Issues in Toxicology

Edited by Bernard Weiss

Aging and Vulnerability to Environmental Chemicals

Age-related Disorders and their Origins in Environmental Exposures

RSC Publishing

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Issues in Toxicology

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Edited by

Bernard Weiss
Department of Environmental Medicine, University of Rochester, NY, USA
Email: bernard_weiss@urmc.rochester.edu

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Preface

Aging. We all do it from the moment we are born and it could be likened to the finest wine reaching its prime. It sure looked like aging was on our side in the beginning. We liked it. Think back to all the things you looked forward to as a child or a teenager, like reaching ''driving age'' and then ''drinking age''. We could not wait until we got ''old enough''. But while all that took place aging kept plodding on in its phantom-like manner. For some, acknowledging aging has not been easy as they sought surgical options to cover it on the surface. But even with or without wrinkles and sags, reality soon sets in when we realize that aging is no longer an asset. And near the end when more and more of our diverse body systems let us down, un-relentlessly limiting our bounds, that is when we really understand what aging is all about.

But that's normal aging. In this book Dr. Bernard Weiss tackles a serious health problem that has long been ignored, rapid aging, by bridging numerous disciplines and leaning on the most eminent scientists in the field of public health for their perspective. In so doing he opens the door for discussion on how could this have happened? And, why, since the 1950s, accelerated aging has become more prevalent and over the same time period many chronic endocrine related disorders have reached pandemic level, at a tremendous cost to society?

This book could not be more timely. Globally, over the past several decades, hundreds of professional society and government meetings have been devoted to rapid aging and endocrine disruption to the point where it appears that it may be impossible to reverse the trend unless something is done immediately. The technology that has provided this information is based on entirely new laboratory protocols that test genes, molecules, cells, and tissue at realistic concentrations encountered each day in the environment. You might call it a bottom up approach. It is rich in its discoveries and the use of new words

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creating a whole new vocabulary and a whole new generation of multi-disciplinary researchers. Despite this wealth of knowledge governments have not changed how they test chemicals for their safety. Currently we are at an impasse because the use of toxicological standards based on risk analysis is deeply embedded in the language of federal regulations. While millions have been increasingly succumbing to early onset of chronic disorders, and early mortality, this new language has not been translated into policy for regulatory purposes. For those doing the research who understand the overarching principles of endocrinology it is as though no one has been listening.

Looking back might help understand how this could have happened. Rachel Carson quoted in her 1962 book, *Silent Spring* "A change at one point, in one molecule even, may reverberate throughout the entire system to initiate changes in seemingly unrelated organs and tissues. This concept, familiar in physics, is gaining validity in all fields of biology and medicine." Then she went on to write how difficult it is to demonstrate cause and effect where the ultimate effect may not be expressed for a long time after the initial change in a molecule, or cell, or tissue. Amazingly, she was describing endocrine disruption.

Carson's citations in *Silent Spring* reveal that she had been reading about the changes that were taking place in medical research in the 1950s. I expect that she was looking for clues about cancer, specifically because of her own condition and trying to determine its etiology. She read about the work that was being done in 50s with the adrenal hormones, cortisol and aldosterone, and the anterior pituitary and ACTH. And it was about that time that hormone replacement therapy was being explored and estrogen had caught the interest of the pharmaceutical industry.

I am certain that if Rachel Carson had lived only a few more years she would have discovered the phenomenon called endocrine disruption and I'll just bet that she would have found a better name for it. And perhaps many of the endocrine disorders such as diabetes, obesity, autism, ADHD, fertility problems, Parkinsons, Alzheimers, and the cancers of the sex organs would never have reached current epidemic proportions. There was a big push in the 50s for fundamental research to understand the living organism in order to provide better diagnosis and treatment — and the need to expand on the concept of medicine as a life science and to include biology (Carson's love). Although some advances along these lines have taken place they were not enough to slow down rapid aging.

But there is another reason why it has taken endocrine disruption with its proclivity for rapid aging so long to become accepted as a major threat to humankind. The same trade associations, other industry funded institutions, and corporations that attacked Rachel Carson are still out there 50 years later protecting their products and padding their bottom lines using some of the largest public relations firms in the world to marginalize the science and vilify those doing this 21st century research. And when one takes into consideration that practically every endocrine disrupting chemical in use today was derived from the toxic by-products from coal, oil, and natural gas it becomes even more evident why today, federal health regulations are still based on the odds of

getting cancer at one in million or a thousand, not on the most unthinkable odds like diabetes where today one out of every third child born — and if you are among a minority group — every other child born will suffer the disease.

Humankind is in the midst of a dire health crisis that requires immediate intensive care to survive. The paradigm upon which current government policies and regulations have evolved has failed to protect us. A new level of discourse is needed immediately between science and decision makers creating a toxic chemicals platform or framework using a disease-driven approach that employs the principles of endocrinology. This entity should over-see the creation of an entirely new set of 21st century public health rules that would enable governments to reverse the current crisis. This could happen by making possible the merging of the dialogue between the most brilliant statespersons with a record of independence and integrity and the brilliant spokes persons within the community of scientists who understand the endocrine system. I see this book providing the first major break through in that dialogue and contributing to an urgently needed paradigm shift in how governments protect public health.

Theo Colborn
The Endocrine Disruption Exchange,
Paonia, Colorado

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Introduction

BERNARD WEISS

Email: bernard_weiss@urmc.rochester.edu

Progressively aging populations introduce a situation never before encountered in human history. Of all the problems this demographic surge creates, the foremost is declining health. As populations age, they impose rising demands on medical care systems and facilities; at the same time, they no longer produce the wealth required to sustain such facilities.

Aging is not a disease. We possess no therapies for it, only for its manifestations. But the stresses it inflicts on society would be more manageable could its burden of disease and disability be diminished or slowed. We have learned during the past four decades that, in fact, it can be. The Framingham Heart study is testimony to that possibility. It identified risk factors that led to new strategies for the prevention and subsequent reduction of coronary heart disease. We have also learned that diet, exercise, and intellectual activity also delay or attenuate the burdens of aging and, in fact, help sustain productive lives. These and other strategies for reducing the health risks of aging now receive profuse publicity.

In this volume, we address another set of risks, one to which we have given hardly more than a glance. These risks arise from the chemical revolution that began about seventy years ago. It flooded the world with chemicals that penetrated every aspect of our lives. Although they have brought us significant benefits, they have also exacted a heavy price. In our ignorance and greed we have so contaminated our environment that we are now exposed to thousands of chemical agents that remain largely untested, despite their residence in our

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bodies and surroundings. Even those that are permanent residents of our environment, such as metals, have appeared in new guises, such as fuel additives, that spawn new questions.

Now we propose to ask how these chemical agents may alter the health status of aging populations. It is a question currently accorded a relatively low priority by investigators and funding agencies. Early development is the period of the lifespan that has dominated research during the past few decades, with occasional attempts to determine how exposures early in life play out during late adulthood and senescence.

Early development, however, is not the only life stage during which we see heightened responses to the adverse effects of chemicals. Vulnerability to toxic processes climbs again late in life and in many ways recapitulates the imperfect defenses deployed by the immature organism. Traced across the life cycle, this progression takes the form of a U-shaped function, with the greatest potential for damage early and late in life. One feature common to both early and late phases is a reduced capacity to activate defenses against toxic effects. Immature organisms do not yet possess robust defense mechanisms. In aging organisms, they have passed into what might be called a post-mature decline. Older bodies are already high-maintenance properties, so exposure to substances with toxic properties may accelerate the process of decline, or exploit their dwindling capacities to resist such effects. ''Aging'' is not a mechanistic explanation for the diminished functions we suffer later in life. Sometimes, the roots of such declines merely unfold late in life, having lain dormant for decades, much like the herpes zoster virus. Sometimes, the waning compensatory capacities that accompany aging magnify vulnerability to exposure, a problem with pharmaceuticals and one which is discussed at length in the medical literature.

