HISTORY IN MEDICINE

Lead nephropathy: early leads from descriptive studies
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Abstract Chronic lead exposure is recognized as a potential cause of hyperuricaemia, kidney damage and hypertension. The fascinating story of lead poisoning and nephrotoxicity illustrates the utility of descriptive studies in the early elucidation of a new disease entity. The pursuit towards understanding lead nephropathy is presented as a successful illustration of human occupational and public health.

In parallel with civilization, the ubiquitous divalent metal lead was known as early as 4000 BC and the history of lead poisoning dates back 2500 years.1 Mischiefous and relentless mankind lead exposure was captured in The Uncommercial Traveller by Charles Dickens; an old Irish lady told him about the women working in the white lead mills in the east end of London, ‘...some of them gets lead-poisoned soon, and some of them gets lead-poisoned later, and some, but not many, niver...’ Over the past decade, kidney damage secondary to lead exposure has received increasing attention.2,3 It is now being recognized that lead exposure shows both acute and chronic toxic effects. Acutely, lead accumulates in the proximal renal tubules, causing aminoaciduria and renal glycosuria due to diminished reabsorption as well as hyperuricaemia secondary to diminished urate secretion and inhibition of guanine aminohydrolase by lead.4 Chronic lead exposure results in progressive tubular atrophy and interstitial fibrosis. Common clinical manifestation includes chronic renal insufficiency with a benign urinary sediment, contracted kidneys and hypertension.2

A long history of controversy intertwining lead exposure and kidney disease illustrates several important roles of descriptive studies in medical research. Descriptive studies are often the first foray into a new disease or area of inquiry – the first scientific ‘toe in the water’.5 Historically, occupational diseases have often first been identified by case reports, then by clusters and ultimately by experimental models in animals and epidemiological studies in subjects.6 Here, we provide an historical overview of the fascinating scientific search for the link between lead poisoning and kidney disease, emphasizing the influence of descriptive studies since antiquity.

Case clustering
Credence for a causal link of lead poisoning from occupational exposure first came from Sir Alfred B. Garrod (1859) who observed that one-third of his gouty patients were plumbers1 and painters, as cited in Nriagu’s book.7 Early descriptive studies provided clues with kidney disease ensuing lead exposure, but failed to differentiate interstitial from glomerular disease.8,9 Clearly, the lack of a clear, specific and measurable case definition of lead nephropathy poses a problem in descriptive epidemiology. Detection or ascertainment bias thus introduced (owing to confusion of lead nephropathy with Bright’s disease, for instance) will reduce the true effect of lead exposure.

Jean-Martin Charcot was credited with the earliest description of experimental lead nephropathy in animals, with the recognition that lead causes interstitial nephritis in guinea pigs in the absence of proteinuria.10 The urine sediments were accurately characterized as bland sediment in lead nephropathy, emphasizing the absence of urinary casts and albuminuria and thus allowing distinction from Bright’s disease.2,3 A clear description of kidney disease with interstitial nephritis came from the
post-mortem examination of a lead-poisoned artist in 1862.\textsuperscript{9,11} Substantial atrophy of the renal cortex and tubular fibrosis was shown in the kidney of an artist who habitually kept a paintbrush in his mouth for a substantial proportion of his day.

