The Importance of Environmental Embodiment for Public Health Professionals:

Stress Triggers, Environmental Toxicants, and Strategies for Education

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A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2015

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School of Public Health

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Abstract

The Importance of Environmental Embodiment for Public Health Professionals: Stress Triggers, Environmental Toxicants, and Strategies for Education

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Human bodies exist as part of ecosystems and can be altered by environmental exposures. Environmental embodiment, the conceptual model described in this work, demonstrates how external exposures can shift body systems in ways that foster disease. Epigenetic mechanisms operate at the interface between externally-derived stimuli and the body's physiologic response making the epigenome especially relevant to explore health implications of adverse environmental exposures. New evidence suggests chronic exposure to psychosocial stress or to common environmental toxicants can disrupt epigenetic processes important for health. The scale of such daily exposures merits closer investigation, especially since epigenetic disruption during fetal development is known to increase a person's disease risk over the life span. Epigenetic disruption is of special importance to public health professionals as we have an ethical obligation to protect the most vulnerable individuals in our communities, in this case our developing children.

While psychosocial stress and toxicant exposures often co-exist, researchers tend to study them as separate phenomena. To facilitate cross-disciplinary collaboration, I describe epigenetic mechanisms that are common to both exposures. Within the context of chronic disease etiology, I reviewed the literature for human examples of environmental embodiment across a range of common environmental toxicants. This synthesis indicates that four exposure groups (air pollution, endocrine disrupting chemicals, heavy metals, and persistent organic pollutants) can disrupt epigenetic mechanisms in

humans and pose a special threat to in-utero development. I also developed an integrated theoretical model to understand the embodiment of chronic stress by drawing on three theories of stress to illustrate the pathway from external stress exposures to epigenetic action and embodiment.

I further investigate the current challenges for understanding, surveying, researching, intervening, and regulating some of the previously-identified epigenetic disruptors. I argue that current environmental policy prioritizes human-centric values that foster false assumptions regarding the safety of low-dose exposures to toxicants and reductionist approaches to investigating risks, thus enabling further exposure. I make recommendations for regulation and public health to take action to address these community-level drivers and provide more support for an already-sufficient body of evidence calling for a precautionary approach to chemical policy.

I then focus on community engagement strategies to inform risk assessment regarding environmental toxicants and to exercise power in pressing for social policy change. The scientific community has a duty to disseminate our new understanding of epigenetic embodiment and use this information to change policy. Our health sciences professions can greatly facilitate this dissemination through community engagement of educational media and through exercising community power. I discuss two cases of community engagement, first the creation of an epigenetic educational video, and second the work of Health Equity Circle.

A broader understanding of this embodiment process can support the health equity movement by equipping public health professions with tools and experience to educate policy makers, educate the public, inform surveillance and research activities, support population-wide interventions, and work with community institutions to change policy. I specifically call for public health support of stronger chemical policy regulation and changes to social policy to reduce environments shaped by the contamination, pollution, threat, unpredictability, and lack of control for all environments that increase

the risk for epigenetic disruptors. I call on academia to provide community engagement opportunities for health sciences students to act on the knowledge they have gained.

Acknowledgments

This work by no means occurred in isolation. My committee has been instrumental in facilitating this work. Dr. Kelly Edwards, I am humbled by your deep commitment to justice, community, and student growth and forever appreciate the space to explore epigenetic education. Dr. Helene Starks, I am inspired by your passion for society's well-being and commitment to student development. Thank you for cultivating my skills for *half a decade*; it has been foundational to my success. Dr. Steven Gilbert, I am motivated by your profound commitment to children's environmental health and advocacy. By keeping the ethics of protection alive in research and community conversations you give voice to those who have none. Dr. Paula Nurius, I am excited to be an interdisciplinarian. The discussion spaces you created were critical to broadening my thinking of the environment, broadening my imagination for collaboration, and empowering me to reach outside of my comfort zone. Dr. Dan Eisenberg, my GSR, thank you for rounding out the team with your lens of evolutionary biology.

Thank you to my external readers: Erika Schreder with Washington Toxics Coalition, Peter Hasegawa at Sound Alliance, and Tom Tousey my rock star, proofreading Uncle. Those early drafts were dense and disorganized yet you still plowed through them. Thank you to my academic colleagues who spent numerous hours helping me work through my thoughts, especially the Renal Disease Working Group: Kate West, Joseph Yracheta, Nini Shridhar, and Taryn Hall.

Thank you to the two focus groups that informed the creation of the epigenetics video described in Chapter 4: Sarah Nelson, Ragan Hart, Kate West, Lizzie Dorfman, Marilyn Hair, and Steve Gilbert.

A special thank you to Joe Chrastil, Peter Hasegawa, and Julia Moen from Sound Alliance and Kelsen Caldwell with the UW School of Medicine. Working with you during the Health Equity Circle experience has been an amazing experience of growth for me. To the rest of Health Equity Circle, those before me and after, keep rocking it! We are doing important work. The School of Medicine has been

providing financial support and much needed resources to Health Equity Circle since our inception in 2008. A special thank you to Kelsen Caldwell for your staff support, commitment to student development, and leadership in the health equity movement.

Institutional support including funding and the ability to converse with leading researchers on ideas, resources, and feedback, comes from the Center for Genomics and Healthcare Equality, School of Medicine, based and NHGRI funded and led by Dr. Wylie Burke; the Center for Ecogenetics and Environmental Health, SPH based and NIEHS funded; and the Interdisciplinary Center on Epigenetics, Science & Society led by Dr. Nancy Press. Funding has also come directly from my husband, Aaron Walker. Thank you all!

Finally, my sincere appreciation to all faculty who have worked tirelessly to create the Public Health Genetics field at UW, the faculty that have been supporting me from grade school through grad school, and my family and friends who have kept me fed, loved, and alive during this time.

Because of all of you, I am forever changed for the better.

Dedication

For Adeline, my dear squiggle bug. This work gained true meaning when you entered my life.

Your smile and light give me hope and determination for a better world.

Above everything else you are loved.

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Chapter One

Introduction

This work began with the question, "How does the human body manifest common environmental exposures as chronic disease outcomes?" I investigated this question across multiple disciplines to assess what we know and what we don't from the perspectives of genetics, epidemiology, social science, policy, ethics, and ecology. As a lens to investigate this question, I used the framework of epigenetic embodiment, defined as the ways by which inputs from the external environment can induce internal physiologic changes that affect population health. The goal of this multi-dimensional exploration was to understand the potential of community-level exposures, specifically environmental toxicants and psychosocial stressors, to induce epigenetic changes that foster chronic disease and cancer and consider the ethical implications (Figure 1). This understanding can facilitate future interdisciplinary teams working to understand, capture, and mitigate the community drivers of chronic disease outcomes.

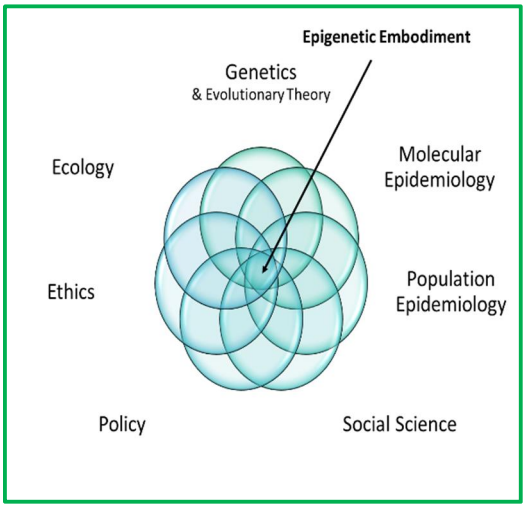


Figure 1: Interdisciplinary Lens of Investigation

I first examine how these two broad categories of exposures affect populations epigenetically and then describe two cases of community engagement I developed as ways to advocate for reduced exposures. Specially, these projects included the creation of an educational video that explains epigenetics with the goal of shifting risk perception to promote citizen engagement, and teaching community organizing and political advocacy skills to health sciences students at the University of Washington as part of their professional development.

This work is a product of training received from the Institute for Public Health Genetics (IPHG) in the School of Public Health at the University of Washington. The IPHG program is an interdisciplinary program that trains public health professionals to use a comprehensive perspective to address complex problems, in this instance the increasing burden of chronic disease and especially how this burden is disproportionally distributed in society. My goal was to enable more complex interdisciplinary investigation across disciplines to foster collaborative communication, use of shared and integrated terminology, and cross-train disciplines to enable teams to generate and investigate hypotheses together. This goal required groundwork including identifying the common theme that would unite disciplines in working together. Assuming I was able to get experts from multiple and diverse disciplines to come together around the same table to address chronic disease, I wanted to co-create an agenda about what would we need to know, what would we need to do, and how would we need to do it.

To accomplish this, I took two approaches. First, I wanted to synthesize the embodiment process in a way that allows multiple disciplines to participate in integrative, interdisciplinary research. Second, I wanted to use this knowledge to act in meaningful ways to reduce the drivers of chronic disease as a means to reduce health disparities. I took a three-paper approach, presented in chapters 2-4. Chapters 2 and 3 investigate epigenetic embodiment of community-level exposures I believed were relevant to the disciplines depicted in Figure 1. Chapter 2 specifically synthesizes epigenetic embodiment of environmental toxicants across multiple types of exposures. Chapter 3 integrates three theories of stress embodiment across multiple disciplines. Chapter 4 discusses two ways I choose to act on the epigenetic drivers I identified in the first chapters. Both are types of community engagement that involved multiple communities.

Before investigating the literature relevant to the first two chapters, I had to do some background work to lay the foundation of the synthesis and integration I wanted to achieve. This groundwork included identifying the problem, the pathway, the population, the scope, and the

perspective for action. The next section describes the background work I completed and demonstrates the thinking that drives an interdisciplinarian.

The Social Determinants of Health

The increasing rates of chronic disease that are disproportionately distributed in society are a growing problem for public health.[1,2] The social determinants of health are community conditions that cause disease.[3] If we look at the drivers of health status, it is estimated that half of our health is affected by drivers not under individual control.[4] Social drivers include policies impacting community-wide poverty and local crime rates, ambient noise levels, overcrowding, location of toxic waste sites, exposure to lead and mercury, outdoor and indoor air quality, housing quality, parks and open spaces, sources of stable daycare, after school programs, transportation options, job opportunities, educational opportunities, and sources of healthy affordable foods.[5–8] In fact, it is now estimated that the primary contributors to over 70% of chronic disease are from environmental (not genetic) factors.[9]

If we think about our own families, most of us have loved ones or personal experiences with chronic disease and cancer in our recent past. We represent the greater picture of society at large which is suffering from chronic disease and cancer. In 2006, the largest drivers of medical expenses were heart disease, cancer, asthma, and mental disorders.[10] Chronic disease consumes our lives: heart disease affects one of every four people and diabetes one in seven.[11] Chronic disease also consumes our resources: 86% of our national healthcare dollars are spent on chronic disease and cancer.[11] The total cost of diagnosed diabetes was $245 billion in 2012 alone.[12] Two in five people will be diagnosed with cancer in their lifetime.[13] Mental disorders also account for a large portion of persons with chronic disease.[10] Almost 20% of the population deals with anxiety, a disorder that has an average age of onset of 11 years old.[14]

Remembering that chronic disease is not inherently genetic, in the last 4 decades, we've seen an increase in the rates of prostate cancer, breast cancer, genital tract deformities, attention deficit disorders, and reduction in sperm counts.[15] In the last three decades we've seen a doubling of rates of obesity and tripling of diabetes.[15] Granted that a portion of this increase has been from better screening and diagnosis, it is clear there are expensive environmental drivers of disease at play, and their effects are increasing. In looking for the non-genetic drivers of disease, we see a spatial segregation of housing and economic policy with health outcomes.

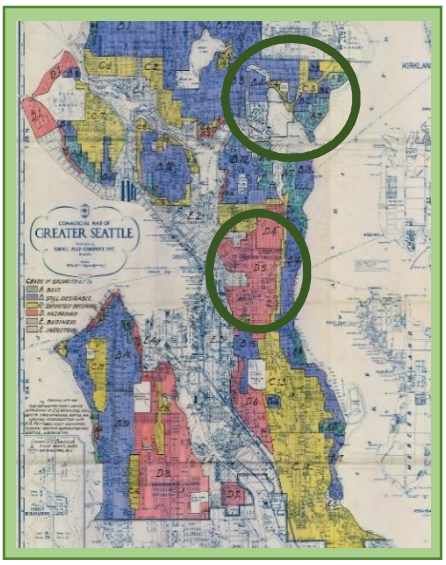


Figure 2: Map of Seattle 1936[16]; Upper circle is Northeast Neighborhood, lower circle is the Central District

For example, of the 12 neighborhood districts in Seattle, two, the Northeast Neighborhood (NE) and the Central District (CD), are just a few miles apart (Figure 2), yet the CD experiences disparities in health outcomes and resource distribution (Table 1). The CD has on average a 7-year lower life expectancy and rates of multiple chronic diseases and cancer. The CD's residents also have lower educational attainment, less household wealth, a higher population density, and

Socioeconomic Drivers	Central District	Northeast Seattle
Population 2010 (% total Seattle population)*	44,407 (7%)	67,415 (11%)
Dominant Ethnicity (White)*	55%	77%
No High School Diploma*	12%	2%
No College Degree*	47%	25%
Below 200% FPL 2012*	33%	27%
% Renters+	66%	35%
Population Density (people / sq. mile)+	13,378	6,936
Median Household Income 2011+	$47,405	$82,654
Households on Food Stamps in 12 months+	1,409 (10%)	697 (3%)
Car transportation to work+	59%	66%
Forcible Rape Counts 2014~	8	2
Robbery (All)~	142	37
Assault (All)~	658	212
Burglary (All)~	462	361
Larceny/Theft (Excluding Motor Vehicles~	2,476	833
Disease States		
Life Expectancy at Birth (years)*	78	85
Cancer (Age-adjusted per 100,000)*	210	138
Heart Disease (Age-adjusted per 100,000)*	142	105
Alzheimer's Disease (Age-adjusted per 100,000)*	53	27
Stroke (Age-adjusted per 100,000)*	45	21
Accidents (Age-adjusted per 100,000)*	40	19
Chronic Lower Respiratory Disease (Age-adjusted per 100,000)*	28	18
Diabetes Mellitus (Age-adjusted per 100,000)*	36	14
Influenza and Pneumonia (Age-adjusted per 100,000)*	16	5
Obese BMI (age 18+)	18%	10%

*Data from Public Health Seattle King County 2012 Report[8]. Rounded down for all.
+City-date for zip codes 98122 (Central) and 98115 (NE Seattle). Rounded down for all.
~Seattle City Police August 2014. Central precincts: C3, E1, E2, G2; NE precincts: U1, U3. Northeast district spans from the UW district north to 95th street and I-5 east to Lake Washington; Central District spans E Madison Ave south to S. McClellan St and a section of I-5 east to Lake Washington

Table 1: Social Determinants and Health Status in Two Neighboring Seattle Districts.

half the income of their neighbors to the north.[16–18] I chose this map from 1936 as a brief acknowledgement of the historical drivers of disparities. In the mid-20th century, the FHA home loan grading system classified the Central District as having predominantly class D rating while the Northeast District earned Class A and B status.[19,20] A significant factor in this rating system was non-white ethnicity of CD neighborhood residents. Home loan discrimination impeded family wealth and community resources needed to support education and other drivers of health.[21–25] Today, there are still ethnic differences between these districts with the Central District representing 17% more Black and twice as many Latino residents.

Embodiment

Bodies tell stories of these experiences. They bear the mark of environmental interactions.[26–28] Embodiment describes how the body incorporates the material and social world into its biology. This process explains the social patterning of disease and captures historical experiences and their implications today. As I looked closer at the relationship between the realm of complex exposures and the realm of chronic disease (Figure 3) it became clear to me that I needed to gain a better understanding of how low-dose chronic exposures were disrupting biological mechanisms in ways that activated chronic disease pathways.

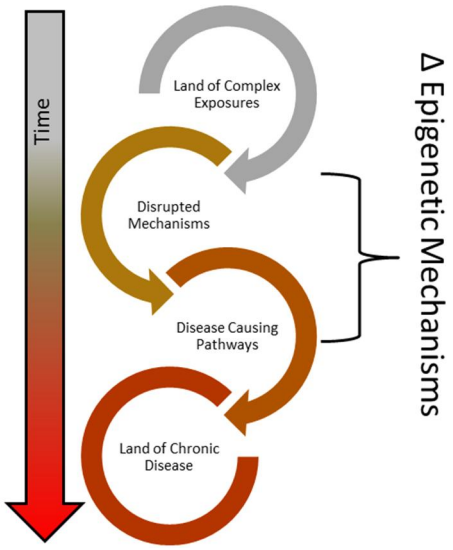


Figure 3: Path of external exposures into disease outcomes.

I believed there was strong indication that embodiment occurred to some extent through epigenetic mechanisms.[29] I suspected that embodiment, occurring through time, incorporates adverse environmental stimuli into epigenetic functioning in a manner that fosters disease etiology. Epigenetic disruption is one link between an environment of complex and chronic exposures and the outcomes of

complex and chronic.[30,31] The example from our country's recent past of use of the prescribed drug Diethylstilbestrol (DES) represents a good example of embodiment. DES impairs cellular migration during reproductive tract development in the developing child. This impairment caused irreversible changes in utero that manifest as reproductive cancers and other disease outcomes later in life (Table 2).[32] Over five million women took DES during the first trimester of their pregnancy in the mid-20th century (Figure 4 depicts how three generations can be at risk during maternal exposures).[33] In this example, the exposed fetus' body bore a mark of the maternal exposure and that mark, embodied in cellular disorganization, increased that child's risk for disease and cancer in adulthood. Thus, the environment became embodied through epigenetic dysregulation in a way that fostered chronic disease over the life span.

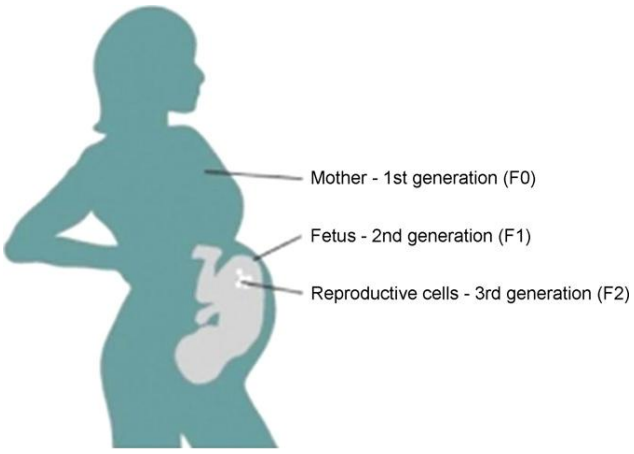


Figure 4: Maternal exposure risks health of three generations.

Risks for DES-Exposed Daughters Compared to Non-Exposed	
Outcome	**Increased Risk**
Clear-cell adenocarcinoma	40 times higher
Neonatal death	8 times higher
Pre-term delivery	4.7 times higher
Loss of 2nd-trimester pregnancy	3.8 times higher
Ectopic pregnancy	3.7 times higher
Stillbirth	2.4 times higher
Infertility	2.4 times higher
Early menopause	2.4 times higher
Cervical intraepithelial neoplasia	2.3 times higher
Breast cancer	1.8 times higher
First trimester miscarriage	1.6 times higher
Preeclampsia	1.4 times higher

Table 2: Health risks for DES exposed daughters.

The Epigenome

This next section explains the importance of the epigenome and the ways it regulates DNA, which is central to my work as these mechanisms are a unifying pathway of embodiment. The field of epigenomics is relatively new and exploding with data. My first task was to understand the functioning and mechanisms of action of the epigenome. The epigenome by definition is a collection of chemical marks and mechanisms that regulates how our genome (our DNA) functions.[34] Figure 5[35] (next page) depicts a strand of DNA (upper left), part of the genome, magnified to 10Mx. The upper right depicts

that section of DNA, such as a gene, that is being transcribed or expressed. This is where a transcription protein accesses the DNA and copies that information into a format for protein production or further gene regulation. The lower image depicts how our active DNA actually exists. There are chemical marks and proteins attached to DNA that govern its expression; this is the epigenome.