This volume has assembled a group of scientists who have thought about and investigated the environmental exposures that may imperil what might be called the natural or optimal course of aging. As editor, what I find most striking is how closely and unexpectedly the different chapters fit together and how they intersect.

Six of the chapters touch on metals: lead (two chapters), mercury, cadmium, manganese, and aluminum. Of these, only cadmium doesn't feature brain function directly. There, it is the kidney that receives the most attention, but lead and mercury also affect kidney function. Kidney function, however, exerts potent effects on brain function. For example, chronic kidney disease may induce neurological disorders, such as ischemic brain injury, as well as cognitive impairment. And patients with chronic kidney disease have a higher prevalence of cardiovascular disease, another chapter topic. The liver, too, cannot be overlooked as a source of neurotoxicity. Hepatic encephalopathy is a classic example. The liver can also be the source of the Aβ-amyloid in the brain that is associated with Alzheimer's disease.

Other chapters also examine brain function, and the chapter on Parkinson's disease discusses manganese in detail, but also examines lead. The chapter on polychlorinated biphenyls (PCBs) is focused on the brain, while the chapter on cardiovascular function features related chemicals, the Persistent Organic

Pollutants (POPs) and plastics, as well as PCBs. The chapter on obesity and diabetes also takes account of brain function because food intake is governed by hormonal processes in brain. It is centered on endocrine-disrupting chemicals (EDCs) and what we have learned about their contribution to the current surge in obesity and allied disorders. But we also know that POPs and similar chemicals are also risk factors for diabetes, as well as for cardiovascular disease. And it has now been established, and discussed in the chapter on air pollution, that adverse cardiovascular effects are a major source of the association between air pollution and mortality.

Hormonal function and EDCs are addressed in other chapters as well. One is an extensive review of the compound bisphenol A and exemplifies the range of questions and issues surrounding EDCs. The chapters on prostate and breast cancer also address EDCs, as does the chapter on cardiovascular disease, and all three point to their association with POPs such as dioxins. Like other chapters, these also emphasize the association between exposures early in life and the emergence of adverse effects decades later, a phenomenon termed "silent damage". One reason for the long latency may be the diminution of compensatory mechanisms late in life. But another may stem from earlier, silent damage that renders the target tissues more vulnerable to a second exposure or "hit". Many of the findings that first pointed us to the possibility of environmental chemicals causing endocrine disruption arose from questions about male reproductive function, the subject of one chapter. Many chemicals, we now know, besides those directly associated with the endocrine system, also exert endocrine-disrupting effects. Cadmium, for example, interacts with the estrogen receptor to induce such actions.

Two organ systems in particular play a large role in how we process and defend against environmental exposures. The liver and the immune system carry out these functions, but both suffer diminished efficiency as we age. Chemicals are processed by the liver to detoxify them, but the products (*i.e.* their metabolites) are sometimes the entities carrying the toxic message. The immune system is also a defense system that may respond in such a fashion that the protective response itself inflicts harm on the individual.

Although lead is the focus of the chapter on osteoporosis, cadmium is also stored in bone, and both have a half-life measured in decades. Cadmium, too, is toxic to bone. And both may contribute to osteotoxicity, not only through their effects on calcium but *via* endocrine-disrupting properties acting on estrogenic receptors. Osteoporosis, in effect, also releases lead stored in bone, raising blood lead levels, and in this way contributes to the neurotoxic effects observed in older populations and described in one chapter.

Figure 1 is a schematic depiction of how the course of aging might be influenced by environmental chemical exposures and other factors. The baseline age is taken as 20 years, a time that health statistics indicate is followed by progressively increasing rates of disabilities such as heart disease, for example. With "normal" aging, functional capacity—the ability of the model organ or system to perform its function—has declined to about 50% of its baseline value (shown by the horizontal line) by age 80 years. Exposed individuals are shown

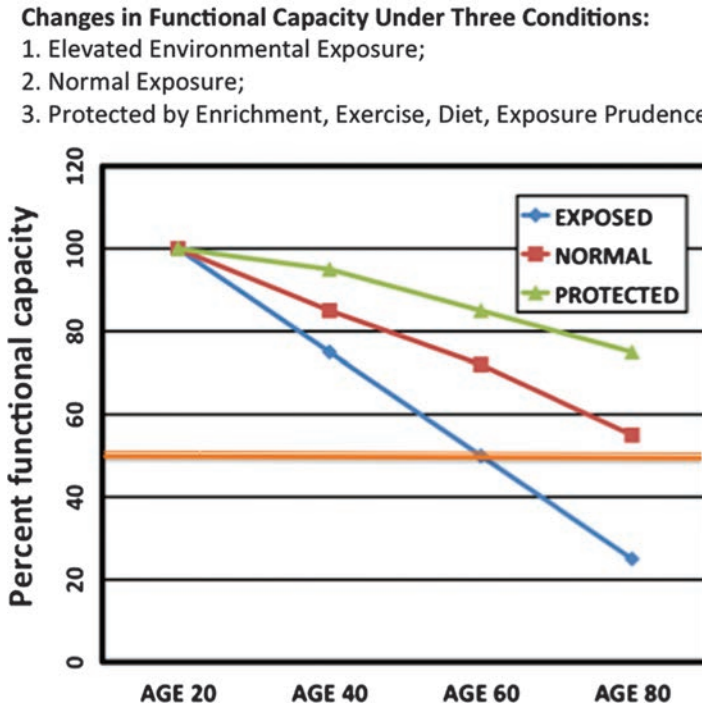

Figure 1 A model depicting changes in functional capacity during the course of aging. Age 20 years is taken as the 100% baseline. Three different progressions are shown: a "normal" rate of decline; a rate accelerated by chemical exposure; and a rate slowed by lower exposures and lifestyle modifications.

to have reached that value by age 60 years, while those who have been able to avoid exposure and undertaken other positive behaviors have suffered a decline of around only 25%. Although only a schematic, the graph emphasizes how different rates of decline can cause the gaps between the different courses of aging to widen with time.

I expect this volume to receive wide recognition and to serve as a foundation for policy decisions. We are all aware of how the combination of aging populations, their health challenges, and rising medical care costs is a priority issue for governments throughout the world. As we gain more knowledge of how our contaminated environment contributes to these disorders and disabilities, I am hopeful that we will act to avert further strains on our beleaguered societies.

The great baseball pitcher Satchel Paige, whose race confined him to the "Negro" baseball leagues until late in his career, was also a philosopher of aging. Taking a somewhat fatalistic view, he observed, "Don't look back. Something may be gaining on you." But he was also sanguine about it, pointing out that, "Aging is a question of mind over matter. If you don't mind, it doesn't matter." This volume aligns itself with those optimists who believe that knowledge gives us the power to make aging matter less.

CHAPTER 1

Exposure to Lead and Cognitive Dysfunction

JENNIFER WEUVE[a,b] AND MARC G. WEISSKOPF*[b,c]

[a] Rush Institute for Healthy Aging, Rush University Medical Center, Chicago, IL, USA; [b] Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA; [c] Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA
*E-mail: mweissko@hsph.harvard.edu

1.1 Lead Exposure: Long at Hand and in Mind

Humans' use of lead dates back at least to 7000 BC.[1] And knowledge of lead's neurotoxicity has been with us since the observations of Nicander, Vitruvius, and the ancient Greek physician, Dioscorides, who wrote that "[l]ead makes the mind give way". Nonetheless, between 1925 and 1980, human exposure to lead in the US environment reached historically high levels owing to the dominance of leaded gasoline for automobile fuel and the widespread use of lead-based paint. In the present US environment, as a result of long-sought regulations that removed lead from gasoline and minimized the use of lead-based paint, exposure to lead happens sporadically, and most individuals' exposures occur at low doses. Nonetheless, exposure to lead remains relevant to the cognitive function of aging adults, because exposures in the past were substantial. These exposures may influence adult cognition either through their effects on the developing nervous system or, because lead is stored in the skeleton for periods of years

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and decades, through re-exposure to lead in adulthood with age-related bone turnover.

