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# *Perspective:* Cell danger response Biology—The new science that connects environmental health with mitochondria and the rising tide of chronic illness

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A B S T R A C T

This paper is written for non-specialists in mitochondrial biology to provide access to an important area of science that has broad implications for all people. The cell danger response (CDR) is a universal response to environmental threat or injury. Once triggered, healing cannot be completed until the choreographed stages of the CDR are returned to an updated state of readiness. Although the CDR is a cellular response, it has the power to change human thought and behavior, child development, physical fitness and resilience, fertility, and the susceptibility of entire populations to disease. Mitochondria regulate the CDR by monitoring and responding to the physical, chemical, and microbial conditions within and around the cell. In this way, mitochondria connect cellular health to environmental health. Over 7,000 chemicals are now made or imported to the US for industrial, agricultural, and personal care use in amounts ranging from 25,000 to over 1 million pounds each year, and plastic waste now exceeds 83 billion pounds/year. This chemical load creates a rising tide of manmade pollutants in the oceans, air, water, and food chain. Fewer than 5% of these chemicals have been tested for developmental toxicity. In the 1980s, 5–10% of children lived with a chronic illness. As of 2018, 40% of children, 50% of teens, 60% of adults under age 65, and 90% of adults over 65 live with a chronic illness. Several studies now report the presence of dozens to hundreds of manmade chemicals and pollutants in placenta, umbilical cord blood, and newborn blood spots. New methods in metabolomics and exposomics allow scientists to measure thousands of chemicals in blood, air, water, soil, and the food chain. Systematic measurements of environmental chemicals can now be correlated with annual and regional patterns of childhood illness. These data can be used to prepare a prioritized list of molecules for congressional action, ranked according to their impact on human health.

"When a deep injury is done to us, we never heal until we forgive."
Nelson Mandela (1918–2013)

## 1. Introduction

Mitochondria sense and respond to changes in the cellular environment. By sensing safety and danger, mitochondria act as fundamental regulators of the cell danger response (CDR) (Naviaux, 2014). The CDR is an ancient and universal response to threat, stress, or injury. Mitochondria are uniquely suited to monitor the environmental and genetic conditions, and the gene-environment (ecogenetic) interactions that regulate the CDR. The mitochondrial proteome consists of about 1300 proteins (Calvo et al., 2016) that are transcriptionally and post-translationally regulated according to tissue-specific needs (Pagliarini et al., 2008), injury (Naviaux et al., 2009), infection (Wang et al., 2011), and presence or absence of environmental pollution (Winckelmans et al., 2017). Chemical, physical, and microbial changes that surround all multicellular life on Earth are translated into changes in mitochondrial structure and function. These changes in mitochondria are used to signal safety or danger in the cell, alter gene expression, trigger the healing response, and adjust fitness and susceptibility to chronic illness (Naviaux, 2019b). These changes even help to adjust the rate of aging in response to environmental stress (Naviaux, 2019a). The term CDR was originally coined to include all levels of the organismal response to stress, including inflammation, immunity, metabolism, microbiome, epigenetics, behavior and memory (Naviaux, 2014). Some aspects of the CDR are studied independently and called the integrated stress response (ISR) (Lu et al., 2004) and the mitochondrial ISR (Khan et al., 2017; Nikkanen et al., 2016; Silva et al., 2009).

When the CDR is triggered, the priorities of a multicellular organism are reset to optimize survival. The CDR is so fundamental to the survival of all living things, that the same core defenses of metabolism, inflammation, immunity, microbiome, brain function, sleep pattern and behavioral changes are activated by many different kinds of threats. These threats can be as diverse as an infection, poisoning, physical, or psychological trauma, and still trigger the same stereotyped sickness behavior (Shattuck and Muehlenbein, 2015). This stereotyped response to danger includes withdrawal from social contact, activation of innate immunity, decreased speech, fragmented sleep, head, muscle and abdominal aches, changes in the gut microbiome, and the increased

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sensitivity to touch, sound, and light that many people experience when they have the flu, or are recovering from a serious injury. It is the CDR that produces these familiar signs and symptoms (Naviaux, 2012, 2019b). At a cellular level, the cell danger response cannot be turned off until the cell receives the final "all clear" signal. Until then, the CDR remains stuck in a repeating loop that blocks further healing in an attempt to eradicate perceived danger. This can lead to long-term suffering, disability and chronic disease. Only when a cell perceives safety can it heal completely.

