define the limits for safe exposure, if such limits really exist. This is a challenge both for study design, data analysis, and biochemical, physiologic, and epidemiologic measuring methods. Research becomes more demanding and more expensive.

However, although research is necessary and sometimes exciting, the key question is the *prevention of toxic effects*, however slight. This does not need sophisticated research anymore—it can be done based on existing knowledge. Lead poisoning is indeed preventable. The problem is to get authorities convinced that efforts are needed and that they are economically defendable. The developing countries, although burdened with tremendous other problems, should also learn from the mistakes made by the industrialized countries. But there are not only mistakes to learn from. We have also seen many examples of successful action, although action usually has come much too late: Lead-free glazes in pottery, the white lead convention, abandonment of lead plumbing, the ban on leaded gasoline, a beginning (finally!) of the sanitation of lead contaminated

housing, reduction of emissions from smelters, and new lead-free technologies, for example, in the printing industry. Many other examples could be listed, not least a general improvement of occupational hygiene. But we must go further in order to be able to also prevent very early effects, and we must support the developing countries with economical aid, know-how and training, rather than by relocating our dirty industries to them. We must not let history repeat itself by neglecting effective prevention where it is most needed. It is a shame if action is not taken when all the ingredients for successful prevention exist.

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