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Ruby Wiener April 12, 2022

FEWER DRUGS, MORE TALKING: RELATIONSHIP-BASED CARE AND INTEGRATIVE SOLUTIONS FOR CHRONIC DISEASE

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Arts with Honors

Interdisciplinary Studies in Society and Culture Department

2022

Abstract

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This paper explores the effect of stress on health, specifically focusing on chronic disease. A current problem in chronic disease treatment is segmentation of treatment. Integrative and relationship-based care solutions bring social determinants of health into the treatment plan. The paper explores the relationship between research and medicine, focusing on integrative and chronic disease research. Lastly, the paper utilizes a case study of a clinical research study (MND-CKD) testing meditation as integrative intervention for chronic kidney disease. This pilot study explores two outcomes mirroring integrative health in practice: self-reported levels of depression, anxiety, and stress and blood pressure and found reductions in all four measurements. The paper ultimately discusses in theory and tests in practice the application of integrative medicine and relationship-based care in chronic disease.

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Acknowledgements

Thank you to the Park Lab, specifically Jinhee Jeong, Cortnie Hartwig and Dr. Park, for all their guidance and support over the last two years and for helping me to grow as a person, student, and researcher.
Thank you to Dr. Eisen for taking on this project and working with me (even on sabbatical).
Thank you to the Interdisciplinary Studies Department and the Institute for Liberal Arts for being my academic home at Emory and inspiring the intellectual curiosities and conversations that spawned this research.

Thank you to my family and friends for helping me to find the right words. I am eternally grateful to each of you.

Table of Contents

There is an animal inside me,
clutching fast to my heart,
a huge crab.
The doctors of Boston
have thrown up their hands.
They have tried scalpels,
needles, poison gasses and the like.
The crab remains.
It is a great weight.

- From *The Poet of Ignorance*, Anne Sexton[1]

It only remains to be added that broadening of our knowledge in these respects is of benefit, not only with regard to the human compulsion to understand, but also to the practical healing art. For man also, in health and sickness, is not just the sum of his organs, but is indeed a human organism.

– Walter Hess, Nobel Prize in Physiology or Medicine Lecture, 1949[2]

[1] Sexton, Anne, "The Poet of Ignorance," *The Paris Review*, accessed December 15, 2021, https://www.theparisreview.org/poetry/3912/the-poet-of-ignorance-anne-sexton.
[2] "The Nobel Prize in Physiology or Medicine 1949," NobelPrize.org, accessed December 15, 2021, https://www.nobelprize.org/prizes/medicine/1949/hess/lecture/.

My fascinations and frustrations with medicine began simultaneously. My mother's battles with chronic illness sparked many questions in me – why does every visit with a new doctor end with a recommendation of some drug that already hasn't worked? Why don't they get to know her and listen to her? When did medicine lose touch with humanity? And one that stuck with me over the years: isn't there a better way? I hope to use this research to imagine a better future for medicine that I want to be a part of – an integrative, relationship-based care approach that places the patient's life at the center of the healing process.

About two years ago, I sat down with Cortnie Hartwig, a post-doctoral fellow in Dr. Jeanie Park's Human Physiology Lab at Emory Medical School, to talk about her research focus which would eventually become my own: chronic stress and its effect on health. Prior to this introduction, my clinical experiences volunteering with marginalized communities had sparked my interest in accessibility to healthy living. The Park Lab is particularly interesting because the interventions they work with, namely meditation and exercise, are accessible means of illness prevention. Further, the lab focuses on research within underserved populations with increased risk of cardiovascular disease and decreased access to means of prevention. My specific project for the Park Lab utilizes measures of cardiovascular health to assess how patients with chronic kidney disease are affected by stress-reduction meditation training compared to both pharmacological and alternative treatments. My first step in gaining footing within the lab and paving a course for independent study was lots and lots of reading.

The biomedical academic community heavily relies on one another's research to fine-tune their own. Most of the literature about meditation and chronic disease, particularly within cardiovascular research, finds that meditation provides significant beneficial reductions in blood

pressure.[3] In reading recent studies on meditation within similar populations, I found a common narrative woven delicately into the introductions and conclusions of method-, graph-, and statistics-heavy papers. Most researchers found a way to suggest that the impetus for their research was bigger than just meditation or illness. They were commenting on the system at large.

This thread left me curious about the implications of modeling a patient-care system using integrative and alternative evidence-based research in conjunction with the more pharmaceutically focused research our medical treatment processes predominantly rely on today. Integrative treatment and relationship-based care forces social determinants of health into clinical conversations because they are patient-centric. By refocusing care on the entire person instead of isolated symptoms, health is examined as an aspect of their life as a whole. This care model combats paternalism in medicine and builds patient-physician relationships which have been demonstrated to improve health outcomes.[4]

The current system falls short for many chronic illness patients. Without proper support, the weight of a diagnosis and the subsequent responsibility of juggling different specialists and prescriptions further burdens patients. By combining practices and treatments from different specialties, be they alternative or conventional, integrative medicine creates cohesion across a treatment plan, alleviating excess stressors. Stress instigates and exacerbates inflammation, which if not the root of the problem, further complicates all conditions.

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[3] Anjalee Thanuja Amarasekera and Dennis Chang, "Buddhist Meditation for Vascular Function: A Narrative Review," *Integrative Medicine Research* 8, no. 4 (December 2019): 252–56, https://doi.org/10.1016/j.imr.2019.11.002.

[4] Sherrie H. Kaplan, Sheldon Greenfield, and John E. Ware, "Assessing the Effects of Physician-Patient Interactions on the Outcomes of Chronic Disease," *Medical Care* 27, no. 3 (1989): S110–27.

Chronic stress at work or home is associated with a 40-50% increase in the occurrence of coronary heart disease;[5] chronic stress induces immune dysregulation, reducing the patient response to vaccines, slowing wound healing, and increasing risk of severe infections;[6] being chronically stressed makes you more susceptible to periodontal disease;[7] chronic stress promotes tumorigenesis and cancer development;[8] and 7 in 10 Americans report that they regularly feel the physical and nonphysical symptoms of chronic stress.[9] It is impossible to ignore its effect on every patient. The cost alone of chronic care for the more than 133 million Americans who live with it totals over $1.5 trillion a year - 75% of all US medical expenses.[10] Chronic stress disproportionately affects marginalized populations and is compounded generationally via epigenetic and social mechanisms I will discuss later. There is a clear need for accessible treatment options and improvements to the existing care model. Even though the health implications of stress are clear, treatment continues to focus on symptoms without addressing stress itself. Interdisciplinary approaches provide more perspectives and richer solutions. Through integrative medicine and relationship-based care, all aspects of the patient's life are addressed in care plans. This change improves treatment by adding care to our existing

[5] Andrew Steptoe and Mika Kivimäki, "Stress and Cardiovascular Disease," *Nature Reviews Cardiology* 9, no. 6 (June 2012): 360–70, https://doi.org/10.1038/nrcardio.2012.45.
[6] Jonathan P. Godbout and Ronald Glaser, "Stress-Induced Immune Dysregulation: Implications for Wound Healing, Infectious Disease and Cancer," *Journal of Neuroimmune Pharmacology* 1, no. 4 (December 1, 2006): 421–27, https://doi.org/10.1007/s11481-006-9036-0.
[7] Kimberly R. Warren et al., "Role of Chronic Stress and Depression in Periodontal Diseases," *Periodontology 2000* 64, no. 1 (2014): 127–38, https://doi.org/10.1111/prd.12036.
[8] Shirui Dai et al., "Chronic Stress Promotes Cancer Development," *Frontiers in Oncology* 10 (2020): 1492, https://doi.org/10.3389/fonc.2020.01492.
[9] "Stress in America™ 2020: A National Mental Health Crisis," accessed March 29, 2021, https://www.apa.org/news/press/releases/stress/2020/report-october.
[10] Victoria Maizes, David Rakel, and Catherine Niemiec, "Integrative Medicine and Patient-Centered Care," *EXPLORE* 5, no. 5 (September 2009): 277–89, https://doi.org/10.1016/j.explore.2009.06.008.

knowledge-base and understanding of disease etiology, correcting the separation of mind and body without losing what we have gained in our understanding of each.[11]

Body- or organ-isolated analysis is common to high-tech medicine and has led to some major leaps in our understanding of the physiological mechanisms of disease. However, the evidence of the mind implicating physiological symptoms is clear in every aspect of illness. Continuing to treat the mind separate from the body is to ignore this reality; continuing to treat symptoms without treating the person with whom they are attached is to ignore this reality. Organ-isolated treatment does not necessarily address the complexity of healing.[12] Integrative medicine comes from a growing recognition that, although highly successful in some areas, high-tech medicine cannot fully address the growing epidemic of chronic diseases.[13] In addition to conventional pharmaceutical or surgical treatments, integrative medicine seeks to include all aspects of healing to restore and foster health: the biological mechanisms of defense and repair, the social unit in which the patient lives, and the patient's own propensity to strengthen and enhance their physical, emotional, social, and spiritual health. Integrative medicine is a means to organize and regulate a holistic approach to medical treatment, a framework within which people will be treated as people instead of disparate minds and bodies, a mechanism for closing the gaps between the biological and humanitarian sides of treatment.[14] It forces a patient's life into the conversation: their cultural beliefs, their work life, their great grandma's homemade salve.

I will focus on stress and its pathophysiology as an exemplar to explore greater issues in social determinants of health and chronic disease. To investigate the ways in which the current

[11] David Rakel and Susan K. Golant, *The Compassionate Connection: The Healing Power of Empathy and Mindful Listening*, First edition (New York: W.W. Norton & Company, 2018).
[12] Richard Gannotta et al., "Integrative Medicine as a Vital Component of Patient Care," *Cureus*, August 4, 2018, https://doi.org/10.7759/cureus.3098.
[13] Maizes, Rakel, and Niemiec, "Integrative Medicine and Patient-Centered Care."
[14] Allen Barbour, *Caring for Patients: A Critique of the Medical Model* (Stanford University Press, 1997).

system can improve chronic disease treatment, I will examine conventional and alternative evidence-based medicine, considering the gaps between research and practice for chronic disease patients.

Chapter 1: Stress and Health

The idea that stress negatively affects health is not new; stress has been called many names, but its associated symptoms have remained the same. In the late 19th century, George Beard (1839-1883), an American neurologist, diagnosed patients with fatigue, anxiety, headache, impotence, neuralgia, and depression with neurasthenia. He explained the disease as being the "result of exhaustion of the central nervous system's energy reserves due to the stresses of modern life."[15] He published an article in the *Boston Medical and Surgical Journal* in April of 1869 and opened with words I now echo when describing my research: "I am to speak tonight of a condition of the system that is, perhaps more frequently than any other, in our time at least, the cause and effect of disease."[16] Neurasthenia was later nicknamed "Americanitis" by William James, a famous American psychologist, who identified the disease with the "hustle and bustle of the American temperament." [17]

Today, stress means many things. For salespersons, it might be the looming quota they have yet to reach. In my experience living and studying in an intellectually competitive environment, "normal" is a state of stress, of constant complaints of assignments and lack of sleep, of a cough that lingers all semester and a CVS whose cold and flu shelves are always sold out. Neurasthenia connects the ill effects of life with these and other chronic symptoms that have become so "normal" they are not addressed as ailments of their own. In a way, this unique diagnosis is the one of the few at the nexus of culture and health.

[15] Jacquelyn H. Flaskerud, "Neurasthenia: Here and There, Now and Then," *Issues in Mental Health Nursing* 28, no. 6 (January 1, 2007): 657–59, https://doi.org/10.1080/01612840701354638.
[16] George Beard, "Neurasthenia, or Nervous Exhaustion," *The Boston Medical and Surgical Journal* 80, no. 13 (April 29, 1869): 217–21, https://doi.org/10.1056/NEJM186904290801301.
[17] Smithsonian Magazine and Greg Daugherty, "The Brief History of 'Americanitis,'" Smithsonian Magazine, accessed October 25, 2021, https://www.smithsonianmag.com/history/brief-history-americanitis-180954739/.