In this chapter, we describe historical and contemporary sources of lead exposure and scientific findings on its effects on cognitive function in adults. We give particular consideration to the history of lead's use in gasoline and the incremental acknowledgement of its neurotoxicity by industrial and regulatory stakeholders. It is this history that underlies an epidemic of elevated lead exposure that spanned several generations and may be responsible for cognitive decrements in many adults. This history is also instructive for how future additives to gasoline and other widely used consumer products should be scrutinized.

1.2 How Humans were and Continue to be Exposed to Lead

1.2.1 Historical Exposures

1.2.1.1 Early Uses: the Emergence of Lead into the Environment

Unlike metals such as iron, copper, and manganese, lead is not essential to physiological function. Yet humans have been introducing lead into their environments—and often directly into their bodies—for millennia.[1–4] In ancient Chinese, Mediterranean, and Middle Eastern societies, lead was a key ingredient in glassware, pots and vessels, solder, paints, cosmetics, eye medicines, and contraceptive methods. It was also used in food and wine as a sweetener and preservative. The Romans, taking advantage of its malleability and availability, made lead the centerpiece of their infrastructure with their extensive web of lead pipes, promoting lead to a quotidian status unprecedented in human civilizations. These uses were joined by new ones—*e.g.*, as an ingredient in inks, ammunitions, and even poisons—and continued throughout the early twentieth century. Then, in the 1920s, humans in the burgeoning US automotive industry, aided and abetted by others in the US government, developed a use for lead that would expose much more of the population, at much higher doses than ever before.

1.2.1.2 How Leaded Gasoline Became the Major Source of Exposure to Lead

The market for automobiles in the US had grown increasingly competitive by the early 1920s, and General Motors (GM) sought to distinguish its automobiles from Ford's reliable but sedate Model T by unveiling new models every year and, critically, improving engine power and efficiency.[5,6] A challenge central to this latter goal was eliminating the pinging "knock" that arose when the fuel ignited prematurely in high-performance, high-compression engines. In

1921, Thomas Midgley, Jr., an engineer at GM, discovered that adding tetraethyl lead (TEL) to gasoline decreased this knock. Curiously, several years earlier, GM's engineers had established that ethyl alcohol (grain alcohol) was also an effective anti-knock agent. However, the competitive advantage of having a proprietary fuel and GM's entwinement with the production of TEL fuel meant that the lead-based agent prevailed while the alcohol-based agent was maligned. This occurred even though, since TEL's first synthesis by a German chemist in 1854, it had a "known deadliness."[7]

In response to protests from industrial hygienists, physiologists, and chemists, the Surgeon General inquired with GM and the DuPont company, a manufacturer of TEL, who responded with evidence-free reassurances. Nonetheless, seeking a governmental "stamp of approval" for their product, GM and DuPont entered into an agreement to study TEL's safety with oversight from the Bureau of Mines.[8] This oversight was merely symbolic, because GM and DuPont negotiated contractual control over all TEL data and any communications regarding it.[5] The first gallon of leaded gasoline was sold in 1923.[5,6]

The momentum behind the ambition of GM and its affiliates was nearly staunched when, in October 1924, five employees at Standard Oil's TEL facility died violent, psychotic deaths, and 35 other workers were smitten with serious neurologic symptoms such as hallucinations, tremors, and palsies. Even though Standard Oil dismissed suspicions with such claims as the victims "had probably worked too hard",[9] officials in New Jersey, Philadelphia, New York state, and New York City were unconvinced and officially banned the sale of leaded gasoline for varying periods – in New York City, the ban lasted for 3 years.[5]

By this time, the Bureau of Mines had formally exonerated leaded gasoline, and yet at the TEL plants, poisonings and deaths continued, many of them closely guarded by industry. Still, the neurotoxicity of lead in these occupational settings was difficult to miss. Among workers at the Standard Oil plant, the TEL building was known as "The Looney Gas Building," and at the DuPont plant, the TEL building was known as "The House of Butterflies," in tribute to its occupants' tendency to have hallucinations involving insects.[6] Yielding to the perception that a governmental body (the Bureau of Mines) was in the pocket of industry, and thus any ill effects of TEL were being ignored, in 1925, the Surgeon General assembled a conference of public health and industry scientists. The argument that prevailed was that TEL would contribute so substantially to the progress of the US as to advance civilization itself, thus making TEL a "gift from God."[5] And although public health advocates argued that it was incumbent on industry to demonstrate TEL's *safety*, ultimately, the Surgeon General commissioned a "Blue Ribbon Panel" to investigate lead's *harm*, giving this panel only seven months to do so.[2] It is not surprising then that the committee concluded that "...at present, there are no good grounds for prohibiting the use of ethyl gasoline...."[5] However, the committee recognized that seven months was insufficient for the job. Presciently, it predicted that, given the insidious and cumulative toxicity of lead poisoning, "[l]onger experience may show that even such slight storage of lead [in the

body] as was observed in these studies may lead eventually in susceptible individuals to recognizable or to chronic degenerative diseases. . . .''[5,6] This was the last time for several decades that the US government would come close to considering major regulatory action on leaded gasoline.[8]

1.2.1.3 Lead-Based Paints Added to the Burden of Lead Exposure

Running in parallel to the emergence of leaded gasoline was the emergence of lead-based paint. Humans have been adding lead to paint for centuries, and the neurologic hazards to children of exposure to lead-based paint have been known since at least the early 1900s.[10] The players in the saga of lead-based paint were the archetypes seen in the saga of leaded gasoline. The paint saga differed in its focus on children, both as potential victims of exposure and as subjects in advertising for lead-based paint manufacturers.[11,12] In a perverse twist, the medical director for the Ethyl Gasoline Corporation advocated reducing children's exposures to lead by eliminating lead from paint, but clearly saw no problem with lead in gas.[11]

1.2.1.4 Leaded Gasoline and Lead-Based Paint Were Phased out, but Many Were Exposed

The US Environmental Protection Agency, born in 1970, instituted regulations that initiated the gradual phase-down of lead content in gasoline for on-road vehicles, beginning in 1976 and concluding with a complete ban in 1995.[2,13,14] (Excluded from this phase-down were fuels used for off-road vehicles and marine vessels, and in farming and aviation. In addition, it was only in 2008 that the National Association for Stock Car Racing completely switched its racing fuels to unleaded varieties.[15,16])

In 1978, the Consumer Products Safety Commission banned the sale and use of lead-based paint.[11] By then, human exposures to lead, primarily from leaded gasoline and paint, had reached common and chronic proportions. As of 1980, the estimated *per capita* consumption of lead-based products in the US was 5.2 kilograms per American per year, around 10 times the estimated exposures of ancient Romans.[2] Over the 20th century, the US had burned an estimated 7 million tons of lead in its gasoline,[7] the source of about 90% of the lead emitted into the environment.[17]

While leaded gasoline and paint were being removed from public consumption, interventions were occurring on other sources of exposure. For example, in the 1970s, many US-based food can manufacturers voluntarily ceased using leaded solder in their cans,[18] which resulted in a substantial reduction in human exposure from this source between 1979 and 1989.[17] In 1995, the US Food and Drug Administration formally banned the use of lead-based solder in all canned food sold in the US, including imported food.[18]

The removal of lead from gasoline, paint, and other sources markedly reduced Americans' lead exposures. For example, in early 1976, at the start of

the phase-down of lead in gasoline, the *average* blood lead level in the civilian, non-institutionalized US population was $15\,\mu g\,dL^{-1}$,[19] well above what is defined today as an elevated level for children (around $5\,\mu g\,dL^{-1}$).[†] (In some areas in the early 1970s, including rural areas, the average blood lead levels among children exceeded $20\,\mu g\,dL^{-1}$.[23–25]) By 1980, the average blood lead level had sunk to $10\,\mu g\,dL^{-1}$,[19] and it had plummeted to $2.8\,\mu g\,dL^{-1}$ about a decade after that.[‡,26] Nonetheless, millions of children and adults had been exposed to biologically relevant doses of lead, often for many years, and emerging evidence was suggesting that while removing the exposures had established health benefits, the legacies of those exposures could go on to influence myriad health risks, including risks for impaired cognition in adulthood.

