

**A city of steel, and a heart of lead: an analysis of lead exposure and its effect on
cardiovascular disease**

by

Andrew Rowley

BS in Biochemistry, Duquesne University, 2017

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This essay is submitted

by

Andrew Rowley

on

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and approved by

Essay Advisor: James Peterson, PhD, Associate Professor, Environmental and Occupational
Health Graduate School of Public Health, University of Pittsburgh

Essay Reader: George Bandik, PhD, Assistant Dean, Department of Chemistry, Dietrich School
of Arts and Sciences, University of Pittsburgh

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Andrew Rowley, MPH

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Abstract

Exposure to lead has long been known as a human health risk, with the hallmark symptom of disease being neurological impairment. However, there have been developments in the field of medicine that suggest exposure to lead also is responsible for cardiovascular disease, both in onset and increasing the severity thereof. With the levels of ambient exposure to lead from our infrastructure, in soil, lead paint, and lead pipes, there is no shortage of routes of exposure to lead both domestically and abroad. It has long been recognized that no safe level of lead exposure exists, especially in pediatric patients, although recent events in Flint, Michigan, and Pittsburgh, PA, have shown that lead exposure is not just a relic of the past, but a problem that still very much exists in the world today (National Public Radio [NPR], 2016; Pieper et al, 2018; Lidsky & Schneider, 2003; O'Connor, 2018; Flora, Gupta, & Tiwari, 2012; USCDC, 2012).). With the global burden of cardiovascular disease resulting in 1 in 3 deaths in this country and being among the top 10 causes of death across the world, combined with growing speculation that lead exposure is related to the severity and incidence of cardiovascular disease, the questions become is there exists enough evidence to prove such a claim, and what methods are available to find the truth if it remains unknown. Finally, should there be definitive proof of this link one day, what would the most feasible and reasonable path forward be?

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Preface

I would like to sincerely thank Jim Peterson, PhD, for his continual advisement throughout the progress of my degree, from the time of enrollment to the culmination of this essay. I would also like to sincerely thank George Bandik, PhD, not only for his role as an advisor on this committee, but also for being a friend and mentor since we first met. Further, I extend my sincere gratitude to every instructor I've had over the course of my degree, who not only made every class interesting and worthwhile, but also were able to weave every lecture seamlessly into other courses throughout the progress of this degree. I also thank my parents, who made sure I stayed the course to earn this degree and to continue pursuing even more letters after my name in the years to follow. Finally, my most sincere thanks and appreciation goes to Julia, who not only tolerated me throughout my undergraduate studies, but then encouraged me to go back for another degree.

1.0 Introduction

Since the dawn of civilization, humans have strived to use the resources around them to their advantage, to improve their own security and to build upon their empires. Humans have long realized that many of the resources found in the natural world are abundant and can be incorporated into many facets of surviving and thriving. From guns, germs, and steel to atoms being split and intelligence being artificially conceived, we have come a long way from our roots as early humans to the societies we live in today. Lead, being an incredibly abundant natural resource, has long been utilized in technological advances, being used since the Roman Empire, and still being used today (Cilliers & Retleif, 2019).

The United States also has a long history of incorporating lead into a variety of products, namely lead pipes, gasoline, and paint, although the deleterious health effects of lead exposure were discovered almost immediately after the incorporation of these products (Rabin, 2008; Eschner, 2016; O'Connor, 2018). With lead being quite malleable, it was used often in modern pipe infrastructure, despite iron, a cheaper option, being available (Rabin, 2008). (Rabin, 2008; Cilliers & Retleif, 2019). While the installation of new lead pipes has been outlawed for over 30 years (Safe Drinking Water Act, 1986), it is still legal to maintain lead pipes with measures to minimize corrosion (American Water Works Association vs Environmental Protection Agency, 1993), with Flint, MI; Newark, NJ; and Pittsburgh, PA being notable examples. Leaded gasoline, first invented in 1921, was known to be dangerous to human health shortly after its inception but was still used for decades afterwards before its eventual ban from the US in 1996 (Eschner, 2016; Dignam, 2019). Leaded paint, while being banned from commercial use in 1978, is still found in

residences built before this date and can pose risk to residents if poorly maintained (United States Environmental Protection Agency [USEPA], 2021).

The purpose of this paper is to provide a perspective on how something often overlooked as a source of health complications, lead exposure, may have lasting effects on the field of cardiovascular disease, determine the extent of such a link between these factors, and provide an appropriate path forward for how to best mitigate the effects and who would be best equipped to do so. With a national emphasis both on monitoring of lead contamination and the prevalence of cardiovascular disease, it has been speculated that lead exposure is related to higher prevalence and worse outcomes for those who suffer them, such as hypertension, heart attacks, and stroke (Brown et al, 2020). With lead having many routes of exposure to humans; be it ingestion of paint chips, crops grown in contaminated soil, occupational exposure, inhalation of dust, or consumption of tainted water from lead pipes; the field of environmental and occupational health is the perfect lens to evaluate the effect of lead exposure on the link between prevalence and outcome. Further, environmental policy makers would be the ideal audience for this evaluation, with those involved in policy being best equipped to respond to the needs for remediation of the issues discussed. Finally, a literature review was chosen for this project due to the minimal understanding and research being done on lead exposure and the effects of cardiovascular health, with a literature review allowing us to better understand the field as it currently is and what areas we should next turn our attention to for a more complete understanding of the issue.