The separation of health from life is a largely Western idea. In very broad strokes, Eastern - specifically Oriental and Ancient Chinese - medical literature has accumulated from millions of practitioners over thousands of years. The Western approach divides health from disease and emphasizes a person's body. While physicians treat disease; detection, prevention, rehabilitation, and therapy are outsourced. The Eastern idea of health and disease is more a question of balance; the physician's job is to promote health and treat disease when it occurs.[18] Eastern techniques today are generally referred to as 'alternative' while Western techniques are 'conventional.' This dichotomy is hyperbolic. Treatment does not flip at a certain longitudinal degree and there are physicians in all parts of the world practicing either one or both ways. Extremes help to highlight key components of each. The neurasthenia diagnosis bringing together culture and health is an example of the blend of the two.

To learn more about the East/West divide, I spoke with Tenzin Namdul, a Tibetan medical practitioner and medical anthropologist. Our conversation centered around a question which is central to his work: why are there so many obstacles to alternative treatment in the West? His work explores the intersection of the biological and cultural components of human health and illness. He believes that western medical practice today focuses on the physical components of illness and therefore prioritizes physical interventions, specifically those operating at the cellular and molecular level. The American cultural unconscious tie between what is new and what is best is ever present in medicine. Namdul believes the focus on the small-scale aspects of physiological disease removes the patient from the picture and, in doing so, removes patient-experience-centric care models like meditation. Integrative medicine brings

[18] Julia J. Tsuei, "Eastern and Western Approaches to Medicine," *Western Journal of Medicine* 128, no. 6 (June 1978): 551–57.

together age-old conceptual understandings of health with modern technological knowledge of pathophysiology and disease mechanisms.

Chapter 1 will explain the mechanism through which stress results in a physiological disease state, discuss the impact of stress on marginalized communities and resulting health disparities, and introduce meditation as an accessible intervention to this cycle.

1.1: Mechanisms through which Stress Causes and Exacerbates Disease

To understand how stress can be seen as both a cause and effect of disease, let us first examine its physiological effect on a healthy body. When your mind detects a stressor, physical or emotional, it enacts a series of cascades to mitigate a response. This is commonly known as the "fight or flight" response. The pathway and residual effects of the system being activated are important for understanding of how chronic stress affects long-term health. For a simple example, consider a splinter. The first line of defense is breached when the splinter pierces the skin and all of the germs and bacteria on the splinter are now inside the body. These germs are recognized as non-self by mast and dendritic cells that sit just under the surface of the skin. Mast and dendritic are immune system cells and will facilitate an inflammatory cascade to stop the pathogenic particles on the splinter from infiltrating further into the body. Common symptoms of inflammation – pain, swelling, heat, and redness – are all caused by this cascade.[19] When the mast and dendritic cells recognize the danger, they release chemokines and chemical transmitters that communicate with the rest of the body via cellular interactions to alert nearby cells of the invasion. When measuring levels of inflammation, levels of chemokines in the blood can show

[19] C. Gabay and I. Kushner, "Acute-Phase Proteins and Other Systemic Responses to Inflammation," *The New England Journal of Medicine* 340, no. 6 (February 11, 1999), https://doi.org/10.1056/NEJM199902113400607.

levels of inflammation in a quantitative way.[20] Certain chemokines are specific to acute responses, while others are much more common in chronic inflammatory states.

For a common example, mast cells release histamine. This may be a pretty familiar term if you have ever taken an anti-histamine when spring allergies hit. Allergies are actually an inflammatory response to foreign substances. When you are jealous of your friends' lack of reaction to all of the pollen in the environment, you are really jealous that their bodies don't recognize pollen as a foreign substance invading the body. Your allergic reaction to the environment is really just a pickier security system. The anti-histamine turns off this reaction to get rid of spring allergy symptoms like a runny nose.

Returning to the splinter example, histamine *is* wanted because the threat *is* real. Histamine causes vasodilation and capillary expansion, causing redness in the area. When the capillary blood vessel walls expand, fluids pool to the area causing swelling. Capillary expansion is caused by the cells of the blood vessel walls growing. This introduces tiny gaps inbetween cells in the walls, allowing for an easier exchange between "helpers" and the invading splinter. White blood cells pool in the area and immune system cells such as neutrophils, which are attracted to histamine, squeeze through the gaps in the capillary walls to digest damaged mast- , dendritic- , skin- cells and bacteria. These are all acute and regional reactions to a stressor, the splinter. In this example, it is evident what the stressor is (the splinter) and why it triggered such a response (splinter's germs). Once the immediate danger has passed and foreign substances are no longer detected, resolution mediators that oppose pro-inflammatory markers switch off the

[20] Jesse Huang et al., "Inflammation-Related Plasma and CSF Biomarkers for Multiple Sclerosis," *Proceedings of the National Academy of Sciences of the United States of America* 117, no. 23 (June 9, 2020): 12952–60, https://doi.org/10.1073/pnas.1912839117.

inflammatory signaling pathways.[21] Stress is good and necessary for your body to respond to threats. It is only problematic when dysregulated. In this healthy example, the splinter is removed, pathogens cleared, and all returns to normal.

When the stressor isn't physical, the inflammatory cascade can still be activated. There are two signaling systems that direct the mental side of the stress reaction: the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis. When a person experiences something stressful, the amygdala is the first to sound the alarm. The amygdala is an area of the brain in charge of processing emotions and sends a distress signal to the hypothalamus. The hypothalamus, a region of the forebrain, controls body temperature, thirst, hunger, and homeostasis.

The hypothalamus is similar to the command center of the brain. It communicates with the rest of the autonomic nervous system, which, as its name suggests, is responsible for automatic bodily functions like breathing, blood, pressure, and heartbeat. It is divided into two competing signaling systems: the sympathetic and parasympathetic. The sympathetic is largely responsible for active, "fight or flight" stress responses, while the parasympathetic stimulates "rest and digest" reactions. These two components work together to regulate the body's stress response and to appropriately turn the response on and off.

After the distress signal is sent to the hypothalamus and the sympathetic nervous system is consequently activated, signals are passed through autonomic nerves to the adrenal glands which respond by releasing epinephrine, commonly known as adrenaline, into the bloodstream.[22] This is what makes your heart beat faster (pushing blood to your vital organs and muscles), your

[21] Michelle A. Sugimoto et al., "Resolution of Inflammation: What Controls Its Onset?," *Frontiers in Immunology* 7 (April 26, 2016): 160, https://doi.org/10.3389/fimmu.2016.00160.
[22] Joshua A. Waxenbaum, Vamsi Reddy, and Matthew Varacallo, "Anatomy, Autonomic Nervous System," in *StatPearls* (Treasure Island (FL): StatPearls Publishing, 2021), http://www.ncbi.nlm.nih.gov/books/NBK539845/.

breathing quicker (lungs taking in as much oxygen as possible with each breath), your senses sharper (to assess the threat), and sugar stores released (supplying energy to the whole body so you can react to the stressor).[23] As stated previously, this is a healthy reaction. We need our bodies to respond to stressors and get adrenaline pumping to react appropriately to our environments. Properly regulated stress ebbs and flows, returning to safe baseline levels when the threat has disappeared. However, when stress levels breach a certain threshold and begin causing harm, this is deemed pathological stress.

For example, let's say that a threshold exists at some arbitrary stress level 100. Every person's baseline stress level when going about day-to-day life is at a different value. The most peaceful person who faces zero obstacles and naps happily on the beach all day long may start at 1. When this person is stressed, their stress level peaks around 20 and returns back to 1 shortly after, never getting close to pathological levels. On the contrary, a person in a constant state of stress may start around 70. The same level threat brings this person to stress level 90 and they may have a harder time bringing their stress level back down. As stress accumulates, it gets harder and harder to lower your baseline level. Soon, your baseline value is much closer to the pathological stress level. A small increase in stress, one which would never affect the health of our beach friend, now places this person in danger. Due to cyclical, systemic factors, marginalized populations are more likely to have higher baseline stress levels, placing them at increased risk for the effects of pathological stress such as cardiovascular disease and immune dysregulation.

[23] Michael J. Joyner, Nisha Charkoudian, and B. Gunnar Wallin, "A Sympathetic View of the Sympathetic Nervous System and Human Blood Pressure Regulation," *Experimental Physiology* 93, no. 6 (June 2008): 715–24, https://doi.org/10.1113/expphysiol.2007.039545.

1.2: The Effect of Chronic Stress on Marginalized Populations

Chronic stress particularly affects marginalized communities and is partially responsible for elevated cardiovascular and chronic disease risk for these populations. Researchers at RAND, a policy based non-profit research organization, constructed a model assessing how stress can accumulate generationally: "an accretion of despair, disinvestment, discrimination, and disparity."[24] This is a societal accumulation of stress. If every person started at stress level 1, these factors would raise baseline stress of marginalized communities solely through external factors. On top of this, stress can be heritable.

Epigenetics is a field of biology that analyzes the switching "on" and "off" of genes in response to environmental factors. These epigenetic on/off markers are one of the ways that the stresses people face throughout their lifetime are encoded. Recent literature has found that changes accumulating throughout a person's lifetime are transmitted to their offspring.[25] A pregnant mother with high stress levels passes on a higher baseline level of stress to her child.[26] This means the child is extra sensitive to stressors and more susceptible to breaching the threshold of pathological stress. A 2020 study found that pregnant women of color are disproportionally more likely to experience chronic stress in the form of discrimination, historical trauma, and acculturation, resulting in psychophysiological ramifications for both the

[24] 1776 Main Street Santa Monica and California 90401-3208, "Stress Accumulates in Marginalized Communities, Generation After Generation," July 8, 2020, https://www.rand.org/blog/rand-review/2020/07/stress-accumulates-in-marginalized-communities.html.
[25] Amy Lehrner and Rachel Yehuda, "Cultural Trauma and Epigenetic Inheritance," *Development and Psychopathology* 30, no. 5 (December 2018): 1763–77, https://doi.org/10.1017/S0954579418001153.
[26] Patrick O McGowan and Stephen G Matthews, "Prenatal Stress, Glucocorticoids, and Developmental Programming of the Stress Response," *Endocrinology* 159, no. 1 (January 1, 2018): 69–82, https://doi.org/10.1210/en.2017-00896.

pregnant women and her child.[27] Gender-based violence and trauma can dysregulate the central nervous, endocrine, and immune systems of survivors, placing them at increased risk for a multitude of health problems.[28] Allostatic load is a term referring to the "wear and tear" on the body a person who is exposed to repeated or chronic stress experiences. People who self-identify as homosexual or bisexual display higher levels of allostatic load than heterosexual individuals.[29] Financially disadvantaged children are more likely to encounter an array of physical and psychosocial stressors.[30] This pattern is mirrored in the racial and ethnic disparities in the prevalence of cardiovascular and chronic diseases in the United States. In 2019, the CDC reported that non-Hispanic Black persons are most likely to have hypertension, obesity, and diabetes.[31] Diabetes provides an example of the ways food insecurity affects the incidence and management of chronic disease; adults living with the most severe levels of food insecurity have more than twice the risk of diabetes.[32] Ethnic minorities and those living below the poverty line have higher incidence and worse outcomes in common chronic diseases such as hypertension, cancer, cardiovascular disease, diabetes, and obesity. Further, racial and ethnic disparities in hospitalizations from chronic conditions have increased in the last 20 years, resulting in over

[27] Elisabeth Conradt, Sierra E. Carter, and Sheila E. Crowell, "Biological Embedding of Chronic Stress Across Two Generations Within Marginalized Communities," *Child Development Perspectives* 14, no. 4 (2020): 208–14, https://doi.org/10.1111/cdep.12382.
[28] Bushra Sabri and Douglas A. Granger, "Gender-Based Violence and Trauma in Marginalized Populations of Women: Role of Biological Embedding and Toxic Stress," *Health Care for Women International* 39, no. 9 (September 2, 2018): 1038–55, https://doi.org/10.1080/07399332.2018.1491046.
[29] Vickie M. Mays et al., "Chronic Physiologic Effects of Stress among Lesbian, Gay, and Bisexual Adults: Results from the National Health and Nutrition Examination Survey," *Psychosomatic Medicine* 80, no. 6 (2018): 551–63, https://doi.org/10.1097/PSY.0000000000000600.
[30] Gary W. Evans and Pilyoung Kim, "Childhood Poverty, Chronic Stress, Self-Regulation, and Coping," *Child Development Perspectives* 7, no. 1 (2013): 43–48, https://doi.org/10.1111/cdep.12013.
[31] "Racial and Ethnic Disparities in Heart Disease," n.d., 2.
[32] Hilary K. Seligman and Dean Schillinger, "Hunger and Socioeconomic Disparities in Chronic Disease," *New England Journal of Medicine* 363, no. 1 (July 2010): 6–9, https://doi.org/10.1056/NEJMp1000072.