The concepts of cellular perception and reactivity are critical. Danger can be real or imagined. From the time we take our first breath, our genes are hard-wired to treat the world as a dangerous place, to anticipate a struggle to survive. When conditions become extreme, one cell can defend itself with powerful chemical weapons, while another may sacrifice itself to save its neighbors by activating a single-cell "self-destruct" sequence. The threshold for cellular reactivity is set by past environmental experience. The perception of safety leads to calm. Perception of danger leads to hypersensitivity.

## 2. Cellular safety

Organismal safety starts with cellular safety—a condition determined by access to adequate shelter and nutrients for growth and repair, effective management of intercurrent infections, absence of chemical, physical, and psychological trauma, and ample opportunities for healthy play. Sending a clear message of child safety early in life is essential for adult health. At a cellular level, anxiety is created when safety is not assured—when there is uncertainty about nutrient resources and support from neighboring cells, or about protection from exposure to a toxin or alarm signal. When cells are threatened, they behave the way nations do when they go to war. They harden their borders and don't trust their neighbors. The biophysical properties of membranes of cells undergoing the cell danger response change dramatically, leading to aggregation of patches of sphingolipids and cholesterol (Lingwood et al., 2008), membrane hardening, and the release of cellular ATP to signal danger and recruit cells needed to fight infection and heal (Burnstock, 2016). Cellular calm is created when environmental uncertainties are removed and the signals of health and safety are restored. It is now well known that a child raised in neglect or extreme adversity carries a lifelong risk of chronic illness and mental health struggles (Cameron et al., 2017). Social adversity can result in physical changes in brain development and other organs that can permanently change the trajectory of child development and can injure a child for life. What is only recently becoming known is that a rising tide of manmade chemicals and other changes to our environment are creating a similar impact on lifelong illness and mental health by threatening cellular safety. Children with chronic illness grow up to be adults with chronic illness. In the past 40 years, the fraction of children living with chronic disease in the United States has risen from approximately 5–10 percent in the 1980s, to 40 percent today. Rising teen depression, suicidal ideation, anxiety and behavioral mental health disorders add another 10–20 percent so that 50% of teens struggle with a chronic illness (Bethell et al., 2011). Sixty percent of adults under 65, and 90 percent of those over 65, now live with a chronic illness, a number that has doubled since the 1980s, and continues to grow (CDC.gov, 2017) (Fig. 1).

## 3. The economic cost of chronic illness

The United States now spends $2.8 trillion annually on medical care for children and adults with chronic conditions. This represents 86 percent of the $3.3 trillion US budget for health care. If the rising tide of chronic illness over the past 30 years continues unabated, the cost of health care in the US is projected to exceed $5.5 trillion by 2025, creating adverse effects that will derail economic prosperity not just in this country, but in many nations around the world (CDC.gov, 2017; CMS.gov, 2017; Khazan, March 15, 2019). What if a new approach to medicine were able to alleviate the suffering and the need for expensive medical care for just 10 percent of people with a chronic disorder? This new approach would return $280 billion (10 percent times $2.8 trillion) back into the US economy each year. This savings in a single year would surpass the annual budgets of the National Institutes of Health (NIH; $37 billion), the Environmental Protection Agency (EPA; $8.7 billion), the Food and Drug Administration (FDA; $5.1 billion) and the US Department of Agriculture (USDA; $151 billion) combined.