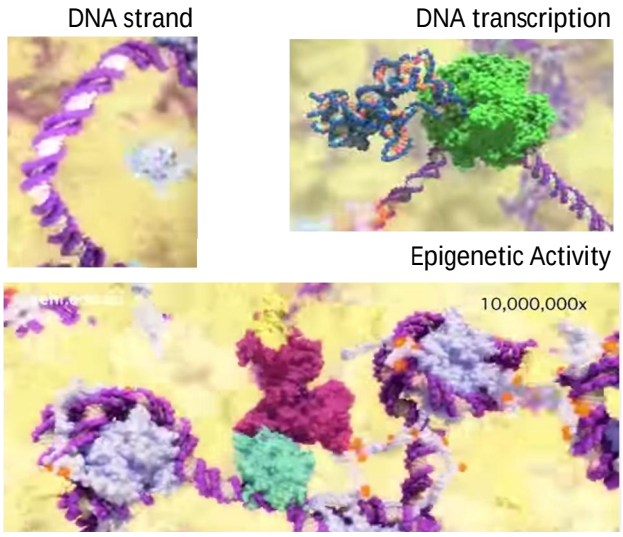


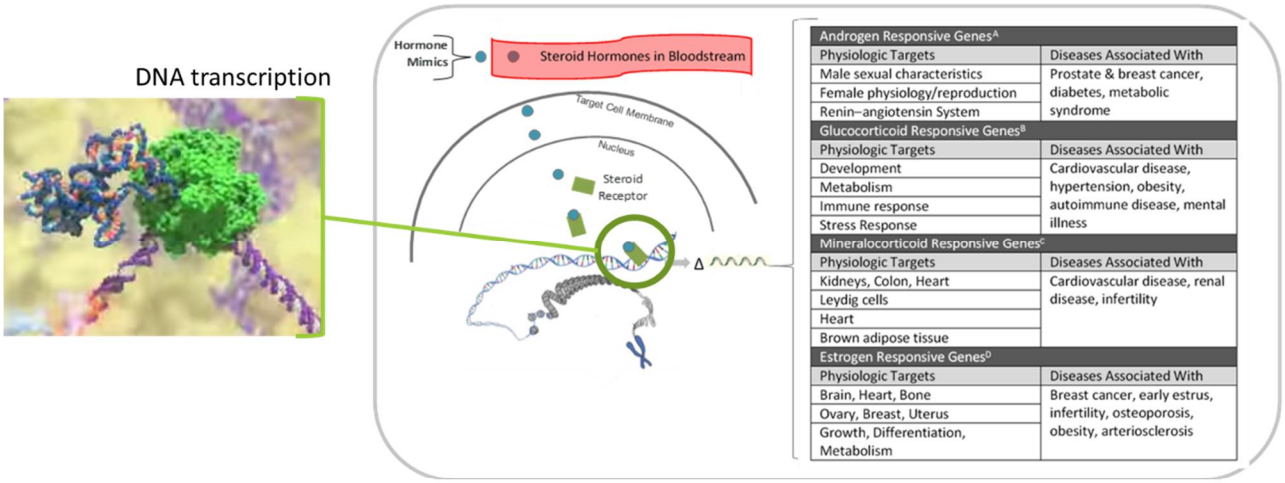
Figure 5: DNA strand, DNA transcription, and active DNA with epigenetic attachments.

It is these epigenetic mechanisms, the epigenome, that govern cell differentiation, identity, and function.[36,37] All human development begins from 1 fertilized egg which divides into a collection of 200 cell types across three trillion adult cells, all of which occurs through epigenetic regulation.[38] Thousands of genes are transcribed around the clock, but in each cell, only a fraction of genes are being expressed. All of this is governed by epigenetic activity.

There are essential features of the epigenome. The epigenome is our body's interface with the genome and is required for most life forms on earth,[36] and has to be heritable between cell divisions and between generations.[39] The accuracy of each division is dependent on the availability of metabolic precursors and enzymes.[40] Importantly, the epigenome incorporates environmental signals into its regulation.[41,42] We see high epigenetic activity during embryogenesis that directs cell differentiation through epigenetically governed developmental pathways.[43,44] Next, I will take a closer look at how external stimuli can affect epigenetic pathways.

Epigenetically-mediated Gene Expression

The epigenome can mediate gene expression such as occurs during hormonal signaling. Hormones released from one place in the body circulate through the blood stream and travel to their target cell (Figure 6). After entering the nucleus of the cell, a hormone binds to its receptor and this complex binds to a corresponding "hormone response element" preceding a target gene on the DNA. This activates gene transcription and the result is a change in protein expression that is dependent on cell type of the target tissue.[45] Through this mechanism, internally-circulating hormones such as androgens, steroids, and estrogen, or their human-made synthetic mimics, can act at low doses to stimulate a physiologic effect. Androgens affect reproductive development, glucocorticoids (such as cortisol) affect development and metabolism, and estrogens affect brain, heart, bone, and breast tissue as well as growth and metabolism. Disruption in these gene networks have been implicated in tissue specific disease. Androgen responsive genes are associated with prostate and breast cancer, and metabolic syndrome. Stress hormones stimulate pathways involved in cardiovascular disease, obesity, autoimmune disease, and infertility. Estrogen responsive genes are associated with infertility, obesity, cancer, and osteoporosis.



Androgen Responsive Genes[A]	
Physiologic Targets	Diseases Associated With
Male sexual characteristics	Prostate & breast cancer, diabetes, metabolic syndrome
Female physiology/reproduction	
Renin–angiotensin System	
Glucocorticoid Responsive Genes[B]	
Physiologic Targets	Diseases Associated With
Development	Cardiovascular disease, hypertension, obesity, autoimmune disease, mental illness
Metabolism	
Immune response	
Stress Response	
Mineralocorticoid Responsive Genes[C]	
Physiologic Targets	Diseases Associated With
Kidneys, Colon, Heart	Cardiovascular disease, renal disease, infertility
Leydig cells	
Heart	
Brown adipose tissue	
Estrogen Responsive Genes[D]	
Physiologic Targets	Diseases Associated With
Brain, Heart, Bone	Breast cancer, early estrus, infertility, osteoporosis, obesity, arteriosclerosis
Ovary, Breast, Uterus	
Growth, Differentiation, Metabolism	

Figure 6: Hormonally activated gene transcription. *Citations: A[45]; B[46]; C[47]; D[48]; DNA transcription[35]*

Epigenetically-controlled Gene Expression

Epigenetic mechanisms can control which genes are expressed or not. For example, the worker bee and the queen bee depicted in Figure 7 are genetically identical.[46] What makes a queen bee a queen is exposure to an epigenetic modifier found in royal jelly. This nutritional exposure activates the expression of queen genes whose activity is responsible for reproductive system development. At the genetic level, when a gene is available, proteins can bind with DNA and transcribe the target gene. When a chemical cap, called a methylation mark, is placed at the beginning of a gene, transcriptional proteins cannot bind and the gene remains silent. Therefore, methylation is an epigenetic mechanism for silencing genes.[47] Cancer is defined by uncontrolled growth of abnormal cells in the body and can be caused by silencing genes required for control of cell growth (tumor suppressor genes) and by activation of genes involved in cell proliferation (oncogenes).[36,42]

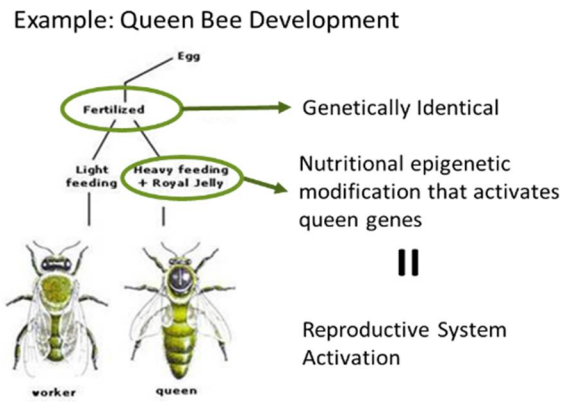


Figure 7: Epigenetic reproductive activation in queen bee.

Epigenetic Defense System

The epigenome, through these methyl marks, also provides our genome with a layer of defense against the activation of disruptive DNA elements.[42,48] Figure 8 depicts the Agouti mouse model,[47] which has become a biosensor for epigenetic activity. In this example, genetically-identical pups are born exhibiting a range of coat colors due to maternal exposure to Bisphenol A (BPA) that induces an epigenetic change that activates yellow coat expression. This activation also stimulates DNA elements responsible for obesity, diabetes, and tumorigenesis.

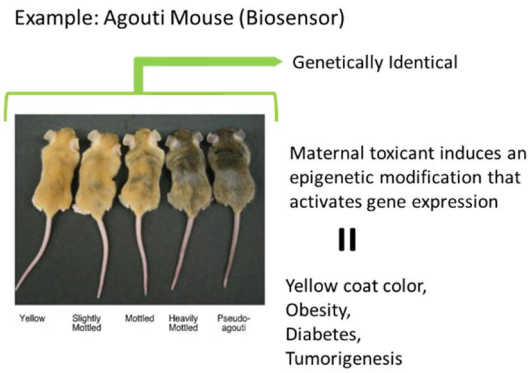


Figure 8: Agouti Mouse

Most genomes carry elements that are not used throughout the life span. These are collectively referred to as transposable elements.[48] In the Agouti mouse model, the source of increased diabetes, obesity, and tumorigenesis is from the activation of one of these elements. Usually silenced through methylation, the exposure to BPA reduces the global level of methylation, thus allowing such elements to become active and this activation results in genomic instability and mutations that increase risk for cancer.[42,49,50]

One third of the human genome consists of such elements with only about 100 that remain functional. This means that when methylation levels drop across the genome, these dormant elements become active by recruiting transcriptional proteins that make copies which then insert themselves chaotically into other regions of DNA, potentially disrupting normally-functioning genes. This insertion happens through a cut and paste mechanism that inherently damages DNA, further increasing the risk for mutation.

Epigenetic Needs: Metabolic Supply

With each cell division, the epigenome must be copied. The ability of methylation marks to silence genes, whether those genes are transposable elements, oncogenes or specific in developmental timing, is dependent on the availability of precursors and enzymes (Figure 9).[48] There is a metabolically-driven supply chain that is responsible for the creation and distribution of methyl marks. When this supply is diminished, there is a corresponding decrease in methylation that associates with an increase in cancer and developmental disorders.[40,48] This is the mechanism through which folate insufficiency increases risk for neural tube defects.

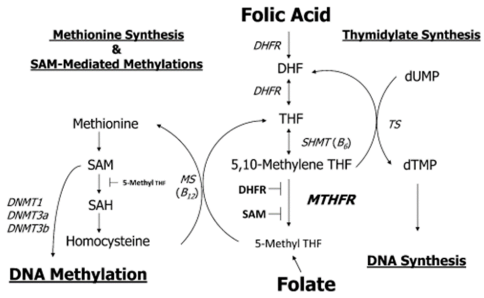


Figure 9: DNA methylation metabolic pathway.

Chromosomal Aging

Finally, epigenetic mechanisms function at scales beyond the individual gene. Chromosomal aging is one of these more complex mechanisms and is a measure of biological aging (Figure 10).[51] Cells must replicate in adulthood for maintenance and repair. With each cell division, DNA is replicated and with each replication, the DNA at the end of the chromosome shortens. Over time, these caps, called telomeres, become shortened to the point of apoptosis (programmed cell death).[52] Processes that accelerate cell divisions and therefore telomere shortening accelerate biological aging, and increase the risk for chromosomal fusion and general genomic instability that fosters cancer.[53]

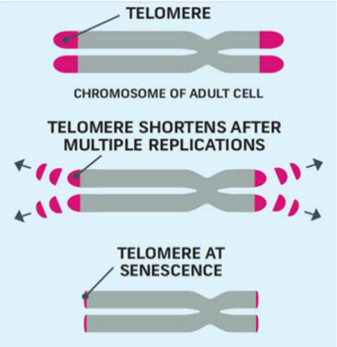


Figure 10: Chromosomal aging through telomere shortening.

Epigenetics in Disease

These examples were the first of many indicating that epigenetic modification occurs upon specific environmental exposure, and, in these examples, during specific windows of development. Since we cannot tinker with humans the way we tinker with animals, researchers turned to twin studies to explore the association of epigenetic changes and disease outcomes. Though they share 100% identical DNA, many identical twins are discordant for disease outcomes. In fact, diseases like schizophrenia and type I diabetes have a 50% discordance rate.[26] Autism is another example, with evidence suggesting that heritable factors account for 38-50% of cases,[54,55] yet identical twins often display behaviors on different ends of the spectrum. When researchers looked closer, they found epigenetic differences between the twins with the affected twin demonstrating changes in gene pathways associated with the disease outcome.[26]

Epigenetic Vulnerability: Development

Epigenetic mechanisms can be altered at any point along the life span, but disruptions during development can have more dramatic effects that persist throughout adulthood. During development,

cells undergo rapid cell division, with each division requiring a duplication of the epigenome. The availability of precursors and enzymes is critical to reducing the error rate in epigenetic replication. Early pregnancy is an important window for establishing epigenetic profiles across differentiating cells.[42,56] This period is especially vulnerable to external stimulation, particularly to hormone mimics.[29] During childhood, children are at risk for a higher body burden from environmental exposures than adults as they have faster breathing rates, and ingest more food and water for their body size as compared to adults.

Community-level Problems

Public health has made significant advances in changing personal behaviors through awareness and intervention campaigns that have reduced smoking, drunk driving, and maternal drinking during pregnancy. Yet despite these efforts, rates of chronic disease outcomes are still on the rise. Advances in technology and research suggest that broad environmental exposures can be drivers of epigenetic disruption that lead to chronic disease when they are experienced chronically at low doses. My understanding of epigenetics suggests that to reduce chronic disease, we in public health must act on community-wide exposures. We should focus on broader exposures that are insidious, relentless, and unavoidable on an individual level.

Interventions at this level are particularly important from the perspective of health equity which aims to secure equal access and opportunities for wealth, status, resources, and other relevant health opportunities. In order to reduce health disparities, we will have to focus on exposures that are disproportionately distributed in society.

Riskscapes

To capture the epigenetic risks in a location we must look at the overlapping risks to health from the physical and social environment – referred to as a riskscape, or a landscape of risks.[57] A simple

example is the riskscape of a child whose parent is a farmworker and lacking childcare, brings his daughter into the fields where pesticides are used. Assessing riskscapes includes understanding the risk from interactions of these exposures, and I argue, how they act on the epigenome. To have any true predictive power, we must capture the environmental stimuli acting across riskscapes that affect biological function, referred to as the exposome.[58] Accurate measurement of the exposome is a daunting task, and will take a great deal of interdisciplinary collaboration because overlapping hazards must be assessed in the aggregate. The exposome includes not only environmental toxicants but also the risks that social stresses place on the body.

Overview of Dissertation Chapters

I develop each of these themes in greater detail in the following chapters. Chapter 2 focuses on the broad spectrum of environmental pollutants and contaminants known to disrupt epigenetic mechanisms in a manner that fosters disease pathology. The ability of low dose, community-level chemical exposures to active epigenetically are not typically categorized collectively. This separation causes patchwork assessment and regulation that has the potential to significantly exacerbate health disparities now and debilitate the healthy genomic function of future generations. This chapter argues for a comprehensive category of "epigenetic disruptors" and examines the values underlying ecologic policies. The goals of this chapter are to: (1) identify epigenetically-active toxicants relevant to human exposure and disease outcomes; (2) understand the epigenetic mechanisms involved in embodiment of these toxicants; (3) demonstrate the range of epigenetic assault across the identified exposures; (4) understand the barriers to reducing exposures; and (5) make recommendations based on these findings. I identified four broad groups of chemicals: air pollution, endocrine disrupting chemicals, heavy metals, and persistent organic pollutants, as examples of human-created environmental toxicants that are known to induce chronic disease, circulate in daily exposures, and act through epigenetic mechanisms. I further identified the range of epigenetic changes known in humans to result from these four exposure

groups. The intended purpose of this work is to provide public health professionals with epigenetic evidence and sound arguments reflecting the ecologic nature of our community environments. This is to enable the advocacy of a precautionary approach in chemical policy to protect children's health.

Chapter 3 focuses on the transactional natures of stressful interactions by drawing upon and integrating concepts from three theories of stress: the transactional model of stress,[59–61] the theory of allostasis,[62,63] and the adaptive calibration model.[64] Put together, these theories can help social and biological sciences researchers work together to understand and map the pathways to embodiment from initial appraisal to disease outcomes, with particular attention paid to the features of adversity that stimulate the stress response and the epigenetic mechanisms involved in embodiment.

The goal of this chapter is to answer three questions. First, what are the features of a stressful environment that provoke a stress response? Second, what happens biologically during a response? Third, how does the stress response foster chronic disease and mental instability; in other words, how is it embodied? In answering these questions, I discuss the concept of stress biasing during development and the impact this biasing has on the health outcomes of developing children. My goal for this chapter is to facilitate interdisciplinary interventions and affect policy on the social drivers that foster chronic disease through embodiment.

Chapter 4 articulates the need for community engagement to shift policies affecting health equity through two case examples. The first case of community engagement describes the process used to create an educational video as an outreach tool designed to increase genetic and environmental health literacy. The second case study explores community engagement through teaching community organizing and advocacy skills to health sciences students and exercising these skills with community members. By organizing health sciences students through experiential learning opportunities on community campaigns, local policy affecting the social determinants of health can be altered to mitigate the stress response pathway detailed in chapter 3. This case study explores how health sciences

students can use the skills of building and exercising institutional power to live out their community values during their professional lives.

I conclude the dissertation with a chapter that explores the policy and practice implications of environmental embodiment and makes recommendations for moving the work forward. Collectively, my dissertation work provides a holistic perspective on how community-level exposures become embodied through epigenetic change to cause or support poor health outcomes, especially in children. The overarching goal is to foster interdisciplinary work to support social changes in favor of health equity by identifying the drivers responsible for embodiment, providing perspective on the scale of overlap in epigenetic action these factors have, especially for developing young, and foster the imagination and skills of public health professionals to incorporate this knowledge into their work.

Chapter Two: Epigenetic Toxicity and Social Responsibility

Introduction

Public health is facing rising rates of chronic disease. In 40 years the diagnoses of prostate cancer have increased by 57%, breast cancer by 40%, penile deformities by 85%, while average sperm count has decreased by 30%.[15] In just 30 years we've seen a doubling of obesity rates and a tripling of diabetes.[15] While better screening and early detection have likely added to this increase, there is a strong indication that community-wide environmental contamination is driving chronic disease outcomes.[15,65–67] Further genetic research estimates that well over 70% of chronic disease is from environmental factors[9] and not a result of inborn genetic errors.[67–69]

Our daily living environments are flush with synthetic chemicals, many of recent human creation. Of the 7 million registered chemicals in existence, about 80,000 are in common use, and almost 3,000 are produced at quantities greater than 1 million pounds annually.[70] Of those in high production, 43% do not have toxicity or safety screening data, 50% have incomplete data, and the remaining 7% that have complete screening data do not meet the data requirements for restricting use. Through daily low dose exposures, chemicals can enter the bodies of young women and pregnant mothers. Chemicals found traveling in the human body including DDT, PCBs, organochloride pesticides, polybrominated diphenyl ethers, phthalates, endocrine disruptors and polycyclic aromatic hydrocarbons.[69,71–76] Nationally, phthalates are found in higher concentrations in children than adults[77] and brominated flame retardants have been found in toddler excrement.[78] There is mounting evidence that these pollutants can disrupt the delicate developmental processes active during pregnancy in ways that increase disease rates later in life.[43,66,75,79,80]

The EPA requires limited, if any, safety data on individual chemicals yet is tasked with understanding the collective impact these chemicals have on health.[70,81] Since the U.S. requires little to

no safety testing for the majority of widely-used chemicals, there is a deficit of information about the health risk that daily low-dose chemical exposures pose, and regulators have been slow to respond.[82,83] Researchers at institutions around the world have been investigating health risks using community-wide epidemiology studies and state of the art animal modeling. As I describe in this chapter, new advances in molecular technology allow researchers to explore how chemical exposures disrupt our genetic processes.

Genetic disruption can occur in more ways than direct mutation (i.e., through radiation). Epigenetic disruption occurs when the regulation of DNA is altered in ways that disturb normal cellular processes. Epigenetic disruption is a hallmark of cancer.[84] This makes a chemical's ability to be epigenetically disruptive important for risk assessment and merits further investigation. I surveyed the literature for evidence of epigenetic disruption across a wide range of everyday chemicals present in the daily environments of pregnant women and found evidence for alarm. I then assessed the value systems and policy needs that allow these threats to remain in the environment. My goal is to both bring attention to the potential for a broad range of chemicals to adversely affect epigenetic processes in ways that deteriorate health and to increase political pressure for chemical testing and stronger regulation. My roadmap for this chapter is depicted in Table 1.

First, I describe the concept of embodiment that serves as a lens for this work (Section 1). I briefly review the epigenome and its relationship to disease (Section 2). Next, I synthesize our targeted literature review of human exposures associated with epigenetic disruption (Section 3). This analysis established the basis for concern that everyday chemicals may be a collective

Roadmap for Chapter
How does chronic toxicant exposure threaten health?
Section 1: Embodiment
Section 2: Epigenetic mechanisms in disease
Section 3: Epigenetic disruptors
Section 4: Exposure sources for pregnant women
Section 5: Assumptions of values in current policy
Section 6: Recommendations for epigenetic disruptors

Table 3: Topic roadmap for Chapter 2.

threat to human epigenetic function. I identify the community-wide risk landscape for these exposures groups (Section 4). I then explore the values underlying assumptions in chemical regulations that allow current exposures to exist (Section 5). Finally, I make recommendations for public health and policy makers to consider (Section 6). To understand why I place an emphasis on epigenetic disruption, I review the concept of embodiment.