430,000 excess hospitalizations among non-Hispanic Blacks compared to non-Hispanic Whites.[33]

The resulting factors of these health disparities are called social determinants of health. These determinants are root causes of chronic stress such as systemic racial inequality; disparities in income, housing, environmental exposures, and education; violence, trauma and abuse. Each lead to the disproportionate prevalence of chronic conditions in marginalized populations. The current system does not always address the complex and intertwined health and social challenges of its patients. This is one benefit to an integrative, relationship-based care approach to treatment. Relationship-based care requires the physician or healthcare worker to consider the patient's entire life, encouraging social determinants into the conversation, as opposed to treating an isolated illness, which in cases of chronic conditions, may not address underlying factors. There are many avenues to reducing chronic stress. While policy reform and action combating stigmatization and foundationally disparate systems fall outside the scope of my thesis, my research uses accessible means of prevention and treatment in hopes of reducing the downstream health effects of chronic stress.

The heritability and systemic nature of chronic stress may seem too big to overcome. However, it is possible to change a person's baseline stress level to move farther away from pathological levels. In the same way epigenetic markers can be turned on, they can be turned off. Studies on meditation have found that participants lower their reactivity to stressors in testing

[33] Riddhi P. Doshi et al., "Racial and Ethnic Disparities in Preventable Hospitalizations for Chronic Disease: Prevalence and Risk Factors," *Journal of Racial and Ethnic Health Disparities* 4, no. 6 (December 1, 2017): 1100–1106, https://doi.org/10.1007/s40615-016-0315-z.

and this change is seen in a decrease in inflammatory markers in the blood and in improvements to cardiovascular health.[34]

1.3: Meditation as a Stress Reduction Intervention

The MND-CKD study in the Park Lab tests meditation as a means of self-regulating a patient's response to stress. The study uses meditation-based stress reduction (MBSR) to test the sympathetic nervous system response in patients with chronic kidney disease (CKD). Chronic overactivation of the sympathetic nervous system is elevated in patients with end-stage renal disease and CKD is a major factor contributing to increased cardiovascular risk, causing hypertension (high blood pressure) and diabetes.

The idea that meditation could be used to override the nervous system's stress activation was initially popularized in 1972 by Herbert Benson, a professor of Medicine at Harvard Medical School. He presented a paper to the National Institute of Mental Health with data supporting the hypothesis that just as there are known physiological stress reactions in the body, there exists an opposing "relaxation response."[35] Even in the 70's, this idea was not entirely new.

In Walter Hess' 1949 Nobel Lecture, he discussed two competing energy systems and denoted these as *ergotropic*, favoring the expenditure of energy, and *trophotropic*, promoting rest and reconstitution of energy stores.[36] His research used electric impulses to track the source of the "vegetative control system," which we now know as parasympathetic. He saw the parasympathetic system as "protective against overloading" of internal organs in their response to stressors. Benson expands on this notion and posits that with meditation training a person can

[34] Thaddeus W. W. Pace et al., "Effect of Compassion Meditation on Neuroendocrine, Innate Immune and Behavioral Responses to Psychosocial Stress," *Psychoneuroendocrinology* 34, no. 1 (January 2009): 87–98, https://doi.org/10.1016/j.psyneuen.2008.08.011.
[35] Herbert Benson, John F. Beary, and Mark P. Carol, "The Relaxation Response," *Psychiatry* 37, no. 1 (February 1, 1974): 37–46, https://doi.org/10.1080/00332747.1974.11023785.
[36] "The Nobel Prize in Physiology or Medicine 1949."

consciously invoke a parasympathetic response. Among other relaxation techniques, Benson focuses on Transcendental Meditation (TM), a silent mantra-driven meditation fathered by Maharishi Mehesh Yogi in India in the mid-1950s.[37] The physiological changes caused by TM are different than a regular resting state. The decrease in oxygen consumption, heart rate, respiratory rate, and muscle tension show parasympathetic activation. A cynic may say this is the same as a stressed-out person just taking a nap. What is special about the relaxation response is that increases in EEG alpha wave activity,[38] characteristic of a wakeful state, in the brain reflect an "integrated hypothalamic response," increased mental alertness and physical rest.[39] I like to think of meditation as sending out lots of little police to navigate the traffic when a busy intersection stoplight is out. The flashing red lights of the stoplight are like the signals reaching the HPA axis saying, "there is still a problem!" However, meditation police are there to calm everyone down and guide the body out of chaos.

In the last fifty years, many researchers have tested the relaxation response in diverse patient and healthy populations, finding decreases in blood pressure in hypertensive patients;[40] lower levels of anxiety, depression, and improve well-being in stressed (otherwise healthy)

[37] Robert Keith Wallace, "Physiological Effects of Transcendental Meditation," *Science* 167, no. 3926 (March 27, 1970): 1751–54, https://doi.org/10.1126/science.167.3926.1751.
[38] Gregg D. Jacobs, Herbert Benson, and Richard Friedman, "Topographic EEG Mapping of the Relaxation Response," *Biofeedback and Self-Regulation* 21, no. 2 (June 1, 1996): 121–29, https://doi.org/10.1007/BF02284691.
[39] Michael C. Dillbeck and David W. Orme-Johnson, "Physiological Differences between Transcendental Meditation and Rest," *American Psychologist* 42, no. 9 (1987): 879–81, https://doi.org/10.1037/0003-066X.42.9.879.
[40] Howard L. Bleich, Emily S. Boro, and Herbert Benson, "Systemic Hypertension and the Relaxation Response," *New England Journal of Medicine* 296, no. 20 (May 19, 1977): 1152–56, https://doi.org/10.1056/NEJM197705192962008.

adults;[41] improvements in sleep quality and anorexia in cancer patients,[42] and more.[43] The specific molecular mechanisms of the benefits of mediation are even beginning to be elucidated.[44]

Medicine today relies on research to inform treatment, a framework termed evidence-based medicine. The most straightforward applications of evidence-based medicine, for example the development and prescription of a drug to treat a known bacterial infection, are incredibly successful. This is rarely the case in chronic disease patients. Alternative, accessible forms of care such as meditation provide an interesting case study into the limitations of pharmaceutically based medicine and organ-isolated research in chronic disease treatment. Examination of the research guiding treatment also helps to highlight missing links in the treatment pathway. Chapter 2 will discuss evidence-based medicine, its successes and limitations in chronic disease treatment, and the ways in which an integrative, relationship-based care approach fills in the gaps between academic unknowns and clinical care.

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[41] Catherine Calder Calisi, "The Effects of the Relaxation Response on Nurses' Level of Anxiety, Depression, Well-Being, Work-Related Stress, and Confidence to Teach Patients," *Journal of Holistic Nursing: Official Journal of the American Holistic Nurses' Association* 35, no. 4 (December 2017): 318–27, https://doi.org/10.1177/0898010117719207.

[42] Mehdi Harorani et al., "The Effect of Benson's Relaxation Response on Sleep Quality and Anorexia in Cancer Patients Undergoing Chemotherapy: A Randomized Controlled Trial," *Complementary Therapies in Medicine* 50 (May 2020): 102344, https://doi.org/10.1016/j.ctim.2020.102344.

[43] Albert J. Arias et al., "Systematic Review of the Efficacy of Meditation Techniques as Treatments for Medical Illness," *Journal of Alternative and Complementary Medicine (New York, N.Y.)* 12, no. 8 (October 2006): 817–32, https://doi.org/10.1089/acm.2006.12.817.

[44] Manoj K. Bhasin et al., "Specific Transcriptome Changes Associated with Blood Pressure Reduction in Hypertensive Patients After Relaxation Response Training," *Journal of Alternative and Complementary Medicine (New York, N.Y.)* 24, no. 5 (May 2018): 486–504, https://doi.org/10.1089/acm.2017.0053.

Chapter 2: Linking Research and Medicine

When chicken hatchlings are born, large commercial hatcheries divide them by gender because the males and females have different diets. Chicken sexers pick up each chick, quickly determine its sex, and sort the chick into the correct bin. The task is famously difficult because male and female chicks look alike. Sorting is based on very subtle visual cues, but even professional sexers cannot describe what those cues are. Instead, they would glance at the chick's rear and simply know which bin to put it in This is how the skill is taught. Professionals stand over the apprentice's shoulder and watch. The student picks up a chick, examines its rear, and tosses it into one bin or the other. The master gives feedback: yes or no.[45] Few professions run successfully on intuition, but before evidence-based medicine informed physician decision making, intuition and experience were primary means of creating treatment plans. Fifty years ago, pregnant women were given enemas to prevent infection during childbirth, a practice which was not only extremely painful, but was later tested and found to have no effect on infection rates.[46] These findings helped to discourage and end what was previously routine medical practice.

Evidence-based medicine is defined by Gordon Guyatt, who coined the term, as the "conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients."[47] Stelian Hodorogea, an obstetrician and assistant professor at the Medical University of Chisinau, explained how evidence-based medicine changed his view of what it means to be a physician: "If I ask five colleagues about their opinion on a case, I get

[45] David Eagleman, *Incognito: The Secret Lives of the Brain* (New York: Pantheon Books, 2011), https://www.yourcloudlibrary.com.
[46] Ludovic Reveiz, Hernando G Gaitán, and Luis Gabriel Cuervo, "Enemas during Labour," *The Cochrane Database of Systematic Reviews* 2013, no. 7 (July 22, 2013): CD000330, https://doi.org/10.1002/14651858.CD000330.pub4.
[47] Ariel L. Zimerman, "Evidence-Based Medicine: A Short History of a Modern Medical Movement," *AMA Journal of Ethics* 15, no. 1 (January 1, 2013): 71–76, https://doi.org/10.1001/virtualmentor.2013.15.1.mhst1-1301.

five different answers, but with evidence-based medicine I know I can find the best current practice."[48] Evidence-based medicine revolutionized the practice of medicine and the purpose and application of biomedical research. In this chapter, I track its development and describe limitations when applied to chronic disease research.

2.1: Evidence-Based Medicine: How Research Asks and Answers Medicinal Questions

Evidence takes on many meanings. In science and in life, not all evidence is equal. Evidence-based medicine (EBM) ranks various methods of research by reliability. This means evidence from some studies is better and more applicable than others. This evidence is then interpreted by physicians, a key step in the process, to help aid in treatment decision making. The process is not so different than the scientific method taught in my elementary school in the 4th grade. First, you make an observation that begets a question. The cycle follows: do some research, come up with a hypothesis, test it experimentally, analyze the data, draw a conclusion, and make a new observation that begets a question based on what you found out. Either your initial hypothesis was right or wrong, but either way the experiment's results lead to new observations, research questions, and hypotheses. There is no final conclusion. The cycle continues and research leads to more research. Every research paper ends with recommendations for future directions. This is how we progress in science and how the community supports each other – by leaning on one another's research to finetune their own.