## 4. Chronic disease and the chemical World—the mixtures that make up the chemosphere

When viewed from far in space, Carl Sagan pointed out that the Earth appears as a pale blue dot (Sagan, 1997). A little closer, when viewed from the orbit of the International Space Station, the totality of livable space on our planet appears as a wispy thin layer of atmosphere, land, and ocean that scientists call the biosphere. Invisibly extending through and beyond the biosphere are the chemicals that make up both the living and non-living parts of the Earth. These chemicals are mingled with every drop of water, every breath of air in the skies, and adsorbed to particles of soil and sediments on land and sea. The chemical world on Earth is called the chemosphere.

The vast majority of the chemosphere is invisible to human eyes, tasteless, and odorless. The majority of what we "sense" of the chemosphere is through subconscious cellular responses to this invisible world that surrounds us. Tens of thousands of chemicals in the chemosphere are manmade and many are toxic even at low doses. Ultimately, the total load (Herbert and Weintraub, 2013)—the collective mixture—of both manmade and natural chemicals in the chemosphere, and other stresses in the biosphere helps determine the population risk of chronic illness. Recent studies have established that mixtures of chemicals can have deleterious effects on metabolism even when no single chemical is present in concentrations defined as "toxic" (Bonvallot et al., 2018). These findings have underscored a need for government agencies to revisit the guiding concepts in environmental toxicology called the "no observed adverse effect level" (NOAEL) and "lowest observed adverse effect level" (LOAEL), since low-level exposures to real-world mixtures of manmade chemicals can be toxic and produce chronic illness even at concentrations well below NOAEL.

Within every population there are sensitive and resistant individuals, and risk of harm is a probability, not a certainty for any given person. Resistant individuals can remain healthy despite exposure at one particular time, but then become vulnerable in another season or after a predisposing event at another time. In sensitive children and adults, whose cell danger response has been primed by a perfect storm of previous chemical, microbial, physical, and/or psychological stresses, the same levels of chemical or biotoxin burden produce pathological and prolonged metabolic, epigenetic, and physiologic responses. This hypersensitive response has two major effects: 1) it leads to disability and chronic illness, and 2) it interferes with the body's natural efforts to heal (Naviaux, 2019b).

## 5. Slow DNA and fast industries

The DNA of *Homo sapiens* changes slowly, and requires generations to adapt to the chemical changes around us. Common new diseases are not the result of mutations in our DNA, but the result of an environment that is changing faster than our genes can adapt. Although important, not even the rapid epigenetic changes regulated by mitochondria (Smiraglia et al., 2008) can fully rescue us from this problem. By evolutionary default, the cellular response to anything unknown or new is to first treat it as a threat. Repetitive activation of the cell danger response can lead to cellular mosaics in which healing has been slowed or incomplete (Naviaux, 2019a, b). In a rapidly changing world, our cells respond to so many chemicals that are new and threatening that it is