Whereas a single report might not raise alarm, clustering of several cases alerted people to the danger of this occupational exposure. As a matter of fact, plumbism was so common in the Victorian era that cattle grazing in fields adjoining white-lead factories died from the contaminated grass in the UK.\textsuperscript{12} The Roman word \textit{plumbum}, denoting lead water spouts and connectors, is the origin of the English word plumbing and of the element’s symbol, Pb. Use of lead pipes in public water systems had prevailed until the 1950s, after which they were gradually replaced by copper or polyvinyl pipes. Thomas Oliver noticed that cattle grazing near the mines ‘died from lead poisoning, fowl could not be reared, and in one instance, a child died after sucking flowers contaminated with lead dust’\textsuperscript{13} He reported that kidney disease was a major cause of death among English lead workers and published the first illustration of the histology of lead nephropathy uncomplicated by gout.\textsuperscript{13,14} The notion of occupational disease compensation emerged as early as 1914 when Oliver asserted that ‘...contracted kidney is the most common pathological event in chronic plumbism. It is undoubtedly the lesion of chronic lead poisoning. Saturnine nephritis has come to be recognized in a court of law as a disease of occupation and compensation has been given to relatives’.\textsuperscript{13,15} Saturn (Saturnus) was a god of ancient Roman mythology, although some have related him to the Greek Cronus who was the father of Zeus. He was the introducer of agriculture and his wife, Rhea, the goddess of sowing and harvest. The eponym saturnism was evidently derived from the designation of Saturn as the god of riches of the earth, including lead. In more common usage, the adjective saturnine is used for a person of sluggish, cold and gloomy temperament, so used because lead is a heavy and sluggish metal.\textsuperscript{16} This is a classic example of how individual case reports give rise to case series, with the aggregation of similar cases suggesting the presence of a new disease entity.

**Studies of epidemics**

Clustering of unusual cases in a short period often heralds a new epidemic.\textsuperscript{5} It was not until the late 1920s when an epidemic in Queensland, Australia, triggered more rigorous investigations and the story of lead nephropathy eventually came into light. Geographically, Queensland is mostly tropical with houses built on high stumps and surrounded by wide open verandas, often with a wooden railing painted with the only paint available in the late nineteenth century – lead pigment-based paint.\textsuperscript{17} Not surprisingly, children frequently played on these cool verandas where large amounts of the leaded paint tended to powder and flake in the hot sun. In addition to ingestion of leaded paint debris, the children licked the sweet-tasting lead-containing rain water collected on the railings. The puzzling high death rate in Queensland young adults who suffered from ‘chronic nephritis’ led to a long investigation and it was alleged that the excess mortality from chronic renal disease in Queensland was due solely to lead absorption (from leaded paint) in childhood.\textsuperscript{17–20}

This was followed by a multitude of reports of renal disease after lead exposure. The early epidemiological evidence suggested a change in the frequency of disease following a specified change in the frequency of exposure. The prototype was recognized in south-eastern USA where individuals consumed lead-contaminated illicitly distilled (moonshine) whiskey and developed significant renal insufficiency accompanied by gout. As most long-term follow-up studies to date have indicated that hyperuricaemia and gout rarely result in renal damage, the observed coincidence of gout and renal failure among these moonshine consumers attested to the common causative factor of lead poisoning.\textsuperscript{4,21} Renal biopsy findings closely resembled the previously reported manifestation.\textsuperscript{20,22–25} It is believed that the increased lead content in ‘moonshine’ whiskey was related to the process of brewing in galvanized tubs and distillation in truck radiators.\textsuperscript{25} Lead battery plates, moth balls or drain cleaners were sometimes added to the mash to accelerate fermentation or to add flavour by ‘making the liquor taste like it is mellowed and aged’.\textsuperscript{26} This finding prompted epidemiological surveillance (mostly passive) in different communities. For instance, nearly two-thirds of 200 hypertensive male veterans admitted to past ingestion of moonshine drinking according to a survey in Philadelphia.\textsuperscript{27}

In retrospect, an increasing incidence of gout among women had been noted after the lifting of rules prohibiting women from drinking wines (which were presumably laden with lead).\textsuperscript{3,28} A high prevalence of gout among subjects with lead nephropathy implicated a close link between lead and hyperuricaemia. Possible mechanisms of saturnine gout include decreased renal clearance of uric acid, crystallization at low urate concentration and lead-induced guanine crystal formation. Subsequently, human studies confirmed greater amounts of mobilizable lead in gouty patients with renal failure (as compared with either patients with gout and normal renal function or those with renal insufficiency and no gout).\textsuperscript{29} These data further suggested a causative role for lead in the development of both gout and chronic kidney disease.\textsuperscript{30}
Ecological correlational studies