1.2.2 Contemporary Sources of Exposure

Lead exposure results from inhalation of air contaminated with lead, or ingestion of food, water, or dust that contains lead. The highest exposures to lead have always been occupational, where workers can experience extremely high levels of exposure. The action level for medical removal from the workplace in the Occupational Safety and Health Administration's (OSHA) standard for blood lead is $50\,\mu g\,dL^{-1}$ or above for construction and $60\,\mu g\,dL^{-1}$ or above for all other occupation settings;[27–29] that is, when workers are found to have blood lead levels above these levels, they are required to be removed from that work environment until two consecutive blood lead measurements are below $40\,\mu g\,dL^{-1}$. This level is still over 10 times greater than the current average blood lead concentration of adults in the US population (see also Section 1.2.1.4).

In the US, while occupational lead exposure has generally been decreasing, it remains a problem in construction,[30] and this sector has become the dominant source of lead exposure for adults (to a large extent the result of lead in paint). Lead paint can contain up to 50% lead by weight, and workers who remove

[†]In May 2012, the US Centers for Disease Control and Prevention altered and, in effect, lowered its recommended pediatric threshold of concern from $10\,\mu g/dL$, the level set in 1991, to any level exceeding the current 97.5th percentile of blood lead levels for children ages 1–5. As of 2012, this was about $5\,\mu g/dL$. Sources: [1] Centers for Disease Control. 1991. Preventing lead poisoning in young children 1991. Centers for Disease Control and Prevention. [2] CDC Response to Advisory Committee on Childhood Lead Poisoning Prevention Recommendations in "Low Level Lead Exposure Harms Children: a Renewed Call of Primary Prevention." 2012. Atlanta, GA.

[‡]Overall, as documented by data from the National Health and Nutrition Examination Survey, blood lead levels in the civilian, non-institutionalized U.S. population dropped from about $15\,\mu g/dL$ in 1976 to $10\,\mu g/dL$ in 1980 and then to 2.3, 1.7, 1.5, 1.4 and $1.3\,\mu g/dL$, respectively, in the 1991–1994, 1999–2000, 2001–2002, 2003–2004 and 2005–2006 monitoring periods. It remained at $1.3\,\mu g/dL$ for 2007–2008. Sources: [1] J. L. Annest, J. L. Pirkle, D. Makuc, J. W. Neese, D. D. Bayse, M. G. Kovar. Chronological trend in blood lead levels between 1976 and 1980. *N. Engl. J. Med.*, 1983; **308**(23):1373–1377. [2] Update: blood lead levels–United States, 1991–1994. MMWR Morb Mortal Wkly Rep. 1997; **46**(7):141–146. [3] Centers for Disease Control and Prevention. Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, February 2012, Atlanta, Georgia.

paint are at extremely high risk of lead exposure.[31] The majority of houses built before 1978 (estimated at 42–47 million houses in the US) have lead-based paint inside and outside,[32] and lead paint was also used in commercial buildings and other structures such as bridges. Scraping and, in particular, sanding lead paint creates a fine lead dust that can be easily inhaled. Absorption of lead is highly efficient following inhalation, particularly if the particles are small. Hand-to-mouth behavior of construction workers, for example eating and smoking cigarettes without prior hand washing, can also lead to significant absorption of lead. Lead dust on the hands can be ingested and absorbed through the gastrointestinal tract as can lead dust on cigarettes, which can be heated during smoking, generating lead fumes that are especially well absorbed by the lungs. Much more commonly in countries outside the US, Canada, and Europe, workers in many other industries, such as battery manufacturing plants, are also at high risk of extremely high lead exposure.

Aside from occupationally exposed individuals, people who present with blood lead levels that exceed the Centers for Disease Control and Prevention (CDC) current pediatric action limit of $5\,\mu g\,dL^{-1}$ were often exposed from sources such as contaminated traditional medications and cosmetics, accidental exposures to lead from commercial uses (*e.g.*, leaded batteries), or use of lead-containing materials in several common hobbies. For example, persons who create pottery and stained glass often use materials that contain lead, which can result in exposure, as can chewing on or making lead bullets or lead fishing line sinkers. Current exposures can also occur as a result of past activities, unfortunately sometimes unwittingly. Recent reports revealed elevated blood lead levels among children in areas where houses were built on the site of former lead manufacturing plants, of which the residents were unaware.[33,34] In other communities, tap water has been inadvertently contaminated due to partial replacement of service lines,[35] or to water treatment processes that render the chemistry of the water more amenable to dissolving corroded lead in water pipes.[36] Outside of the US, many more examples of very high lead exposures of non-workers are found. A very recent and devastating example of this was the death of an estimated 400 children, and severe lead poisoning of many more, in Nigeria as a result of artisanal gold ore processing in their family compounds.[37,38]

Common current sources of environmental lead exposure in the United States and around the world include lead in plumbing (which can contaminate drinking water), lead paint in older housing, contaminated house dust, contaminated soil, lead crystal, and lead-glazed pottery. However, past exposures to lead are still an important consideration. By far the predominant past general environmental exposure to lead was through exposure to lead in air, which was very largely a result of lead in gasoline. Although a few countries, including Canada and Japan, led the US in banning leaded gasoline, bans in other parts of the world have occurred more recently or not at all, and in these countries, past cumulative exposures are likely to have been much higher.[39–42]

There are many reasons why—even in the US—we may still be seeing the effects of those past high levels of environmental exposures. First, for those who were alive during the times of leaded gasoline, toxic effects of lead

exposure at that time may manifest as health impairments later in life. For example, the cumulative exposure to lead in the past could have caused neurotoxicity at the time, which in turn may result in more rapid cognitive decline in later years. Second, while lead initially enters the bloodstream after being inhaled or ingested—from where it is delivered to different tissues and causes different toxicities—the major repository for lead in the body is the skeletal system. Lead deposited in bone stays there a long time—the half life of lead in bone is of the order of years or decades, depending on the bone type[43]—but it is slowly resorbed into blood as bone turnover occurs. Thus bone turnover leads to a remobilization of lead, from exposure potentially many years earlier, back into the bloodstream, where it can again exert toxic effects on other tissues.[44] In fact, in the present environment, in the US and many other countries, of low levels of lead, the current major exposure to lead for many older people may be from lead in their own bones.

1.3 Mechanisms of Neurotoxicity

Several mechanisms by which lead can cause central nervous system dysfunction exist. These have been reviewed elsewhere in greater detail,[45–47] but we will touch on some key aspects of particular relevance to the nervous system here. Many of the neurotoxic actions of lead relate to lead's ability to substitute for calcium, and to a lesser extent zinc. At a very broad view level, nerve cells generally communicate by releasing compounds (neurotransmitters) from one cell (the pre-synaptic neuron) to act on a neighboring cell (the post-synaptic neuron) in some way. The release of these neurotransmitters is finely tuned to the activity of the pre-synaptic neuron in ways that are critically dependent on calcium-dependent mechanisms. The released neurotransmitter acts on the post-synaptic neuron by setting off signalling systems within the neuron; these can have a myriad effects on the intracellular state of the neuron, including altering cytoplasmic molecules as well as intranuclear molecules. Many of these intracellular signalling processes are *also* calcium-dependent. These processes underlie basic neural communication and functioning and underlie the ability of the nervous system to change. This includes changes that drive the establishment and refining of neural architecture during development and the changes that occur in the adult as a result of experience, changes that are thought to underlie learning and memory. Lead is recognized by many of these molecules in much the same way calcium is recognized, but because lead then either blocks or disrupts the function of the protein it interacts with, lead disrupts communication in the nervous system, with the ultimate concern that it thereby disrupts behaviors that are dependent on those neural processes, behaviors such as adult cognitive function.