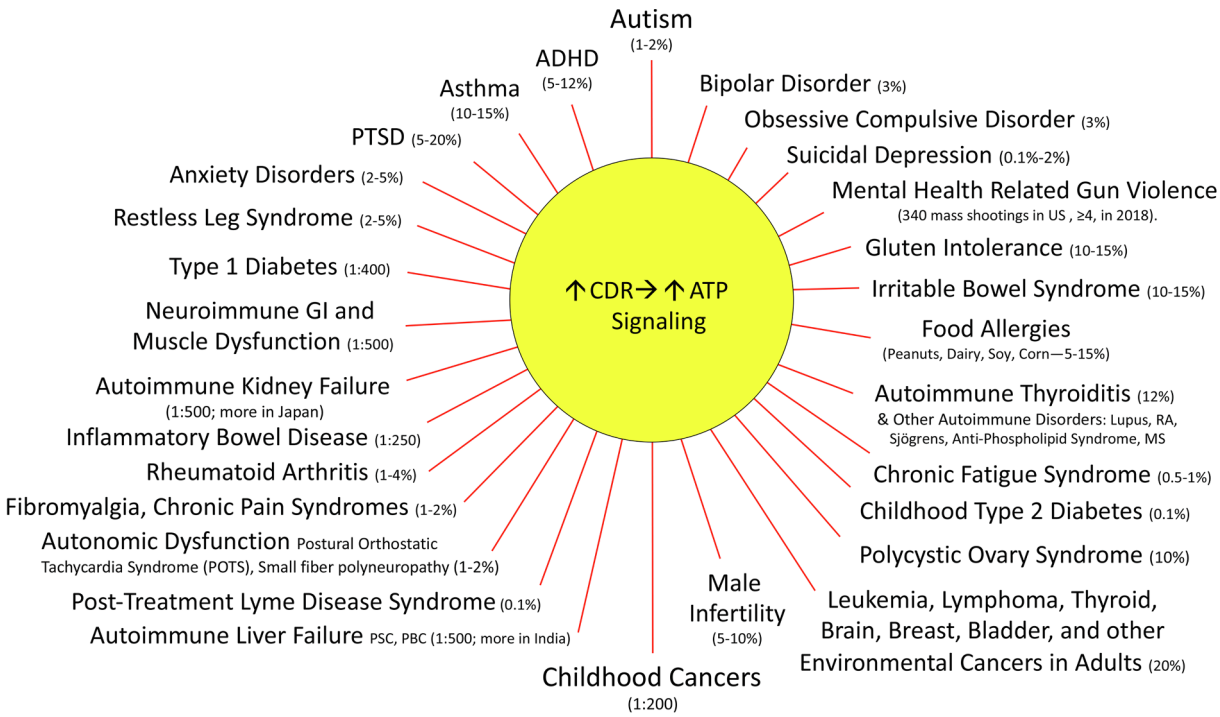


**Fig. 1. Chronic Health Disorders that have Increased 2-100 times since the 1980s.** Forty percent of children born in the US today and 60 percent of adults under 65 live with at least one chronic illness. ATP signaling is also known as purinergic signaling (Burnstock, 2018; Naviaux, 2018). **Abbreviations**: CDR, cell danger response; ATP, adenosine triphosphate; ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; PTSD, post-traumatic stress disorder. Numbers reflect the population prevalence of each illness in the United States in 2018.

becoming increasingly difficult to heal completely after any common injury caused by the common cold, the flu, accidental poisoning, allergens or physical trauma. In much the same way that repeatedly ripping the scab from a skinned knee delays healing and leaves a scar, repeated exposure to a toxic world means that cellular safety and "all clear" signals are becoming harder to sustain. The absence of safety signals leaves a mark. Children and many adults are left in a state of primed hypersensitivity. New pesticides, plasticizers, antibiotics, food additives, dyes, solvents and other pollutants that our genome and our microbiomes have not yet evolved mechanisms to detoxify are entering our food chain, water supply and air like an invisible but poisonous chemical tide—a miasma of our own making.

## 6. Generational transmission

A study conducted by the Environmental Working Group in 2005 found that the umbilical cord blood of newborn babies in the United States already contained an average of 287 pesticides, pollutants and other environmental chemicals (Houlihan et al., 2005). The methods used at that time allowed the authors to look for 413 molecules from 9 different chemical classes. Other studies that have looked for a smaller number of pesticides or persistent organic pollutants have documented the presence of dozens of pollutants in newborn blood samples from around the world (Cabrera-Rodriguez et al., 2019; Silver et al., 2015). Similar pollutant loads have been documented in the placenta and found to change mitochondrial DNA content (Vriens et al., 2017). These studies show that when a child is born, they inherit a sample of their parents' chemical exposure history. Many chemicals are biomagnified in fat, bone and reproductive organs, accumulating over years of exposure to levels that can be hundreds of times higher than the concentration in any given environmental source of air, water or food (Drouillard et al., 2001). Many banned pesticides like DDT and industrial chemicals like PCBs can still be found in people decades later (Montano et al., 2013). If a child is born today with a burden of 300 manmade chemicals, in 25 years that child will add to their inherited burden by accumulating new toxic chemicals from their environment as they grow to reproductive maturity. As adults, they will then pass on a new sample of both their inherited and their newly-accumulated environmental chemicals to their children. If a net increase of 50 environmental pollutants occurs in the umbilical cord blood with each generation, and is added to the current number of 300, the toxic chemicals passed on to our children will soon have more devastating effects on human health than any mutation in DNA, leading to escalating infertility rates, miscarriages, childhood and adult chronic disease.