2.0 Review

Historically, lead has been ingrained into infrastructure of many major powers, with the Roman Empire being associated with the lead pipes that transported water within their borders (Cilliers & Retleif, 2019). The United States has also used lead pipes throughout its history, with 70% of established cities having lead pipes by 1900 (Rabin, 2008). While other more cost-effective materials were available for constructing pipes, such as iron, lead is more malleable, making it better for large infrastructure projects like city plumbing (Rabin, 2008). Additionally, lead is useful in other, more modern applications as well, such as increasing the octane rating for gasoline (Bellinger, 2016) and in paint to increase durability and decrease drying time (Bellinger, 2016; Schroder, Tilleman, DeSimone, 2015; Crow, 2007). However, the deleterious health effects of using lead in such products have been well established, with the effects of lead paint being known since the early 20th century (Gibson, 2005) and leaded gasoline being recognized as dangerous shortly after its inception in 1921 (Schrader, 1925; Schroder, Tilleman, DeSimone, 2015).

With the monumental developments in medicine over the last century, more developed nations have largely been able to overcome the so-called “double burden of disease,” where nations face health crises from both quickly moving infectious disease and dormant chronic illnesses (Boutayeb, 2006). With some notable exceptions, the United States has largely been able to mitigate the spread of infectious disease, with heart disease, cancer, stroke, and diabetes being among the leading causes of mortality within the nation in 2019 (United States Centers for Disease Control and Prevention [USCDC], 2019). With cardiovascular disease (i.e., heart disease and stroke/cerebrovascular disease) comprising an estimated 809,000 deaths in the United States in

2019, it is apparent that cardiovascular disease is an issue of great interest to public health at large (USCDC, 2020).

2.1 The effects of exposure

With heart disease historically being the top cause of mortality in the United States, it is perhaps the premier health issue the nation faces (Lanphear et al, 2018). Causing 1 of every 3 deaths in the nation, and costing an estimated \$300 billion annually, the factors typically associated with are diet, exercise, smoking behavior, and hypertension (Lanphear et al, 2018). This has led to inquiries about the effects lead exposure, which can facilitate hypertension, has on the prevalence and severity of (Lanphear et al, 2018). It is suspected that lead is responsible for 10.3% of the global burden of hypertension disease, 5.6% of ischemic heart disease, and 5.6% of the global burden of stroke (WHO, 2019), although relatively few studies have been performed to truly determine the extent to which lead and the cardiovascular system are related.

Domestically, lead exposure-based heart disease is estimated to influence an annual 256,000 deaths from (28.7% of all cases), and 185,000 deaths from ischemic heart disease (37.4% of all cases) (Lanphear et al, 2018). Sadly, the effects of lead on the cardiovascular system have been known for over 100 years, although our understanding of the correlation is still in its infancy (Navas-Acien et al, 2006). Generally, while lead is tied to hypertension, which is correlated to cardiovascular disease and ischemic heart disease (Lanphear et al, 2018; Navas-Acien et al, 2006) hypertension is not seen as the hallmark disease related to exposure- rather, lead has historically been viewed as a neurotoxin (Cory-Slechta, 1996; Flora, Gupta, & Tiwari, 2012). In addition to hypertension, lead exposure has been recently correlated to other complications with health, such

as abnormalities in electrocardiography, left-ventricle hypertrophy, and peripheral heart disease (Lanphear et al, 2018).

When looking abroad, while lead regulations, and ultimately the severity of outcomes, may differ from the United States, the trend becomes more apparent. For example, a cohort study conducted in Korea showed a positive association in occupational lead exposure and hospitalization for ischemic heart disease, cerebrovascular disease, angina/chest pains, and stroke (Min & Ahn, 2017). In another study, it was found that among hospitalized stroke patients in Iran, patients had an average blood lead level (BLL) of 20.65 micrograms per deciliter (mcg/dL) relative to healthy controls with levels of 2.65mcg/dL (Mousavi-Mirzaei et al, 2020). When comparing the odds ratio of stroke between hospitalized patients and their healthy gender and age-matched controls, it was found that for every 1.0mcg/dL increase in BLL among patients, the odds of disease increased by 4% (Mousavi-Mirzaei et al, 2020). Further, in China, a study showed that among women with varying levels of lead exposure, higher BLLs were associated with higher likelihood of prevalence (Chen et al, 2017). Regarding levels of exposure, women in the study within the highest exposure quartiles (BLL quartiles of < 2.5mcg/dL, 2.501-3.770mcg/dL, 3.771-5.46mcg/dL, and >5.46mcg/dL), a trend of prevalence emerged, with those in the lowest exposure quartile having a prevalence of 3.9%, while the highest exposure quartile having a prevalence of 10.3% (Chen et al, 2017). When considering factors that also affect onset and severity, such as obesity, diabetes and smoking status, an odds ratio of 1.93 between the lowest and highest exposure quartiles was calculated (Chen et al, 2017).