1. Embodiment

Embodiment describes the process by which external environmental exposures can stimulate physiologic reactions; it captures how the body incorporates the material and social world into its biology.[27,28,85] Bodies tell stories of their experiences; they bear the mark of environmental interactions that we can now measure in more detail.[26,30] As environmental chemicals become embodied, they can disrupt biological processes such as tissue formation and maintenance[29,36,42,86] to activate the disease causing pathways[31,47,63,87] that foster disease.[69,88,89] Though they can disrupt health through many routes, epigenetic disruption appears to be a common feature of embodiment (Figure 1).[30,42,63,90]

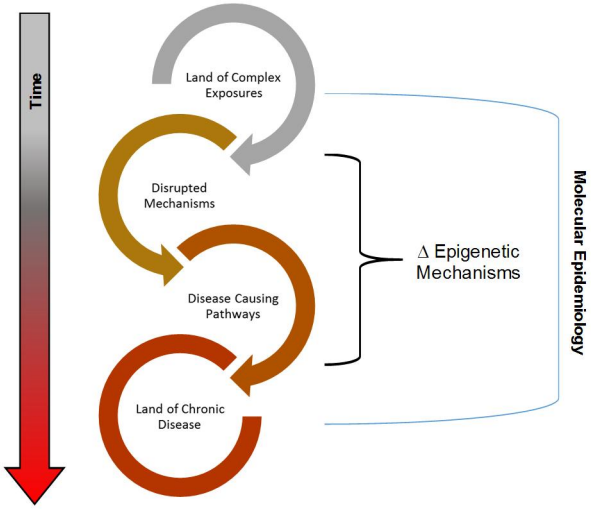


Figure 11: Epigenetically mediated embodiment. Environments with complex chemical exposures are suspected to act on the human body to cause pre-disease states. Through time these states can manifest as chronic disease and cancer.

Examples of epigenetic embodiment are in our nation's past. During the mid-20th century over 5 million women took the prescribed drug Diethylstilbestrol (DES) during their first trimester of pregnancy. Children exposed in utero, especially daughters, were found to have significantly higher rates of negative health outcomes (Table 2 next page).[32] In the 1990's, using new technology, researchers found

DES worked through epigenetic mechanisms to change gene expression of signaling (*WNT7A* family) and regulatory (*HOXA10*) genes.[29,91] Drug exposure during the window of reproductive system development impaired cell's ability to migrate and communicate. Decades later, the disorganization manifested as cancer and disease once the reproductive system was activated in adulthood. In this example, the bodies of those exposed bear a physiologic mark of their exposure, embodied as cellular disorganization, that negatively affected their adult risk for disease.

Manipulating the epigenome for study is unethical in humans, so the epigenetic research community must rely heavily on animal models to explain causal relationships. These models complement human association studies since evolutionary theory validates the use of animal models to explain human mechanisms.[92–94] Recently, molecular technology has enhanced our ability to explore the epigenetic mediation in the exposure-disease trends we see in human populations.[30,43,50,87,95,96] Next I describe the epigenome, important epigenetic mechanisms for chemical induced disease, and epigenetic vulnerability during development.

Risks for DES-Exposed Daughters Compared to Non-Exposed	
Outcome	**Increased Risk**
Clear-cell adenocarcinoma	40 times higher
Neonatal death	8 times higher
Pre-term delivery	4.7 times higher
Loss of 2nd-trimester pregnancy	3.8 times higher
Ectopic pregnancy	3.7 times higher
Stillbirth	2.4 times higher
Infertility	2.4 times higher
Early menopause	2.4 times higher
Cervical intraepithelial neoplasia	2.3 times higher
Breast cancer	1.8 times higher
First trimester miscarriage	1.6 times higher
Preeclampsia	1.4 times higher

Table 4: Disease risk for women who were exposed to DES in utero as compared with unexposed women. [40]

2. Epigenetics and Disease

The Epigenome

In the cell, DNA is attached to chemical marks and proteins (see Chapter 1 for more detail). By definition, the epigenome is this collection of marks and their regulatory mechanisms that control how our genome (DNA) functions.[34,94] There are essential features of the epigenome. First, the epigenome regulates cell differentiation which enables most life forms on earth to use their genomes. Epigenetic

mechanisms govern cell differentiation, cell identity, and function.[36,37,84] Thousands of genes are transcribed around the clock, but in each cell, only a fraction of genes are expressed. The development of one fertilized egg into a collection of 200 cell types across 3+ trillion adult cells happens through epigenetic regulation.[38] Second, the entire epigenome must be reliably replicated between cell divisions and between generations[39,48] otherwise disease ensues. The accuracy of each division is dependent on the availability of substrates and enzymes to build each new copy of the epigenome.[40] Third, the epigenome incorporates environmental information into developmental programming.[41,86] In utero, the body is setting metabolic, immune, and hormonal baselines in reference to the perceived environment.[43,44,67,79,92] By responding to environmental cues, the epigenome allows for diverse and complex phenotypes to develop from the same common static genotype.[97,98] During the first trimester of human development, the epigenome is in a state of maximal plasticity.[44] Its pliability during development makes the epigenome more responsive to environmental inputs[42,56] and therefore more vulnerable to environmentally-induced disruption.[43,44,97]

Epigenetic mechanisms have been directly implicated in multiple disease pathways. Numerous human studies find epigenetic disruption in most cancers, allergic reactions, cardiovascular disease, asthma, and neurological disorders.[26,42,67,87] Next I describe the epigenetic mechanisms that are disrupted to create disease pathways.

The Epigenome in Human Disease

To understand the relationship between epigenetic disruption and disease, researchers turned to human twin studies. Though they share 100% identical DNA, many identical twins do not develop the same diseases. In fact, diseases like schizophrenia and Type I Diabetes have a 50% discordance rate.[26] While autism is highly heritable, identical twins often display behaviors on different ends of the spectrum. When researchers looked closer, they found epigenetic differences between twins, with the affected twin demonstrating changes in gene pathways known to associate with the disease outcome

(Table 3). The animal studies detailing such epigenetic pathways have evolved into drug targets. The FDA approved the first epigenetic drug in 2004 and has approved human trials for numerous drugs, all designed to alter the epigenome in ways to restore cells to pre-disease states, especially in a range of cancers.[56,99] These drugs are reported to show promise, especially when used in combinations with each other or as a complement to existing therapies.

Twin Disease (Discordance)	Epigenetic Mechanism	Epigenetic Changes (Human Genes)
Systemic Lupus (low)	Δ Methylation; Δ Expression	49 DMR; (*IFNGR2)*
Type 1 Diabetes (50%)	Δ Methylation; Δ Expression	132 DMR; *(HLA-DQB1)*
Autism Spectrum (10%)	Δ Methylation; Δ Expression	Loss Imprinting; Serotonin Transporter; *(BCL-2, RORA)*
Schizophrenia (50%)	Δ Methylation; Δ Expression	*(OxIt, SMUGIt*, *GGN, T6GALNAC1)*
Cancer (30%)*	Δ Methylation; Δ Expression	Tumor Suppressor/Oncogenes Transposable Elements

Table 5: Genes with epigenetic changes in twin discordant for disease. [26]
**Heritability estimate.*

Next I briefly discuss the relevant mechanisms that become disrupted with chemical exposures. They are more thoroughly discussed in Chapter 1.

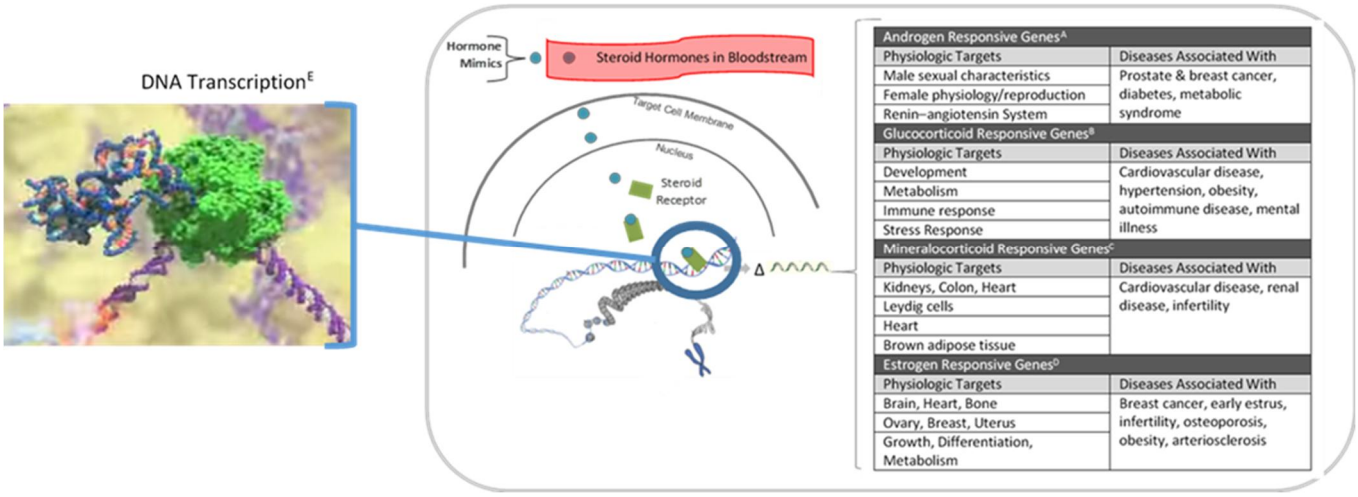
Epigenetic Mechanisms

Epigenetic mechanisms are complex and far from being fully cataloged and understood. There are, however, three well-studied types of epigenetic alterations I found relevant for our assessment of chemical embodiment. I organize these actions into 1) epigenetically-mediated gene expression, 2) epigenetically-controlled gene expression, and 3) the metabolic supply chain that fuels epigenetic activity and replication. Next I briefly describe each of these in order and rely on Chapter 1 for a complete description.

Epigenetic Mediation

The epigenome can mediate gene expression during hormonal signaling. Hormones released from one organ in the body circulate through the blood stream to their target cell.[100] They migrate to the cell nucleus where the DNA is stored and bind to their receptor. This complex binds to a

corresponding “hormone response element” preceding a target gene on the DNA strand.[45] The complex becomes an epigenetic mark that activates gene transcription to change protein production in cell specific ways.



Androgen Responsive Genes[A]	
Physiologic Targets	Diseases Associated With
Male sexual characteristics	Prostate & breast cancer, diabetes, metabolic syndrome
Female physiology/reproduction	
Renin–angiotensin System	
Glucocorticoid Responsive Genes[B]	
Physiologic Targets	Diseases Associated With
Development	Cardiovascular disease, hypertension, obesity, autoimmune disease, mental illness
Metabolism	
Immune response	
Stress Response	
Mineralocorticoid Responsive Genes[C]	
Physiologic Targets	Diseases Associated With
Kidneys, Colon, Heart	Cardiovascular disease, renal disease, infertility
Leydig cells	
Heart	
Brown adipose tissue	
Estrogen Responsive Genes[D]	
Physiologic Targets	Diseases Associated With
Brain, Heart, Bone	Breast cancer, early estrus, infertility, osteoporosis, obesity, arteriosclerosis
Ovary, Breast, Uterus	
Growth, Differentiation, Metabolism	

Figure 12: Epigenetic mediation of hormonally-stimulated gene expression. Citations: A[61,62]; B[63]; C[60]; D[64], E[65]

Androgens stimulate gene expression in reproductive development, glucocorticoids (such as cortisol) stimulate genes involved in development and metabolism, estrogens stimulate genes in the brain, heart, bone, and breast tissue and affect metabolism (Figure 2). Through this mediation, androgens, steroids, estrogens, or their mimics, can act at low doses to stimulate a physiologic effect.[92] Disruptive expression of androgen-responsive genes are associated with prostate and breast cancer, and metabolic syndrome; stress hormones with cardiovascular disease, obesity, autoimmune disease, and infertility; and estrogen-responsive genes are dysregulated in infertility, obesity, cancer, and osteoporosis (Figure 2).

Epigenetic Control

Epigenetic mechanisms do more than mediation, they can directly control if genes are being expressed or silenced. When a gene is available, proteins can bind with DNA and transcribe the target gene. When a molecular cap, a methylation mark, is placed at the beginning of a gene, transcriptional proteins cannot bind and the gene remains silent.[101] In carcinogenesis, oncogenes are unmethylated

(activated) and tumor suppressor genes are methylated (silenced). This results in unregulated cell growth and formation of cancer.[36,42,102] Therefore, methylation is an epigenetic mechanism for controlling gene expression (see queen bee development in Chapter 1).

Epigenetic Defense

Methyl marks do more than regulate if a gene is on or off. They collectively provide our genome a layer of defense against the activation of disruptive DNA elements.[49,103] Primate genomes carry old DNA elements not used through the life span. These are collectively referred to as transposable elements and are heavily silenced by methylation.[104]

In the human, a third of our genome consists of transposable elements.[105] While most have lost function, about 100 elements are still capable of being expressed.[48] When the levels of protective methyl caps drop across the genome, these elements begin making copies. These copies can insert themselves chaotically into other regions of DNA potentially disabling working genes.[42,50] This destabilizes the genome and supports carcinogenesis.[42,49,105] Additionally, the DNA strand is broken in the process, also increasing the risk for genetic mutation at that site. Measuring the total level of methylation across the genome (usually in blood cells) is a proxy for this activity, and can inform risk estimates and cancer staging during treatment assessment.[42,106]

Figure 13: Agouti mouse, a biosensor for transposable elements. Mice are genetically identical.

The Agouti mouse model has become a biosensor for this epigenetic mechanism. In Figure 3, genetically identical pups are exposed in utero to Bisphenol A (BPA), a common estrogen mimic found in food can linings and water bottles.[107] BPA interferes with the methylation of transposable elements in utero. More-exposed offspring were born with lower total methylation levels. The decrease in methylation increased the expression of the gene for yellow coat color and the transposable element responsible for obesity, diabetes, and tumorigenesis (yellow mouse in Figure 3).[47]

Epigenetic Metabolic Supply

With each cell division, all methylation marks in the epigenome must be copied onto the newly created DNA. The ability of methylation marks to silence genes, whether those genes are transposable elements, oncogenes, or specific to developmental timing, is dependent on the availability of methyl donors and enzymes.[42,44,48] There is a metabolically-driven supply chain responsible for the creation and distribution of methyl marks. When this supply is diminished, there is a decrease in methylation that is associated with an increase in cancer and developmental disorders.[44,49] Through this mechanism, folate insufficiency early in pregnancy increases the risk for neural tube defects.[40]

3. Epigenetic Disruptors: Synthesis of the Literature

I sought to identify the toxicants of interest, understand their causal pathways, demonstrate a collective threat, understand the barriers for regulation and public health, and make recommendations to mitigate this risk.

Methods

I surveyed the literature for human and animal examples of epigenetic alterations associated with a broad range of exposures. I used this scope to further examine the relationship between epigenetics and human disease in the context of the exposure-disease pathway. I relied on additional literature to answer questions specific to exposures, disease outcomes, and epigenetic mechanisms. Lastly, I explored literature relevant to ecosystem policy or policy on the exposures of interest. This interdisciplinary investigation resulted in analysis of 122 articles, as depicted in Figure 4.

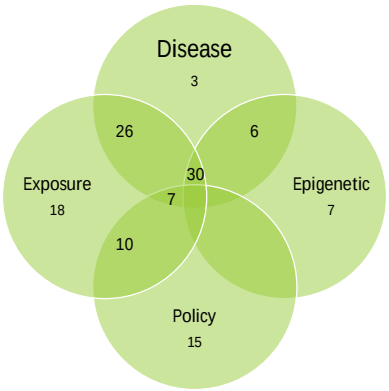


Figure 14: Interdisciplinary investigation for this Chapter

When I surveyed the human examples of exposures associated with epigenetic disruption, I found examples across four chemical groups: air pollution, endocrine disrupting chemicals (EDCs), heavy metals, and several persistent organic pollutants (POPs) (Table 4).

Chemical Exposure Groups of Interest			
Air Pollution	EDCs	Heavy Metals	POPs
Black Carbon (BC)	Pesticides	Mercury	Organochloride Pesticides
Sulfates	Flame Retardants	Lead	PCBs
Polycyclic Aromatic Hydrocarbons (PAH)	Phthalates	Cadmium	Furans
Particulate Matter 10 (PM_{10})	Surfactants	Arsenic	Dioxins
Particulate Matter 2.5 ($PM_{2.5}$)	Bisphenol A		Polybrominated diphenyl ethers
Cadmium			Polychlorinated Biphenyls
Benzene			

Table 6: Exposure groups explored for epigenetic disruption.

I assessed the ability of chemicals in these exposure groups to change the three epigenetic mechanisms discussed above: gene expression, defense against transposable elements, and reduction to metabolic supply. The findings are summarized in Table 5 with highlights for each group listed below.

Evidence for Epigenetic Disruption

Air Pollution

Air pollution is a complex mix of toxicants and has become a major public health concern.[108,109] Composed of black carbon (BC), sulfates, particulate matter, and polycyclic aromatic hydrocarbons (PAHs), air pollution is known to negatively affect health across the life span.[30,44,50,87,96,108,110,111]

Epigenetic Mediated Dysfunction				
	Air Pollution	EDCs	Heavy Metals	POPs
Gene expression	X	X	X	X
Transposable Elements	X		X	X
Metabolic Supply	X	X		

Table 7: Evidence for epigenetic disruption.

In my review, air pollution was found to alter gene expression[30,44,87,110] especially in inflammatory pathways, decrease protection against transposable elements,[30,50] disrupt the metabolic supply needed for epigenetic replication,[87] and advance

chromosomal aging (described earlier in Chapter 1).[96] These disruptions increased the risk for cardiopulmonary diseases, cancer, asthma, neurological disease, and early aging.[44]

Polycyclic aromatic hydrocarbon (PAH) exposure altered the methylation status in many genes causing a disruption in their expression. Of the 30 genes found differentially-methylated with PAH exposure, the *ACSL* and *IFNG* genes were affected. Non-human studies demonstrate that disruption in these genes fosters asthma development.[44]

Human studies demonstrate that black carbon and $PM_{2.5}$ are associated with hyperhomocysteinemia, a state of low methyl-donor availability[50] that can disrupt epigenetic replication and gene expression. Cadmium, a component of particulate matter, can interfere with enzymes that add methyl groups during normal cell cycle processes.[87]

Children exposed to air pollution had significantly lower levels of total methylation in the DNA of cord blood collected at birth and in cells collected at age 3.[44] Black carbon, indicative of traffic particulate, also reduces methylation in adults with high exposure.[50] In humans, benzene, a known carcinogen found in motor vehicle exhaust,[112] can decrease the expression of specific genes while also increasing the activity of transposable elements.[42] These findings are especially concerning from an environmental justice perspective since people of low socioeconomic status and people of color experience disproportionately higher levels of air pollution.[113–115]

Endocrine Disrupting Chemicals (EDCs)

Endocrine disruptors (EDs) are exogenous chemicals that interfere with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body.[66,116] Human epidemiology and detailed animal studies have identified causal links between environmentally relevant doses of EDCs and poor birth outcomes,[42,56,92,117] reproductive alterations and disease,[117–119] abnormal behaviors,[80] childhood chronic disesase,[43,44] immune dysregulation,[92] cell proliferation and death,[92] and

metabolic disorder.[44,97,118] Acting through the pathway depicted in Figure 2 above, endocrine disrupting chemicals mimic natural hormones and can inadvertently stimulate hormonal pathways at inappropriate times.[43,120,121] My review found that prenatal exposure to EDCs can permanently disrupt gene expression during organ development[44] and during critical developmental windows.[90,117] Prenatal exposure can alter hormonal signaling pathways[44,92,118] in ways that persist into adulthood.[43]

There are several phthalates that have been implicated in "phthalate syndrome," which is measured by a shorter ano-genital distance and incomplete testicular descent. This syndrome occurs in the population at levels consistent with the maternal phthalate body burden.[75] When females are exposed to dibutyl phthalate (DBP), a common plasticizer, between pregnancy weeks 7 through 15, the activity of several networks responsible for male reproduction development are disrupted. DBP interferes with *INSL3* production and this disrupts the full descent of the testis (cryptorchidism). DBP affects testosterone levels in Leydig cells and this disruption leads to malformation in duct tubing.[122] Phthalate syndrome is also known to interfere with gene networks responsible for proper prostate formation and sperm production.

In human studies of children and their mothers, first trimester exposure to the phthalate DEHP was directly associated with a 4-5% change in ano-genital distance.[123] In girls, phthalate exposure is associated with precocious puberty and early breast development (thelarche) and alterations in vaginal development and uterine size.[118] Animal models demonstrate that DEHP can alter gene expression in several ways. DEHP can stimulate receptors in cells involved in sperm development[45] and disrupt the production of testosterone leading to infertility.[15] DEHP exposure in utero altered the methylation of two critical imprinting genes, insulin-like growth factor 2 receptor (*Igf2r*) and the paternally-expressed gene 3 (*Peg3*) to affect oocyte development.[117] DEHP can disrupt methylation of *Lhx8* gene, interfering with folliculogenesis.[117] DEHP can disrupt androgen induced testes formation by altering methylation of the mineralocorticoid receptor gene (Figure 2), a steroid receptor widely distributed in the body.[44,45]

Further, specific phthalates can change methylation of the estrogen receptors. Estrogen receptors are part of a complex signaling system and are expressed in different quantities in different cell types depending on organ needs.[92] By altering the level of receptors available in this hormone-signaling pathway, phthalates can disrupt signaling networks across the life span.