## 7. Increasing human impacts on the chemosphere and biosphere

The problem of environmental accumulation of toxic chemicals has been noted since the beginning of the industrial revolution in the 1700s, but has been accelerating since the rise of industrial scale farming and other large-scale industries since World War II. Rachel Carson was the first to call attention to the ecological effects of this accumulation in her landmark book *Silent Spring* (Carson, 1962), which first appeared in 1962. The title of her book referred to the decrease in the songs of birds in the spring because of pesticide accumulation in their food chain. Since that time, 30% of all birds in North America have been lost (Rosenberg et al., 2019). In 1962, the world's human population was 3.1 billion people. Today, the population is 7.7 billion and is growing at a rate of about 1% per year—about one billion people every decade. To glimpse the sheer magnitude of the ecological footprint of humans on the Earth, we need only look to the north Pacific Ocean to find a garbage patch of plastics and other manmade debris now twice the size of Texas, the exponential increase in plastic deposits in ocean floor sediments that has occurred since World War II (Brandon et al., 2019), or to the dying swaths of coral in the Great Barrier Reef (Kroon et al., 2016) the size of cities. The hopeful message is that by cleaning up pollution from the environment, the next generation can begin to off-load their inherited burden at a rate faster than they accumulate new toxins.

## 8. Canaries in the coal mine

Children are most susceptible to this menacing tide because their cells are growing rapidly and their metabolism, brain and endocrine systems are more sensitive to disruption. Children are like canaries in the coal mine—the first responders to environmental change. Many chemicals pass safely through adults, but strike our children during their periods of rapid growth in the womb and first few years of life, leaving them with chronic illnesses like asthma, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). In the case of ASD, the prevalence has risen from 1 in 5000 (20 in 100,000) in the 1970s to 1 in 59 (1700 in 100,000; an 84-times increase) in 2014 (Baio and Investigators, 2018). It has been calculated that 60% of the apparent increase can be explained by changes in the diagnostic criteria for ASD over the past 40 years (Hansen et al., 2015). However, even with this conservative correction, the adjusted prevalence of ASD of 1 in 59 children today represents an absolute increase of 34 times ($84 \times 0.4 = 34$) from the 1970s (Fig. 1).

Chemical exposures in childhood can have many other lifelong effects, even when the same exposures in adults produce no obvious effect. A *Lancet* Commission study from 2016 reported that 940,000 children die each year around the world as the result of manmade pollution (Landrigan et al., 2018; Landrigan et al., 2019). This report also found that pollution was responsible for 9 million premature deaths each year—a number that continues to grow (Fuller et al., 2018; Martin and Landrigan, 2017). In addition to the deaths, which occur in only 1–10 percent of those exposed, it can be estimated that ten to hundred times these numbers—nearly 1 billion people around the world—are sickened annually from exposure to manmade pollution. For many, the illnesses caused by exposure to pollution will remain with them for the rest of their lives.