This process is incredibly successful in some instances, which is why it has been around so long. The first antibiotic was developed by the chemist Paul Ehrlich as a treatment for syphilis. He sought out an intervention that targeted the disease entity, a bacterial basis of

[48] "Evidence-Based Medicine – a New Approach to Childbirth," accessed January 17, 2022, https://www.euro.who.int/en/health-topics/Life-stages/maternal-and-newborn-health/country-work/republic-of-moldova/evidence-based-medicine-a-new-approach-to-childbirth.

syphilis that had recently been discovered, and eliminated it. Observation: bacteria is responsible for the disease. Hypothesis: there is a particular chemical that could bind to these bacteria and kill them. He eventually found such a chemical and proved it to be effective in eliminating the syphilis bacteria and thereby alleviating symptoms of the disease.[49]

Ehrlich tracked down one disease to one bacterium, but things are not always quite so simple. Some diseases are too complex for this approach. For example, autism disorder is not really one disease, but a set of symptoms that appear together. Depression is not really one disease, but rather a set of symptoms that could be traced back to many different causes. Many of the "diseases" we treat today are not single cause diseases, and even if they were, chronic conditions often travel in groups. The complexity of chronic diseases is reflected in the complexity of the methodology used to research and ask questions about treating them. However, the general scientific method process remains the same.

There are some components of clinical studies your average 4th grader may not take into consideration. Testing with humans is more difficult to control so science has guidelines to mitigate biases. The more biases a study eliminates, the "better" or more reliable the evidence is said to be. Systematic reviews or meta-analyses of randomized-controlled trials (RCT: participants are randomly assigned to one or more different clinical interventions) [50] are best, followed by individual RCTs, cohort studies, case-control studies, case series, case reports, and lastly, opinion. The hierarchy of evidence reflects the reliability of the evidence it provides.

[49] Jacob Stegenga, *Care and Cure: An Introduction to Philosophy of Medicine* (Chicago: The University of Chicago Press, 2018).
[50] A. K. Akobeng, "Understanding Randomised Controlled Trials," *Archives of Disease in Childhood* 90, no. 8 (August 1, 2005): 840–44, https://doi.org/10.1136/adc.2004.058222.

Figure 1. Randomized Control Trial Methodology

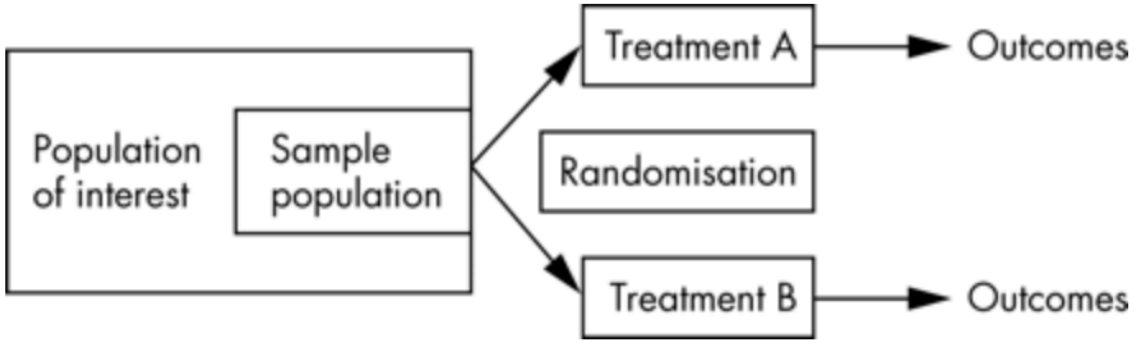

Figure 1 Randomized Control Trial Methodology. Figure 1 shows a standard randomized control trial (RCT) methodology. Within the population of interest, a sample population large enough to be representative and statistically powered is taken. Randomization divides this sample population into two treatment groups, labeled A and B. Measurements are conventionally taken before and after treatment with baseline levels used to measure change due to treatment. Outcomes from both treatment groups can be compared to one another and to baseline values.

The only difference between the two groups - A and B shown above - is the intervention or treatment. At the end of the study, the groups are analyzed in terms of outcomes previously defined. The random assignment prevents selection bias. If the scientists just wanted to see the result they were looking for and placed participants more likely to achieve that result in one of the two groups, they may find the outcome they were looking for, but the intervention would not have been solely responsible for that outcome. Randomization ensures distribution of participant characteristics so that the outcome can only be explained by the intervention. It is impossible to eliminate all biases and confounding variables, but scientists seek to control as many as possible. There are many other types of biases that may affect results and are thus controlled for in RCTs. For example, patients who are aware they are receiving a new treatment may report being "better" than they are. Physicians who expect treatment A to be more effective than B may be clouded in favor of what they perceive to be the more effective treatment. Conversely, physicians

may provide more care and attention to those they believe to not be receiving the best treatment to compensate for this perceived disadvantage. Blinding prevents this by ensuring that neither participants nor physicians know which treatment group any participant is in.[51] For a study to have statistical power and detect a difference between treatment groups when such a difference exists, a large sample size is needed. When a sample size is too small, the difference between treatment groups may be from differences in the individual people rather than the treatment. The best evidence in the eyes of EBM come from meta-analyses of RCTs. This means that many, many RCTs all investigating the same population and interventions are pooled together and analyzed to estimate an overall effect of the intervention. Some disagree and believe large RCTs provide better evidence than meta-analyses of many individual smaller RCTs, but regardless, the gold standard in clinical studies is RCTs. [52]

2.2: Limitations of RCTs within Chronic Disease

In RCTs, scientists must be extremely specific with their sample populations. If your study is testing a new treatment for diabetes, the ideal participant only has diabetes and not kidney or cardiovascular disease as well. Researchers determine exclusion criteria at the outset to make sure it is, in practice, targeting the disease it sought to. In doing so, participants who reflect the reality of the disease and comorbidities that come with it are eliminated from enrolling in the study. Few RCTs published in the last 15 years included patients with multiple chronic conditions. A 2016 study analyzing exclusion of patients with concomitant chronic conditions in ongoing randomized controlled trials found that among 319 ongoing RCTs, 79% of trials

[51] "Blinding in Clinical Trials and Other Studies | The BMJ," accessed January 26, 2022, https://www.bmj.com/content/321/7259/504?hwoasp=authn:1369647604:4223573:1446970149:0:0:4lLHYzv2ujxaVryjzwQeDA%3D%3D.

[52] Christina M. Scifres et al., "Meta-Analysis versus Large Clinical Trials: Which Should Guide Our Management?," *American Journal of Obstetrics and Gynecology* 200, no. 5 (May 2009): 484.e1-484.e5, https://doi.org/10.1016/j.ajog.2008.09.873.

excluded patients with concomitant chronic conditions. 91% of patients with coronary heart disease (CHD) have a concomitant chronic condition, but 69% of trials targeting CHD excluded such patients.[53] Research crafting clinical practice guidelines for single chronic conditions are not relevant for people with multiple chronic conditions.[54] This approach often results in polypharmacy, defined as the chronic co-prescription of several drugs - the "consequence of the application of disease specific guidelines, targeting disease specific goals, to patients with multiple chronic diseases."[55] Imagine a study created a pharmaceutically-based solution for what was tested as an isolated disease, when in reality, patients with said disease often have many other associated comorbid diseases or symptoms. If each symptom is treated with a different drug and all these drugs were tested in isolation, you end up with lots of different prescriptions. Given the possible drug-to-drug and disease-to-disease interactions that remain unexamined, the evidence gathered by RCTs examining isolated conditions is of limited value to guide decisions about medication use by patients with multiple chronic diseases.[56] A 2015 study of UK national clinical guidelines of prescriptions for type 2 diabetes, chronic kidney disease, and heart failure found that positive drug-disease interactions were uncommon, while serious drug-drug interactions[57] were common.

[53] Céline Buffel du Vaure et al., "Exclusion of Patients with Concomitant Chronic Conditions in Ongoing Randomised Controlled Trials Targeting 10 Common Chronic Conditions and Registered at ClinicalTrials.Gov: A Systematic Review of Registration Details," *BMJ Open* 6, no. 9 (September 27, 2016): e012265, https://doi.org/10.1136/bmjopen-2016-012265.
[54] Lloyd D. Hughes, Marion E. T. McMurdo, and Bruce Guthrie, "Guidelines for People Not for Diseases: The Challenges of Applying UK Clinical Guidelines to People with Multimorbidity," *Age and Ageing* 42, no. 1 (January 2013): 62–69, https://doi.org/10.1093/ageing/afs100.
[55] Alessandra Marengoni and Graziano Onder, "Guidelines, Polypharmacy, and Drug-Drug Interactions in Patients with Multimorbidity," *BMJ* 350 (March 11, 2015): h1059, https://doi.org/10.1136/bmj.h1059.
[56] Alejandro R. Jadad et al., "Consideration of Multiple Chronic Diseases in Randomized Controlled Trials," *JAMA* 306, no. 24 (December 28, 2011): 2670–72, https://doi.org/10.1001/jama.2011.1886.
[57] Between drugs recommended for highly prevalent comorbid diseases

A patient with cardiovascular disease (CVD) may be taking beta-blockers and ACE inhibitors to reduce blood pressure, aspirin to prevent blood clots, and statins to lower cholesterol. Evidence from the RCTs rarely goes beyond a few years of follow-up, but patients are often given continuous treatment with multiple drugs well into old age.[58] A CVD researcher's attention was drawn to the issue when he – who was on beta-blocker drug for 15 years, ACE inhibitor drug for 10 years, and aspirin for 20 years – developed a sinoatrial block from the beta-blocker, a cough from the ACE inhibitor, and aspirin-induced gastrointestinal bleeding. His study aptly summarized the dangers in long-term use of cardiovascular disease drugs: (1) Unclear guidelines, specifically regarding use after myocardial infarction and for how long these drugs should be prescribed; (2) Knowledge gap regarding long term use, as RCTs provide short-term follow-up; (3) Problems with polypharmacy, namely the aforementioned drug-drug interactions; (4) Long-term medication in the elderly, especially because older patients are under-represented in RCTs and age is a common exclusion criteria; and (5) lack of drug withdrawal trials.[59]

A natural intuition when faced with the problem of over-prescription may be to turn away from drugs entirely and consider solely alternative methods. There is much disagreement over the efficacy of various complementary and alternative methods (CAM) and even disagreement over what counts as alternative in the first place. Under the umbrella CAM, there are many quite different methods, from acupuncture to meditation. The more common a treatment is in Western medical practice, the more conventional it is. These types of treatment are often newer with a technological flare. However, complementary and alternative methods have been on the rise with

[58] Xavier Rossello, Stuart J. Pocock, and Desmond G. Julian, "Long-Term Use of Cardiovascular Drugs," *Journal of the American College of Cardiology* 66, no. 11 (September 15, 2015): 1273–85, https://doi.org/10.1016/j.jacc.2015.07.018.
[59] Rossello, Pocock, and Julian.

many patients personally seeking out alternative care to replace or complement the conventional care they receive.[60] As CAM gained popularity in use, it gained popularity in research. In October of 1991, U.S. Congress passed legislation (Public Law 102-170) that provided $2 million in funding to establish an office within the National Institutes of Health (NIH) to investigate and evaluate unconventional medical practices.[61] In October of 1998 the National Center for Complementary and Alternative Medicine, now the National Center for Complementary and Integrative Health (NCCIH), was born. In May 1999, the center awarded its first research project grant.[62] Many important findings have come from the center and in 2021 the NCCIH budget was $154.1 million of the NIH's 51.96 billion (about 0.3%).[63] This boom in integrative medicine research did not come without controversy.