Many other effects of lead are relevant to adult cognitive function. Gene expression is critical to the normal function of any cell, including neurons, and is also thought to be critical for encoding learning in the brain. Lead can disrupt gene expression in different ways. Many gene transcription factors

require calcium or zinc as co-factors, therefore lead's ability to substitute for calcium and zinc can lead to disruption of resultant gene expression.

An exciting new direction of research related to gene expression actions of exposure to lead and other environmental chemicals is epigenetics. Epigenetics refers to several different ways that the read out of the underlying DNA sequence (gene expression) can be modified without an alteration in the DNA sequence itself. An example of this is methylation of the DNA at particular sites. More methylation tends to be associated with less gene expression and *vice versa*. Critical to the importance of epigenetics is that the epigenetic pattern can be altered by the environment and, at the same time, epigenetic changes can persist after the environmental modifier is gone. And in fact these changes can be heritable, *i.e.* passed on to daughter cells. Lead exposure has been found to be associated with increased concentrations of homocysteine.[48] Increased homocysteine reduces the demethylation of *S*-adenosylmethionine (SAM)—which provides methyl groups for DNA methylation—thus possibly reducing DNA methylation levels. In fact, lead exposure has been shown to induce global hypomethylation of hepatic DNA in rats, which was associated with an increase in cell proliferation.[49] Two recent studies in humans found that higher bone lead levels were associated with patterns of lower DNA methylation in adults and the cord blood of newborns.[50,51] Of particular note, epigenetic effects have been proposed to potentially underlie intriguing findings from recent animal studies that link *in utero* and neonatal exposure to lead to Alzheimer's disease neuropathology in later life.[52–54] These findings are related to amyloid beta (Aβ) plaques, which are the pathological hallmark of Alzheimer's disease.[55–57] Aβ is the amyloidogenic product derived from the amyloid precursor protein (APP), with the help of the β-site APP-cleaving enzyme, BACE1. Early life lead exposure—but not later life exposure—in rats has been found to be associated with increased expression of the *APP* gene, increased activity of the Sp1 transcription factor that regulates the *APP* gene, and increased levels of APP and Aβ.[58] Similar changes are seen in early life lead-exposed monkeys, as is increased BACE1 mRNA and amyloid plaques.[59] Moreover, it has been suggested that age-related demethylation—perhaps with a contribution from lead exposure—is related to Aβ production in the brain.[60]

Lead also adversely affects the central nervous system (CNS) through the many ways in which it causes cell damage and death. Lead causes oxidative stress through several pathways, including: the inhibition of enzymes in the heme synthesis pathway (δ-ALA synthetase, δ-ALAD, and ferrochelatase); stimulation of ferrous ion initiated membrane lipid peroxidation;[61,62] changes in the fatty acid composition of membranes;[63] and increased activation of NAD(P)H oxidase.[64,65] Lead also disrupts enzymes involved in antioxidant defense systems. Lead has been shown to alter the function of superoxide dismutase, catalase, glucose-6-phosphate dehydrogenase and enzymes involved in glutathione metabolism, glutathione peroxidase, glutathione-*S*-transferase, and glutathione reductase.[66] Lead also accumulates in and damages the mitochondria, causing release of calcium and apoptotic cell death.[67–70]

In addition to the actions of lead within the nervous system, lead may also affect neural function indirectly: for example, *via* effects on the cardiovascular system. There is abundant evidence of effects of lead on the cardiovascular system, including increasing homocysteine levels, atherosclerosis, blood pressure, and risk of hypertension.[48,71] Homocysteine is toxic to the CNS by influencing neurotransmitter synthesis, and causing excitotoxicity and cell death.[72,73] Atherosclerosis, increased blood pressure, and hypertension can all contribute to silent (or not) cerebrovascular damage, leading to neuronal death. These types of cardiovascular factors are suspected to result in neurobehavioral disturbances and may play a role in other brain disorders as well.

1.4 Assessment of Lead Exposure

The primary biological assessment of exposure to lead is to measure lead in whole blood. The half-life of lead in blood is approximately 30 days, thus a single blood lead concentration measurement only provides a metric of recent exposures, although if external exposures are constant over time, a single blood lead measurement can provide an estimate of exposure to lead over longer periods. In occupational settings where exposures are expected to be high, serial blood lead measurements are often taken at regular intervals for surveillance. These are measured to identify incidents of possible high level exposures (see Sections 2.2 and 2.6), but serial measurements can also be used to construct an index of cumulative exposure over longer work periods, which can be useful for studies of exposures of longer or varying durations. Some epidemiological studies evaluate the effect of lead exposure on the health of workers without access to blood lead measurements. Instead, these studies use job exposure matrices (JEMs), which link specific jobs and tasks to different levels of likely exposure to lead. These exposure levels are inferred from studies in other settings where more direct measures of exposure—*e.g.* workers' blood lead measurements or air lead measurements—are available. In these settings, the relation of specific jobs and tasks to lead exposure levels can be determined to construct a JEM that can then be applied in settings where actual measurements are not available.

Determining exposure levels among those exposed non-occupationally is much more difficult without biomarkers because exposure levels are typically much lower and sources of exposure are more widespread and varied. Although blood lead concentration is by far the most commonly used biomarker of lead exposure, this measure is less useful when one wants to consider the effects of cumulative exposure to lead over a longer time period. While serial blood lead measurements have been used to quantify lead exposure over longer durations in occupational settings, this practice is less commonly used in non-occupational settings as it is time-consuming and labor intensive to implement if not required for surveillance. This conundrum created problems for the study of the effects of lead on cognitive function, and the literature related to blood lead measurements was quite inconsistent.[74] Great advances in these research

endeavors came with the development of technology to non-invasively measure lead in bone: x-ray fluorescence (XRF).[44]

Bone is the primary reservoir for lead in the human body, and measures of the concentration of lead in bone provide an integrated estimate of long-term, cumulative exposure to lead. The half-life of lead in the patella—which comprises mainly trabecular bone—is of the order of years, while the half-life of lead in the tibia—which comprises mainly cortical bone—is of the order of decades.[43] It is important to keep in mind however, that bone lead measurements cannot provide information on the temporal pattern of exposures during the years over which it integrates exposure. For example, two people may have the same bone lead concentration, but one may have had uniformly low exposures to lead except for one or more short periods of high exposure, while the other may have experienced a constant level of moderate lead exposure over the same time frame. We may not know whether those differences in exposure patterns matter for the health outcome of interest, but we need to keep in mind that if they do, these are distinctions we cannot make based on bone lead. Distinguishing different effects of those two patterns of exposure would be possible however with serial blood lead measurements.

1.5 Cognitive Effects of Lead Exposures in Adults

Prior to the mid-20th century, the prevailing view of lead poisoning was one of an acute clinical event—involving tremors, vomiting, encephalopathy, and anemia, among other signs—that, if treated prior to encephalopathy, would have no enduring neurologic effects.[75,76] Work in 1943 by Randolph Byers and Elizabeth Lord contradicted both these assumptions.[75] They documented 20 cases of lead exposure among children, most of whom did not exhibit the most severe effects of lead exposure and none of whom exhibited the severe extreme neurologic symptoms believed to be indicative of lead poisoning. However, all of the children exhibited demonstrable neurologic problems, including attention deficits, behavioral problems, and impaired motor function. Over the years that they were followed by their physicians, some of the children's problems resolved, but most had impaired intellectual development and many developed new behavioral problems. In most cases, these enduring effects occurred even after the exposures, mainly from eating chips of lead-based paints, and were removed and treatment given. Indeed, a clinical trial conducted nearly 60 years later indicated that chelation therapy was ineffective at reducing the neurologic effects of lead exposure.[77]

In this section, we describe research on the relation of lead exposure to cognitive function in adulthood. The studies discussed document effects on cognition and subserving brain structures resulting from lead exposure at levels far lower than the doses associated with acute lead poisoning. This body of evidence also extends the pioneering work of Byers and Lord by showing that the cognitive effects of lead exposure may continue well past the point at which the exposure has ended.