The persistent cell danger response caused by environmental chemical exposure has the power to change human thought and behavior. Because the brain controls metabolism (Naviaux et al., 2017; Naviaux et al., 2016; Naviaux et al., 2019), the persistent CDR that was originally triggered by mitochondria and reached the brain, feeds back on peripheral mitochondria using neuroendocrine and autonomic circuits from the brain, to amplify the cellular response to environmental change in an attempt to eradicate danger and restore safety. If the danger is not successfully eradicated, persistence of an activated CDR creates a cellular form of anxiety that can bubble up to create psychological anxiety and fear of change. In many people, the anxiety translates to a fear of strangers, outbursts of anger and violence, repetitive and obsessive-compulsive behaviors, and rigid imposition of past rules regardless of current circumstances in an effort to preserve the safety associated with earlier times. In others, the pervasive anxiety can lead to chronic pain, suffering, and drug addiction. I believe the rising tide of depression, suicide, gun violence, mental health issues, chronic pain and the opioid crisis reflects the changing set-point for the CDR in America. This new set-point creates a loss of past resilience to disease. The new set-point of the CDR is primed to react to smaller and smaller threats that arise by repeated exposures to a toxic mix of manmade chemicals, and acoustic and electromagnetic pollution in our increasingly industrialized cities, food chain, water and air.

## 9. A Second Book of Medicine

To treat the rising tide of chronic disease, a *Second Book of Medicine* is needed (Naviaux, 2019b). The *First Book of Medicine* contains the corpus of medical knowledge from the past 5,000 years of written history. From the *First Book of Medicine*, doctors learned how to treat acute illnesses caused by infections, poisonings and physical injuries. Typical acute illnesses last less than six months. The topic of the *Second Book of Medicine* will be the cause and treatment of chronic diseases that last longer than six months. In this book, a new chapter in pharmacology will be needed. A new class of medicines that might be called "armistice therapies" can now be developed (Naviaux, 2018). This new class of medicines will help doctors adjust the set-point of the CDR so it is no longer hypersensitive to chemicals and other threats that are below the threshold required to cause harm. The new medicines will help send the chemical message that the "war is over," allowing a child or adult struggling with a chronic illness to return to the "peace time" activities that permit healing, recovery and health. This new class of medicines will have fewer side effects than drugs from the *First Book of Medicine* because the new medicines will target biological processes that are most active under conditions of illness, when healing is incomplete. Once the illness or injury has healed, armistice medicines of the *Second Book of Medicine* will become inert because their targets will have receded or disappeared once health has been restored, and the use of adaptogens can help maintain and strengthen resilience (Panossian, 2017).

## 10. Environmental health for human health

Unfortunately, unless the environment can be cleaned up, and the repeated exposures to chemical, acoustic and electromagnetic triggers of the CDR are reduced, modern medicine will not be able to completely cure most chronic illnesses. Regular efforts to rejuvenate and heal by reconnecting with the natural world through walks in the park, or in a forest as is now prescribed in Japan as preventive medical care in the practice known as *shinrin yoku (*Miyazaki, 2018*)*, are steps in the right direction, but will not be able to hold back the tide. Incomplete healing occurs in part because many environmental chemicals block the body's ability to heal. Without restoring the environment, chronic illnesses will not heal completely, but will instead become relapsing-remitting disorders. Instead of putting a condition like a broken leg in the past—cast off, leg good as new—many people with chronic illness will remain at risk for recurrence throughout life. For example, a person who has recovered from diabetes would become a "recovering diabetic" for life, and someone with post-traumatic stress disorder (PTSD) who has been successfully treated and has recovered full function would still be at risk of relapse for the rest of their life.

Precision medicine will soon be able to use personal genome and serial metabolomic analysis to identify points of vulnerability in each person that might be strengthened with supplements, drugs, diet, exercise, restorative sleep and other measures. However, these advanced tools will only identify weak links in the personalized chain under tension. Ultimately, every chain has a breaking point. The ongoing accumulation of manmade changes in the environment is like a hydraulic winch that steadily adds tension to the chain of every citizen. Some chains will break before others, but ultimately, all living organisms are affected.