Some claim that confirmation bias and the natural course a disease takes exacerbates the benefits of CAM. Confirmation bias means that those participating in or studying the treatment believe the treatment to be successful and this expectation effect results in a false beneficiary outcome. It would be difficult to have a blind experiment, controlling for this confounding variable, when participants are not simply taking drug A or drug B. However, RCTs using CAM have found significant results controlling for as much bias as possible. Further, supporters of CAM argue that the efficacy of an alternative treatment is not due to one aspect (i.e. one chemical compound) of the treatment. When undergoing alternative treatment, the relationship

[60] Institute of Medicine (US) Committee on the Use of Complementary and Alternative Medicine by the American Public, *Integration of CAM and Conventional Medicine*, *Complementary and Alternative Medicine in the United States* (National Academies Press (US), 2005), https://www.ncbi.nlm.nih.gov/books/NBK83807/.
[61] "Text of H.R. 3839 (102nd): Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations … (Passed Congress Version)," GovTrack.us, accessed March 1, 2022, https://www.govtrack.us/congress/bills/102/hr3839/text.
[62] "National Center for Complementary and Integrative Health (NCCIH)," National Institutes of Health (NIH), July 10, 2015, https://www.nih.gov/about-nih/what-we-do/nih-almanac/national-center-complementary-integrative-health-nccih.n
[63] "Welcome to the Office of Budget," accessed March 1, 2022, https://officeofbudget.od.nih.gov/.

between the provider and patient is regularly seen to have a positive effect. Inability to isolate the explanation should not be sufficient evidence to discard an entire realm of treatment modalities. Instead of using the downsides of alternative treatment research to justify marking the entire realm of treatment modalities as illegitimate, the proof of the benefits should be applied to existing "proven" treatment methods. An integrative system that combines the benefits of both is particularly applicable to chronic disease because of the discussed issues existing in the treatment framework as it exists today.

Integrative medicine can be seen as a reaction to polypharmacy and the ceaselessly growing epidemic of chronic diseases, but it is not new. In conjunction with our modern understanding of health, age-old techniques like meditation get a new life. Regardless of the specific technique, integrative medicine's focus on relationship-based care encourages a holistic approach to treatment. This model can be aptly summarized in four words: fewer drugs, more talking.

Chapter 3: MND-CKD - A Case Study in Integrative Medicinal Research

When synthetic drugs first entered the clinical realm, physicians knew very little about pharmaceuticals and consequently relied on the manufacturer's advice when prescribing. Over time, the problems with this model became apparent and the onus for appropriate prescription and treatment decision-making was placed back on the physician. To do so, knowledge of the benefits and side effects of different drugs was needed.

In the 1970s, a collaboration between a physician and scientist led to the discovery of statins, a class of drugs that inhibit cholesterol production and have saved millions of lives. Together, they investigated the disease's molecular basis, tracked the problem down to a single missing piece (lack of LDL receptors), and developed a solution.[64]

Evidence-based medicine, in theory, uses this model to bring the best treatment options to patients. However, a physician knowledge gap in alternative treatment creates a chasm between evidence and medicine. Much of this knowledge gap comes from how physicians are trained and the absence of alternative treatment discussion in curricula. A 2021 review of medical school curricula found that complementary and alternative medicine teaching in medical education was "widely inconsistent."[65] If curriculum is based on the evidence-based medicine research, what threshold do alternative treatment EBM have to breach to break the stigma around their use in clinical practice? Integrative medicinal research continuously seeks to prove that alternative techniques deserve to be taught side-by-side with conventional ones.

While testing integrative methods in clinical settings is more complex, it is not impossible. The MND-CKD study in the Park Lab is an ideal case study to examine the ways

[64] Thomas P. Stossel, "The Discovery of Statins," *Cell* 134, no. 6 (September 19, 2008): 903–5, https://doi.org/10.1016/j.cell.2008.09.008.
[65] Mary Soliman and Justin Bilszta, "Teaching Complementary and Alternative Medicine in Undergraduate Medical Education: A Scoping Review," *International Journal of Medical Education* 12 (July 27, 2021): 140–49, https://doi.org/10.5116/ijme.60e2.f3ed.

clinical studies can overcome the challenges in researching chronic disease to perform research that can result in better practices in clinical treatment.

3.1 Background

One of the primary functions of the kidney is to regulate blood pressure. This regulatory system is severely hindered in patients with chronic kidney disease. Many patients with CKD are also diagnosed with high blood pressure. In general, CKD patients are at a five- to fifteen-fold increased risk of cardiovascular disease. Stress-induced elevated activation of the sympathetic nervous system (SNS), as detailed in chapter 1 section 1, can increase risk of cardiovascular disease and exacerbate symptoms in diagnosed patients. As discussed, this effect is more prominent and poses a higher risk for individuals whose threshold to pathological stress is much lower. The narrower window of healthy stress in conjunction with lessened ability to regulate responses to stress poses major risks for this population. This research comes from the need to develop new methods to better regulate SNS over-activity and ultimately improve clinical outcomes in this highly prevalent and high-risk patient population.

Existing therapeutic strategies have been unsuccessful in addressing SNS regulation and come with a laundry list of side effects and unwelcome drug-drug and drug-disease interactions. Mindfulness meditation (MM) is an apt therapy in the ways it addresses multiple contributing factors without these negative side effects. MM is noninvasive, safe, accessible, inexpensive and may have real biological effects on blood pressure and SNS activation. Previous studies of the effects of meditation on cardiovascular risk included those investigating physiological response to stress, blood pressure reduction, insulin resistance, endothelial function, and prevention of

cardiovascular disease. Findings suggested an overall positive benefit but had never been tested in chronic kidney disease.[66]

The MND-CKD study is a randomized control trial to determine the effects of meditation on blood pressure and SNS activity in people with CKD. As a lab member, I was fortunate enough to experience all aspects of the study including recruitment and observing and aiding in screening, EndoPAT, and Micro visits. With the help of my mentor within the lab, Jinhee Jeong, I independently performed analysis of pilot data detailed below. These pilot data investigate two aspects of the study: the effect of MBSR on blood pressure and the effect of MBSR on self-reported mental health measurements.

3.2 Methods

Using the graphic model of RCTs detailed in chapter 2, the MND-CKD methodology is outlined below:

Figure 2. MND-CKD Protocol

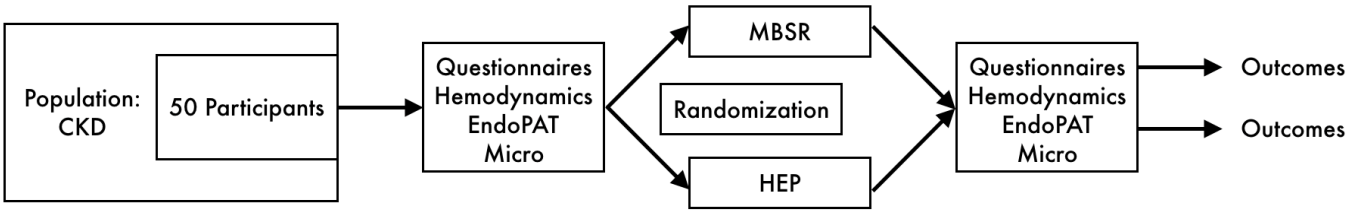

Figure 2 MND-CKD Protocol. Figure 2 shows MND-CKD study protocol and is mirrored after the methodology in Figure 1. The sample population is 50 chronic kidney disease participants. Baseline measurements of 8 questionnaires, hemodynamics (blood pressure, heart rate), an EndoPAT test, and Micro test are taken. Randomization sorts the sample population into two interventions: MBSR and HEP. After 8 weeks of MBSR or HEP courses, participants return to lab for end of study testing and measurements from the baseline are repeated (questionnaires, hemodynamics, EndoPAT, micro). Outcomes are compared within groups and between groups. *Chronic Kidney Disease (CKD), Endothelial Peripheral Arterial Tone (EndoPAT), Microneurography (Micro), Mindfulness-Based Stress Reduction (MBSR), Health Enhancement Program (HEP)*.

[66] Glenn N. Levine et al., "Meditation and Cardiovascular Risk Reduction," *Journal of the American Heart Association* 6, no. 10 (September 28, 2017): e002218, https://doi.org/10.1161/JAHA.117.002218.

Patients continue to take medications they were prescribed before enrolling in the study as meditation is an additional treatment therapy, not a replacement. This provides an accurate model and mirrors integrative medicine in practice. Randomization and double-blinding prevents biases in experimentation and analysis. Participants are randomized into either the Mindfulness-Based Stress Reduction (MBSR) or Health Enhancement Program (HEP) treatment groups which are courses that meet for 2.5-hours weekly for 8 weeks. This controls for the positive effect on health that might come from meeting with a group of peers.

Study Population

The study population consisted of 14 total participants (age range 49-71) with CKD Stage III, defined as an estimated glomerular filtration rate (eGFR) between 30 and 59 ml/min/1.73 m^2 as calculated by the modified Modification of Diet in Renal Disease (MDRD) equation. While exclusion criteria for participant selection is necessary, the study does not exclude common comorbidities of CKD such as hypertension and diabetes. This ensures clinical relevance of the findings and applicability to real patients. The sample size for the entire study is large enough for the study to be statistically powered to meet its primary outcome of determining whether mindfulness meditation improves sympathetic function in CKD. Note that for my particularly pilot data, sample size is too small to be statistically powered, but gives indication to numerical trends that may continue as the study progresses.

Measurements and Procedures

Questionnaires. There are 8 different questionnaires participants fill out wherein they record self-perceived metrics of mindfulness and stress, along with their daily routines and typical diet, sleep, and exercise. The Course Experience Questionnaire (CEQ) and Client Satisfaction Questionnaire (CSQ) are used for internal means to ensure patients are satisfied with

the course and their participation in the study and are only used at the end of the 8 weeks. CEQ was initially developed in 2001 with the intention of measuring course satisfaction for university graduates.[67] CSQ was used in a study investigating the effect of MBSR for anxiety and was effective in gathering information for researchers to improve their program.[68] The Depression, Anxiety, and Stress Scales (DASS) and Five-Faceted Mindfulness Questionnaire (FFMQ) are the most helpful in measuring changes in mental health and mindfulness before and after intervention. The DASS was found to be valid and reliable to discriminate depression, anxiety, and stress levels between "normal" and clinical populations and has been used in a multitude of studies to assess changes in depression, anxiety, and stress over relatively short periods of time.[69, 70] The FFMQ has been used over the last twenty years to assess changes in mindfulness before and after various mindfulness-based interventions. The questions are aimed to measure a person's ability to observe and describe their emotions, act with awareness, and to be non-judgmental and non-reactive towards their thoughts. The Short-Form Questionnaire (SF-36) measures the physical limitation or disability a patient feels regarding their illness before and after intervention. The Pittsburgh Sleep Quality Index (PSQI), Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH), and Dietary Screening Questionnaire (DSQ) measure a patient's habits and are used to ensure no drastic lifestyle changes are made over the

[67] Craig Mcinnis and Patrick Griffin, "Training and Youth Affairs CONTENTS Development of the Course Experience Questionnaire (CEQ)," n.d.
[68] Elizabeth A. Hoge et al., "Treatment for Anxiety: Mindfulness Meditation versus Escitalopram (TAME): Design of a Randomized, Controlled Non-Inferiority Trial," *Contemporary Clinical Trials* 91 (April 1, 2020): 105965, https://doi.org/10.1016/j.cct.2020.105965.
[69] Ahmet Akin and Bayram Cetin, "The Depression Anxiety and Stress Scale (DASS): The Study of Validity and Reliability," *Educational Sciences: Theory and Practice* 7, no. 1 (January 2007): 260–68.
[70] R. Beiter et al., "The Prevalence and Correlates of Depression, Anxiety, and Stress in a Sample of College Students," *Journal of Affective Disorders* 173 (March 1, 2015): 90–96, https://doi.org/10.1016/j.jad.2014.10.054.

course of the study.[71,72,73] The eight questionnaires and their primary outcomes are summarized in Table 1 below.

Table 1. MND-CKD Questionnaire Information

Questionnaire	**Measures**
Course Experience Questionnaire (CEQ)	credibility and patient expectation
Client Satisfaction Questionnaire (CSQ)	Satisfaction with MBSR/HEP course
Depression Anxiety Stress Scales (DASS)	Depression, anxiety, and stress
Five Facet Mindfulness Questionnaire (FFMQ)	Mindfulness
Short Form Questionnaire (SF-36)	Health in relation to sickness (pain, limitations, quality of life, etc.)
Pittsburgh Sleep Quality Index (PSQI)	Sleep quality, sleep habits
Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH)	Daily activities, physical activity
Dietary Screening Questionnaire (DSQ)	Nutrition intake

Table 1: MND-CKD Questionnaire Information. Table 1 summarizes each of the 8 questionnaires participants fill out before and after the experimental (MBSR) or control (HEP) intervention. Column 1 states the name of the questionnaire and column 2 summarizes what the questionnaire measures.