Phthalates are suspected obesogens, which can alter fat cell development and lipid metabolism by binding to peroxisome proliferator-activated receptors.[124] By stimulating these receptors, signaling during metabolic development is disrupted. A recent cohort study of over 1,237 women and their children demonstrated that phthalates are circulating in 1st trimester maternal blood and cord blood at birth. Both contained the phthalate metabolites MEP, MBP, MBzP, and MCPP. High MCPP exposure in utero was associated with a higher odds (3.5x) of raised leptin levels, a marker of disrupted metabolic function.[124]

Brominated flame retardants (BFRs) are found in many of our everyday household products (i.e., foam cushions, electronics, clothing, and building materials) and our bodies.[73,78,125,126] When humans and animals ingest or absorb these compounds, they must be detoxified. Detoxification of BFRs requires substrates that are also used in DNA methylation, creating a demand on the epigenome's metabolic pathway.[37] Some BFRs can change gene expression in utero to disrupt fat cell differentiation.[127]

Heavy Metals

Environmental metal contamination has many sources including fluorescent lamps,[128] wood preservatives,[90] brake pads,[129] air pollution,[130] leaded gasoline,[130] contaminated children's products,[130] and industrial waste.[131] Metals may accumulate in the placenta[44] and are correlated with poor birth outcomes including higher infant death, lower birth weight, and developmental abnormalities, as well as various cancers, mild retardation, and neurodegenerative outcomes.[42,44,132] There are many ways metals can disrupt the body to foster disease.

Epigenetically, metals can disrupt fetal epigenomes.[42,44] Animal models demonstrate how methylmercury changes expression of the *Bdnf* gene in the hippocampus of the brain, an important factor for behavioral learning.[44] Arsenic-increased methylation of *TP53* (p53*)* and *CDKN2A* (p16*)* has been found in cord blood and mothers, effectively silencing these tumor-suppressor genes.[44] In cell models, arsenic inhibits methylation by impeding the availability of methyl donors, risking the activation of transposable elements.[30] Cadmium can alter gene-specific methylation patterns similar to those in lung cancer.[42]

Exposure to heavy metals (i.e., arsenic, mercury, copper, iron, aluminum, nickel, and cadmium) also inhibit DNA repair mechanisms.[133] This makes metal exposure a double threat to chromosomal health since metals both foster the activation of transposable elements and inhibit repair of their damage.[133] This increases genomic instability, increasing the risk of cancerous growth.[42,133]

Persistent Organic Pollutants

Persistent organic pollutants (POPs) include organochloride pesticides (i.e., DDT), polycyclic aromatic hydrocarbons (PAHs), brominated flame retardants (i.e., PBDEs), dioxins, furans, and polychlorinated biphenyls.[134,135] They travel the globe[90,92] with some bioaccumulating through the food chain,[74,136] crossing the mammalian placenta,[44] contaminating mammalian breast milk,[73,74,137] or circulating in fetal environments.[134] POPs exposure is associated with cognitive and developmental disabilities in separate cohorts of children,[79,89,138] can disrupt fetal growth,[139] and impair adult sperm.[44,140] Animal models demonstrate several POPs-induced disorders including altered sexual differentiation, kidney function, and infertility pathologies.[42,44] The range of chemicals categorized into persistent organic pollutants have differing effects on the epigenome.

POPs generally disrupt methylation marks on genes in disease pathways indicative of cancer formation,[42] especially in blood-forming tissue,[30] autoimmune disorders, and reproductive disorders.[44,90,92,118,141,142] They disrupt estrogen-responsive gene expression to affect estrogen signaling

pathways,[43] alter imprinted gene expression,[43] and disrupt epigenome regulation.[141,142] This disrupts a range of gene expression in cardiac,[43] ovarian,[43] sperm, skeletal, and liver tissue.[42,43,79,118] Changes in these methylation patterns support the development of tumors and malignancies that increase for non-Hodgkin's lymphoma.[142] Methoxychlor can disrupt expression of the estrogen receptor gene and DNMT3b, an important methylating enzyme.[43] DDT metabolites in Belgian girls were associated with early onset of puberty. This is believed to result from DDT's properties as an endocrine disruptor, effecting estrogen signaling in gonadal development.[118] DEET, DDT, and hydrocarbon mixture (jet fuel JP-8) are known to change the sperm epigenome after fetal exposure.[79,143]

Animal models prove PCB and pesticide exposures decrease methyl donor availability and methylation enzyme levels.[141,142] In humans, persistent organic pollutants are also associated with less methylation protection against transposable elements, which increases the risk of cancer in blood-forming tissues.[30] High levels of DDT, DDE, oxychlordane, mirex, and several PCBs were found in the plasma of Greenland's Inuit community and were directly associated with a reduction in total methylation.[136] It was suspected that DNA methylation was inhibited by the creation of reactive oxygen species,[30] a known factor for genome instability and driver of carcinogensis.[90]

In-utero and life course exposures to perfluorooctane sulfonate (PFOS), an extremely persistent chemical that has been used widely over the last 50 years,[144] can disrupt DNA methylation of specific genes and of repetitive elements to foster cancer.[42] Dioxin can disrupt the expression of cardiac genes, genes in sperm, skeletal muscle and liver tissue, and alter the expression of epidermal growth factor receptors in developing animal models.[43] Permethrin and vinclozolin alter gene specific methylation patters.[43] Vinclozolin, a common fungicide, was found in umbilical cord blood from growth restricted newborns in a rural cohort.[44] This pesticide binds to androgen receptors and disrupts sexual differentiation. Animal models show vinclozolin induces disease between generations through epigenetic transmission. In part by altering methylation of important imprinted genes, vinclozolin can

disrupt spermatogenesis indicative of infertility pathologies, disrupt reproductive function indicative of polycystic ovarian syndrome, and impact kidney development.[44] In animal models, methoxychlor (an alternative to DDT) exposure during development can silence the estrogen receptor beta (*ER-β*) gene leading to adult ovarian dysfunction,[43] changes in sexual behaviors,[118] and abnormalities in vaginal development.[118] Further, POPs increase the oxidative stress a cell experiences.[30] Oxidative stress is a direct pathway to epigenetic dysregulation and a known driving factor in genome instability that accompanies carcinogensis.[90]

After assessing the biological effects of chemicals in these four groups, I believe there is a realistic potential for a wide range of everyday chemicals to act negatively in the body, especially in utero through epigenetic disruption.[56,67] Regardless of their source, route of exposure, or complex internal stimulation, ultimately, it is the internal burden that must be assessed for risk. Only through understanding the totality of exposures, called the exposome, will our assessments have predictive value.[9,145] Researcher are shifting focus to better understand the exposome.[145] Instead of assessing exposures in isolation, investigation includes multiple routes of exposures, how those exposures interact with the body, and how those interactions have different effects over the life span. This review captures the impact that epigenetic changes can have in early life and how their disruption can foster disease in adulthood, a field of study now referred to as the Developmental Origins of Health and Disease.[66,90,146,147] To better identify the potential for exposures to the epigenetic disruptors described above, I explore the potential environmental risks for pregnant mothers.

4. Exposure Sources for Pregnant Women & Developing Children

Today, exposure to human-made synthetic chemicals span both poles and most life inbetween.[30] Most human breastmilk is contaminated with a wide variety of these chemicals.[74,137,148] Some of these pollutants persist and accumulate in the environment magnifying human exposures

through additive routes.[134,144] Others have short half-lives, but their pervasive presence[30] in our food, water, and air makes exposure ceaseless.[95] Figure 5 demonstrates what a pregnant woman may be exposed to on a daily basis. Epigenetic disruptors circulate through vehicle and industrial exhaust[149] that pollutes indoor and outdoor air, pesticides in fresh fruits and vegetables,[140,150] food contact materials[151] like butter wrappers and packaging,[152] off-gassing from semi-volatile flame retardants[126] in our electronics, couches, and mattresses, and building materials such a vinyl flooring, contaminants in our fish,[153] aircraft fuel used by small planes,[154] children's clothing and products like nursing pillows and changing pads, surfactants and fragrances in our personal products,[121] pollutants from roadway paint,[149] and personnel care products.[121,155] We also know food spices used locally have been found to contain excessive levels of phthalates probably from contamination during manufacturing.[156] These exposures are traveling through all the contact pathways we have with our environment.

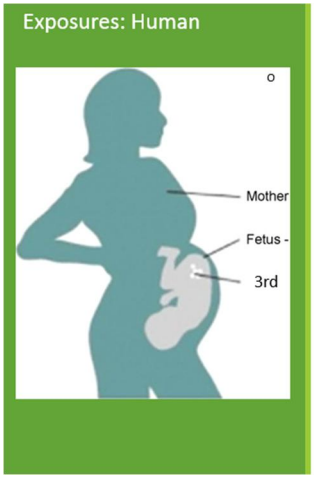


Figure 15: Daily exposures to epigenetic disruptors. Citations: A[44,76,110,118], B[111,114], C[112,113], D[88], E[90], F[37], G[91], H[92], I[88,92], J[119], K[87,88], L[83,116], M[88], N[120], O[121].

Locally, Seattle has subpopulations of fertile and pregnant women and their children that are exposed to chemicals from every group of epigenetic disruptors identified above. First, toxics from air pollution is above most national sites increasing the number of air toxic related cancers by an additional 450 cases (per million) in the Duwamish Valley and 360 cases (per million) in Beacon Hill.[108] All of these women are also exposed to endocrine disruptors from a variety of sources. Women of child bearing years have phthalate levels 12-200x the referenced population, mainly from the use of phthalate-containing products found in perfumes, lotions, nail polish, and hair spray.[117] Such personal care products do not rinse off immediately with showering, leaving a residue that takes days to wash away.[157]

Because Washington State law allows children's products to be tested for chemicals of high concern, we know many of these products contain phthalates and metals. Fourteen products contained metal levels above 100ppm; 2 products had levels of cadmium above the 40ppm limit, 3 above the 40ppm lead limit, and 11 had at least 1 phthalate above the 1,000ppm limit.[158]

Persistent organic pollutants stored in maternal fat cells is transferred to the infant during breastfeeding. Depending on duration, breastfed infants get 18% more exposure to PCBs that those who are formula fed and bank pollutants in their fat stores at exposures up to 50 times the adult daily equivalent.[137] This creates a quandary for public health professionals who recognize the enormous benefits breastfeeding has to lifetime health of the mother and child.[159] During childhood, kids are at risk for a higher body burden from environmental exposures than adults as they have faster breathing rates, and ingest more food and water for their body size as compared to adults.[160]

Threat to Children's Health

The process of embodiment discussed above demonstrates a real and current threat to our children's health.[88] These chemicals pose an untested risk in combinations found against our skin,[157] throughout our diet,[151] and in our air.[161] Their effects on the epigenome can occur at any point across the lifespan,[42] but the greatest risk for adverse outcomes from embodied toxicants occurs during developmental windows in utero.[97] Epigenetic changes during developmental periods (i.e., embryogenesis, fetal development, and early childhood) have more pronounced effects on risk for adult cancer, autoimmune diseases, metabolic disease, and neurological disorders.[42,66] We have an ethical duty to act on knowledge of this risk, no matter how difficult action or regulation might seem.[162] By not acting, we are passively allowing this health risk to continue. In order to make recommendations for action, I analyzed the assumptions made by policy makers that allow for epigenetic disruptors to circulate untested in our environment.

5. Assumptions that Inform Policy

The complexity, scale, and integration of environmental exposures into our body makes the concept of ecosystems an appropriate framework to understand the values that drive relevant policies.[163] Conceptualized in the 1930's, an ecosystem framework acknowledges the relationship of the human experience with its corresponding community of non-human organisms and their environments. In looking across ecosystem policy over the last fifty years, human-centric values have predominately shaped ecological policy (Box 1).[164,165]

Human-centric Values:
- Only humans have intrinsic value
- Humans are external to their environments
- Resources are for human development
- The environment should be preserved for future generations and their economic needs *(recent addition)*

Dualistic Values:
- Humans and ecosystems have intrinsic value, though humans are dominant and most valuable
- Humans are an integral part of ecosystems
- Management should be balanced and sustainable
- Society's relationship with the ecosystem and our interactions
- Humans have the role of stewards of our ecosystem

Box 1: Values in Ecosystem Policy.

Human-centric values allow the exploitation of the environment as a human resource, assigning the environment to the status of service provider primarily as a resource for consumption.[165] This assumes that human actions are external to our ecosystem ignoring how environmental pollution cycles back to us becoming embodied through complex environmental relationships. This value fails to recognize that low dose exposures can become embodied collectively. Recent evidence highlights this failure indicating that exposure combinations can reach the threshold to initiate cancer.[166] Shifting to a more inclusive, or dualistic, set of values acknowledges human interaction and dependence on the ecosystem.

Current policy is based on a reductionist approach to modeling the effects of exposures to environmental toxicants and assumes a linear dose-response curve, where lower doses are predicted to have smaller, and therefore safer effects. Safety testing conducted by industry relies on endpoints from higher exposures and extrapolates these results to low doses to estimate safe thresholds for single exposures. There is good evidence that these assumptions are false, especially for hormonal mimics and other endocrine disruptors.[92] In reality, hormonal signaling patterns are non-monotonic, enabling

disruptors to have more pronounced effects in the low doses that are typical of human environments.[92,166] Other assessments of safety rely on false or untested assumptions, or are simply not done. An important example is the lack of routine assessment of the effects of environmental exposures across multiple generations, in either animal or human studies.

The patchwork nature of regulatory policies divides regulatory authority across agencies even though the substances they regulate are in shared waters, air, and soil and individual bodies.[165] Ultimately, our monitoring, intervention, and regulatory systems do not categorize epigenetic disruptors together thereby missing the large cumulative risk of exposure. In addition, analyzing safety and exposure thresholds with the reductionist set of assumptions places the burden onto individuals to control exposures. Avoiding exposure by changing personal behaviors alone is nearly impossible. The sources of toxicants are ubiquitous and individuals are not empowered to exercise choice, in part because of confusion and obfuscation in how chemical products are labeled, limited public access to toxicity data, and limited clinical guidance about prevention and personal protection strategies.

Public health surveillance is also missing. Routine surveillance measures have very little data on epigenetic disruptors. There is recognition of the problem but not enough political will to address it. For example, the national toxics program from the National Institute for Environmental Health Sciences (NIEHS) states some concern of BPA's ability to disrupt development, and the EPA lists certain phthalates as "suggestive of carcinogenic potential," yet these chemicals are still in wide circulation.[167,168] The U.S. Department of Agriculture (USDA) is responsible for meat and dairy but does not test or provide guidance on any phthalates in the food supply chain yet plastics are commonly used in the production of milk. The FDA has not expanded its total diet study to include flame retardants[169] nor addressed measuring exposures from contact with food packaging materials.[151] Further, there is much more to be done by the FDA and the EPA to mandate quantifying the effects of large-scale drug contamination in public wastewater as one criterion for drug approval.[170] Despite strong evidence of the

epigenetic harms associated with flame retardants, there are no regulations for use in commerce, even though they have been found in high quantities in products like butter.[152]

6. Recommendations

Launching a global campaign to eradicate all epigenetic disrupting chemicals from our environment is probably unrealistic. Instead, public health and regulation can focus on reducing exposures for those who are pregnant, nursing or early in development. My recommendations are outlined in Table 6.

I recommend fast-tracking regulatory authority for increased surveillance to the WA Department of Health, the WA State Department of Ecology water quality program[171] and FDA's Total Diet Study[169] to monitor our bodies, environments, and food for epigenetic disruptors.[151] I recommend providing ongoing funding of interdisciplinary research teams who would be tasked with understanding the interactions of these low dose disruptors in the exposome. I recommend this research stretch the lifespan from pre-conception to old age.

Recommendations for Public Health and Policy
Comprehensive Surveillance
Interdisciplinary Exposome Research
Stronger Chemical Regulation and Enforcement
TSCA Reform
Taxation Instead of Allowance
Industry Funded NIH Studies
Precautionary Approach
Incorporation of Epigenetic Effects into Risk Assessment

Table 8: Recommendations for Policy and Public Health.

I recommend taking a harder stance on chemical regulation and better enforcement of current regulation. I specifically support reforming the Toxic Substances Control Act (TSCA) that incorporates a more precautionary approach.[93,172,173] The U.S. Government Accountability Office has already called for legislation to strengthen EPA's chemical assessment process.[81] TSCA must be revised to include precautionary values that respect each state's domain and prohibit preemption of state regulations by federal agencies. For example, Washington State's chemical policy is stricter than most other states,[174]

especially for children's products. This protection is lost if federal chemical policy is weaker that the state's since federal policy pre-empts state regulation.

I recommend direct taxation of polluters to hold them accountable for all levels of pollution. A weakness of current allowance schemes (which permits a fixed amount of discharge) is they permit numerous polluters to distribute low doses into the environment, especially for the 3,000+ high-volume production chemicals (> 1 million pounds produced annually).[70] I also recommend shifting the financial burden of safety testing to the chemical manufacturer by requiring them to fund research on epigenetic disruption and longitudinal children's health studies. This would help to offset the financial burden borne by taxpayers that fund activities such as EPA's Tox21 program,[175] a high-speed robotics approach to chemical screening and prioritization for health assessment, or the NIH's Environmental Influences on Child Health Outcomes longitudinal study (ECHO).[176] A shift in costs would also incentivize industry to explore greener alternatives.

I recommend shifting away from human-centric values and towards dualistic values (Box 1) by taking a precautionary stance in regulation. Policy makers should ask "is it necessary" instead of asking "is it safe."[177] This acknowledges that safety is a moving target.[167,178,179] For example, when California policy makers assess appropriate pesticide application, parameters for assessment are different for airport runways than for daycare play yards.

Consumer awareness of necessity has already started to shift industry practices with changes in Kraft's Mac'n Cheese, Apple's electronics products, and Home Depot's flooring, but the change must be holistic.[180–182] Otherwise, chemicals of concern such as BPA will be replaced by equally alarming chemical cousins such as BPS.[183] Or we end up allowing formulations of flame retardants believed to be safe even though they break down in the environment into more dangerous compounds.[184]

Realistically enacting precautionary values will require an integration of disciplinary knowledge and strategic method choices across multiple disciplines.[93,185] Research teams can start from a common

place of epigenetic embodiment to unite their investigation. The genome-wide toxicant-specific "annotations" induced by exposures, known as epigenetic signatures, hold considerable promise as new molecular biomarkers.[110] DNA methylation marks are relatively stable, are relatively cheap to amplify, and are known to reside in specific regions of the genome.[42,102] These marks can be obtained from body fluids (plasma and urine) or excised tissue[42] and should serve to enrich public health surveillance and research.

Finally I recommend assessing and regulating epigenetic disruptors collectively to better inform risk assessment and policy reform.[186] Ultimately it is the internal exposure, the embodiment of our environment, that must be assessed and mitigated.[79,90] When the chemicals above are classified as single exposures or ignored in their capacity to shift epigenetic activity, we miss the totality of the physiologic burden. We also miss our opportunity to understand the complexity of our physical environment. Grouping chemicals that disrupt epigenetic programming under the umbrella of 'Epigenetic Disruptor' will assist public health professionals in assessing and understanding the totality of epigenetic risk to developing babies and exposed communities. This unifying classification should be used in assigning research funding, fostering cross-disciplinary research, regulating policy, public health surveillance and intervention.

Limitations

The biomarkers assessed as part of this literature review are relatively new. Unlike genetic mutations, epigenetic changes can fluctuate through time. Epigenetic signatures are tissue-, exposure-, and age-specific. There is substantial variation between people so we need better largescale efforts to understand how inheritance and environmental exposures change before these signatures can be completely understood (see Chapter 5 for deeper discussion).[187]

Our knowledge of the epigenome grows every day and is far from comprehensive. This calls for epigenetic expertise in biomarker use and interdisciplinary participation in biomarker interpretation.

The translation of effect from animal models to human outcomes is not direct and will require more robust epidemiologic data from human surveillance and longitudinal studies.

Conclusion

Chronic disease rates continue to rise despite large scale public health measures to change personal behaviors. The evidence from this review demonstrates that numerous chemicals in our everyday environments disrupt the human epigenome in ways that manifest as chronic disease. Exposures are ubiquitous and outside the realm of individual protection strategies. The consequences to population health of epigenetic disruption for developing young demands that public health and policy makers respond with better protections and surveillance.

By assessing and regulating epigenetic disruptors collectively, we can better inform risk perceptions and policy reform.[186] The totality of this action would seem impossible a decade ago. Today, advances in epigenetic biomarkers of embodiment provide internal proxies for both exposure and pre-disease states.[188] By incorporating these biomarkers into ongoing public health surveys, environmental surveillance protocols, and risk assessment strategies, we can better capture the signals of complex exposure and early physical dysregulation.[9] Regulators need not wait until the epigenetic markers are better understood as there is plenty of available evidence now.[162] Government agencies can strengthen enforcement of current chemical policy, increase chemical exposure awareness, and act with precaution, such as requiring water and air filtration systems for all low-income housing. A precautionary stance in chemical policy reform is well supported until we have a better assessment of the health implications for this generation and those to come.

Chapter Three: Healthy Bodies Reflect Healthy Communities

Introduction

The rise of chronic disease is a complex and growing problem for public health in the U.S.[10–14] Stress, particularly exposure to long-term chronic stress, is associated with a variety of chronic health conditions.[189] Recent advances in brain-body imaging demonstrate that negative emotional states, such as those caused by chronic stress, deteriorate physical health.[190] Both the sources and frequency of stressors are not distributed equally in society with heavier burdens borne by those with less advantage, further compounding disparities in health.[1,2,191] For public health to intervene, we need a multi-level, cross-disciplinary understanding of how stressful environments can affect long term health outcomes. Intervention will require interdisciplinary teamwork.