When evaluating the effects of lead exposure on human health, we tend to associate its worst effects with children, due to the deleterious effects exposure has on proper neurological and central nervous system development and function (Cory-Slechta, 1996; Flora, Gupta, & Tiwari,

2012). However, when evaluating the effect of lead exposure through the lens of cardiovascular disease, the frame shifts to young and middle-aged adults (18-44 years old classified as young adults, 45-65 years old classified as middle-aged adults), with higher levels of exposure being tied to higher rates of poor health outcomes related to cardiovascular disease, namely manifesting in increased blood pressure and higher cholesterol (Obeng-Gyasi, 2019).

With regards to lead exposure, it is well known that lead is unsafe in any capacity to human life, especially regarding children under the age of 6 (Lidsky & Schneider, 2003; O'Connor, 2018; Flora, Gupta, & Tiwari, 2012; USCDC, 2012). However, in recent years the views on what is constituted an actionable level of contamination has been modified. Prior to 2012, the CDC recognized BLLs of 10mcg/dL or higher as within the “level of concern,” although that has since been modified to be lower, at 5mcg/dL (USCDC, 2021). Prior to the reclassification, BLLs under 10mcg/dL were not required to be reported to parents, although this has since been modified (USCDC, 2021). While the step to report increasingly lower BLLs is a step in the right direction, the uncertainty remains about lead exposure and its implications extending into the realm of cardiovascular disease (USCDC, 2012; Obeng-Gyasi et al, 2018). One such study in adults found that when evaluating the effect of cardiovascular disease incidence across various levels of BLL contamination (0-2, 2-5, 5-10, and 10+ mcg/dL), there appeared to be increased incidence of cardiovascular disease across cohorts, showing that even any level of contamination, even below 2mcg/dL, could potentially be a factor in cardiovascular disease development (Obeng-Gyasi et al, 2018).

Overall, while there is evidence suggesting there may be a link between cardiovascular disease and lead exposure (Chen et al, 2017; Mousavi-Mirzaei et al, 2020; Obeng-Gyasi et al, 2018), these studies have not yet firmly established a link between the two. We remain unsure at

this time how much of a role lead plays on cardiovascular disease (Chen et al, 2017; Mousavi-Mirzaei et al, 2020; Obeng-Gyasi et al, 2018), and while many efforts have succeeded in reducing the levels of lead exposure overall (Dignam, 2019), we will see that lead exposure is far from a relic of the past, and even is an issue that has affected us in our own neighborhood.

2.2 Flint, Michigan, and Pittsburgh, PA

While lead exposure comes in several forms, such as lead dust, paint chips, and lead-additives in gasoline, perhaps the most notorious route of contamination is lead pipes resulting in contaminated drinking water (Farfel, Chislom, Rohde, 1994; O'Connor et al, 2018; Schroder, Tilleman, DeSimone, 2015; Bellinger 2016). We don't have to look far back in history to see lead pipes rearing their ugly head- Flint, Michigan propelled the issue to the national spotlight in 2014 (Bellinger, 2016). The story is well known at this point-in pursuit of a fiscal responsibility for the city of Flint, the city switched the water supply from Lake Huron to the Flint River, and the anti-corrosion agents required by the Environmental Protection Agency's (EPA) Lead-and-Copper Rule were abandoned (Bellinger, 2016; USEPA, 2007). Further, the city incorporated the use of ferric chloride into their water treatment regiment, with the factors combining to increase the corrosiveness of the water by 19-fold (Bellinger, 2016). With the change in water supply and the methods used to treat it, the lead pipes which the water flowed through began to degrade rapidly, resulting in lead leeching into the water supply and harming the city's residents (Bellinger, 2016). While the city had lead contamination prior to the switch, the prevalence of children with BLLs above 5mcg/dL more than doubled, from 2.4% in 2013 to 4.9% in 2015 (Hanna-Attisha et al, 2016). Additionally, in some areas of the city, more than 25% of water samples taken had a

concentration above 15ppb, and these areas saw an increase of children with elevated BLL (i.e. 5mcg/dL or higher) from 4.0% to 10.6% (Hanna-Attisha et al, 2016). In one such residence, sampling taken throughout the crisis showed lead concentrations ranging from 217-13200 ppb from the water supply, with 5,000 ppb being classified by the EPA as hazardous waste (Pieper et al, 2018).

While we would like to think that Flint's water crisis was an isolated incident, it tragically was not. There are over 3,800 communities in the country that have been found to have evaluated childhood BLL rates double the rate of Flint, and 1,300 communities have quadruple the levels of elevated childhood BLLs that Flint does (Pell, 2017). While Flint is perhaps the most notable recent example of lead contamination through the water supply, Newark, New Jersey seemed to immediately follow the tragedy of Flint, garnering national news shortly after the first story (Lytle et al, 2020) When I first began my degree in 2019, Pittsburgh was one of these communities, with an average lead concentration of 17ppb (Pittsburgh Water and Sewer Authority [PWSA], 2019). The increased levels of lead in the city's water supply can be traced back to 2012, when Pittsburgh hired the French management company Veolia North America, the same company the city of Flint hired for their water management before their crisis (Lurie, 2016).