This is qualitative data because it is self-reported and subjective. It tells the scientist how the person is feeling, which is incredibly important in clinical practice, but is enhanced when complemented with quantitative data; for example, an increase in mindfulness being mirrored by a decrease in blood pressure. Quantitative measurements of blood pressure and muscle sympathetic nerve activity are taken using the following protocols.

[71] Tatyana Mollayeva et al., "The Pittsburgh Sleep Quality Index as a Screening Tool for Sleep Dysfunction in Clinical and Non-Clinical Samples: A Systematic Review and Meta-Analysis," *Sleep Medicine Reviews* 25 (February 2016): 52–73, https://doi.org/10.1016/j.smrv.2015.01.009.
[72] Bregje L. Seves et al., "Test-Retest Reliability and Concurrent Validity of the Adapted Short QUestionnaire to ASsess Health-Enhancing Physical Activity (Adapted-SQUASH) in Adults with Disabilities," *Journal of Sports Sciences* 39, no. 8 (April 2021): 875–86, https://doi.org/10.1080/02640414.2020.1850983.
[73] Frances E. Thompson et al., "Development and Evaluation of the National Cancer Institute's Dietary Screener Questionnaire Scoring Algorithms," *The Journal of Nutrition* 147, no. 6 (June 2017): 1226–33, https://doi.org/10.3945/jn.116.246058.

Blood pressure. Baseline blood pressure is measured with an automated sphygmomanometer (Dinamap PRO series) while the participant is seated, after 5 min of quiet rest, using standard technique. Baseline BP is the mean of three consecutive readings separated by 3 minutes.

Muscle sympathetic nerve activity. A tungsten microelectrode (tip diameter 5–15 μm) (Bioengineering, University of Iowa) was inserted into the nerve, and a reference microelectrode was inserted subcutaneously 1–2 cm from the recording electrode. The signals were amplified (total gain 50,000 –100,000), filtered (700 –2,000 Hz), rectified, and integrated (time constant 0.1 s) to obtain a mean voltage display of sympathetic nerve activity (model 662C-4, Nerve Traffic Analyzer, University of Iowa, Bioengineering) that was recorded by the LabChart 7 Program (PowerLab 16sp, ADInstruments). Continuous electrocardiogram (ECG) was recorded simultaneously with the neurogram using a bioamp system. All MSNA recordings met previously established criteria.[74, 75, 76]

Interventions

Mindfulness based stress reduction. MBSR is a meditation technique codified in the 1970's by Jon Kabat-Zinn, a PhD scientist, writer, and mindfulness leader. The course was designed to manage mental health and chronic pain in patients who were non-responsive to conventional therapy and has since been used by healthy and sick persons alike to reduce stress and improve mindfulness in daily life. In his book, *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness*, Kabat-Zinn writes that you can choose

[74] W. Delius et al., "General Characteristics of Sympathetic Activity in Human Muscle Nerves," *Acta Physiologica Scandinavica* 84, no. 1 (January 1972): 65–81, https://doi.org/10.1111/j.1748-1716.1972.tb05158.x.
[75] Delius et al.
[76] Tadaaki Mano, Satoshi Iwase, and Shinobu Toma, "Microneurography as a Tool in Clinical Neurophysiology to Investigate Peripheral Neural Traffic in Humans," *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 117, no. 11 (November 2006): 2357–84, https://doi.org/10.1016/j.clinph.2006.06.002.

not to go into fight-or-flight mode when stressed and mindfulness, a "moment-to-moment awareness," allows you to exert control over your reactions to stressors.[77] MBSR is delivered in 8 weekly 2.5-hour group sessions and a one day-long retreat. MBSR teaches to become more aware of thoughts, feeling, and sensations, and to skillfully respond to stressors. Each of the sessions includes education about mindfulness and stress; experiential mindfulness practice, and discussion of participants' experiences with mindfulness practice. Participants learn formal mindfulness practices, such as meditation, yoga, body scans, as well as informal, such as awareness of breath, thoughts, or emotions, and mindfulness of daily activities. Participants receive digital audio (MP3) downloads with guided mindfulness meditation practices, a home practice manual, and handouts with each week's assignments. Daily home practice consists of 40-45 minutes of recorded practice.

This specific type of meditation was chosen for the study because the coursework has a pointed focus on the fight-or-flight response compared to other techniques which, for example, may spend more class time focusing on gratitude, relaxation, or visualization. Further, MBSR has an extensive evidence base. Systematic reviews of MBSR have shown improvements in measures of anxiety and depression.

Health enhancement program (control). The health enhancement program (HEP) is designed to provide a structurally parallel, active control intervention to MBSR with health benefits of its own, while omitting any components of mindfulness. HEP participants meet with a health educator in a group setting for 8 weekly 2.5 hour sessions with a day-long retreat. HEP matches MBSR in structure and content. Classes consist of music therapy, nutritional education, posture and balance movements, walking, and stretching. Work with all practices, group

[77] Jon Kabat-Zinn, *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness*, Revised and updated edition (New York: Bantam Books trade paperback, 2013).

discussion, and exercises during the retreat match that of MBSR. HEP participants also receive MP3 downloads on a tablet from which adherence measurements are taken. The recordings are 40-45 minutes and cover health education topics. Participants are also given a home listening manual and weekly handouts with each week's listening assignments.

Experimental Protocol

All participants are studied a minimum three times (Screening, Micro, EndoPAT) before randomized into either MBSR or HEP courses, and twice following (Micro, EndoPAT). All are separate study visits in a randomized controlled design. For each visit, participants were instructed to take their antihypertensive medications at the same time before the study and no medication changes were allowed between studies.

Screening. At the first visit, participants are screened – heart and respiratory rate and blood pressures taken, questionnaires filled out, urine samples taken, and a 24-hour ambulatory blood pressure (24h-AMBP) run. The first are standard hemodynamic measurements, the questionnaires reflect their current state of mindfulness and daily habits, urine for measuring kidney health and the 24h-AMBP shows blood pressure on a continuous basis. Participants are screening 1-3 times before completing Micro and EndoPAT visits.

Microneurography. The second visit is called "Micro Day." A participant's heart and respiratory rate and blood pressures are taken, blood is drawn, and then the experimental part begins. As discussed, the experiment seeks to determine if 8 weeks of MBSR leads to a reduction in sympathetic nervous system activity (MSNA). The sympathetic nervous system is activated by stressors. In our testing, both physical and mental stressors are used. To stress the participants mentally, they answer fast-paced mental math questions. To stress them physically, participants squeeze a hand grip for three minutes followed by placing their hand in ice water. All the while,

they are hooked up to a machine taking hemodynamic measurements and muscle sympathetic nervous activation via a muscle neurography electrode in the participant's calf. This device allows us to quantify the extent to which a person's sympathetic nervous system was active. By comparing pre- and post-intervention MSNA data, the lab can determine if the intervention altered SNS activation or regulation.

Endothelial Peripheral Arterial Tone. On the third testing day, within three weeks of Micro Day, participants are given the Endothelial Peripheral Arterial Tone (EndoPAT) test. EndoPAT testing measures endothelial function. The endothelium is a one-cell-thick lining in blood vessels that controls blood pressure and is important in regulating cardiovascular health and the inflammatory response. On EndoPAT day, a participant's heart and respiratory rate and blood pressures are taken as usual, blood is drawn, and the participant's measurements (waist, hip, Inbody) are taken before the EndoPAT test. The EndoPAT device is a finger cuff that detects the functioning and health of arteries and blood vessels via state-of-the-art micro-electronics which measure pulsatile fingertip volume changes. Simply put, it measures cardiovascular health by tracking blood moving through the finger.

Then, participants are ready to begin 8 weeks of either MBSR or HEP classes. At the end of the 8 weeks, participants return to the lab for another Micro and EndoPAT test. The lab visit schedule and testing information is summarized in Table 2 below.

Table 2. MND-CKD Study Visit Protocol

Screening	Micro Day	Endothelial Day
• 3 BP and HR, 1 RR • Questionnaires • 24h-AMBP • Urinalysis	• 3 BP and HR, 1 RR • Blood drawn • MSNA	• 3 BP and HR, 1 RR • Blood • Waist/Hip measurements • Inbody • EndoPAT
*1-3 Screening Visits	within 3 weeks of one another	

Table 2: MND-CKD Study Visit Protocol. Table 2 summarizes the three testing visits (Screening, Micro, and EndoPAT), specifying logistically when the visits occur and measurements taken at each visit.

Data analysis. A Wilcoxon-rank sum test was used to determine p-values because data is not normally distributed due to small and unequal sample size.

Table 3. MND-CKD Participant Baseline Characteristics

	MBSR (n=11)	HEP (n=3)	p-value
Age, yr	66.2 ± 7.2	59.3 ± 7.9	0.70
Male, n	10	3	0.73
Height, cm	177.3 ± 8.04	180.3 ± 2.71	0.09
Weight, kg	100.8 ± 22.1	100.8 ± 5.6	0.46
Hypertension, n	9	1	0.52
Veteran, %	100	66.7	0.08
Diabetes, %	27.2	66.7	0.26
PTSD, %	9.1	0	0.73

Table 3: MND-CKD Participant Baseline Characteristics. Table 3 reports baseline characteristics of participants. Column 2 shows averages for the MBSR group and column 3 averages of HEP group participants. Column 4 reports the p-value for between-group difference. No p-values are statistically significant indicating no significant differences in baseline characteristics exist between the two intervention groups.

3.3 Results

Baseline characteristics. Table 3 depicts the baseline characteristics for study participants. Participants were all CKD Stage III (mean eGFR of 43.7 ± 10 $ml \cdot min^{-1} \cdot 1.73m^{-2}$). Most participants were obese, with a mean body mass index (BMI) of > $30kg/m^2$.

Table 4. Antihypertensive medications taken by study participants

Medications	*n*
Beta Blockers	6
ACE/ARB	11
DCCB	9
NDCCB	1
Diuretics	5
PDE	2
Alpha blockers	1
Hydralazine	1
Statin	2

Table 4: Antihypertensive medications taken by study participants. Table 4 reports the antihypertensive medications taken by study participants. Column 1 names the medication and column 2 reports how many study participants took said medication. Participant medication did not change throughout the study. *Angiotensin Converting Enzyme/Angiotensin Receptor Blockers (ACE/ARB), Dihydropyridine Calcium-Channel Blockers (DCCB), Non-Dihydropyridine Calcium-Channel Blockers (NDCCG), phosphoediesterase (PDE)*

Table 5. MND-CKD Hemodynamic Data

	MBSR			HEP			MBSR vs. HEP
	Baseline	End of Study	In-group	Baseline	End of Study	In-group	Between Group
SBP	121.4 ± 14.	110.4 ± 11.6	0.09	123.9 ± 10.2	125.3 ± 17.7	1	0.13
DBP	77.1 ± 11.9	63.8 ± 12.4	0.04*	69.7 ± 10.1	67.7 ± 6.03	0.7	0.38
MAP	92.0 ± 11.6	79.3 ± 11.2	0.03*	87.7 ± 8.11	87.1 ± 7.47	1	0.19
HR	70.3 ± 9.54	64.6 ± 10.5	0.30	61.2 ± 10.9	56.7 ± 7.57	0.4	0.92
RR	16.1 ± 3.64	16.4 ± 3.16	0.47	16.7 ± 2.52	16 ± 1.73	1	0.91

*Statistically significant

Table 5 MND-CKD Hemodynamic Data. Table 5 reports average values of hemodynamic measurements by group. Columns 2, 3 and 4 report values for the MBSR group. Columns 5, 6, and 7 report values for the HEP group. Columns 4 and 7 report p-values for within-group changes between baseline and end of study measurements. Column 8 reports p-values for the change between baseline and end of study between the MBSR and HEP groups. Statistical significance is indicated with an asterisk (*) for p-values below 0.05. *Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean Arterial Pressure (MAP), Heart Rate (HR), Respiratory Rate (RR)*