Stress embodiment is the concept that frames this work. Embodiment is the idea that physical and social experiences can change how the body functions; that external experiences can become integrated into a person's biology through physiologic change.[27] I use *stress* embodiment to capture the pathway that stressful interactions take from the social transaction through the brain's appraisal system, into a physiologic response that, through time, shifts the body's functioning in a way that fosters chronic disease. The goal of this chapter is to integrate ideas from three theories of stress, each from a different discipline, into one pathway that helps to understand the embodiment of stress. This understanding can be the foundation for interdisciplinary investigations among researchers across social and biological sciences who wish to act on the drivers of stress-induced chronic disease. To accomplish this integration, I draw on the transactional model of stress[59–61] from the social sciences, the theory of allostasis[62,62,192] from the biological sciences, and the adaptive calibration model[64] from an evolutionary perspective.

Background

Roadmap for this work.
Overarching question: What is stress embodiment?
Section 1: Embodiment
Section 2: Social Ecologic Model
Section 3: Appraisal
Section 4: Physiologic Stress Response
Section 5: Chronic Activation of Stress Response
Section 6: Biasing of Stress Response
Section 7: Epigenetic Tools
Section 8: Public Health Importance

Table 9: Roadmap for understanding stress embodiment.

This work describes how negative social transactions can change internal biological mechanisms in the disruptive ways that foster the development of chronic disease pathways. To fully understand stress embodiment, or how stressful transactions can change body functions, I ask and answer several questions (Table 1). I begin with a background section on the concept of embodiment (Section 1) by answering the question, "What is embodiment?" I then focus on the question of "How does an individual's position in society make him vulnerable to stress response stimulation?" This requires the lens of the Social Ecologic Model and the concept of overlapping risks (Section 2). With this background I then focus on stress embodiment. I first answer the question, "What makes an environmental transaction stressful?" The Transactional Model of Stress and Coping provides details of the mental appraisal that determines if a transaction is stressful, while the Adaptive Calibration Model identifies the basic features relevant to this appraisal (Section 3). If a transaction is determined to merit a stress response, I ask "How does the body respond to a stressful environmental transaction?" To answer this, I rely on the theory of allostasis to understand the body's stress response and review the biological changes that occur in the body and how they act through epigenetic mediation (Section 4). Next, I ask "How is chronic stress activation destructive to health?" This is answered by exploring how chronic stress activation fosters pre-disease states (Section 5).

With stress embodiment described in one path from the external source to the health outcome, I ask the question "What is the risk to health from chronic stress activation during early development?" To answer this I take a targeted look at how the stress response system is biased early in life as this biasing can itself increase the risk for chronic disease over the life span (Section 6). Finally, I ask "What

minimally invasive epigenetic tools might aid interdisciplinary teams to better monitor *changes* in internal states of stress embodiment?" by exploring how epigenetic marks might aid interdisciplinary investigation (Section 7). Communities differ by their values, ideals, experiences, interactions, and needs, and yet bodies are quite similar in their stress response.[61] Because of the uniqueness of community context, and the uniformity of the stress response system, it is critical that public health professionals understand the features of environmental experiences that foster chronic disease and act on them (Section 8). Action requires interdisciplinary teamwork between social and biological disciplines that can be facilitated with this knowledge of stress embodiment.

As an overview, Figure 1 (next page) represents my conceptual model of how all of these questions tie together during stress embodiment. I briefly introduce and explain the relationships between the different components of my model here and then provide more details and examples in the following sections. Stressful transactions can arise from multiple levels of the social determinants of health (Figure 1, A: Social Ecological Model). Each transaction has characteristics that are appraised by the brain against one's perceived internal and external resources (Figure 1, B: Appraisal). If this appraisal determines the transaction is uncontrollable, unpredictable, or in any way threatening, the brain initiates a stress response in the body (Figure 1, C: Stress Response). During this response, biochemical mediators flood the blood stream, enter tissue-specific cells (Figure 1, C^1: Cellular Response), and initiate a change in gene production. The resulting physiologic stress response in cardiac, immune, and metabolic systems results in large part from shifting gene products of cells in these tissues (Figure 1, C2: Physiologic Response). Through repeated or chronic activation of these gene networks by circulating hormones, body systems become dysregulated in ways that increase risk for chronic disease outcomes (Figure 1, C^3: Disease Outcomes). This figure shows the pathways that chronic stressors take in the body

to manifest as chronic disease outcomes through time. The sections that follow explain this in more

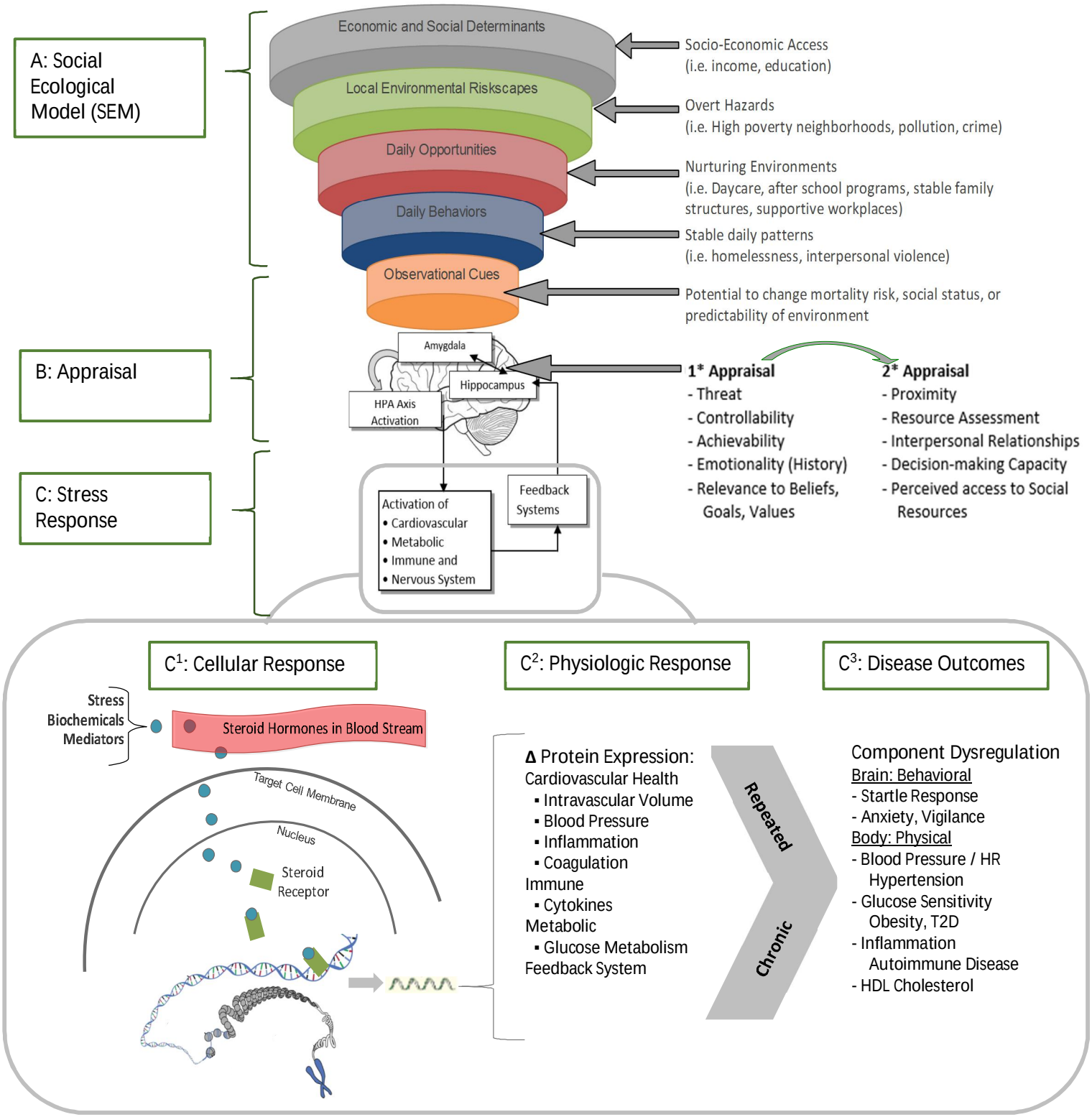


Figure 16: Stress embodiment pathway.

detail.

What is stress embodiment?

1. Embodiment

It is well known that systems of inequity create differences in health outcomes, known as health disparities.[3,193–195] Through ongoing interactions with inequitable social systems, individuals experience a chronic state of negative arousal both emotionally and physically. Through time, environmentally-induced distress drives the physiologic dysfunction that deteriorates health and resilience. This process is referred to as weathering.[196] Just as a flag that weathers many storms begins to fray, so too does the body when directly exposed to the environments of social inequity.[197] The health outcomes are chronic disease, morbidity, and premature death.[189]

Bodies tell stories of their experiences; they bear the mark of environmental interactions. Embodiment occurs when the body incorporates the material and social world into its biology.[27,28,85] Though this concept has existed for decades,[27,198] along with a call for social change,[3] the biological understanding and measurement of the embodiment process has only recently been detailed.[9,26,30,110,197,199–202] There is a strong indication that embodiment occurs through a disruption in biological development processes, such as tissue formation and maintenance[29,36,42,47,86] and through activation of disease-causing pathways.[31,63,87] Through ongoing repeated challenge, the body may incorporate negative environmental stimuli into epigenetic functioning in a manner that fosters disease etiology.

2. Social Ecological Model

The Social Ecological Model of Health Promotion[203] (SEM) and the concept of riskscapes describe the multiple levels of external demands that elicit a stress response from social experiences. The SEM bridges social and biological disciplines that have historically functioned in separate spheres.[203] The SEM

was first conceptualized in the 1970's to describe how factors that occur in a nested set of levels, including the biological (cellular), individual, interpersonal (familial), communal (neighborhood), and societal, influence health and well-being. The SEM is particularly useful as a model that allows researchers to study stressors from the micro scale (i.e., cellular) to the macro scale (i.e., social policy), positioning their work in the larger social ecological context.[85,204] In Figure 1, A: SEM, I have relabeled these levels from the original model to show the stressors occurring at each level.

The levels of potential adverse experiences and their interactions often result from broad social policy (see Box 1) that impact local environments and daily opportunities, and influence daily health behaviors (see Box 2 next page).[205,206] Environmental characteristics at each level can serve as observational cues regarding the potential adversity of an environment.[207]

Housing Policy in Seattle

The broadest policies impact entire communities and can affect large proportions of the population by shaping the risks to health communities' experience. Such policies include those altering economic development, influencing poverty, and facilitating racial segregation. For example, the lack of rent caps in Seattle combined with the recent inundation of software developer capitol has created a financial incentive for real estate developers to demolish low income housing and replace it with top dollar condos. The wave of rent hikes resulting from changing property values has priced many families out of safe reliable housing and increased Seattle's homeless population by 20% in just 24 months[A]. National studies relevant to Seattle indicate for every $100 increase in monthly rent there is a resulting 15% increase in homelessness[B]. This has pushed low income families out of their neighborhoods. Worse, as people of color proportionally are more affected by homelessness, on-going attempts to restrict homeless residents of Seattle to industrial neighborhoods far from resources, and far from the new privileged society that forced them out, reminds us that this country's legacy of racism is still in effect.

Local policies that facilitate gentrification directly shape the environments where individuals live, work, and learn. For families priced out of housing the options for a safe reliable location for their food, belongings, and ability to eat and sleep are minimal. Teachers from an overcrowded elementary school in Seattle report up to 20% of their student body is homeless.[C] The daily experience of these families includes inconsistent access to refrigeration and food storage restricting fresh fruit and vegetables that make healthy diets. Multiple moves in an attempt to stay warm, dry, and safe means commutes to work and school can take several hours a day. Longer commute times reduce opportunities for family bonding, parental role modelling, and directly inhibits physical activity. The unpredictability and disruption to daily patterns adds an additional daily layer to the stressors already experienced.

Box 1: Social policies that create adverse health environments. Citations A[45]; B[46]; C personal communications.

Public health requires more integrated approaches that incorporate researchers across all levels of the SEM framework. These researchers need to be sufficiently capable of understanding phenomena across levels and identify mechanisms through which factors at one level can exert causal effects on factors at other levels.[185,208] This is required as the factors operating at each layer of the SEM function in

relationship to each other and can operate through structured social arrangements to trigger complex cascades of processes that affect the biological capacity of people within these contexts.

Policies such as those described in Box 1 (previous page) create overlapping risks to health. A riskscape, or landscape of risks, captures the overlapping vulnerabilities to health occurring in a physical location.[57] Box 2 aims to "walk through" hypothetical examples of how, layer by layer, interconnected chains of conditions and responses carry the effects from broader societal policies into daily experiences that ultimately affect health outcomes. Neighborhoods with higher concentrations of poverty experience, for example, restricted access to resources that impact social and physical conditions,[1] and often have higher crime rates, more noise, overcrowding, more toxic waste sites, higher exposure to lead and

Navigating Riskscapes

Let's track a hypothetical family who experiences poverty-induced stressful transactions arising from inequity in resource distribution and status. The day starts with an increase in traffic noise from a nearby freeway that boarders blocks of low income housing units. As kids wake for school, one parent is coming home from nightshift work while another makes breakfast. A limited family food budget makes cereal and milk a staple meal. In the hustle to catch the morning bus, less frequent due to city budget cuts, parents' time is focused on packing for a long day instead of homework and mentoring. After two bus rides, the kids are off to stay at a friend's house close to school until the school day begins while one parent sleeps after work and the other begins a laborious day as a housekeeper. As the kids wait for their school bus, the house is crowded with low adult supervision. Kids must stay indoors as there are neighborhood gangs that run the streets.

At school, the kids are hungry well before lunch and have trouble focusing. In the classroom, classes are full with low staff support creating chaotic and noisy environments. The school lunch is heavy on sugar and fat and does not provide the needed nutrition required for learning and development. Old plumbing put the kids at risk for lead exposure in the drinking water and the ventilation system is old. After school, the kids make their way to another home to wait until dinner when their mother gets off work. This house is generally unsupervised and older kids smoke cigarettes, engage in sexual activity, and show abusive tendencies. Hours earlier, their father awoke, showered, and started his part-time job until his fulltime night position begins.

At work, the mother is required to cycle through numerous rooms handling trash and soiled linens. Middle management pressures her to work faster and does not listen to concerns of inadequate supplies such as gloves and healthy cleaners. During the lunch hour, she has to decide how to spend her limited funds between bus fare, household groceries, rent, and school clothes. In order to save for unexpected events, she forgoes a nutrient-rich lunch for a fast food hamburger next door. When she gets off her shift, she buses to get her kids, buys a bucket of fried chicken, corn and mashed potatoes, and gets everyone home by 8pm.

On the ride home, she and her kids are objects of negative attention from other passengers who comment on their worn jackets, their outgrown clothing, and deteriorating shoes. The bus route travels through a more affluent area of town. Here her kids witness others who are playing in parks, eating at restaurants, driving cars, buying clothes, and generally enjoying life. Her kids used to ask her why they do not live there, but now they just sit in silence looking out the window. As the bus enters their impoverished neighborhood, sprawling open spaces are replaced with abandoned buildings, community centers are replaced by vacant lots, and open air grocery stores are replaced by strips of fast food buildings alongside highways.

At home, the kids are craving personal space, parents are exhausted, and the family struggles to find the energy to address homework, sports, and hobbies. This family will have to deal with the additional pressures of reduced income when a parent is sick or injured, helping disabled family members without resources, and pressure to relocate due to rising rent costs. This family has to make decisions daily about how to distribute limited resources across numerous demands and navigate the power differential that gates these resources. The ability to move into management positions or change careers to secure more income requires more education. Both parents do not have time due to work pressures or resources such as childcare to take on skill development. This family is experiencing an environment that repeatedly stimulates the stress response system.

Box 2: Stressful transactions in negative riskscapes.

mercury, more freeway traffic and air pollution, poorer indoor air quality, poor-quality housing, fewer parks and open spaces, fewer sources of stable daycare, fewer after school programs, limited transportation options, reduced access to medical care, and fewer sources of healthy affordable foods.[5–8,115] Minority status, age and gender further interact to increase risk for disease.[200] Individuals experience additional adversity when they live amid wealth and affluence but do not share those resources. They become acutely aware of what they lack in comparison, which shapes how they interpret and emotionally experience the characteristics of the environments in which they live, work, and raise their families.[209] All of these can impact health status and interact together in the aggregate.

Of all the daily interactions a person has with his social environment, it is the human mind that determines what is stressful and what is not. To better understand this, I now described how these environmental experiences are appraised by the brain to trigger a stress response.

3. Stress Appraisal

A transaction becomes stressful when an individual cannot address an external pressure with internal resources.[61,210] To borrow a fitting definition from material sciences, stress is load relative to supporting surface.[210] For a transaction to be stressful, it must elicit a physiologic stress response.[211] First the brain must recognize and assess the social interaction. This appraisal is the gate keeper of stress activation. The core emotional regions of the brain (areas of the hippocampus, amygdala, and prefrontal cortex) perceive the environmental change (Figure 1, B: Appraisal).[64] These regions conduct a quick assessment to determine if there is a discrepancy between the external condition and one's own individual characteristics (i.e., needs, perceptions, values, resources, and skills).[63,212,213] This assessment includes contextual features such as adverse social position, daily hassles, and discrimination. If the primary appraisal assesses a discrepancy between external demand and internal capacity, then a secondary appraisal follows. In secondary appraisal, the assessment takes personal and community resources, stressor proximity, social capital, interpersonal relationships, and individual capacity for

decision making into account (i.e., resources that support adaptive coping and resilience).[212] The core features of person-environment transactions that stimulate a stress response are threat, lack of control, and unpredictability.[61,64] Specifically, the brain is assessing the potential for threat (i.e., physical injury, death, or threat to beliefs and values), unpredictability of external conditions, and controllability[64] (i.e., personal mastery, achievability) as well as the negative emotionality in the transaction[61] (i.e., relationship to values, goals, and beliefs).

Figure 1 (A: SEM) describes levels of the SEM as characteristics of social determinants that can signal the activation of a stress response. Policies that affect economic and social determinants (top level) may create adverse social positions that decrease access to income and education, and have powerful effects on neighborhood riskscapes.[1,206] These policies shape disparities such as poverty, pollution and crime rates, which each can create a negative perception that an individual has of her local environments (second level)[200] by increasing the perceived threat, decreasing perceived predictability, and reducing perceived control (i.e., when stressors are inescapable). Independently, lack of political power in itself is a form of lack of control. Daily opportunities (third level) create or suppress nurturing environments and govern the frequency and intensity of daily hassles (known as microagressions[214]) an individual must tolerate. As we move from the macro to the micro, important features of the stressful interactions include unstable daily behaviors and patterns (fourth level) (i.e., homelessness) or unpredictability and threatening daily interactions (i.e., interpersonal violence). As these pressures funnel down from the political to the institutional to the individual, they become observational cues (fifth level) that the environment is threatening, unpredictable, or uncontrollable and merit appraisal for a stress response.[64] Once a situation is perceived as stressful and one that imposes demands that are beyond the individual's capacity to meet, a physiological stress response is stimulated in the body. This is explained further in the next section on the stress response system.

4. The Stress Response System (SRS)

Upon activation, the brain sends signals to the body to mount a stress response (Figure 1, C: Stress Response).[61,62,191,201,210,213] This response system is evolutionarily old and has been shaped by the environmental experiences of thousands of preceding generations. Through millennia of adverse environmental challenges, adaptations, and collective evolution, humans have developed a sophisticated SRS.[64] It is a complex network of coordinated physical and behavioral responses that have proven to be successful for survival in diverse local social and physical environments.

Though the cause and effect of a stressor may vary, as well as each person's appraisal of an experience, the stress response is more universal.[61] The resulting biologic reaction is evolutionarily programmed and functions similarly across complex lifeforms .[64,215] This response involves a network of tissues coordinating across the parasympathetic nervous system, the sympathetic nervous system, and hypothalamic-pituitary-adrenal (HPA) axis[63] that collectively activate a complex physiologic response across the cardiovascular, metabolic, neuroendocrine, and immune systems.[216,217]

Just as the SEM helps us contextualize complex and interrelated external stressors active in the environment, the theory of allostasis helps us understand the complex and interconnected stress response occurring in the body.[216] Life requires some physiologic conditions to remain within stable and reliable limits (i.e., pH levels, body temperature, oxygen levels) whereas others can change based on environmental demand, such as the SRS.[62] When the appraisal system deems an interaction to be threatening, the brain sends out a set of signals that cascade through every body system. The internal shift effectively musters the internal resources to fight or flee the external pressure (Figure 1, C: Stress Response).[212]

This intense system-wide shift involves a panoply of signaling mediators (hormones and neurotransmitters),[216,218] some of which flood blood vessels to be pumped vigorously to organ systems throughout the body.[61] These biochemical signals have fast effects. Increased epinephrine and

norepinephrine levels dilate the eyes to enhance vision, increase breathing and dilation of the bronchi, blood pressure, heart rate, blood volume, and clotting factors in anticipation of intense physical activity and injury. Peripheral blood flow is reduced, digestion halts, sodium and water retention levels change, and the body is primed with increased access to energy stores and alertness. Soon into this process, stress hormones (i.e., cortisol) are released, which shift metabolic processes to utilize non-carbohydrate sources of energy, increase cell growth and proliferation, and prime the immune system to be reactive. This coordinated biological response is known as an allostatic response[219] (Figure 1, C^2: Physiologic Response).[62,200,201,213,216,218,220]

In healthy doses and supportive environments, perceived stress can stimulate allostatic responses that foster learning.[64] However, as part of a response to toxic or adversarial experiences, the allostatic response can manifest as chest pain, heart palpitations, headaches, dysphagia, intestinal cramping, anxiety, panic, immobility, frustration, muscle tension, and inflammation.[212] These reactions can be exhausting and imprint a strong memory of fear on the brain.[221]

Physiologic shifts following stressful exposures occur in large part through hormone-activated gene expression (Figure 1, C^1: Cell Response).[45,222,223] For example, when the steroid hormone cortisol is released by the adrenal glands into the blood stream, it targets glucocorticoid responsive genes in tissues distributed throughout the body[45,217] including the central nervous system, metabolism, immune, cardiovascular, endocrine, and renal system.[223,224] Within each cell nucleus, the steroid hormone binds with its receptor and this complex binds to a stretch of DNA called a hormone response element.[45,225] This activates gene expression (Figure 1, C^1: Cell Response) to shift the physiologic activity of the target cell (Figure 1, C^2: Physiologic Response).