1.5.1 Effects of High-Dose, Occupational Exposure

1.5.1.1 Evidence from Studies of Cognition and Cognitive Decline

With the accrual of several decades of research, it is clear that exposure to lead exerts adverse cognitive effects on cognitive functioning in adulthood. The TEL-related events of the 1920s and beyond were sentinels that eventually led to studies focused on adults who experiences high-doses and/or frequent exposures as part of their occupations. The most rigorous early meta-analysis of these study findings included 12 studies, published between 1977 and 1997, that reported quantitative information about the exposed participants' levels of exposure and the cognitive scores, in addition to accounting for age and "premorbid intelligence." Participants' blood lead levels were relatively high by today's standards; among the occupationally exposed participants, study cohort *averages* exceeded $30\,\mu g\,dL^{-1}$, and in over half of the "unexposed" participant groups, the averages exceeded $10\,\mu g\,dL^{-1}$. Overall, higher blood lead levels corresponded to worse performance on tests of visuospatial ability, memory, and motor function.[78] Although these conclusions were contested,[79] the findings were consonant with a subsequent review,[80] as well as several studies that have confirmed and extended these findings by distinguishing the acute effects of exposure from the effects that remain after exposure has ceased and by exploring the realms of cognitive decline over time, cerebral vascular ischemia, and brain volumes.

Since 1997, 16 new studies emerged that, in addition to measuring exposures using blood lead, also measured cumulative exposures.[80] All of these studies were adjusted for several potential sources of confounding, including age (and, unless otherwise specified, this is true of all the other studies that we will discuss in the remainder of this section). In some of the 16 studies, the cumulative exposure estimates came from integrating serial blood lead concentrations. Other studies measured lead concentrations at specific bone sites, taking advantage of *in vivo* K-x-ray fluorescent (KXRF) spectroscopic methods that had been refined for use in research settings (see Section 1.4). As described in a review of these studies,[80] higher blood lead concentration—a measure of recent exposure—predicted worse performance on tests of cognition among workers currently exposed in their occupations. Measures of cumulative exposure were not as strongly associated, a finding that the reviewers attributed to acute effects masking the effects of chronic or past exposures. By contrast, among workers whose occupational exposures had ended, measures of cumulative exposure were more strongly associated with poor performance on cognitive tests than were measures of current exposure (*e.g.* blood lead level). Lead exposure appeared to adversely affect a wide range of cognitive functions, most notably visuospatial ability, executive function, and verbal memory. Higher exposures were also associated with worse performance on tests of motor ability, including dexterity.

Among these studies were two investigations of change in cognition over time. This outcome is of interest because it distinguishes effects of lead that

persist over time—*i.e.* cognitive function remains diminished but does not continue to worsen after the exposure ends—from effects that worsen over time.[81] Moreover, decline in cognitive function is more directly related than poor cognition to the pathogenesis and progression of dementia. In these studies, higher cumulative exposure, indicated by tibia bone lead concentration, corresponded to greater decline in several cognitive functions, even after the occupational exposure had ended.[80] These findings were consistent with a subsequent study of 83 previously exposed workers in lead battery plants and 51 unexposed workers.[82] In spite of this study's small size—and even after accounting for factors such as current blood lead level, years of employment with lead, age, education, income, alcohol intake, smoking history, and blood pressure—exposed workers with higher peak tibia lead levels (current tibia bone lead concentration corrected for time since last occupational exposure) experienced significantly faster declines over 22 years on measures of visuospatial ability, general intelligence, and memory ability, as well as overall cognition. Higher peak tibia lead level was also associated with more rapid cognitive decline among the "unexposed" workers, but these findings were not statistically significant.

1.5.1.2 Evidence from Brain Imaging Studies

To further explore the mechanisms by which lead exposure may influence cognitive function and decline in occupationally exposed adults, several researchers have examined findings on brain imaging. A study of 536 men who previously had worked in organolead (*e.g.* tetraethyl lead) manufacturing plants found that higher cumulative exposure to lead, indicated by peak tibia lead level, was associated with significantly elevated cerebral ischemic burden, as assessed by white matter lesion score on magnetic resonance images.[83] This observation provides support for a vascular mechanism underlying at least some of lead's cognitive effects.

In this same study, higher cumulative exposure also appeared to be linked to structural differences in the brain, including reduced total brain volume and total grey matter volume. In addition, frontal, cingulate gyrus and insula volumes were smaller with higher cumulative lead exposure, but cerebellar and occipital volumes were not, consistent with the observed associations of lead exposure with decline in cognitive functions, such as learning and executive abilities, that are subserved by these affected regions.[83] Indeed, a subsequent study found evidence that reduced volumes in brain regions specified *a priori* seemed to explain the association between lead exposure and impaired visuoconstruction ability. Similar but weaker evidence was found for eye-hand coordination and executive function.[84] By contrast, when the investigators examined *changes* in these imaging indices over a five year interval among 362 of the original 536 participants, they found little association with cumulative lead exposure.[85] It is possible that lead exposure has progressive effects on cerebral ischemia and brain structure but that these effects are too modest to be observed in a study of this size that is reliant on these measures of exposure and

outcomes. It is also possible that lead's effects on these outcomes are merely persistent rather than progressive and that the progressive effects seen on cognitive function are attributable to other mechanisms, such as effects on microstructure and neural function.

Magnetic resonance spectroscopy (MRS) is another brain imaging technique that integrates data on brain metabolites and structural features of an imaged brain. Because MRS can assess brain metabolites, it can potentially detect changes in brain metabolism that occur before changes in the volume of brain structures can be seen. Using this technique in a study of 71 year old identical twin brothers, Weisskopf and colleagues found additional evidence for the neurotoxic effects of lead.[86] Both twins were retired painters but differed in the extent to which they were involved in paint removal, a task that involves high levels of exposure to lead *via* inhaled leaded paint dust. Despite the twins' many similarities, the MRS results showed lower levels of *N*-acetylaspartate (NAA)—a brain metabolite indicative of neuronal density—in frontal and hippocampal regions in the more highly lead-exposed twin, as well as greater dysfunction on learning, memory, and executive function tasks, which are dependent on frontal and hippocampal regions. A subsequent study of 22 workers at a lead paint factory in Taiwan, along with 18 controls, found similar results, with higher levels of blood and patella lead concentrations exhibiting associations with decreased NAA, particularly in the frontal lobe.[87]

1.5.2 Effects of Low-Dose, Non-Occupational Exposure

Against the backdrop of evidence suggesting that the cognitive effects of earlier occupational exposures linger well into middle and old age, the hypothesis that protracted non-occupational ("community-level"), and therefore lower-level, exposure might also influence cognitive function and cognitive decline in adulthood emerged. This hypothesis is particularly important in light of two demographic phenomena. The first is that an enormous number of individuals experienced relatively high levels of these types of exposures between the 1920s and 1980s, merely by virtue of being exposed to emissions from leaded fuel, lead-based paint, or both. The second demographic feature is the impending surge, fuelled by the aging of the post-war "baby boom" population, in the number of adults expected to develop dementia over the coming decades.[88,89] Impaired cognition and, to a greater extent, cognitive decline in adulthood both signal future dementia risk.[90–93] Thus understanding the relation of community-level lead exposure to impaired cognition and cognitive decline may offer direction toward ameliorating lead's effects among those already exposed and impetus toward continuing to minimize exposures among future generations.