After Veolia North America began their work in Pittsburgh, some 81,000 residences were notified of elevated lead levels (i.e. 15ppb lead or higher) in their water supply, with 17% of all samples being above the limit during the testing period (Lurie, 2016; USEPA, n.d.) Veolia North America largely deflected any blame, saying "some people may be sensitive to any water," although lead levels in city supplied water samples, even with existing lead pipes, were as low as 6ppb in 2001, then reaching 14.8ppb a year after the switch (Lurie, 2016; PWSA, 2016). Further, the treatment regimen for the water was altered by Veolia, changing the anti-corrosion agent from

soda ash (sodium carbonate) to caustic soda, (sodium hydroxide) a cheaper alternative (Lurie, 2016; National Center for Biotechnology Information, 2022; Eggeman, 2000).

Specifically in Pittsburgh, among the 10,184 children under the age of 2 tested for elevated BLL in 2017, the prevalence of elevated BLL (confirmed BLL values of 5.00-10.0+ mcg/dL) affected 220 patients in 2017, with another 144 patients with suspected but unverified levels above 5.0mcg/dL, amounting to a possible 364 pediatric patients with elevated BLLs diagnosed in 2017 (Pennsylvania Department of Health [PADOH], 2017). Among the 10,184 children under 2 tested, with 220-364 possible patients with elevated BLLs, this correlates to an elevated BLL incidence of 2.16-3.57% (PADOH, 2017). Further, when considering the rates of cardiovascular disease within Alleghany County relative to the state of Pennsylvania (2015-2019), Alleghany County had rates higher than the rest of the state, with a prevalence of 186.5/100,000 in the population against 175.3/100,000 for the state (PADOH, 2021).

2.3 The facts and the future

While the city of Flint, Michigan was in the national spotlight for their infrastructure leading to lead exposure to many of their citizens, the levels of exposure are not uniform across even the same geographic area. In 2016, a study conducted in Alleghany County with 100 randomly selected residences found that 45 residences were found to have no detectable lead in their water supply, 38 had levels of lead under the EPA action limit of 15ppb, 17 had levels above 16ppb, and 4 residences had lead concentration between 50 and 75ppb (PWSA, 2016). However, since the Pittsburgh crisis began, remedial actions have been taken, including switching to anti-corrosion agent orthophosphate to prevent the further degradation of the existing lead pipes, and

replacement of all remaining lead pipes by the year 2026 (PWSA, 2021b). This resulted in the city having the lowest level of lead concentration in their water supply in the last 2 decades (5.1ppb), with 19.9 miles of lead line replacement being achieved in 2020 (despite restrictions related to COVID-19 shutdowns) (PWSA, 2021b). While the success is palpable, and in some cases ahead of schedule, there remains the issue of the estimated 8,000 remaining homes in Pittsburgh affected by lead pipes, with efforts being made to replace all public owned city lead lines by the end of 2025 (PWSA, 2021a).

After evaluation of the evidence, while the correlation between lead exposure and cardiovascular disease is still an underappreciated field of interest, evidence has long existed that lead affects the cardiovascular system (Lanphear et al, 2018). Mainly seen as a toxic agent affecting neurologic and central nervous system, lead has long been associated with hypertension, although it is not typically seen as the hallmark condition set on by exposure (Cory-Slechta, 1996; Flora, Gupta, & Tiwari, 2012). It is widely accepted that no level of lead exposure is safe, especially for patients under the age of 6 (Lidsky & Schneider, 2003; O'Connor, 2018; Flora, Gupta, & Tiwari, 2012; USCDC, 2012), and with the persistence of heart disease and stroke among the main causes of death in the nation, a question is emerging- is lead correlated to an increase in heart disease, stroke, and other various forms of cardiovascular disease? (Lanphear et al, 2018; Obeng-Gyasi et al, 2018; USCDC, 2020). The routes of exposure are abundant and often can occur in the background- lead dust from degrading paint, lead contamination in soil, and lead leeching into drinking water (Farfel, Chislom, Rohde, 1994; O'Connor et al, 2018; Schroder, Tilleman, DeSimone, 2015; Bellinger 2016). As such, our strategy must not only include determining the level of impact that lead exposure has on cardiovascular disease development and severity, but

also, where feasible, find ways to reduce exposure to lead in the first place, and once exposure occurs, how to best prevent the manifestation of unfavorable outcomes.