As shown in Table 5 row 2, participants in the MBSR group experience a statistically significant reduction in diastolic blood pressure (DBP) from an average of 77.1 mmHg to 63.8 mmHg (p-value 0.04). This change was not seen in the HEP group whose average DBP measurements before and after intervention are 69.7 mmHg and 67.7 mmHg (p-value 0.7). This

reduction in DBP in the MBSR group is clinically significant and has been supported by evidence from other studies.[78] Mean Arterial Pressure (MAP), a measurement of the average arterial pressure in one cardiac cycle, systole, and diastole, also experiences significant reduction in the MBSR group. Mean MAP values change from 92.0 mmHg at baseline to 79.3 mmHg following 8 weeks of MBSR (p-value 0.03). On the contrary, no statistically significant changes in hemodynamic measurements were noted in the HEP group. This may be due to the small sample size within the HEP group. Column 8 on the far-right of Table 5 reports p-values for the change in measurement over the course of the study between the MBSR and HEP groups. While no values are statistically significant, we expect to see significance as the sample size of each group grows. Overall, findings align with evidence of MBSR-reduced blood pressure in hypertensive populations.[79]

Table 6. MND-CKD Questionnaire Data

	MBSR			HEP			MBSR vs. HEP
	Baseline	End of Study	In-group difference p-value	Baseline	End of Study	In-group difference p-value	Between Group Difference p-value
Depression	6.09	2.25	0.63	6.00	7.33	0.7	0.75
Anxiety	6.27	1.625	0.12	3.00	1.32	0.27	0.60
Stress	7.09	5.00	0.97	6.67	5.67	1.00	0.76
FFMQ	106.8	106.75	0.74	99.3	111.7	0.38	0.18

Table 6: MND-CKD Questionnaire Data. Table 6 reports mean values of depression, anxiety, stress taken from the DASS questionnaire and mean value of mindfulness calculated as the sum of points from five-faceted mindfulness questionnaire (FFMQ). Columns 2, 3 and 4 report values for the MBSR group. Columns 5, 6, and 7 report values for the HEP group. Columns 4 and 7 report p-values for within group changes between baseline and end of study values. Column 8 reports p-values for change in values over the course of the study between the MBSR and HEP groups.

[78] Joel W. Hughes et al., "Randomized Controlled Trial of Mindfulness-Based Stress Reduction for Prehypertension," *Psychosomatic Medicine* 75, no. 8 (October 2013): 721–28, https://doi.org/10.1097/PSY.0b013e3182a3e4e5.

[79] Javad Momeni et al., "The Effects of Mindfulness-Based Stress Reduction on Cardiac Patients' Blood Pressure, Perceived Stress, and Anger: A Single-Blind Randomized Controlled Trial," *Journal of the American Society of Hypertension* 10, no. 10 (October 1, 2016): 763–71, https://doi.org/10.1016/j.jash.2016.07.007.

Statistical significance would be shown by p-values less than or equal to 0.05. While no changes in depression, anxiety, stress, or mindfulness within or between groups are statistically significant (likely due to small sample size), the MBSR group values reported in Table 6 show numerical reduction in depression, anxiety, and stress. This numerical reduction is supported by evidence in other studies showing MBSR reduces depression, anxiety, and stress.[80]

This preliminary hemodynamic and questionnaire data reflect the trends seen in other studies.[81] As the study progresses, larger sample sizes will likely allow for statistical significance and emphasize existing trends. Further, data from the lab not explored in this preliminary analysis, such as MSNA data and inflammatory marker data, will likely support trends seen in other populations.

3.4 Discussion

Preliminary data from the first two years of research reflect trends from other studies investigating the mental and physical effects of MBSR. In a study testing the effect of MBSR on fibromyalgia, a chronic pain syndrome, the meditation practice was shown to reduce sympathetic nervous system activation as measured by skin conductance. This research built on the Park Lab's previous work showing MBSR reduces depressive symptoms in fibromyalgia patients.[82] A 2018 study narrowed in on physiological indications of stress in stressed, but otherwise healthy, working people and found that mindfulness meditation benefitted autonomic balance, increased

[80] Yeoungsuk Song and Ruth Lindquist, "Effects of Mindfulness-Based Stress Reduction on Depression, Anxiety, Stress and Mindfulness in Korean Nursing Students," *Nurse Education Today* 35, no. 1 (January 2015): 86–90, https://doi.org/10.1016/j.nedt.2014.06.010.
[81] Ciro Conversano et al., "Is Mindfulness-Based Stress Reduction Effective for People with Hypertension? A Systematic Review and Meta-Analysis of 30 Years of Evidence," *International Journal of Environmental Research and Public Health* 18, no. 6 (March 11, 2021): 2882, https://doi.org/10.3390/ijerph18062882.
[82] Elizabeth Lush et al., "Mindfulness Meditation for Symptom Reduction in Fibromyalgia: Psychophysiological Correlates," *Journal of Clinical Psychology in Medical Settings* 16, no. 2 (June 2009): 200–207, https://doi.org/10.1007/s10880-009-9153-z.

heart rate variability, and improved immune function.[83] The link between mental and physical health is supported by many different studies. Most report on depression and anxiety as those are among the most common mental health illnesses,[84] are highly linked, and often comorbid with chronic illness.[85] MBSR was found to significantly reduce depression and anxiety in healthy and sick populations. A meta-analysis of MBSR for healthy individuals found that "changes in mindfulness and compassion measures correlated with changes in clinical measures."[86] The MND-CKD study is a joint investigation with both the Emory Medical School and Atlanta VA and many participants are veterans with PTSD. Common symptoms of PTSD include overactivity of the amygdala and decreased ability to regulate negative thoughts and emotions. MBSR showed improvement of depressive symptoms, mindfulness, and quality of life for PTSD patients in multiple different RCTs.[87,88,89] These findings are encouraging and align with preliminary data from the lab.

Inflammation exacerbates the effect of stress on the cardiovascular system and chronic kidney disease. Inflammatory markers in the blood provide a measure of the "level" of inflammation present and can be used to analyze changes over time. While inflammatory marker

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[83] Rachael A. Heckenberg et al., "Do Workplace-Based Mindfulness Meditation Programs Improve Physiological Indices of Stress? A Systematic Review and Meta-Analysis," *Journal of Psychosomatic Research* 114 (November 2018): 62–71, https://doi.org/10.1016/j.jpsychores.2018.09.010.

[84] CDCTobaccoFree, "Depression and Anxiety," Centers for Disease Control and Prevention, January 7, 2022, https://www.cdc.gov/tobacco/campaign/tips/diseases/Depression is more than just feeling down or having a bad day. When a sad mood lasts for a long time and interferes with normal, everyday functioning, you may be depressed.

[85] Ned H. Kalin, "The Critical Relationship Between Anxiety and Depression," *American Journal of Psychiatry* 177, no. 5 (May 2020): 365–67, https://doi.org/10.1176/appi.ajp.2020.20030305.

[86] Bassam Khoury et al., "Mindfulness-Based Stress Reduction for Healthy Individuals: A Meta-Analysis," *Journal of Psychosomatic Research* 78, no. 6 (June 2015): 519–28, https://doi.org/10.1016/j.jpsychores.2015.03.009.

[87] Melissa A. Polusny et al., "Mindfulness-Based Stress Reduction for Posttraumatic Stress Disorder Among Veterans: A Randomized Clinical Trial," *JAMA* 314, no. 5 (August 4, 2015): 456–65, https://doi.org/10.1001/jama.2015.8361.

[88] David J. Kearney et al., "Effects of Participation in a Mindfulness Program for Veterans with Posttraumatic Stress Disorder: A Randomized Controlled Pilot Study," *Journal of Clinical Psychology* 69, no. 1 (January 2013): 14–27, https://doi.org/10.1002/jclp.21911.

[89] Abdollah Omidi et al., "Efficacy of Mindfulness-Based Stress Reduction on Mood States of Veterans with Post-Traumatic Stress Disorder," *Archives of Trauma Research* 1, no. 4 (2013): 151–54, https://doi.org/10.5812/atr.8226.

data from the MND-CKD study is not yet powered to reach preliminary conclusions about the effect of MBSR on inflammation, this research has been done in other populations. Breast cancer survivors who participated in six weeks of MBSR courses experienced a statistically significant reduction in the pro-inflammatory cytokine interleukin-6 (IL-6) and in salivary cortisol, a stress hormone. This physiological reduction was paralleled by a reduction in perceived stress and increase in self-reported quality of life.[90] A 2019 study investigating the effect of MBSR on generalized anxiety disorder found a significant reduction in adrenocorticotropic hormone (ACTH), which stimulates the release of cortisol, and pro-inflammatory cytokines TNF-alpha and IL-6.[91]

There have been some efforts to uncover the neurological basis of MBSR. Neuroimaging using fMRI shows what areas of the brain are activated during testing. Participants in a study's brains were scanned while they were presented with negative self-beliefs for 12 seconds and then cued to shift their attention to their breath, mirroring MBSR course guidance, before and after attending MBSR classes. They found post-MBSR, patients had decreased social anxiety, depression, rumination, and increased self-esteem. The changes were seen all over the brain: in the prefrontal cortex, which is in charge of processing, in the emotion-control center amygdala, in visual processing, and in the hippocampus which has a major role in learning and memory. Interestingly, post-MBSR patients had decreased amygdala response even before the researchers

[90] Cecile A. Lengacher et al., "A Large Randomized Trial: Effects of Mindfulness-Based Stress Reduction (MBSR) for Breast Cancer (BC) Survivors on Salivary Cortisol and IL-6," *Biological Research for Nursing* 21, no. 1 (January 2019): 39–49, https://doi.org/10.1177/1099800418789777.
[91] Elizabeth A. Hoge et al., "Randomized Controlled Trial of Mindfulness Meditation for Generalized Anxiety Disorder: Effects on Anxiety and Stress Reactivity," *The Journal of Clinical Psychiatry* 74, no. 8 (August 2013): 786–92, https://doi.org/10.4088/JCP.12m08083.

gave a cue to shift patient attention to their breath. When faced with phrases meant to trigger a stress response, post-MBSR patients' brains were less stress reactive.[92]

Based on the data, physicians should be passing out prescriptions for meditation to all of their patients – stressed, healthy, sick, or otherwise. The disconnect between clinical research and clinical practice spans all treatment modalities, but the gap is widest with alternative treatment research. The many physicians I have spoken to about alternative treatment do not object to the efficacy of the modality, but rather use their lack of experience with these treatments as rationale to prescribe conventionally instead. Integrative medicine enters at the root of the problem, seeking collaborative care between patient, physician, and various caregivers with different specialties– be they MBSR coaches or MDs. In data, blending patient experience with quantitative data makes for a stronger case. Integrative medicine puts this research to practice, bridging the gap between research and treatment.

I am grateful to have spent the last year speaking with physicians building a better healthcare system from their relationships with their community, patients, and peers. There are countless numbers of people with stories like my mom's – people frustrated with doctors, frustrated sickness, and frustrated that nothing seems to be helping. Integrative medicine focused on relationship-based care is a model I believe will improve chronic disease patient experience and health outcomes. Research in integrative methods is important work that must continue to shift the narrative around alternative treatment and blend our technological advancements in medicine with accessible interventions that have worked for thousands of years. My research has allowed me to imagine a better system, one I want to be a part of. I hope to continue to advocate

[92] Philippe R. Goldin and James J. Gross, "Effects of Mindfulness-Based Stress Reduction (MBSR) on Emotion Regulation in Social Anxiety Disorder," *Emotion (Washington, D.C.)* 10, no. 1 (February 2010): 83–91, https://doi.org/10.1037/a0018441.

for and support marginalized communities in healthcare as I grow as a student, researcher, and future physician.

Bibliography

Akin, Ahmet, and Bayram Cetin. "The Depression Anxiety and Stress Scale (DASS): The Study of Validity and Reliability." *Educational Sciences: Theory and Practice* 7, no. 1 (January 2007): 260–68.