Once the stressful experience passes, the feedback system in the brain registers the amount of circulating stress mediators (hormones and neurotransmitters) and terminates the stress response.[64,217] Timely termination of the stress response and restoration to pre-stress response states is important to

protecting the body's long-term health.[226] Positive stressors allow termination of the stress response system before internal weathering begins. Chronic, ongoing, relentless triggering of the stress response system is what pushes the body into pre-disease states. To better understand why, I next explore the internal weathering from chronic activation of the stress response system.

5. Chronic Activation of the Stress Response System

The daily stressors that individuals experience have features such as frequency, duration, intensity, source, target, and proximity. These characteristics inform the extent of the internal stress response. The severity of the stressor, the stress response, and the physiologic and behavior changes that arise in response, as well as the duration of each, have an internal effect on the body and can increase an individual's risk for physical and mental burnout. A reasonable level of environmental demand elicits a healthy range of biochemical mediators that are required for development. This level of SRS functioning stimulates mental and physical performance (i.e., learning) when it occurs in safe and controlled surroundings.[64] Individuals assessing an unreasonable stressor, either frequently or chronically, will elicit a higher intensity or longer duration of biochemical mediators (high internal burden).[201,219] As external transactions sustain the stress response, biochemical mediators continue to flood the body, delaying the onset of restorative repair. Without sufficient intervening periods for rest and catabolic repair, the stress mediators active in an allostatic response can become destructive and create a state of allostatic overload.[62,227–229] Over time this

Secondary Dysregulation

The stress response system activates the sympathetic nervous system, which increases several parameters of the cardiovascular system including blood pressure and renin enzymes. Over years of sustained chronic stress response activation, an individual experiences years of sustained increased blood pressure and sodium and water retention. The arterial system must accommodate this sustained average increase through time during both daily resting and physical activities and during the times of stress activation. The cardiovascular system accommodates this sustained increase in blood pressure by thickening the arterial walls. These individuals are more likely to develop hypertension and kidney distress. Both are pre-disease states and additional risk factors for cardiopulmonary and renal disease. Through time, the physiologic dysregulation of pre-disease states becomes the biological background that environmental pollutants act on (i.e. air pollution). This taxes a body already in a state of dysregulation and further increases the risk for disease.

Box 3: Secondary dysregulation .

pressure forces body system to adapt in ways that foster pre-disease states (Figure 1, C3: Disease Outcomes).[61,216,227]

In weathering, each body system must adapt to the internal pressure created by ongoing exposure to stress mediators. These secondary changes serve as a coping mechanism in response to the internal demand (Box 3 previous page).[61] The equivalent dysregulation described for the cardiopulmonary system is occurring across body systems involved in metabolism, mental functioning, autoimmune response and aging. Secondary changes can include increased startle response, anxiety and vigilance, change in body mass index and visceral fat, glucose sensitivity, immune suppression, and changes in HDL cholesterol levels (Figure 1, C3: Disease Outcomes).[61,213,216] If stress remains chronic, these changes foster dysregulation and increase risk for negative physiologic health outcomes (i.e., cardiovascular disease, asthma, metabolic disorder, renal disease, cancer), psychologic health outcomes (i.e., anxiety, depression), and behavioral health outcomes (i.e., aggression, isolation, addiction).[63,216,226] Through this process, prolonged or chronic activation of the SRS causes weathering that is an insidious erosion of health status.[201,227]

Chronic Stress Activation in the Context of the SEM

Activation of the stress response reflects the stress landscape where we live and grow. Problematic life circumstances created by low educational attainment and poverty create daily sources of distress. Lower social classes experience longer durations of chronic stress (i.e., lengthy unemployment, institutionalized discrimination). Stress response stimulants can include interactions with barriers to achievement of life goals (i.e., high cost of educational programs, lack of childcare options), inadequate recognition and rewards for invested effort in the workplace or personal qualification (i.e., gender pay differences). Higher poverty neighborhoods have riskscapes that include violence, crime, overcrowding, noise, and homelessness. Minorities and women in these riskscapes are

exposed to more chronic stressors than their white male counterparts due to differential expectations resulting in role strain and interpersonal conflict.[196,210,230,231]

Ultimately, the systemic adversity created through inequitable social policies manifests as chronic activations of the stress response system (illustrated in Box 2). Over long periods of time, this average burden of stress response (allostatic load) and its physiologic responses create local states of dysregulation.[213] As years turn into decades, the physiologic changes (i.e., hypertension, metabolic disorder, anxiety) may become irreversible often increasing co-morbidities, potentially increasing maladaptive coping mechanisms (i.e., social aversion, drug and alcohol dependence) and decreasing life expectancy.[189,232] It is through these mechanisms that social structures can get under the skin, become embodied, and support disease and loss of vigor. The loss of productivity and financial burden of systemic disease further erodes family and community resilience, especially when the chronic stress starts in childhood.[233]

Because the intensity and duration of the stress response can have long-term impacts on risk for chronic disease, I next explore how the stress response system is programmed early in life.

6. Biasing of the Stress Response System

The stress response system responds to environmental signals even before birth[41] and is especially sensitive during hormonal programming early in development.[217] The intensity and duration of the internal response is known as stress responsivity and varies in the population.[63,222] Individual variation is determined by genetic predisposition[234] and informed by previous experiences, beginning with maternal stress signals in utero.[64] Responsivity can shape brain development (Box 4).[235] High responsivity

Stress Effects on Brain Development

Researchers of a longitudinal study followed 49 children until the age of 24.[87] They found that those in stressful environments, resulting from the inequities of poverty, experienced changes in brain morphology that impaired cognitive, emotional, and learning skills. The high stress environments had layering psychosocial (i.e., child-family separation, violence, and family structure unpredictability) and physical characteristics (i.e., noise, crowding, and housing quality). These exposures increased amygdala function, which enhances fear, anxiety, and emotional dysfunction while it decreased prefrontal cortex function, which participates in regulating and terminating the stress response.

Box 4: Stress-induced changes in brain development

is not an inherently negative attribute. In positive environments, this amplification can enhance mental and social learning, increase memory and improve decision-making and is generally characterized by openness to information. Highly responsive individuals demonstrate better learning and health outcomes in supportive environments and worse health outcomes in high adversity environments.[236] In positive environments there is adequate time for stress response termination. In negative environments, high responsivity magnifies the internal load of each interaction, increasing the risk for weathering over the life span (Figure 2, Box B).[226] High stress responsivity in adverse environments can make individuals hypersensitive to social feedback and psychological manipulation, both capable of detracting individuals from achieving set goals.[64] This increases the risk for future stressful experiences, further increasing the risk for weathering. This exacerbates the propensity for stress perpetuation and mental and physical burnout.

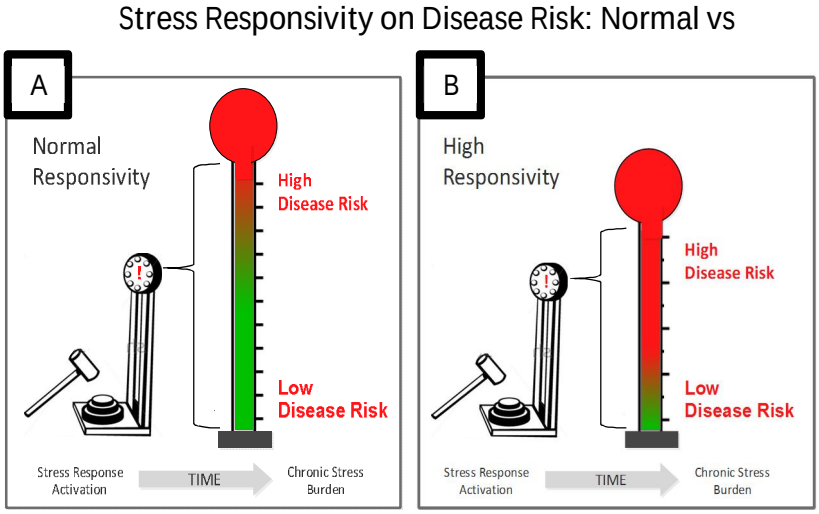


Figure 17: High stress responsivity in adverse environments increases risk for chronic disease.

Highly responsive people have an increased risk that a stressful transaction will add to the internal burden of stress mediators and allostatic load.[237] Figure 1 depicts stress responsivity and its implications for health outcomes over time. The typical responsivity (Figure 2, Box A), can be modified by genetic predisposition[234] but is generally neither amplified nor repressed.[64] This neutral programming is optimal in moderately stressful environment where life is not overly threatening nor consistently safe. Over an individual's life, neutral programming is optimal in balancing the risk for internal burnout from repetitive stress burden and survival in adverse environments long enough to maximize periods for

mating and parenting.[64] When early life experiences signal that the environment is unpredictable, threatening, or uncontrollable, the stress response system may be reprogrammed becoming blunted (see Del Giudice, 2011) or may be programmed to be sensitized and thus more responsive (Figure 2, Box B and described next).[64]

Responsivity is informed by the number of steroid receptors available during stress termination.[36,217] Glucocorticoid receptors are found in most fetal tissue and in the placenta suggesting they are capable of responding to maternal cortisol in utero. The feedback system in the brain, specifically cells in the hippocampus, have glucocorticoid receptors that, once filled, signal the termination of the stress response. When there are fewer glucocorticoid receptors in these cells, it takes a higher circulating quantity of cortisol to terminate the stress response.

The number of receptors available in the feedback system is dependent on how many proteins are produced in that cell. This is determined by the availability of the receptor gene to be transcribed into proteins. Signaling mediators circulating in maternal blood and during early life can alter the glucocorticoid receptor gene to be permanently downregulated, causing less receptor proteins to be produced.[217] The gene's activity is governed by the epigenetic mechanism of methylation (discussed in Section 7) and influences the stress system to be more responsive.[36,217]

As a species, this range of stress responsivity enables us to succeed across a variety of environmental demands. To the individual, there is a cost for high responsivity. Early life stressors that reshape the brain affect hippocampal and amygdala development that can affect a child's transition into adolescence. Chronic early stress impacting social learning may predispose teens to depression and substance abuse, both feeding into adult chronic diseases.[63] This is one vicious cycle of early childhood adversity. The stress that parents experience can have direct influences on a child's biological capacity in responding to future stressful situations.[222] The parent-child relationship, in utero and through development, provides experiential information that programs stress responsivity.

Stress Biasing Affects Health

Stress responsivity shapes the intensity of weathering and has implications for later adult health outcomes.[63,64,97,238] If responsivity is biased towards under- or over-reactivity, it can predispose children to adult disease (Figure 2).[239] Overexposure to maternal stress hormones in utero is known to restrict birth weight and predispose developing young to hypertension later in life.[97,217,240] Products of parental stress, such as reduced opportunities for bonding and distant parent-child relationships, significantly increase the risk up to fourfold for adult onset anxiety, depression, diabetes, and heart disease.[222,235] Parental bonding, when present, is also a resilience factor to protect offspring from the adverse effects of poverty on emotional and cognitive development.[241]

With exposure to chronic stress, the brain changes shape by reducing connections that support nuanced cognitive function, self-regulation, and memory; a process that is less reversible at older ages. Through these changes, chronic stress increases the likelihood of aggression, vigilance, and anxiety.[63] Through stress biasing, the social determinants can become multigenerational stimulants of chronic disease.[36,235] Higher prenatal glucocorticoid exposure is directly associated with higher circulating glucocorticoids in adulthood and both are associated with increased hypertension and hyperglycemia and changes in adult behaviors.[242]

The stress embodiment pathway depicted in Figure 1 integrates multiple disciplines through a common understanding. There are new techniques that show promise for capturing the embodiment process that may further assist interdisciplinary teams in surveillance, research, and intervention to understand and mitigate the stressful transactions occurring in local riskscapes.[9] I now touch on how the field of epigenetics may become a source of biomarkers for future interdisciplinary efforts.

7. Epigenetic Marks of Stress Embodiment

Recent evidence suggests that epigenetic disruption is an important link between the environment of complex and chronic exposures and the outcomes of complex and chronic diseases (Figure 3).[30,31,63] By definition, the epigenome is a collection of chemical marks and mechanisms that regulate how our genome (i.e., our DNA) functions.[34] DNA does not exist in isolation in the cell. Instead, it is bound to an expansive set of proteins and chemical marks that control gene regulation and consequently protein production. The epigenome is sensitive to environmental stimuli[56] and can act in the signaling pathway between environmental exposures (i.e., stressful transactions) and the activation of responding body systems.[97] Circulating hormones can stimulate a change in gene expression (Figure 1, C^1-C^2) by binding to target DNA and directly altering gene transcription. Chronically high levels of stress mediators from repeated environmental stressors can shape the brain and body's disease trajectories through epigenetic mechanisms (Figure 1, C^3).[63] These mechanisms have already been associated with maternal mood, early life socioeconomic status, abuse and parental stress.[41,243] Capturing these epigenetic changes, or biomarkers, can provide information as to the production state of cells (i.e., using methylation status) or reflect the biological weathering a community has experienced (i.e., using telomere shortening; for a deeper discussion of the epigenome, please refer to Chapter 1).

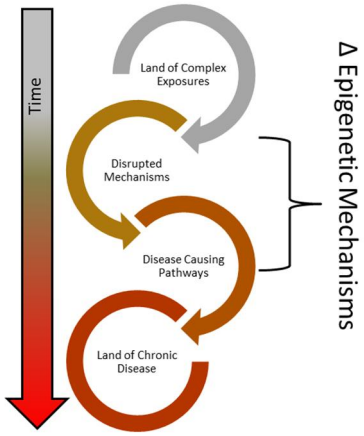


Figure 18: Path of external exposures to disease outcomes.

Epigenetic biomarkers are coming to fruition in ways that can assist public health professionals to better understand how local environments can modify genetic expression and thus, how they are embodied.[68,243] Surveillance efforts, epidemiologic studies, and intervention programs focused on reducing the stress burden could use epigenetic biomarkers as measures of weathering, to identify local stressors, and as short term assessments of an intervention's success. As the field of epigenetics

continues to advance, the barriers to using epigenetic data (i.e., cost, biomarker validity, reliability, and interpretation) are quickly declining.[244] However, because epigenetic biomarkers are new tools, it is important to involve a biomarker expert in planning, collection, and use of these tools (see Chapter 5). I briefly disucss below how some epigenetic biomarkers have advanced our understanding of stress embodiment in human populations.

DNA Methylation

DNA methylation is common to most life on earth and is an epigenetic mechanism that controls if a gene is silenced, or not expressed.[94] When a chemical tag called a methyl group is enzymatically added to a gene, transcriptional proteins cannot bind to DNA. This inhibits the gene's ability to be expressed, making it silent. In utero, cells develop into distinct cell types all from the same DNA code. Through silencing and activation of different genes at different times, DNA methylation is critical to the complex process of development in utero and after birth.[97] Disruption in methylation patterns of specific genes during development can disrupt tissue development in ways that foster cancer and chronic disease during adulthood.[29,67,91] Total DNA methylation in circulating blood cells has also been associated with cancer risk in humans and causally-linked to cancer development in animals.[42,103] As such, total DNA methylation can collectively be a separate measure of disease susceptibility across the life span.[42,245]

There are several ways DNA methylation is being used to understand the embodiment of stress. Researchers rely on detailed animal models to demonstrate the causal association between psychosocial stressful events, methylation changes to genes in the brain, and disease outcomes.[246] These pathways then inform human investigation. Animal models demonstrate how maternal stress affects stress response-epigenetic activity in ways that predispose offspring to the risk factors for chronic diseases.[97] Human associations have been found between lifetime stress and social mobility and methylation changes in inflammation-related genes,[247,248] as well as childhood socioeconomic status and the methylation of stress-related genes.[248] Research also demonstrates that methylation changes are

associated with exposures (i.e., perceived stress), cortisol output, and early-life low SES.[243] Most recently, methylation of the oxytocin receptor was associated with both callous-unemotional traits in youth and prenatal parental risks (i.e., maternal psychopathology, criminal behaviors, substance use).[249]

These associations provide a testable link between psychosocial stress, biochemical mediators, epigenetic alterations, and physiologic responses. This field has only recently been able to utilize epigenetic tools to assess environmental factors and disease outcomes with epigenetic change; collecting these measures on a population level is important to growing this knowledge base for future assessment. One specific gene whose methylation directly affects the responsivity of individuals is the glucocorticoid receptor (GR).

GR Methylation and Stress Reactivity

Exposure to maternal stress hormones and maternal stress behaviors appears to directly affect stress responsivity. When these exposures occur during developmental windows, time periods when stress sensitivity is being programmed,[217] stress signals can decrease the number of cortisol receptors (glucocorticoid receptors) in hippocampal brain cells that are involved in the feedback loop. Rodent models are exemplars for research as receptor number programming is still in flux after birth.[235]

In highly challenging environments shaped by loss of control and physical threat, rodent mothers reduce their affectionate interactions with pups. This behavior is an environmental cue that changes the stress programming in offspring. Brain dendrites shorten and change production levels of steroid receptors for stress hormones.[63,64] The expression change is mediated by heavy methylation of

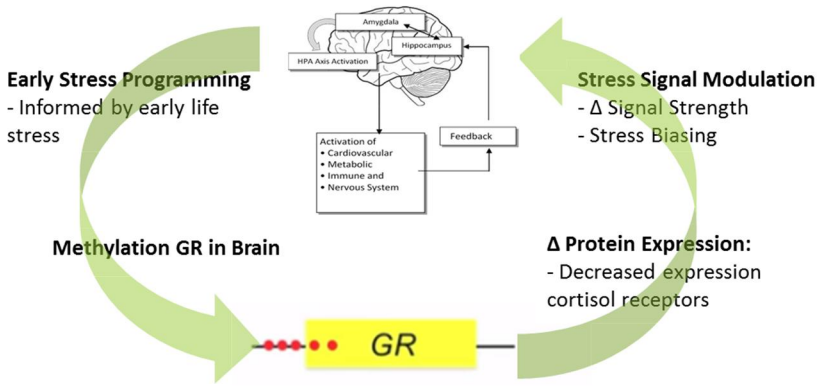


Figure 19: Glucocorticoid receptor (GR) methylation programming during development.

the glucocorticoid receptor gene (Figure 4 previous page). Methylation inhibits production of glucocorticoid receptors. When receptor production is down regulated, as in the pups receiving low affection, there are fewer receptors available in feedback cells of the brain to sense increasing levels of cortisol. Therefore higher levels of cortisol must circulate before the feedback off-switch is triggered. Through this methylation, pups receiving less affection had a higher stress responsivity.[222] Though adaptive for navigating local threatening environments, this epigenetic change is maladaptive for long-term learning and health.[64] Behaviorally, the less nurtured offspring are less likely to venture into new landscapes. Reluctant individuals avoid novel learning and socializing opportunities that, in humans, translates into increased risk for learning delay, fewer social ties, and a greater risk for disease.[226]

We rely heavily on animal models to understand this early life stress programming since sampling a core of human brain is not an option, but we do have direct human associations. The brains of suicide completers show epigenetic changes in the glucocorticoid receptor gene[250] as well as methylation changes in other important genes.[251,252] Newborns of mothers with depressive symptoms during pregnancy also demonstrated increased methylation of the GR gene in the umbilical cord blood cells. As 3 month old infants, these children had higher levels of salivary cortisol.[41]

Stress Impacts on Telomere Length

Telomere length in specific blood cells is becoming a biomarker for cellular aging that is closely associated with age-related and chronic diseases (see Chapter 1).[253] This biomarker holds the promise of capturing population-level weathering occurring in communities. For example, a study of 9 year old boys found that adverse riskscapes shaped by low income, low maternal education, unstable family structure and harsh parenting were associated with a 19% shortening of white blood cell telomeres as compared to a cohort in more nurturing environments. Children with the most sensitivity (i.e., high responsivity) to stress showed the longest telomeres in advantaged environments and the shortest in disadvantaged environments.[234]

Epigenetic biomarkers are relatively new and as such, their use should be well thought out as our current understanding of the epigenome is incomplete. Epigenetic signatures are tissue- and even cell-specific and there is substantial variation between people on what these signatures mean in terms of human health. We need better large scale efforts to understand how inheritance and environmental exposures change before that signature can be completely interpreted at the level of an individual person.[187]

Setting the temporary limitations of developing biomarkers aside (see Chapter 5 for a deeper discussion)[243] epigenetic biomarkers are showing promise as a tool for public health surveillance efforts.[254] Telomere length in blood cells is correlated to those in saliva making them easy to collect.[53] This sample collection could be added to the NHANES sampling protocol. Expanding the collection of telomere length and methylation status beyond research populations would increase comparative statistics and enable a broader range of demographic-specific associations, thus further increasing the reliability of these tools. Understanding biological aging in the aggregate among populations can better inform surveillance efforts for targeting prevention and intervention assessment, as well as capturing indices of future population-level health trajectories.