3.0 Analytical

While a firm link between lead exposure and cardiovascular disease has yet to be firmly established, we should nonetheless address methods to minimize exposure to lead at the individual, institutional, and policy levels. Individually, there are options to minimize lead exposure within the home, with one of the possible first steps being the minimization of exposure to lead paint, with encapsulation and abatement being among the most well-known strategies (Farfel, Chisolm, Rohde, 1994). Regarding abatement, one study found that among 13 residences, abatement of lead paint saw a reduction of 16% of lead dust on floors, 10% on windowsills, and 4% in window wells 3.5 years after abatement was performed (Farfel, Chisolm, Rohde, 1994). Further, the study found that 78% of readings taken within abated residences were below the state's interim clearance standards for lead exposure (Farfel, Chisolm, Rohde, 1994). However, the authors note that efforts of partial abatement of paint lead to levels of lead dust being similar to pre-abatement levels 9 months after efforts were made, and paint removal performed with caustic chemicals saw the highest concentration of lead dust upon reevaluation (Farfel, Chisolm, Rohde, 1994). It should be noted that the cost for lead paint removal has been estimated at approximately \$7,000 per household in the United States, (O'Connor et al, 2018) perhaps making abatement prohibitively expensive for individuals when other options remain viable. Lead paint encapsulation (the practice of covering lead paint with appropriate sealing paint agent) is also recognized practice (USEPA, 2022) and is likely the more cost-effective option when compared to complete abatement. It should also be noted that current EPA clearance levels are 10ug/ft² and 100ug/ft² for floors and windowsills, respectively (USEPA, 2022), down from 40ug/ft² and 250ug/ft² in 2020. Overall, while lead paint abatement would be best for complete prevention of lead presence in the home,

and with consideration for the more stringent EPA standards on lead paint in residences, encapsulation of lead paint or even maintaining leaded paint to prevent degradation, is often sufficient to minimize risk while also being more economically advantageous (USEPA, 2021).

Soil contamination in lead is also an issue that can be corrected at the individual level, although it can be undertaken at community level in communal areas such as parks (von Lindern et al, 2003). Lead soil exposure typically occurs via ingestion, often conceptualized through unwashed hands being part of hand-to-mouth activities or consuming produce grown in gardens with lead-laden soil (von Lindern et al, 2003). One common tactic for minimizing lead soil concentration is abatement of contaminated topsoil by removal and replacement of the top 10-46cm (4-18”) in the region of interest, with perceived risk and location being factors in determining the depth of soil replaced (Laidlaw et al, 2017). The abatement of lead soil has shown positive results ranging from several months to several years after remediation efforts (Clark et al, 2011). However, it should be noted that lead naturally occurs in topsoil, with average concentrations ranging from 10-50ppm, and urban settings often having higher lead concentrations in the topsoil, ranging from 150-10,000 ppm (Penn State, 2010). These elevated lead levels in urban centers are often caused by the previous usage of leaded gasoline and/or the presence of lead paint along the home (Penn State, 2010). While lead occurs naturally in topsoil, CDC recommendations suggest a limit of topsoil lead concentration not exceeding 400ppm in children’s play areas, and not exceeding 1,200 ppm for non-recreation areas, such as garden beds [Agency for Toxic Substances and Disease Registry (ASTDR), 2020]. Additionally, the cost of lead soil abatement ranges greatly, with treatment options ranging from approximately \$22/m³ to \$194/m³ for projects that cover lead soil, such as clean topsoil placement without abatement, while abatement and replacement of contaminated soil costs an estimated \$338/m³ (Laidlaw, et al, 2017) With this in mind, while

covering or abating soil with lead contamination can reduce the levels of lead exposure by up to 30% (von Lindern et al, 2003), levels of lead in soil are already well regulated, and ultimately there is not sufficient evidence to further lower the level of lead in soil at this time.

3.1 Secondary prevention strategies

Methods of minimizing initial lead exposure, such as abatement of lead laden soil and paint, are considered “primary prevention” strategies, which involve preventing lead exposure at the source (Desai et al, 2021). However, it should also be considered that while minimizing lead exposure could be beneficial (USCDC, 2012; Flora, Gupta, & Tiwari, 2012) it is not feasible to eliminate all sources of lead exposure in all facets of life, be it an exposure from an occupational source, source in the home, ambient exposure from the environment or elsewhere. With this in mind, we must also address the various methods of “secondary prevention,” where we consider remediation efforts after exposure to lead has occurred but strategies to minimize the harm done by such exposures (Desai et al, 2021).

As mentioned previously, chelation therapy is one such method of individual lead exposure remediation, with the goal of minimizing damage after lead exposure has occurred (Lamas et al, 2013; Roussel et al, 2009). While chelation has been suggested as a potential treatment for heart disease, evidence of its efficacy is limited, showing the highest level of improvement in patients with diabetes (Lamas, et al, 2013). Further, the use of chelation therapy has often been accompanied by high dose oral vitamin supplementation, such as vitamin C, to provide additional therapeutic effects alongside chelation therapy (Lamas et al, 2013; Roussel et al, 2009). Additionally, with various chelation agents available, there are multiple options for treatment that

either can be achieved by taking oral medications, intramuscular (IM), or intravenous (IV) injections (Schroder, Tilleman, DeSimone, 2015).