## 11. Toward sustainable health

Just as the body resets its priorities to face new threats that activate the cell danger response, nations of the world in the 21st century must reset their priorities to respond to new threats to our health caused by the changing chemistry and climate of our planet. Individual health must be given priority over corporate profit. Both are possible if both are valued equally and measures are taken to protect all the stakeholders. As part of this effort, it has been recommended that a portion of all land and ocean habitats be set aside in its natural state to preserve the biodiversity needed to recycle and purify the planet's water and air (Wilson, 2016). Without such actions, both profits and nations will fall as citizens sicken. New legislation is needed to regulate technological and industrial practices that promote safety and sustainability. The over-extraction and over-consumption of the Earth's resources and the discharge of pollutants into the environment can no longer be written off as economic "externalities" by industry and agriculture. Both resource usage and waste production need to be tracked with the same assiduous attention now paid to monetary profits. Governments of the

21st century must find ways to encourage all farms and businesses to comply with pollution-prevention standards to create a greener economy, and to financially reward businesses with the best sustainability practices.

Environmental protection agencies around the world must reinvigorate their mandate to monitor, record and remediate the crushing impact of the human footprint upon Earth's ecosystems, and minimize or prevent future impacts. If this doesn't happen, the consequences of political apathy, ignorance, or economic short-sightedness will be well-engrained, and Earth-scale processes thus set in motion will develop unstoppable momentum before we can finally agree there is a problem and can unite to make a change. In 2014, a study published in the *Proceedings of the National Academy of Sciences (USA)* found that 42 percent of lakes and rivers in Europe were already contaminated with enough chemicals to cause chronic illness in freshwater animals (Malaj et al., 2014). A similar study of waterways in the US has not yet been conducted. This failure to act has occurred in America despite early wakeup calls like the Cuyahoga river near Cleveland, Ohio catching fire several times from 1952 to 1969 because of industrial pollution, tap water igniting in Pennsylvania because of fracking (Tollefson, 2013), and harmful algal blooms from farm and city runoffs that create dead zones in rivers, lakes, and ocean fisheries that are decimating local economies (Diaz and Rosenberg, 2008; Grattan et al., 2016), making people sick, and are occurring more frequently each year.

Plastic waste in the US now exceeds 83 billion pounds/year (38 million metric tonnes) (Ritchie and Roser, 2018) and produces toxicity and impacts on human health by several mechanisms (Barboza et al., 2018; Wright and Kelly, 2017). Over 3,000 chemicals are made in or imported to the US in amounts over 1 million pounds per year (Landrigan and Landrigan, 2018). Another 4,000 are made in amounts over 25,000 lb per year. The rate of production of manmade pollutants now exceeds the rate at which the Earth can recycle them. This has led to a toxic rising tide that is entering ground water, soil, lakes, rivers, oceans, and the air. Fewer than 5% of these chemicals have been tested for their long-term effects on child development and health. Still thousands more are made in amounts less than 25,000 lb per year. These include widely-prescribed antibiotics, pharmaceuticals, hormones, and chemicals found in personal care products that are being found increasingly in our ground water and food chain (Bacanli and Basaran, 2019; Peng et al., 2014). Many of these manmade chemicals are biomagnified over years of exposure in our fat, bones, and reproductive organs to levels far above the concentration found in any single environmental source. If systematic scientific monitoring and recording, and regular reassessment of the chemistry of both people and the environment are not done, we will not have the tools to ward off the future of looming poor health. People around the world will fall prey to chronic illness in greater numbers; the land and seas will become disease-causing waste dumps; our faltering immune systems will make us vulnerable to untreatable microbial infections and disabling autoimmune diseases; new chronic and degenerative diseases will emerge; and the costs from illness and threats to our social fabric will bankrupt communities, states and nations.

## 12. The right to be born into a healthy environment

We often take for granted the freedoms afforded to us by good health. This must change, or thriving health will become rare, and plagues, wars and mental health struggles will become the new normal. If the activities of a nation poison its own people, then those activities must be changed. What is more important to the health of a nation than the health of its citizens? This question has motivated a call for a new constitutional amendment to invest each citizen with a new right: the right to be born and live in an environment that does not cause chronic disease. Readers can learn more at: http://naviauxlab.ucsd.edu/the-28th-amendment-project/.

## Dedication

This work is dedicated to Olivia, a young lady with ASD whose spirit and imagination shine as a bright light of hope for children and families around the world.

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## Conflicts of Interest

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