Public Health Importance

The stressful interactions described in this chapter are created by adverse social conditions beyond individual control. In neighborhoods with numerous risks, individuals become deeply entwined in power differentials affecting many levels of the Social Ecological Model. Most of the interventions should be directed towards community and societal levels. However, there are some interventions that have been shown to support resilience at the individual level by reducing the biological burden caused by repeated stress responses. Breathing techniques and mindfulness practices have assisted elementary and high school students, especially in adverse inner city environments.[255] A conscious focus on

breathing becomes a signal to the brain that we are safe and in control of our environment. This results in termination of the stress response and shifts biochemical mediators into a restorative phase[256] that appear to have drastic effects on in school performance.[255]

The community-level stressors require community-level interventions, especially because the individuals who are most affected by chronic stress have little control over changing its drivers. This is complex and complicated for public health professionals to navigate.

Being able to understand both the features of social inequity that stimulate a stress response and the pathway that these signals activate in the body through epigenetic mediation will assist public health professionals in many ways. First, a broader awareness of how social policies can be embodied will provide a new perspective for policy makers who are making local and national policy decisions. Second, a biological understanding of stress embodiment provides a new collection of biomarkers to capture population-level markers of exposures and pre-disease states. Public health as a whole is eager to incorporate more genomic techniques into prevention efforts[257] and epigenetic biomarkers can facilitate translation of this new resource.[9] This capacity will facilitate interdisciplinary teams across biological and social sciences and enable them to ask more complicated questions. Third, this knowledge can assist outcome evaluation for intervention efforts that might otherwise take decades to materialize. Fourth, public health population surveillance can provide a richer description of their community's biological health.

Communities across the nation have worked hard to build resilience in the face of systemic pressure. Public health as an institution has a responsibility to alleviate the institutional pressures that create environments of chronic stress. Primary focal points for policy should include stabilizing access to housing and local quality nutrition, reducing discrimination, providing opportunities for community voice and living wage, access to violence-free spaces to support physical health and social connectedness, and access to quality education and childcare. By focusing on the daily experiences

created by lack of privilege and power born out in differential access to resources, differential access to opportunity, and feelings of threat, public health can target the most egregious drivers that foster poor health outcomes. A mindset of creating low stress living environments will have a broad impact on disease and empower community resilience for this generation and those to come.

Chapter Four: Strategies for Community Engagement on Health Equity

Introduction

I fear for our next generation's health. Through environmental embodiment, insufficient or discriminatory social policies threaten human health, sometimes starting before birth. The preceding chapters describe how long-term common exposures to environmental contamination and stressful encounters travel into the body and through the epigenome predisposing our bodies to disease.

This threat invokes a moral imperative to take action. Because public health professionals value human life, I argue that the institution of public health has a duty to act by protecting developing children from the most egregious disruptors in our environment, environmental toxicants and chronic stress. Because of the scale and complexity of epigenetic disruptors in our environment, broad action will require a social movement to make the systemic changes in policy necessary to protect health.

The health equity social movement values the absence of systemic disparities in health through equitable access and opportunities for wealth, status, and resources for health.[258,259] For public health, health equity is our movement. The call for health equity is gaining strength across government and civil sectors nationally and is salient to a broad range of health equity institutional allies in media, research, medicine, public health departments, education, and the organized civil sector.[260]

For the health equity movement to be successful, personal behaviors must change, policy expectations must shift, communities must engage, and political action must be taken.[261] Public health as an institution has a role in supporting the health equity movement by fostering active citizenship. It is after all the citizens who have to support any new social policy, fiscally or behaviorally, and pressure their policy makers to initiate change, often drawing on their own collective resources to leverage that power.[261] Public health can include more citizens in this conversation if we can shift personal norms.[262]

Citizen action is in part based on one's own personal norms. Personal norms govern how a person views his feelings of self-worth and obligation to others in ways that activate him to act in favor of social change. These norms are more malleable than values or beliefs because they are revised when presented with new information.[186,261] Educational strategies that target an individual's personal risk assessment can shift her personal norms and motivate her to become politically engaged.[186] This shift is especially important for a social movement whose values are counter to the prevailing social policy. By educating the public as to the potential and prevalence of epigenetic disrupters, we can help citizens understand the threat to children's health and motivate them to take action.

To advance the health equity movement further, I found two opportunities for academics to engage community members. First, with its pulse on the recent advancements in genomics, students and faculty in schools of public health have an opportunity to use epigenetic embodiment as a teaching tool to broaden the general public's understanding of how common exposures become embodied. Second, health sciences students are learning to exercise their political power through relationships with local community institutions and policy makers. I describe these two cases below as methods for health sciences students to support the health equity movement. The first case focuses on the creation of the educational video "Your DNA, the Environment, and Epigenetics" by the University of Washington Center for Ecogenetics and Environmental Health. The second case describes the teaching and community engagement of students in the University of Washington Health Equity Circle.

Case One: Educational Outreach

The problem

The genomic revolution has catapulted the scientific community forward expanding our understanding of DNA and the evolutionary tree our species sits on. Evolutionary theory, much like gravitational theory, informs how processes occur at every level of the relationships we are nested in: genetic, cellular, physiologic, behavioral, familial, communal, societal, and global.[263] The last 50 years of

genetics research recently hit a flashpoint with the Human Genome Project. We now have a detailed and complex living record of the evolutionary tree for all living organisms in our global ecosystem.[264] With genomic knowledge we have come to appreciate the importance of the epigenome to regulate our genome in a way that is responsive to the environment.[37]

The synthesis and awareness of the genome has remained for the most part within specialized research and clinical communities, inhibiting community members and policy makers from making informed decisions during risk assessment.[186] Society as a whole has been left behind struggling to assess disjointed information received in spurts through media headlines and news coverage. Currently, citizens and policy makers have the confusing task of incorporating extremely complex, complicated, and often inaccessible research findings into their personal risk assessments. The lag time that exists between discovery and dissemination has fueled a lack of public consensus on topics of community concern (i.e., climate change, vaccinations, low-dose toxicants). Opponents of regulation who have large financial interests capitalize on this confusion by redirecting important community discussions away from risk assessment and instead to anti-regulation and anti-tax values.[261,263,265] As opposing perspectives are discussed in public discourse, unified public action to prevent risk-increasing exposures has been slow.[263] Combined with the historical, human-centric view that assumes humans operate independently of their environment,[165] often mining it as a resource, we have created a large and looming environmental threat to children's health.

Epigenetic awareness is especially important for individuals to understand how community-wide exposures (i.e., air pollution, pesticides) can shape health outcomes. Risk communication involves a dialog between the public health officials responsible for mitigating a risk and community members who may be affected by the outcomes of the risk. Effective dialog requires a baseline common knowledge between participating parties. Risk assessment and health policy can now benefit from recent genomic

advances, but more efforts to increase the public capacity to participate in risk communication are needed.

The Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) recognized the need to actively translate genetic findings into readily used public information with a call to action for public health professionals to increase genetic literacy specific to disease prevention.[266] In an attempt to bridge the current genomic knowledge gap in a manner relevant for health, I lead the creation of a 4 minute animated educational video to teach community members about an epigenetic mechanism in the context of community-wide environmental exposures. I explicitly wanted to focus on exposures that were not easily controlled by individual choice to raise awareness of the impact that broader community level exposures pose, while still recommending action on the individual level. I next describe our process, dissemination, and lessons learned.

Video Creation

Figure 1 depicts the process our team took between recognizing the need for epigenetics education and having the final video product. After searching online and speaking with colleagues, it became clear that a simple straightforward educational video demonstrating epigenetic activity did not exist. The UW Center for Ecogenetics and Environmental Health (CEEH) decided to fund the creation of a video, which was matched with in-kind support from the Center for Genomics

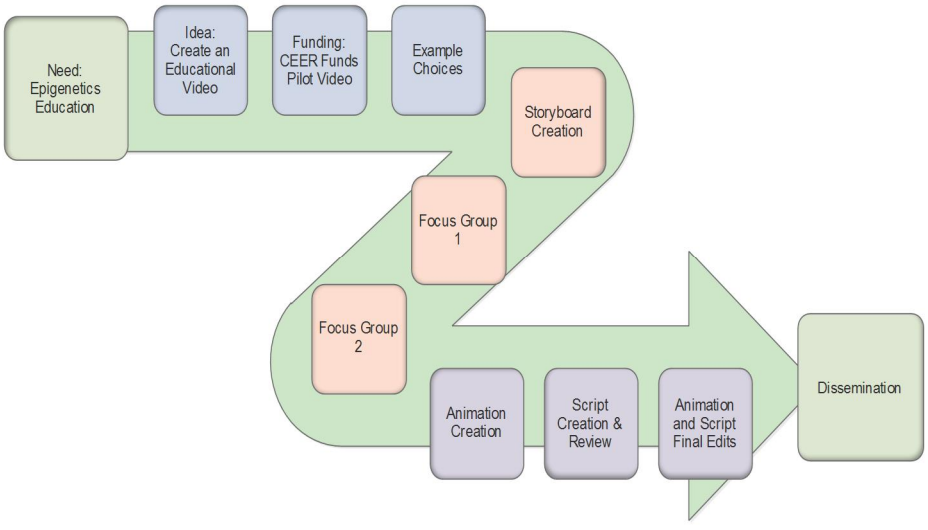


Figure 20: Steps in video creation.

and Healthcare Equity. The CEEH then partnered with Evan Stuart Productions, a previous collaborator in educational video creation.

Phase 1: Formulating objectives and training collaborators

In preparation, I reviewed the literature from the domains of health literacy, risk communication, and health promotion for guiding principles and known barriers to inform the educational strategy for this tool, listed in Table 1 and 2 respectively. The literature identified several barriers I wished to avoid at the onset and set scope on both the scientific educational side of the tool as well as informing the public health action. Table 3 (next page) lists our purpose, intent, evidence, strategy, and vison outline I sought to accomplish.

Barrier	Features
Scientific Understanding is Complex	Increasing knowledge of the natural world, tends to produce more questions of increasing complexity[267].
Discipline Specific Language	Scientific concepts span multiple domains of research, each containing heavy domain-specific terminology.
Concise Messaging	Claims must be correct and streamline but not too simplistic.
General Literacy is Limited	1/3 Americans have limited literacy[268]
Institutional Barriers and Cultural Appropriateness	Health disparities stem from institutional barriers to education and resources that disproportionally affect people of low SES and people of color.

Table 10: Phase I Literature Review Barriers

Guiding Principles	Examples from the tool
Plain Language	Chemical tags, methylation marks too complex
Accurate, Accessible & Actionable	Discussing epigenetic action and not genes of interest
Visual Cues	Adding magnifying glass and farm worker
Avoid Hot Button Language	Evolution / Dirty Dozen
Storytelling	Contextualizing development using a pregnant woman and then her child

Table 11: Phase I Literature Review Principles

Because of the scientific complexity involved, the writing team decided to be direct and specific by depicting an actual epigenetic mechanism instead of using an analogy. I chose DNA methylation as it is scientifically the most understood of epigenetic mechanisms and is responsive to common exposures.[42,269] Additionally, the on/off nature of gene expression controlled by DNA methylation made it appealing for an educational video. The writing team (Figure 2) then spent several meetings better understanding how this mechanism worked.

Knowing 36% of U.S. adults have basic or below basic health literacy skills and that limited health literacy disproportionately affects lower socioeconomic communities and minority groups[268], the production team (Figure 2) decided an animated cartoon would provide important visual cues to contextualized the more complex scientific concepts we wished to cover. The writing team envisioned two parts to the video: the educational knowledge of an epigenetic mechanism and actions individuals could take from a public health perspective.

- Purpose: Inform the general educated adult public, including policy makers, on the key concepts of DNA methylation.
- Intent: Facilitate understanding of the impacts community level exposures have on health outcomes through epigenetic changes.
- Evidence: Validated animal studies with strong human associations of exposures that alter DNA methylation. Exposure scope was limited to community-level environmental toxicants.
- Strategy: Create an animated educational video designed generally as a standalone for broad consumption and specifically to support risk communication efforts.
- Vision: Embed this work in a larger strategy to educate average citizens as to the mechanisms of action (embodiment) that link the social determinants of health to chronic disease outcomes. Broader public awareness will support risk assessment that reshapes personal norms and activates citizens to exercise power for policy change.

Table 12: Drivers behind video.

Ideally, I wanted this video to be accessible to the broader voting public, but the reality of pilot funding led us to target an educated audience with either a college education or a high school biology course in the last 5 years. Though I hope the viewing audience does not require a science background to understand the video's message, the content does require secondary education.

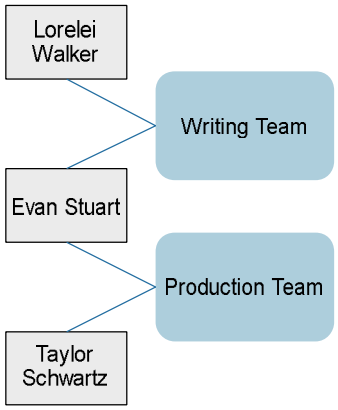


Figure 21: Writing and production team.

Phase II: Focus Groups

With this foundation, the writing team created storyboards and scripts for both the epigenetic education and the public health messaging portions of the video. After getting the team to a common understanding, we presented the boards and script in two focus groups. The perspectives represented in these groups included toxicology, biostatistics,

bioethics, clinical research, public health, genetics, scientific outreach, social science, and genetic epidemiology and all sourced from within the academic community.

The focus group participants made recommendations that informed which examples of methylation to use. They supported the positive frame of describing methylation's actions as part normal cell functioning and healthy development instead of the negative frame of methylation's actions in protecting us from the activation of dormant genetic elements (transposable elements described in Chapter 1).

The focus group participants also identified potentially confusing language. For example, the terms "chemical cap" and "methylation" were changed. "Chemical" was used only when referring to environmental contaminants. The term "gene regulator" replaced methylation with recommendations to depict the regulator as physically instructing genes to function when it was their "turn." Language such as silencing and activation was changed to "off" or "on."

Participants also recommended that the video begin with the definition of the main concept, epigenetics, and that the public health recommendations focus on buying safe conventional food recognizing that the recommendation to buy organic may not be feasible for resource-limited communities. Participants also voiced a desire to see a social justice perspective and recommended visually identifying there are workers exposed to pesticide applications.

Phase III: Animation Creation

In this phase, the production team took the revised storyboards and created an animated product. The writing team worked closely with the production team switching the order of boards to streamline the message on several occasions. Early animations were distributed with the proposed script to specialists in scientific outreach, bioethics, toxicology, and allied sciences. Specific feedback during the individual review was that a visual cue be added to indicate that pesticide residue is too small

to be seen and thus should not be confused with the food itself; that the public health message not use language associated with more extreme advocacy groups (i.e., "dirty dozen") as it might not be appropriate for NIH-funded work; and that the exposure language was too deterministic. After these discussions, the public health recommendations for the video were to purchase foods with low pesticide residuals, doing your part to reduce air pollution, and becoming an informed voter on chemical reform policy.

Phase IV: Dissemination

Within a six month period from the final rendering of the video, the video had accrued 1500 hits on YouTube. Dissemination of the YouTube link happened at presentations, poster sessions, and across virtual networks (Table 4). What was most striking about the dissemination discussions was how quickly diverse audiences grasped the epigenetic concept. High school students were just as engaged and imaginative as children's environmental health practitioners. The viewers clearly connected their own experiences to the story. Many comments expressed shock and awe being able to grasp how epigenetic mechanisms affect the genome's function and how these mechanisms can be changed by outside exposures. One public health professional asked, "Is this really true?" in the context of exposures being able to physically change methylation marks. I believe this speaks to the value of disseminating the information coming out of the human genome revolution. However, this is my opinion only as the video has not been formally evaluated.

In person dissemination	Virtual Networks
Washington State Public Health Association	LinkedIn: Epigenetics, Epigenetics Psychology, HELIX
Children's Environmental Health Working Group	Working Groups: Pesticide Worker Interventions, USF Integrative Biology, CEH-WA
CEEH Center Investigator Meeting	Video Sites: YouTube, VIMEO, smt-source.com
High School Honors Students	Listservs: UW School of Public Health, Kids Enviro Health
NHGRI CEER Regional Conference	Twitter: @ecogenetix, @USC_EH_Outreach, @PHCafe, @ScienceEduc, @Science_teacher, @Science_Ed, @STEMduc
Public Health Genomics Conference	

Table 13: Phase IV Dissemination Networks

Lessons Learned

Looking back, there are features of the video that are problematic but were not originally apparent. There is an implicit message that industry is dirty and incompatible with healthy landscapes, a message that could unproductively position stakeholders against each other, instead of working together to make industry greener. This is especially important since industrial jobs are a critical source of income for families and employment can act as a support against the health effects of poverty. Another common comment was that the call to action was weak. A stronger call to action is difficult with the restraints against advocacy language, funding restrictions against lobbying, and targeting exposures that are not under individual control. One suggestion was to point out that citizens fund the ongoing research that informs the knowledge depicted in this video and include a call to action that builds the base for NIEHS support. This was indeed a missed opportunity for identifying the importance of NIH-funded research.

Finally, during the video creation, we attempted to be cognizant of cultural differences and our own biases. For example, when depicting the farm worker, we opted to not explicitly depict race, age, or gender. Our efforts were not entirely successful as when the storyboards went to animation it became apparent the protagonist in the video directly resembled the lead creator, a younger Caucasian woman with red hair who was pregnant at the time. This was unexpected since all communications were done by phone, but indicated unidentified stereotypes existed within our team.

I have received other feedback that, though important, fell outside the scope of this video's purpose. Several individuals questioned our choice of air pollution, BPA, and pesticides over exposures like smoking and poverty/stress. As mentioned earlier, I wanted to bring awareness to community-wide common exposures and avoided those that could be modified by personal behaviors alone (i.e., smoking). This project was funded by the National Institute of Environmental Health Sciences, making toxicant exposure more in line with their mission verses psychosocial stress or nutrition. Other

comments included the risk that viewers might focus only on the toxicants covered in the video and might miss the broader set of exposures that have direct impacts on health outcomes (i.e., lead). Though I absolutely agree, the scope of this video was constrained by funding and the evidence for epigenetic disruption from other exposures has not matured. Finally, several individuals asked why I did not depict the disease endpoints of such exposures. Our team individually, and with support from the focus groups, did not want to overwhelm the viewer with a laundry list of alarming diseases. I also did not want to depict causal actions of single exposure types as this might imply a reductionist understanding of what are very complex interactions.

Case 1 Conclusion

There is a need to increase genomic knowledge and environmental embodiment across the populous. This video was a pilot to increase genetic literacy and enable risk communication in the context of environmental embodiment. Overall, it has been well received with interest in incorporating it into discussions between researchers and their participants' results, outreach efforts, or as a means to increase awareness of alternate epigenetically important environmental exposures. The next steps for this tool include the creation of stakeholder-specific educational guides and an evaluation of this tool's ability to shift risk perception and personal norms in a manner that activates citizens to participate in the health equity movement.

Case Two: Health Equity Circle

Effective movements, judged by their ability to shift policy into meaningful action,[270] capitalize on political opportunities, act through social groups and institutions, and use resonate frames that appeal to social values.[260] The health equity movement cannot rely only on increased education to activate citizens. To change policy, citizens must organize utilizing relationships between a broad array

of institutions, all with ownership in the movement.[270] These relationships further network groups of political or financial power with groups that have time, energy, and people.

The field of public scholarship materialized from an understanding that new knowledge doesn't flow directly from the university to the larger community.[271] Translation of this information into something actionable requires an understanding of what the community values, struggles with, and views as important. To support the public health movement, academia can build the institutional capacity to foster community relationships in ways that act on political opportunities to expand health equity. The next case is one of community engagement by empowering UW health sciences students with the experience to organize institutionally in the health equity social movement.

Social movements require political allies.[261] Individual citizens cannot easily gain access to the political system to change policy but require the collective power to make political relationships.[270] Once in relationship with policy makers, citizens can activate these relationships towards a political goal. One method is to organize institutionally. Unlike individual or issue-specific organizing, institutional organizing works to bridge divides in American politics through building relationships between civil institutions and organizations all working for their common good.[19]

The registered student organization, the Health Equity Circle (HEC), now active in the University of Washington Health Sciences Schools, in Spokane, and in Portland. HEC believes health is more than healthcare and that we must act together to exercise the power needed to change policy. As such, medical students have been organizing on local campaigns since 2008. This started in the School of Medicine recently expanded across several of the health science schools and now includes undergraduate participation.