While there are several mechanisms for treatment, chelation is not without its shortcomings. First, chelation therapy is affected by multiple factors, such as iron deficiency or if the patient has an empty stomach at the beginning of treatment (Schroder, Tilleman, DeSimone, 2015). Secondly, the duration of treatment can vary based on the agent selected and the route of treatment (IV/IM vs oral). While oral treatments are less invasive than their injectable counterparts, treatment duration is considerably longer, lasting up to 12 weeks rather than 2-7 days for IM and IV treatments (Schroder, Tilleman, DeSimone, 2015). It should also be noted that different agents require different frequencies of administration, with some drugs like Dimercaprol (2,3-Dimercaptopropanol/BAL in oil) requiring administration every 4 hours, while other agents such as succimer (Meso-2,3-dimercaptosuccinic acid/DMSA) being administered every 8 hours to begin treatment and reduced to every 12 hours after initial treatment begins (Schroder, Tilleman, DeSimone, 2015). D-penicillamine, another chelation agent, while not approved by the Food and Drug Administration for lead poisoning, is able to be administered once daily through oral administration, albeit with a longer treatment duration of 4-12 weeks depending on severity (Schroder, Tilleman, DeSimone, 2015). Finally, chelation therapy is typically reserved for pediatric patients with BLL >45mcg/dL, although therapies at this level have similar effectivity as removing sources of lead in children with moderate levels of exposure (Ruff et al, 1993; Schroder, Tilleman, DeSimone, 2015).

The idea of chelation therapy being used to minimize or even prevent cardiovascular disease incidence has been clinically tested before with the Trial to Assess Chelation Therapy (TACT) study (Lamas et al, 2013). The study was conducted to determine if patients who had a

history of cardiovascular disease, namely myocardial infarction (heart attack), would be less likely to suffer from future incidences of cardiovascular disease when given treatment of disodium EDTA chelation therapy relative to patients who also had a history of such disease but received a placebo treatment instead (Lamas et al, 2013). Over the 8 years of the study, the overall mortality rate of the two cohorts was roughly equal, and there was no statistical significance in prevalence of cardiovascular disease (stroke, heart attack, coronary revascularization, angina/chest pains) (Lamas et al, 2013). While the results were not statistically significant, the results did show modest benefits for the group receiving chelation, suggesting further studies may be beneficial for testing efficacy in the future, especially with diabetic patients (Lamas et al, 2013).

In addition to chelation, it has been suggested that proper nutrition could be beneficial as a method of secondary prevention for lead exposure, especially in children (USCDC, 2012; Kordas, 2017). In particular, secondary prevention of lead exposure has been tested with Vitamin C, iron, zinc, and calcium dietary supplementation (Kordas 2017) With lead competing with multiple biological metals, there has been speculation that diets higher in competitive binding metals, such as iron, zinc, or calcium, may prevent lead absorption into the body after exposure (Kordas 2017). In particular, lead competes with divalent metals, namely iron and calcium, through uptake via Divalent Metal Transporter 1 (Kordas, 2017). With regards to iron competition with lead, several studies have been conducted to evaluate the effect of an iron supplement in patients with lead exposure, as both lead and iron are both considered divalent metals which compete for absorption in the gastrointestinal tract (Kordas, 2017). Several studies have tested the efficacy of elevated dietary intake iron and have found that while BLLs are lower when given elevated dietary iron, the source of dietary iron (heme iron/animal-based vs non-heme/plant and supplement based)

may affect the efficacy of such a regimen, and as such, is in need of further exploration before effective policies can be recommended (Kordas, 2017).

Another divalent metal, zinc, has been considered as a means of secondary prevention against lead absorption (Kordas 2017). Notably, there are minimal clinical studies regarding zinc supplementation impeding lead absorption, as there currently are not reliable methods to determine subclinical zinc deficiency (Kordas 2017). Further, while zinc and lead are both divalent metals, there is no evidence at this time of competitive absorption between these two agents. However, there have been several animal studies testing the efficacy of higher dietary zinc supplementation to suppress the absorption of lead (Kordas 2017). It is notable, however, that the levels of zinc supplementation provided in rodent studies typically ranged from 200-300g of zinc/kg of diet, the recommended upper limit for adults is 40mg/day, with the lowest observable adverse effect limit (LOAEL) being 60mg/day (Trumbo, 2001). In children, this tolerable upper limit is even lower, ranging from 4-34mg for daily intake depending on age (Trumbo, 2001). Overall, the evidence of secondary prevention of lead absorption through dietary means is not a widely adopted method and is not recognized by the Centers for Disease Control and Prevention (CDC) as a means of secondary exposure to lead at this time.

3.2 Community, institutional, and policy level interventions

Now that several individual methods of primary and secondary prevention have been discussed, let us turn our attention to community and governmental level interventions to prevent lead exposure and absorption. As mentioned above, perhaps the most well-known method of exposure to lead is through lead pipes, a route of exposure that can result in 20-60% of all lead