Evidence that the effects of long-term, "low-level" exposure to lead early in life may reverberate to impaired cognition later in life has begun to emerge in studies of animals[52–54] and humans.[94] Additionally, in a recent follow-up study of adults who had participated in a study of prenatal lead exposure, blood plasma indices of Aβ production and deposition were higher among those who

had elevated early life blood levels.[95] One mechanism underlying these observations is irreversible change to neural structures and function caused by early exposure. This mechanism may be especially relevant in situations in which exposures have ceased. A second mechanism may involve the cumulative burden of long-term exposure. Such exposure may be exogenous, as for an individual who endured decades of exposure to ambient lead from leaded gasoline. Exposure may also be endogenous, because about 95% of lead in the body is stored in the skeleton (see Section 1.4). The duration of its storage there is a function of the bone characteristics and other metabolic factors that influence the rate of bone turnover. However, when lead-containing bone is resorbed, that lead re-enters the circulation, from where it may access the brain and other susceptible organs and tissues (see Section 1.2.2).

1.5.2.1 Evidence from Studies of Cognition and Cognitive Decline

In comparison with studies of occupational lead exposure, studies of community-level lead exposure and cognitive outcomes in adults are relatively few. However, aided by KXRF technology, their numbers have been increasing. Blood lead levels of most participants in these studies were less than $10\,\mu g\,dL^{-1}$, much lower than those in the occupational studies. A review of 6 such studies, published between 1998 and 2007, in which researchers assessed participants' recent and cumulative exposures to lead, found that higher levels of cumulative exposure—as assessed by KXRF-based bone lead measurements—were associated with worse performance on tests of a variety of cognitive functions, including visuospatial abilities, verbal learning and memory, executive functioning, eye-hand coordination, and overall cognitive ability.[80] Blood lead levels were associated with significantly worse performance on some cognitive tests in some studies, but, overall, these findings were less consistent than those for bone lead.

Since this review, several other studies of community-level exposure to lead and adult cognition have been conducted. In a study of 1812 adults, aged 65 and over and living in rural China, concentration of lead in blood plasma was associated with worse combined performance on 6 cognitive tests, but this result was not statistically significant.[96] Similarly, a study of older adults, aged 60 and over, participating in the US-based National Health and Nutrition Examination Survey (NHANES) found that blood lead levels were associated with increased likelihood of self-reported confusion and problems with memory (N=7277) and worse performance on a test of working memory and attention (N=2299), but neither of these findings was statistically significant.[97] In spite of the large study populations, the findings from these studies are not necessarily surprising. The study in China relied on plasma lead concentrations. Although it is thought that the fraction of lead in plasma represents the most bioavailable lead in blood,[98] levels are typically very low, and this concentration is notoriously difficult to measure.[98,99] Indeed, a large

proportion of participants had plasma lead levels that were effectively zero. In the NHANES study, concentrations of lead in whole blood ranged between 0.18 and 54 $\mu g\,dL^{-1}$, but average (2.45 $\mu g\,dL^{-1}$) and median (2.00 $\mu g\,dL^{-1}$) concentrations indicate low levels of recent exposure in most of the study population. More importantly, neither of these studies employed indices of cumulative exposure to lead. These measures would likely have revealed past exposures to leaded gasoline, a major source of community-based exposure in both study's countries, and which had been officially banned by the time these studies were conducted.

Measures of cumulative exposure were available in 3 other studies of community-exposed adults. In a pilot study of 47 adults, aged 55 to 67 years, investigators gauged participants' cumulative exposure to lead by using KXRF-based measurements of lead concentrations in sites representative of both cortical (tibia) and trabecular (calcaneus) bone.[100] They administered a battery of cognitive tests assessing visual memory, as well as the Montreal Cognitive Assessment (MoCA), a separate battery assessing cognitive functions such as visuospatial ability, attention, executive function, and language. Participants with higher calcaneus lead concentrations performed worse on all of the visual memory tests, two of which were borderline significant ($P < 0.10$). Findings for the tibia were somewhat similar but less consistent and not statistically significant. In unadjusted analyses, neither bone lead concentration was significantly associated with MoCA score.

A larger study of 587 women, aged 47 to 74, participating in the Nurses' Health Study measured lead concentrations in tibia and patella (representative of trabecular) bone as well as in whole blood.[101] In general, higher levels of all three exposure biomarkers were associated with worse performance on the 6 individual cognitive metrics assessed, which included tests of verbal memory, attention, and executive function. Curiously, the only result that was statistically significant was the single association indicating better performance (on a test of phonemic fluency) with higher exposure (as measured by patellar lead). The investigators also evaluated associations between the lead biomarkers and global cognition, accounting for scores on all cognitive tests completed. They repeated these analyses without the aforementioned fluency test, which was supported by a significant formal test of heterogeneity. Higher levels of all three exposure biomarkers was associated with worse global cognition. In particular, although the women's current exposures to lead were quite low (as indicated by an average blood lead level of 2.9 $\mu g\,dL^{-1}$) higher tibia lead level corresponded to significantly worse global cognition when the fluency test was excluded. (Preliminary data from a subsequent cycle of cognitive testing have failed to confirm the patella lead-fluency association.)

The third study—the Baltimore Memory Study, a population-based cohort of men and women living in a racially diverse collection of neighbourhoods in Baltimore, Maryland—involved 1140 participants, aged from 50 to 70.[102] Investigators measured participants' tibia bone lead concentrations and assessed their cognitive functioning at three study cycles approximately 14 months apart, allowing them to evaluate cumulative exposure to lead in relation

to cognitive decline. Decline in all six cognitive domains tested was generally worse with higher levels of tibia lead, although only the association with decline in eye-hand coordination was statistically significant. However, higher tibia lead levels were significantly associated with persistently worse performance on the tests over time (*i.e.*, worse performance but not greater declines in performance). With further adjustment for socioeconomic status, the associations corresponding to executive function, verbal memory, and visual memory remained significant. Nonetheless, in analyses stratified by race, the deleterious association between tibia lead and cognitive function was present only among white participants (and statistically significant only for eye-hand coordination and executive function) and not among African-American participants.

1.5.2.2 Evidence from Brain Imaging Studies

In contrast to the brain imaging research conducted among occupationally exposed individuals, brain imaging research has been scarce among community-exposed individuals. To date, the only such study conducted examined the associations of both patella and tibia bone lead concentration to brain metabolites measured with MRS in 31 older men, none of whom had dementia, participating in the Normative Aging Study.[103] Higher concentrations of lead in both bone sites corresponded to higher levels of hippocampal myoinositol, a metabolite believed to be related to glia (non-neuronal cells in the brain that fill roles including immune function and structural and biochemical support). By contrast, bone lead levels were not associated with neuronal density, as indicated by levels of NAA. While one might expect a reduction in NAA with increasing lead exposure if lead exposure ultimately results in neuronal loss, it is intriguing that others have suggested that one of the earliest spectroscopic signs of Alzheimer's disease is an increase in myoinositol without a change in NAA.[104]

1.5.3 Modification by Psychosocial Factors

An emerging body of animal data suggests that early life exposure to psychological stress may further exacerbate lead exposure's effects on cognitive outcomes.[105–107] This interaction is potentially important because psychological stress and lead exposure frequently occur together in community settings. The mechanism underlying this enhanced susceptibility may involve actions by both factors on the hypothalamic–pituitary–adrenal (HPA) axis, which, via the alteration in cortisol homeostasis[108] and other pathways, is linked to cognitive functioning.[109] Exposure to lead and psychological stress may amplify each other's effects on the HPA axis: lead exposure may alter reactivity to psychological stressors,[110–112] and psychological stress may promote the mobilization of lead from bone into the blood,[113] thus making more lead available to act on the HPA axis and other systems. Both lead and psychological stress also act on the dopaminergic and glutamatergic systems in the brain's mesocorticolimbic regions, which encompass key structures and functions involved in cognition.[105,106]

Because lead exposure and psychological stress may both occur repeatedly over different stages of the lifespan, evaluating their joint effect on cognitive outcomes in adulthood is enormously challenging. Nonetheless, two studies in community-exposed populations offer a start—importantly, using measures of cumulative lead exposure. Their results provide evidence to suggest that adverse effects of lead on cognitive function are worse among persons exposed to greater psychological stress. In a study of 1001 participants, ages 50 to 70 years, of the Baltimore Memory Study, the associations of tibia lead level with poor performance on tests of language, processing speed, and executive function were significantly stronger among those living in neighbourhoods characterized by greater psychosocial hazards (*e.g.* 9-1-1 emergency calls, violent crime).[114] A study of 811 men (mean age, 68 years) participating in the Normative Aging Study found associations between lead exposure biomarkers and performance on a test of global cognition that were more deleterious among men who had experienced greater levels of perceived stress than among men with lower levels of perceived stress.[115] These differences in association were significant or, borderline significant, for both patella bone lead level and blood lead level.