Student Skill Building: Community Organizing

HEC organizes as an institutional member of Sound Alliance. The Sound Alliance is an independent, nonpartisan, nonprofit organization representing faith institutions, labor unions, education associations, and other civic associations in the Puget Sound area.[272] Their member institutes (Box 1) are united in serving the common good by strengthening each institution and building power to act publically towards that good. The Sound Alliance is a member of the Industrial Areas Foundation (IAF) with affiliates throughout the US, Canada, Australia, Germany, and in Great Britain.[273] Through this network and its mentorship, Health Equity Circle students have learned the skills of organizing (Box 2) and have worked on campaigns effecting local policy regarding jobs, immigration, health care access, homelessness, and now early prevention funding.[274,275] Health Equity Circles now exist in Seattle, Spokane, and Portland in several health professional schools. In two locations, HEC students instruct an elective course within the health sciences curriculum. Through collaborative effort between Sound Alliance, the School of Medicine Staff, and HEC, the Seattle chapter taught two quarters of the 1-credit UCONJ 624: Health equity and community organizing course during the 2014-2015 academic year. During this course students

Sound Alliance Member Institutes
Amalgamated Transit Union Local 587
CASA Latina
Diocese of Olympia - Episcopal Church in Western Washington
FUSE
Health Equity Circle
IBEW Local 46
International Association of Heat & Frost Insulators & Allied Workers
Kent Education Association
M.L. King County Labor Council
Northlake Unitarian Universalist Church
Saltwater Church
Seattle Education Association
Seattle Firefighters Union
Sheet Metal Workers Local 66
Society of Professional Engineering Employees in Aerospace (SPEEA)
St. Vincent de Paul Catholic Church
Summit UniServ Council
Bethel Education Association
Fife Education Association
Franklin Pierce Education Association
Puyallup Education Association
Swedish Family Medicine Residency Cherry Hill
Tacoma Dominican Sisters and Associates
Tahoma Education Association
UA Plumbers & Pipefitters Local 26
UA Plumbers & Pipefitters Local 32
University Unitarian Church
Washington State Building & Construction Trades Council
Washington Pipe Trades

Box 1: Sound Alliance Member Institutes

Health Equity Organizing Practices[260]	
1	Building Relationships
2	Narrative Storytelling
3	Strategizing on how to make change
4	Translating strategy into meaningful action
5	Designing structures that allow for collaboration

Box 2: Health Equity Organizing Principles

worked with community members to hold a listening event, a research action, and a 100+ assembly, and engaged students through activities that integrated disciplines.

During the last two years, HEC has successfully organized on several occasions. Students stood with the Alliance to change detainment practices for undocumented immigrants that were creating barriers for community safety and health. Community members fearful of deportation were avoiding police and emergency services. Sound Alliance efforts successfully pressured city council members to remove immigration reporting for non-violent misdemeanors. Another project involved advancing our Tent City Collective through the class. This campaign works to bring tent city encampments for the homeless to campus, with the ultimate goal of ensuring appropriate and affordable housing for all. Student-driven pressure changed a critical city council member's vote in favor of creating more tent cities without redlining these residents to industrial zones. Most recently, HEC students negotiated with a Senior County policy maker to gain a public commitment for transparency in reporting of funding distribution of a substantial property levy funding early childhood prevention. That work furthered a relationship with the County Executive, an important relationship for future political activities. This work led to a campaign (described next) to increase prevention funding in King County, WA for health equity.

Student Skill Building: Best Starts for Kids Campaign

In 2014, Health Equity Circle students and all Sound Alliance institutions participated in a listening campaign to learn what the current local pressures are on our members' families. The problems that surfaced related to mental illness, educational readiness, homelessness, lack of funding for public services, and incarceration costs. HEC students heard stories particularly related to the potential closure of 4 public health clinics serving South King County including one in Auburn and one in Federal Way. As a result of a $15M annual deficit in the county budget, these clinics were unable to secure the financial resources to continue serving over 10,000 pregnant women and children. These clinics served primarily disadvantaged populations comprised of people of color, high poverty,

historically uninsured, and a significant percent of homeless persons.[276] The combination of critical maternal support services and disadvantaged populations being affected by this proposed closure became an area of interest for Health Equity Circle and the Sound Alliance.

Students joined Sound Alliance institutional leaders in research actions to break these overwhelming problems into issues that were concrete, specific, and winnable. After several months, we learned of the Best Starts for Kids Levy soon to be proposed by King County Executive Dow Constantine.[277,278] The county was proposing a six-year property tax levy to raise $350 million to fund Maternal Support Services (MSS) in King County Public Health, early intervention and prevention programs for children 0-5, homelessness prevention, and to expand the Community of Opportunity program. Recognizing the importance of passing this levy for the Health Equity movement, HEC through Sound Alliance efforts has taken two strategies: awareness and political pressure.

Sound Alliance has committed to briefing over 4,000 of its institutional members between July and October 2015. These briefings, unlike presentations, are designed to provide space for community members to understand the importance of prevention funding and relate it to their own experiences and values. Within the space of 30 minutes, trained leaders from each institution talk with community members about how these downstream outcomes have touched their lives, using personal stories to relate their own experience to the need for prevention funding in the areas targeted by the Best Starts for Kids Levy. Then by participating in an interactive activity developed largely by HEC students, community members learn how adverse childhood experiences shape risk for disease and incarceration and how these outcomes are modified by upstream prevention funding. Health Equity Circle students played an instrumental role in developing the health equity portions of this briefing and are in the process of training students to conduct briefings within Health Equity Circle and county wide. Students will also work alongside community members during action assemblies targeting key political figures to publicize support for this levy.

The relationships that have been made in this process will last beyond these participants' student status and has become a meaningful way for health sciences students to contribute to the well-being and health of their community. The ability to exercise the power to change policy is a powerful motivation for health sciences students who have a substantial understanding of the health effects of detrimental social and environmental policy but are ill equipped to make meaningful change alone. Feeling individually powerless is an overwhelming feeling often shaped by a lack of control, unpredictability, and even threat, all capable of increasing the stress burden these students will experience over their professional lifetime. Institutional community organizing has provided health sciences students including myself more than hope, it has taught us the skills to take action.

Case 2: Conclusion

Of all the lessons learned from this type of immersive community engagement, the most important is that to make local change, you must exercise collective power. This demonstration requires an understanding of community experiences as citizens become invested when the issues affect them directly and when there is a clearly articulated obtainable step they can take towards the solution. With the complexities created by the web of relationships, power, and money that shape local policy, empirical research alone will never be translated into a social good. Academia must provide the opportunities for students to learn these skills and that requires providing the funding and space for students to get political. This means moving beyond professional development opportunities focused on direct service and advocacy and teaching organizing.

By entering relationships with community partners through institutional organizing, the academic institution can become a supportive participant at a very important table. The institutional power academia holds is enormous, and when tactfully harnessed, becomes a great vehicle to teach students how to work with the community for the common good. The civil sector gains partners that have access to didactic knowledge that can better inform campaign awareness, strategy, and

educational actions. Moreover, the alliance of institutions becomes stronger based on the work done by members working in partnership to win on local issues. Academia brings people and money to the table, both of which increase a community's political power. To successfully enter these relationships, academic institutions must carve out the financial and administrative spaces for these activities to occur. This includes funding student organizations with budgetary, logistical, and administrative resources. It also means creating the space for faculty and staff to interact and mentor students in these activities. By embracing and supporting the work exemplified above, academic institutions would be better poised to realize their values of social justice and community engagement.

Conclusion

Both cases provide examples of ways academia can engage communities to further the Health Equity movement. By increasing individual awareness of the biological effects of environmental toxicants and the social determinants of health, community members are better equipped to understand the implications of prevention funding and make more informed decisions for the health of their community. By providing the opportunities for health professional students to exercise the principles of community organizing and to act together on local issues, students enter the workforce with both the social determinants of health mindset and the tools to alter its upstream drivers. Both are necessary to redirect the values that drive distribution of resources and status in our community. Professional education administrators can learn from these cases in order to develop the same experiential spaces at their institutions.

Chapter Five: Conclusion

Understanding how the epigenome is changed by environmental exposures to create pre-disease states is of special importance to advancing environmental justice and neighborhood disadvantage.[279] Epigenetic disruption, especially during fetal and early childhood development, can alter gene expression profiles, metabolic pathways, and hormone-responsive organ development.[42,56,66,79,80,87] The effects of disruption can destabilize the genome and alter tissue development in ways that increase adult susceptibility to pathologies such as cancer, heart disease, type 2 diabetes, obesity, neurological and reproductive disorders long after the exposure has passed.[15,43,44,67,95,97,107,280] Further, epigenetically disruptive exposures can also increase disease risk when experienced in adulthood. In environments with multiple exposures over the life span, epigenetic disruption creates a vicious cycle with each new exposure acting in the context of, and possibly interacting with, susceptibilities created from past exposures.

The preceding chapters describe a complex set of threats to our epigenome and can assist risk management in finding actionable strategies to reduce community-level hazardous exposures through better understanding the epigenetic contributions to health disparities. Public health professionals must act to mitigate the risks of epigenetic disruptors in daily exposures as a foundational step in redirecting health trajectories toward positive health outcomes.

Ethical Imperative, Economic Burden, and New Classification

Ethical Imperative

The processes contributing to the embodiment of chronic stressors demonstrate a real threat to our children's health. This threat invokes a moral imperative for public health professionals to take action because they value human life. The genome is one of the oldest sources of life's knowledge and its function is required for childhood development. Environmental embodiment of toxicants and stress

disrupts epigenetic mechanisms and affects the genome in ways that deteriorate health. This disruption poses a special threat to children. I argue that we have a duty to act on our value of human life by protecting our epigenome from the most egregious disruptors in our environment.

Being Reactionary is Costly

By not acting, we fail communities both morally and economically. Recent findings from Europe illustrate some of these effects. In 2007, the EU shifted to a heavily precautionary approach in its chemical assessment and regulation and conducted an assessment of the burden that Endocrine Disrupting Chemicals (EDCs) have on their citizens. By capturing exposures, outcomes, and using new methods established by the climate change community, the EU quantified the community cost of pesticides, phthalates, BPA, and flame retardants.[69,281,282] The results are staggering. Experts are directly attributing the subtle shifts in physiologic functioning caused by EDC exposure to a silent epidemic of reproductive and neurocognitive disorders reported to cost $175 billion annually. Health outcomes attributed to EDC exposures include IQ loss, autism, attention disorders, childhood and adult obesity, male infertility and early mortality.[281]

Classification of Epigenetic Disruptors

Though the EU's assessment is broad, it only captures a subset of the disruptors discussed in the preceding chapters. Grouping chemicals that disrupt epigenetic programming under the umbrella of 'Epigenetic Disruptor' will create a more comprehensive category that can assist public health professionals in their assessment and understanding of the totality of epigenetic risk to exposed communities. This unifying classification should further shift research funding to more expansive studies, require interdisciplinary collaboration, allow for reassessing policies, expand public health surveillance, and shift intervention targets to entire communities. This comprehensive category will also support the development of policy and interventions that can better protect the public from local toxicants, especially exposures in fertile and pregnant women.

Though I have argued the importance of understanding embodiment through the epigenetic lens as a reason for action, practitioners must still proceed with caution in measurement, in interpretation, and in messaging outcomes.

Cautious Advancement Scientifically and Ethically

Public health is excited about the prospect of epigenetic biomarkers to better assess community-level exposures and understand their health implications, especially as a means to address health disparities.[279] Epigenetic biomarkers are becoming available through cheap and easy-to-collect means but should be used with caution as this field is in its formative years and how these mechanisms operate is still under investigation.[283]

The field itself is working through methodological issues regarding the validity and reliability of current genetic[284] and epigenetic[188] biomarkers, making current interpretation of findings complicated and unclear. Epigenetic assays often involve reactions that are sensitive to ambient conditions making them susceptible to batch effect errors. Study design requires attention to determining a sufficient number of internal controls and study findings should be validated using assay different techniques.[285]

Interpreting valid findings can also be confusing. For example, arsenic exposure both increases and decreases DNA methylation making it hard to interpret results. More recently the field has realized such carcinogens act by reducing overall methylation levels while increasing methylation at key genes. This one-two punch increases risk for cancer by first reducing the methyl group protection against transposable elements thus increasing genomic instability (discussed in Chapter 1), and second by directly silencing key tumor suppressor genes with methyl marks.[283] Without the broader understanding of how epigenetic mechanisms operate in carcinogenesis, the biphasic findings of arsenic were thought to conflict each other when they act synergistically.

In addition, epigenomes vary between cell types, age, ethnicities, and exposures. Scientists working in epigenetics must address methodological issues as a community to come to consensus on confounding molecular processes, cell subtype composition, and how to integrate animal models into epidemiological studies.[286,287] Tissue purity is another important factor to monitor since different cell types have different epigenetic signatures. Defining what is meant by methylation as it is used in specific instances requires attention. Methylation is a binary measure, but when it is assessed from multiple cells as part of tissue methylation status is averaged across several thousand copies of DNA.[283,285]

As part of study design, study teams must capture relevant community characteristics, individual phenotypes and behaviors, with the targeted epigenetic measure. The field of bioinformatics can assist this process often employing advanced statistical applications to what will be terabytes of data. The complexity and flux of epigenetic findings requires that investigators from a range of disciplines represented across the levels of the Social Ecological Model must be invested in the entirety of the project.

Problems extend beyond what is captured in the study design. Attempting to provide individual-level interpretations of disease risk when using epigenetic findings in the context of public health messaging is problematic since many environmental exposures that are relevant to the epigenome may be outside of individual control. Special attention should be given to the ethical landscape when interpreting epigenetic biomarkers. Epigenetic investigators must think carefully about framing the messaging and meaning of their findings to avoid setting up a "blame the victim" scenario.[288] For example, a pregnant woman is assumed to be the gatekeeper responsible for choosing which exposures her growing child will experience. This might be a reasonable expectation for personal behaviors such as smoking, drinking, and exercise, but this responsibility cannot extend to adverse exposures that are socially determined. When researchers find that a mother's diet can put her child at risk for disease, the call for action can either focus on what mothers choose to eat or on what society has made available, or

both. An interpretation that faults a mother experiencing poverty for her poor diet and not the systemic disparities that create food deserts is unethical and should be called out during the funding and review process. I argue that we need to keep the focus of action regarding epigenetic mechanisms on interventions that target the social determinants that cause chronic disease and refrain from targeting individual behavior as the sole solution. This is especially important in the short term as the field works out how to interpret conflicting findings from epigenetic biomarkers.

We need a better context of exposures. Genetic and epigenetic studies lack the depth of investigation needed to capture the complex interactions of stressors that originate outside the body and ultimately become embodied. For example, stress and air pollution both increase inflammation, a mediator in the pathology of asthma[289] and should be assessed together to better understand health disparities in children.[290] Interdisciplinary teams must include experts from the social sciences in order to capture the same nuance and complexity that defines internal marks of exposure, physiologic confounders, and disease states.[151] We need a better understanding of low dose, long-term exposure periods across larger populations of society, especially in aggregate. We need longitudinal assessment of outcomes with detailed measures of duration, frequency, and intensity for a wide range of relevant exposures. Assessing exposures in isolation will not reflect the burden created by synergistic interactions. Combined assessment has not been a regulatory priority leaving scarce options for sophisticated models to explore how multiple contaminants interact.[88,166]

Next Steps: Interdisciplinary Partnerships

The changes that environmental exposures can make to the body over time involve a complex non-linear relationship between the environment, genes, and behavior.[15,65,66] To identify the upstream causes of disease, research teams need to have knowledge of geographic distribution of exposures and disease rates, human behaviors, human relationships, time trends, environmental sources, animal

models, and physiologic disease pathways to determine when evidence is sufficient to suggest causation.[93] Epigenetic disruption allows public health professionals from diverse knowledge bases a common starting point to work on interdisciplinary teams. Interdisciplinary investigation allows public health professionals to have a more comprehensive perspective of complex problems, such as the problem of chronic disease.[204]

Interdisciplinary teamwork is critical to assessing the preponderance of evidence necessary to infer harm. This integration has the potential to transform individual thinking and produce more comprehensive solutions to public health problems. Unlike a multidisciplinary team where each domain retains its identity and vocabulary in the working relationship, an interdisciplinary relationship among public health professionals truly integrates the knowledge base. Each discipline's methods have limitations and constraints. Interdisciplinary teamwork requires each investigator to be open to the merits of other disciplines to develop hypotheses that transcend each discipline's current understanding of research findings.[93]

Environmental embodiment spans a wide range of public health disciplines that cross government, industrial, and civil domains.[291] The Children's Environmental Health movement is a domain that has already begun to think and work interdisciplinarily and is broadening its public awareness campaign using education to shift risk perception.[186] Local to Seattle, the Children's Environmental Health Working Group[292] provides an illustrative example of interdisciplinary partnerships within the domain of public health intervention. As part of the Collaborative on Health and the Environment for Washington State (CEH-WA), this working group is embedded in the national discussion regarding children's health.

The CEH-WA working group's mission is: *"To work collaboratively with diverse groups to eliminate children's harmful environmental exposures in the Puget Sound region and beyond during their most critical developmental years: pre-conception to age eight."* To accomplish this mission, the working

group explicitly recruits public health professionals across any domain affecting children's health. Through an active listserv and monthly meetings, members update each other on recent scientific findings, outreach events, tools and resources, public health needs, and funding opportunities. Members collaborate on what the current health gaps are affecting children's health locally and discuss what activities are currently available to address these gaps. This collaboration streamlines efforts by allowing professionals in different public health sectors to access available resources and interventions they would not have known about otherwise.

The workgroup interactions also create the space for novel thinking on how to use group knowledge, time, and resources to better support children's environmental health. For example, this collaborative has launched a campaign to teach green cleaning techniques to school nurses and teachers in several Seattle school districts and daycare centers across our region. Green cleaning decreases asthma triggers in the classroom and decreases dermal and inhalation contact with epigenetic disruptors. This working group produced interdisciplinary activities including the Healthcare Provider Outreach Project, 3 biannual forums, and a wealth of educational and administrative resources.[292] Box 1 lists the professional affiliations of the most recent attendees. Their work has been successful in broader education.

Sample CEH-WA Participants 2015
- KC Hazardous Waste Management Program
- Environmental Coalition of South Seattle
- Evergreen State College
- WA State Department of Health
- Puget Sound Clean Air Agency
- NW Pediatric Environmental Health Specialty Unit
- EPA Region 10
- American Lung Association
- UW School of Public Health
- Seattle & KC Public Health
- Tribal Health Home Network
- Change Your Food, Change Your Life!
- WA State Department of Ecology
- Human Resources and Services Administration
- Institute of Neurotoxicology & Neurological Disorders

Box 1: Sample CEH-WA Participants 2015

Getting Political

Society is arguably tolerant of social injustice.[293] The Environmental Protection Agency was designed to regulate what level of industrial pollution is tolerable,[294] but has limited powers of enforcement, in part because some of the regulatory authority in the hands of individual states.[167] This

approach is positive when it gives local jurisdictions more control over their environment, but can also undermine efforts to regulate exposure sources that originate outside state borders.[295] Concurrently, centuries of racist segregation of social resources still leaves its print on housing policy, educational investment, hiring practices, healthcare access, incarceration, research, and nutritional policies.[296]

Education alone cannot fuel the health equity movement. Citizens must have access to the political system in ways to exercise collective power.[261] Community organizing, through institutions, is a method for uniting community voices in solidarity to influence political decision-making. An academic-civil sector relationship through community organizing rooted in accountability and the common good is synergistic to the interests of both parties. Academia seeks new opportunities for community engagement and service learning to foster student growth and development. Students seek a portal to disseminate research findings, understand broader community pressures, and participate in local policy. The civil sector gains partners that have access to didactic knowledge to inform campaign awareness, strategy, and educational actions. Moreover, the alliance of institutes becomes stronger based on the activities of their members working in partnership to win on local issues. By creating a space and support for students to participate in community organizing, the academic institution would also be better poised to act on its value of social justice.

We Need Action

The reality of daily contaminant exposures carries a risk to health that is 'grossly underestimated' (President's Cancer Panel).[166] Human-centric values have fueled rational self-interests that allow privileged individuals to deplete common resources in a manner contrary to the best interests of society at large. This is by definition a tragedy of the commons.[297] The tragedy is born out in health disparities where inequitable distributions of environmental contamination and social resources are deteriorating our communal health, starting in utero. In moving towards dualistic values, policies would

need to focus on sustainability and stewardship. These values support the adoption of the precautionary approach to chemical regulation.

Being able to understand the features of social inequity that stimulate the stress response system and track the pathway these signals take through the body into the genome will assist public health professionals in many ways. A broader awareness of how social policies are impacting health through biological embodiment will assist policy makers in designing policies that reduce stressful transactions within a community and/or promote resilience. A biological understanding of embodiment will help public health professionals collaborate to identify better biomarkers of exposures and pre-disease states and ask more insightful questions. This knowledge can assist intervention efforts, outcomes evaluation, and population surveillance for public health professionals focused on chronic disease prevention.

The goal of this work was to broaden public health efforts and political support for the health equity movement by 1) explaining environmental embodiment through epigenetic disruption to understand how social stressors and environmental toxicants can affect health at the population level, and 2) exploring opportunities for community engagement to act on these drivers. All communities, regardless of inequity, have developed different strategies of resilience. Using the lens of environmental embodiment, public health as an institution is better positioned to act on our duty to foster health by removing the socially derived causes of disease.

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