exposure (USEPA, n.d.). This is an approach that has already seen mainstream adoption, with the Pittsburgh Water and Sewer Authority (PWSA) replacing lead pipes with a goal of total lead line replacement by 2026 (PWSA, 2021). As mentioned earlier, the PWSA has historically been ahead of schedule for their 2026 total replacement goal, with 855 lead pipes replaced nearly 10 months ahead of a hard deadline during the Fall 2019 semester (PWSA, 2019; PWSA, 2021). While total lead line replacement is the most permanent solution to waterborne lead exposure, the addition of anti-corrosion agents to water treatment is a temporary but more cost-effective option to minimize waterborne lead exposure (American Water Works Association [AWWA], 2017). While the options vary, such as soda ash and caustic soda, it has been found that phosphate-based agents, namely orthophosphate, is generally seen as the best option for balancing cost-effectiveness, preventing lead leeching from pipes, and posing minimal risk to human health (AWWA, 2017). To this end, both Pittsburgh and Flint currently employ orthophosphate in their water treatment regimens (PWSA, n.d.; Zahran et al, 2020). While it is typical to have a concentration of 1mg/L of orthophosphate in treated drinking water (ex. Detroit), the most recently available data shows Flint uses a level of approximately 3.5 milligrams/Liter, which is believed to further prevent the degradation of lead pipes (Zahran et al, 2020). However, while the inclusion of additional orthophosphate may minimize lead pipe degradation, it is not a perfect one-size-fits-all solution. While orthophosphate is generally useful in reducing the levels of lead that leech from pipes into the water supply, there are a multitude of factors that affect the effectiveness of orthophosphate addition, such as pH, additional substances in the water, and the disposal of the water after use (USEPA, 2016). Regarding pH, orthophosphate is generally seen as effective in the pH range of 7.2-7.8, with lower levels of effectiveness at 8.0-8.5, and an

upper limit on effective treatment at 9.0, with adjustment for treatment being needed outside of the 7.2-7.8 range (USEPA, 2016).

Further, aluminum can react with orthophosphate before it reacts with the lead in the pipes, resulting in less orthophosphate being available to prevent lead leeching (USEPA, 2016). Finally, it has been shown that orthophosphate being added to treated water can result in increased levels of phosphate being observed in wastewater treatment plants (USEPA, 2016). With roughly half of surveyed wastewater treatment plants not removing phosphorous from their water during treatment, there is the risk of increased levels of phosphate being introduced to water-based ecosystems, with the addition of phosphorous resulting in increased algae growth (USEPA, 2016; Ye et al, 2017). Through a process called eutrophication, the growth of algae blooms, enhanced by additional phosphorous, saps available oxygen supplies from the water, resulting in local fish and other aquatic species getting insufficient levels of oxygen for themselves, and harming the ecosystem at large (Ye et al, 2017).

While lead line replacement is a viable option to prevent lead exposure from occurring, there exists a caveat: total lead line replacement is the optimal solution, but partial line replacement is perhaps more deleterious than not replacing the lead lines at all (Wang et al, 2012). Paradoxically, the partial replacement of lead lines increases the levels of lead found in the water supply for the following days or months, perhaps related to the disruption of corrosion scales or galvanic corrosion (Wang et al, 2012). Galvanic corrosion, also known as “dissimilar-metal corrosion,” occurs when metals with dissimilar electrochemical potentials are connected (such as copper and lead service lines being connected with brass instead of another material, like plastic) and come in contact with an electrolyte, allowing oxidation-reduction reactions to occur (Wang et al, 2012). This can occur when lead service lines are removed from the municipality, although the

private residence owner does not replace the lead pipes on their own property. Quite often, the cost of replacing lead pipes within one's private residence falls on the property owner, and with costs ranging from \$3,000-15,000, many private citizens choose not to replace their portion of lead pipes at all, meaning that replacement of pipes from the municipality may increase lead exposure from drinking water (Mendoza, 2019; Wang et al, 2012).

It is also worth mentioning that while lead exposure has decreased over the last 50 years, there has been a decrease in lead exposure with the passage of federal legislation, there too has been a decrease in cardiovascular disease (Mensah et al, 2017). While the decrease in cardiovascular disease mortality had occurred before federal bans on common lead products, it could in part be related to diminishing lead exposure as public perception of lead began to change. In the 1960's, thousands of children were hospitalized annually with lead encephalopathy, with one in four children dying after diagnosis (Lanphear, 2007). Thankfully, this number has greatly decreased over the following decades, and the decrease in lead exposure occurred in the same timeframe as a national decrease in mortality from cardiovascular disease (Lanphear, 2007; Jones and Greene, 2012). While this association may be coincidental, cardiovascular disease remains an area where a multitude of factors influence incidence and severity of disease, with lead exposure possibly being an under-studied risk factor (Chen et al, 2017; Mousavi-Mirzaei et al, 2020; Obeng-Gyasi et al, 2018).

When considering the various options for mitigation of lead exposure and absorption, via primary or secondary prevention methods, there is no single solution that would eliminate all exposure. Rather, a multi-pronged approach may be the most fortuitous method, minimizing, if not eliminating, all sources of lead exposure where possible, and when necessary, employing methods to minimize the potential uptake of lead absorbance once it is entered into the body. While

is unlikely that every single source of lead exposure in the world, be it from our manufactured goods, our infrastructure, and in the ambient environment, could be eliminated, any effort made to minimize exposure should be considered where feasible.

4.0 Conclusions

Lead exposure has long been a problem regarding human health. Being naturally abundant and malleable, humans have sought to find ways to incorporate this natural resource into many applications, such as cosmetics, medicine, food and drink, and the pipes they drank from (Cilliers & Retleif, 2019). While we tend to think of lead as an agent that affects the brain, there is increasing evidence that suggests it may also be linked to the cardiovascular system (Lanphear et al, 2018; Obeng-Gyasi et al, 2018). With a growing need to address cardiovascular health as a cause of disease and death, it is important to learn more about what potential factors contribute to it, and how to best minimize if not prevent the severity of cardiovascular disease in the population (USCDC, 2020).