In the wake of the foregoing evidence, correlational studies were undertaken to look for an association between lead exposure and outcome in populations as opposed to individuals. A comparison of mortality statistics in Queensland and other Australian states led to the conclusion that the excess mortality from chronic nephritis was accounted for by the action of a nephrotoxic agent, which affected Queensland children between 1870 and 1920. Further follow-up of mortality and incidence of renal disease was undertaken in those who had been hospitalized between 1915 and 1935 with a diagnosis of lead poisoning in Brisbane. An excess of mortality from vascular and renal disease was shown. Among these 400 children with acute lead intoxication, more than one-quarter had chronic renal failure or hypertension and an additional 20 children had hypertension and proteinuria or proteinuria alone, indicating a vast increase in renal and vascular disease above average. To further support the postulated link, it was shown that patients without other obvious cause of chronically contracted kidneys had significantly higher bone lead levels than those with an established cause of renal disease. Over a period of 30 years after legislative exclusion of lead from paints, a steady decline in the mortality from renal disease was shown in Queensland.

Similarly, in another survey of death certificates from 7032 battery and smelting workers, there was a consistent excess of deaths classified as ‘other hypertensive disease’ and ‘chronic nephritis or other renal sclerosis’. Furthermore, from Shoshone County, Idaho (where the Kellogg lead smelter is located), a fivefold to sixfold higher prevalence rate of end-stage renal failure was quoted as compared with other individual counties in the five-state Health Care Financing System end-stage renal disease network.

Although these correlational studies cannot prove a causal relationship, they make a strong case for a plausible link between lead poisoning and renal damage.

One final word about the evidence: most of these observations and conclusions were accomplished without the use of the ethylenediaminetetraacetic acid lead mobilization test (apart from the correlation study of gout and lead burden quantification) and without early markers of renal tubular damage such as urinary excretion of low molecular weight proteins or N-acetyl beta-D-glucosaminidase. One famous, albeit crude by current standards, chemical analysis in the eighteenth century was carried out by George Baker who evaporated the urine to dryness; the residue was heated to obtain molten lead. Alternatively, a test solution was added to produce a precipitate in the presence of lead. Advances in lead toxicity research made possible by new tools in testing body lead levels were perhaps best illustrated by the mysterious death of the US president Andrew Jackson. Jackson died in a state of anasarca and probably in chronic renal failure in 1845; he was described as ‘perfect jelly from toes to the upper part of my abdomen, in any part of which a finger can be pressed half an inch and the print will remain for minutes’. Concern was subsequently expressed about his regular ingestion of sugar of lead (lead acetate) and plumbism secondary to two lead bullets retained in his left lung and left shoulder (with close proximity to synovial fluid in the joint space). A significantly increased lead level was shown by retrospective hair spectrophotometry analysis more than one century after his death, emphasizing the distinct possibility of lead nephropathy.

Recently, further evidence of a correlation between the body lead burden and kidney disease came from a well-designed landmark randomized study, in which patients with low-level environmental lead exposure and chronic renal insufficiency were found to have significantly improved renal function and slower decline in glomerular filtration rate following chelation therapy. A 4-year prospective longitudinal study of 121 patients with chronic kidney disease further showed the strong and dose-dependent associations between both body and blood lead burdens with the progression of renal decline. The findings of this study lend credence to the suggestion that environmental lead exposure accelerates progression of chronic kidney disease. In another prospective study patients with type II diabetic nephropathy, blood lead levels at baseline and body lead burden, were found to be the most important risk factors in predicting progressive diabetic kidney disease. In addition, patients randomized to chelation therapy had significantly lower rates of decline in glomerular filtration rates than the control group. Although critics may argue that these studies were not designed to prove the causality of nephropathy following lead exposure, they might offer the best insights about lead poisoning and kidney disease.

In summary, all this fine investigative work and compelling evidence achieve a certain triumph in unravelling the enigma of lead nephropathy. Although at present, neither descriptive nor observational studies can provide a definite answer to the precise correlations between lead exposure, hypertension and renal disease, they are a rational basis for hypothesis generation and search for more robust evidence.

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References