1.5.4 Modification by Genes

Identifying genetic variants that modify the health effects of lead can, in theory, define sub-populations with elevated susceptibility to lead's effects. For example, in the previously discussed cohort of former organolead workers, the adverse association between tibia lead concentration and several cognitive abilities was heightened among men carrying at least one ε4 variant— a variant whose association with increased risk of late-onset alzheimer disease has been well-documented—of the apolipoprotein E gene.[116,117]

Genetic studies may also provide insights into the molecular mechanisms by which cumulative exposure to lead may affect adult cognition. A particularly clear example of this type of inquiry was in a study of variants of the hemochromatosis (*HFE*) gene.[118] Two *HFE* variants are associated with hemochromatosis, a disease of iron overload and consequently excess oxidative stress. Among a group of 358 men in the Normative Aging Study, those who carried at least one of these alleles experienced significantly faster rates of decline in global cognition, compared with non-carriers, for a given increase in bone lead (tibia or patella). These findings provide support for the role of oxidative stress and, potentially, iron–lead interactions in lead's relation to cognition.

These two sets of findings have not, however, been replicated in other settings thus far. And, on the whole, reports on lead–gene interactions have either been isolated, as for the aforementioned interactions, or shown inconsistent results. A well-characterized variant in the gene encoding δ-aminolevulinic acid (ALAD) has received the most attention. This variant, known as *ALAD-2*, produces an enzyme sub-unit that is more electronegative than that produced by the wild type *ALAD-1* variant.[119] Thus lead may have greater affinity for the isozyme composed of a greater number of ALAD-2 sub-units.[120] Whether *ALAD-2*

carriers are more susceptible to lead's cognitive effects is unclear. The more electronegative ALAD-2 isozyme could more effectively distribute lead throughout the body or, conversely, bind lead so tightly as to reduce its bioavailability.[121] In addition, lead inhibits ALAD, resulting in an increase in the neurotoxic substrate, 5-aminolevulic acid (ALA). The lead-induced increase in plasma ALA is more pronounced in *ALAD-1* homozygotes,[122–124] implying decreased cognitive susceptibility in *ALAD-2* in carriers. For a given increment in lead exposure biomarker, one study of older adult men found more deleterious associations with cognitive function among *ALAD-2* carriers, although none of these lead exposure-*ALAD* genotype interactions was statistically significant.[125] Findings in two other studies were mixed.[126,127] A fourth study of occupationally exposed and unexposed middle-aged adults found greater susceptibility to lead's effects on motor function among *ALAD*-1 homozygotes.[128]

An emerging area of inquiry, that may produce more promising findings, is how lead exposure affects cognitive function through its effects on the epigenome. Specifically, lead may influence when and how much a particular gene is expressed,[50,51] providing a potentially powerful way, above and beyond lead's interaction with traits of the static genome, for understanding lead's effects on neurodevelopment and cognitive function over the lifespan. (For further discussion on the epigenetic effects of lead, see Section 1.3.)

1.5.5 Does Exposure to Lead Contribute to Dementia Risk?

Taken as a whole, in combination with new findings on childhood lead exposure and adult cognitive functioning, the findings on cumulative exposure to lead among both occupationally and non-occupationally exposed individuals suggest that lead exposure earlier in life has residual neurocognitive ramifications many years later. A mechanistically logical extension of lead exposure's associations with impaired cognition and accelerated cognitive decline is that lead may be associated with increased risk of dementia. Because studies with high-quality assessments of lead exposure rarely also entail high-quality assessments of dementia, and *vice versa*, the data required to answer this important public health question is essentially absent. A few studies have attempted to evaluate this association, but the exposure assessments in these studies were poor, and the studies were underpowered to detect subtle effects, which are common in the study of environmental toxicants on health. With increased interest in the late life effects of early and mid life exposures, more opportunities should arise for addressing the effect of lead exposure on dementia risk.

1.6 Closing Remarks: Shifting Exposures, Continuing Risks

The removal of lead from gasoline and the prohibition of lead-based paint use resulted in substantially reduced exposures for millions of children and adults.

While this achievement has been hailed as a public health victory, the excruciatingly slow pace at which it came about has incurred great costs to the intellectual capacity and economic productivity of the United States,[129] and likely other countries as well, prompting one observer to bemoan the victory as a pyrrhic one.[130]

A surprising dimension of this success is that as average exposure levels have fallen over time, researchers have continued to identify adverse cognitive effects on children at progressively lower levels of exposure.[76] In a recent pooled analysis, adverse effects on children were detectable at levels below $30\,\mu g\,dL^{-1}$ (the screening threshold from 1975–1985), and in fact, the steepest interval of the dose-response curve appeared at the lowest levels of exposure, below $10\,\mu g\,dL$.[131] With these discoveries of cognitive effects at lower blood lead levels, the CDC has lowered its pediatric screening threshold repeatedly over time.[20–22,76] Following advocacy for lowering the threshold even further,[132] the CDC recently changed its recommendations to intervene on children whose levels fall in the 97.5th percentile, effectively reducing the threshold in 2012 to around $5\,\mu g\,dL^{-1}$.[20–22]

In contrast, in occupational settings in the US, the blood lead level thresholds that trigger various actions (*e.g.* removal from the workplace) were last promulgated in an era in which addressing acute toxicity was the primary goal as far as adult health was concerned. The Occupational Health and Safety Administration (OSHA) last set these standards in 1978 and 1993 respectively for construction and general industry. But, as argued by Schwartz and Hu, as well as the American College of Occupational and Environmental Medicine, these current standards may still permit too much risk, especially in light of data that has emerged in the past 15 years.[133,134] For example, a worker with a single blood lead level exceeding $60\,\mu g\,dL^{-1}$ must be removed from further exposure; this level is far in excess of the level at which lead exposure exerts its cognitive effects. In 1978, the average blood lead level in the population exceeded $10\,\mu g\,dL^{-1}$,[19] and even though it had dropped substantially by 1993,[135] most workers who were covered by these standards had started working when average blood lead levels were what are now considered elevated.[133,134]

All told, while lead exposures in the US have been decreasing, they remain relevant to the cognitive well-being of several generations of adults who have sustained substantial exposures during at least parts of their lives. Nearly 90% of US children in 1976 had blood lead levels exceeding $10\,\mu g\,dL^{-1}$.[136] And by the time the most recent OSHA standards for lead exposure came into effect, in 1978 and 1993, most adults had already accrued substantial exposures. Moreover, progress in preventing exposures and their cognitive aftermath will likely not occur at the same pace in all population sectors. Within the US, historic exposures to lead followed marked racial and socioeconomic gradients, with higher exposures more common among individuals of minority race or ethnicity and/or who were economically disadvantaged.[136–138] These gradients have lessened over time, but to a modest degree still remain.[139–141] Progress outside of the US is likely to be uneven as well (see Section 1.2.2). Clearly, the cognitive legacy of lead exposure will likely be a protracted one, as sources of exposure persist or new sources emerge over time.

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