As the saying goes, an ounce of prevention is worth a pound of cure, and with cardiovascular disease on the rise in the United States, it's important to leave no stone unturned and truly find out the role lead plays in cardiovascular health. As we redouble our efforts to eliminate lead exposure from our daily lives, we must also consider the public perception of lead as it relates to our health and wellbeing and who it can and does bring harm to. As was seen with the national outrage with Flint, we largely believed lead exposure to be a problem that was dealt with in the past. However, as history has shown, it is not just a relic of the past, but an issue of the present, and if we're not diligent, the future too. Just as lead exposure does not discriminate based on time, is it not an issue that affects people based solely on their age, income, or zip code. With 3,800 communities having lead exposure double that of Flint, and 1,300 of those having quadruple the levels, this is an issue that affects far more people than we realize (Pell, 2017). When we couple this with the prevalence of cardiovascular disease, and the hardships it can create, be they physical,

mental, or social, we realize the effects of lead exposure go beyond the manifestation of neurological harm. The 809,000 deaths resulting from cardiovascular disease in 2019 alone are a heavy burden for the United States to carry, and the elimination of heavy metal contamination might lighten the load (USCDC, 2020).

Overall, while there is some evidence suggesting a link between cardiovascular disease and lead exposure, there has yet to be any concrete studies showing a link in the same way lead exposure and neurological disease are associated (Radulescu & Lundgren, 2019; Begovic et al, 2008; Lidsky & Schneider, 2003). This forces us to ask, where do we go from here? Should we go all in to eliminate all lead we can once and for all, or should we pause and be more methodical at the risk of acting more slowly? I believe that to conduct an appropriate analysis of lead exposure and cardiovascular disease incidence and outcomes in the US, more research should be performed to determine the extent to which lead affects cardiovascular disease and learn exactly how lead affects the cardiovascular system on a more cellular level. While some studies, namely the TACT study (Lamas, 2013), have investigated a possible clinical outcome from lead exposure on cardiovascular health, there is more work to be done. There is a lack of bench-top cellular or animal studies on the matter, which would serve as a starting point to see if there's something to lead and the cardiovascular system. For instance, while zinc may have a role in the prevention of lead being absorbed into the body upon exposure, there is a lack of subclinical tests to determine deficiency, and the same is true for how plant-based vs animal-product based iron affects the uptake of lead in the body (Kordas, 2017). Learning the mechanisms for how lead affects the body on a more cellular level and what lines of defense our body has will give us a clearer picture of what lead's role is on cardiovascular health and what we can do to prevent or at least minimize the chance of disease from manifesting. From there, occupational studies based on populations that have a higher

risk of lead exposure, such as those involved in industries that use lead (solder, battery, auto repair, and other manufacturing industries) (Pranjić, Mujagić, & Pavlović, 2003), or hobbyists in fields where lead is commonly used (ex. wild game hunting/fishing, where lead ammunition is used in 95% of hunts, and 13 million individuals hunt annually in the US (Bunez and Parry, 2018), may show if lead exposure is tied to cardiovascular disease in ways we haven't fully considered before. With cardiovascular disease being the leading cause of death in the US, it should be a priority to determine how to limit the severity and incidence of such health outcomes, and the role of lead in such disease should also be investigated more thoroughly to truly determine the role it plays (USCDC, 2019). While we have estimates surrounding the effect lead exposure has on cardiovascular disease, these numbers may not truly explain the role lead has on cardiovascular disease, and more effort should be placed on determining the linkage between these factors and what effect current lead exposure, and the extent to which, has on the incidence of cardiovascular disease. It should also be noted that while international studies have been conducted and have found some evidence of a link, different standards for lead exposure exist in every nation, and perhaps different confounding standards within studies as well.

While lead exposure has long been on the decline in the US, it has not yet been fully eliminated, adding to the complex legacy of one of the world's oldest known toxic agents. Our efforts should be to truly find the role of lead on the cardiovascular system on a more granular level, perhaps starting more research about how lead affects the cardiovascular system on a cellular level, and once a more clear picture is formed, move onto occupational studies from workers in fields where lead exposure is routine, such as those involved in battery manufacturing, factories, and auto repair (Shabani et al, 2020; Occupational Health and Safety Administration [OSHA], 2020), or in populations where lead exposure from hobbies like hunting may be underappreciated

and underdetected (Watson and Avery, 2009; Bunez & Perry, 2018). From there, we can determine what steps are appropriate for addressing the matter at hand and have a better idea of what steps may or may not be ultimately necessary to address the issue. Finally, while we cannot expect to eliminate all lead exposure from our daily lives, we have come a long way in scaling its presence down (Dignam, 2019). We owe it to ourselves to do what we can to improve the health of the public at large, and with cardiovascular disease being among the top causes of mortality in the country (Lanphear et al, 2018), the time is upon us to learn more about the role lead plays in the development and severity of this disease.

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