Akobeng, A. K. "Understanding Randomised Controlled Trials." *Archives of Disease in Childhood* 90, no. 8 (August 1, 2005): 840–44. https://doi.org/10.1136/adc.2004.058222.

Amarasekera, Anjalee Thanuja, and Dennis Chang. "Buddhist Meditation for Vascular Function: A Narrative Review." *Integrative Medicine Research* 8, no. 4 (December 2019): 252–56. https://doi.org/10.1016/j.imr.2019.11.002.

Arias, Albert J., Karen Steinberg, Alok Banga, and Robert L. Trestman. "Systematic Review of the Efficacy of Meditation Techniques as Treatments for Medical Illness." *Journal of Alternative and Complementary Medicine (New York, N.Y.)* 12, no. 8 (October 2006): 817–32. https://doi.org/10.1089/acm.2006.12.817.

Barbour, Allen. *Caring for Patients: A Critique of the Medical Model*. Stanford University Press, 1997.

Beard, George. "Neurasthenia, or Nervous Exhaustion." *The Boston Medical and Surgical Journal* 80, no. 13 (April 29, 1869): 217–21. https://doi.org/10.1056/NEJM186904290801301.

Beiter, R., R. Nash, M. McCrady, D. Rhoades, M. Linscomb, M. Clarahan, and S. Sammut. "The Prevalence and Correlates of Depression, Anxiety, and Stress in a Sample of College Students." *Journal of Affective Disorders* 173 (March 1, 2015): 90–96. https://doi.org/10.1016/j.jad.2014.10.054.

Benson, Herbert, John F. Beary, and Mark P. Carol. "The Relaxation Response." *Psychiatry* 37, no. 1 (February 1, 1974): 37–46. https://doi.org/10.1080/00332747.1974.11023785.

Bhasin, Manoj K., John W. Denninger, Jeff C. Huffman, Marie G. Joseph, Halsey Niles, Emma Chad-Friedman, Roberta Goldman, et al. "Specific Transcriptome Changes Associated with Blood Pressure Reduction in Hypertensive Patients After Relaxation Response Training." *Journal of Alternative and Complementary Medicine (New York, N.Y.)* 24, no. 5 (May 2018): 486–504. https://doi.org/10.1089/acm.2017.0053.

Bleich, Howard L., Emily S. Boro, and Herbert Benson. "Systemic Hypertension and the Relaxation Response." *New England Journal of Medicine* 296, no. 20 (May 19, 1977): 1152–56. https://doi.org/10.1056/NEJM197705192962008.

"Blinding in Clinical Trials and Other Studies | The BMJ." Accessed January 26, 2022. https://www.bmj.com/content/321/7259/504?hwoasp=authn:1369647604:4223573:1446970149:0:0:4lLHYzv2ujxaVryjzwQeDA%3D%3D.

Buffel du Vaure, Céline, Agnès Dechartres, Constance Battin, Philippe Ravaud, and Isabelle Boutron. "Exclusion of Patients with Concomitant Chronic Conditions in Ongoing Randomised Controlled Trials Targeting 10 Common Chronic Conditions and Registered at ClinicalTrials.Gov: A Systematic Review of Registration Details." *BMJ Open* 6, no. 9 (September 27, 2016): e012265. https://doi.org/10.1136/bmjopen-2016-012265.

Calder Calisi, Catherine. "The Effects of the Relaxation Response on Nurses' Level of Anxiety, Depression, Well-Being, Work-Related Stress, and Confidence to Teach Patients." *Journal of Holistic Nursing: Official Journal of the American Holistic Nurses' Association* 35, no. 4 (December 2017): 318–27. https://doi.org/10.1177/0898010117719207.

CDCTobaccoFree. “Depression and Anxiety.” Centers for Disease Control and Prevention, January 7, 2022. https://www.cdc.gov/tobacco/campaign/tips/diseases/Depression is more than just feeling down or having a bad day. When a sad mood lasts for a long time and interferes with normal, everyday functioning, you may be depressed.

Conradt, Elisabeth, Sierra E. Carter, and Sheila E. Crowell. “Biological Embedding of Chronic Stress Across Two Generations Within Marginalized Communities.” *Child Development Perspectives* 14, no. 4 (2020): 208–14. https://doi.org/10.1111/cdep.12382.

Conversano, Ciro, Graziella Orrù, Andrea Pozza, Mario Miccoli, Rebecca Ciacchini, Laura Marchi, and Angelo Gemignani. “Is Mindfulness-Based Stress Reduction Effective for People with Hypertension? A Systematic Review and Meta-Analysis of 30 Years of Evidence.” *International Journal of Environmental Research and Public Health* 18, no. 6 (March 11, 2021): 2882. https://doi.org/10.3390/ijerph18062882.

Dai, Shirui, Yongzhen Mo, Yumin Wang, Bo Xiang, Qianjin Liao, Ming Zhou, Xiaoling Li, et al. “Chronic Stress Promotes Cancer Development.” *Frontiers in Oncology* 10 (2020): 1492. https://doi.org/10.3389/fonc.2020.01492.

Delius, W., K. E. Hagbarth, A. Hongell, and B. G. Wallin. “General Characteristics of Sympathetic Activity in Human Muscle Nerves.” *Acta Physiologica Scandinavica* 84, no. 1 (January 1972): 65–81. https://doi.org/10.1111/j.1748-1716.1972.tb05158.x.

Dillbeck, Michael C., and David W. Orme-Johnson. “Physiological Differences between Transcendental Meditation and Rest.” *American Psychologist* 42, no. 9 (1987): 879–81. https://doi.org/10.1037/0003-066X.42.9.879.

Doshi, Riddhi P., Robert H. Aseltine, Alyse B. Sabina, and Garth N. Graham. “Racial and Ethnic Disparities in Preventable Hospitalizations for Chronic Disease: Prevalence and Risk Factors.” *Journal of Racial and Ethnic Health Disparities* 4, no. 6 (December 1, 2017): 1100–1106. https://doi.org/10.1007/s40615-016-0315-z.

Eagleman, David. *Incognito: The Secret Lives of the Brain*. New York: Pantheon Books, 2011. https://www.yourcloudlibrary.com.

Evans, Gary W., and Pilyoung Kim. “Childhood Poverty, Chronic Stress, Self-Regulation, and Coping.” *Child Development Perspectives* 7, no. 1 (2013): 43–48. https://doi.org/10.1111/cdep.12013.

“Evidence-Based Medicine – a New Approach to Childbirth.” Accessed January 17, 2022. https://www.euro.who.int/en/health-topics/Life-stages/maternal-and-newborn-health/country-work/republic-of-moldova/evidence-based-medicine-a-new-approach-to-childbirth.

Flaskerud, Jacquelyn H. “Neurasthenia: Here and There, Now and Then.” *Issues in Mental Health Nursing* 28, no. 6 (January 1, 2007): 657–59. https://doi.org/10.1080/01612840701354638.

Gabay, C., and I. Kushner. “Acute-Phase Proteins and Other Systemic Responses to Inflammation.” *The New England Journal of Medicine* 340, no. 6 (February 11, 1999): 448–54. https://doi.org/10.1056/NEJM199902113400607.

Gannotta, Richard, Shaista Malik, Alvin Y Chan, Kamran Urgun, Frank Hsu, and Sumeet Vadera. “Integrative Medicine as a Vital Component of Patient Care.” *Cureus*, August 4, 2018. https://doi.org/10.7759/cureus.3098.

Godbout, Jonathan P., and Ronald Glaser. “Stress-Induced Immune Dysregulation: Implications for Wound Healing, Infectious Disease and Cancer.” *Journal of Neuroimmune*

Pharmacology 1, no. 4 (December 1, 2006): 421–27. https://doi.org/10.1007/s11481-006-9036-0.

Goldin, Philippe R., and James J. Gross. "Effects of Mindfulness-Based Stress Reduction (MBSR) on Emotion Regulation in Social Anxiety Disorder." *Emotion (Washington, D.C.)* 10, no. 1 (February 2010): 83–91. https://doi.org/10.1037/a0018441.

Harorani, Mehdi, Fahimeh Davodabady, Zohreh Farahani, Ali Khanmohamadi Hezave, and Fatemeh Rafiei. "The Effect of Benson's Relaxation Response on Sleep Quality and Anorexia in Cancer Patients Undergoing Chemotherapy: A Randomized Controlled Trial." *Complementary Therapies in Medicine* 50 (May 2020): 102344. https://doi.org/10.1016/j.ctim.2020.102344.

Heckenberg, Rachael A., Pennie Eddy, Stephen Kent, and Bradley J. Wright. "Do Workplace-Based Mindfulness Meditation Programs Improve Physiological Indices of Stress? A Systematic Review and Meta-Analysis." *Journal of Psychosomatic Research* 114 (November 2018): 62–71. https://doi.org/10.1016/j.jpsychores.2018.09.010.

Hoge, Elizabeth A., Eric Bui, Luana Marques, Christina A. Metcalf, Laura K. Morris, Donald J. Robinaugh, John J. Worthington, Mark H. Pollack, and Naomi M. Simon. "Randomized Controlled Trial of Mindfulness Meditation for Generalized Anxiety Disorder: Effects on Anxiety and Stress Reactivity." *The Journal of Clinical Psychiatry* 74, no. 8 (August 2013): 786–92. https://doi.org/10.4088/JCP.12m08083.

Hoge, Elizabeth A., Eric Bui, Mihriye Mete, Samantha R. Philip, Caroline Gabriel, Meredith J. Ward, Rebecca Suzuki, Mary Ann Dutton, and Naomi M. Simon. "Treatment for Anxiety: Mindfulness Meditation versus Escitalopram (TAME): Design of a Randomized, Controlled Non-Inferiority Trial." *Contemporary Clinical Trials* 91 (April 1, 2020): 105965. https://doi.org/10.1016/j.cct.2020.105965.

Huang, Jesse, Mohsen Khademi, Lars Fugger, Örjan Lindhe, Lenka Novakova, Markus Axelsson, Clas Malmeström, et al. "Inflammation-Related Plasma and CSF Biomarkers for Multiple Sclerosis." *Proceedings of the National Academy of Sciences of the United States of America* 117, no. 23 (June 9, 2020): 12952–60. https://doi.org/10.1073/pnas.1912839117.

Hughes, Joel W., David M. Fresco, Rodney Myerscough, Manfred H. M. van Dulmen, Linda E. Carlson, and Richard Josephson. "Randomized Controlled Trial of Mindfulness-Based Stress Reduction for Prehypertension." *Psychosomatic Medicine* 75, no. 8 (October 2013): 721–28. https://doi.org/10.1097/PSY.0b013e3182a3e4e5.

Hughes, Lloyd D., Marion E. T. McMurdo, and Bruce Guthrie. "Guidelines for People Not for Diseases: The Challenges of Applying UK Clinical Guidelines to People with Multimorbidity." *Age and Ageing* 42, no. 1 (January 2013): 62–69. https://doi.org/10.1093/ageing/afs100.

Jacobs, Gregg D., Herbert Benson, and Richard Friedman. "Topographic EEG Mapping of the Relaxation Response." *Biofeedback and Self-Regulation* 21, no. 2 (June 1, 1996): 121–29. https://doi.org/10.1007/BF02284691.

Jadad, Alejandro R., Matthew J. To, Mohamed Emara, and Jennifer Jones. "Consideration of Multiple Chronic Diseases in Randomized Controlled Trials." *JAMA* 306, no. 24 (December 28, 2011): 2670–72. https://doi.org/10.1001/jama.2011.1886.

Joyner, Michael J., Nisha Charkoudian, and B. Gunnar Wallin. "A Sympathetic View of the Sympathetic Nervous System and Human Blood Pressure Regulation." *Experimental*

Physiology 93, no. 6 (June 2008): 715–24. https://doi.org/10.1113/expphysiol.2007.039545.
Kabat-Zinn, Jon. *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness*. Revised and Updated edition. New York: Bantam Books trade paperback, 2013.
Kalin, Ned H. "The Critical Relationship Between Anxiety and Depression." *American Journal of Psychiatry* 177, no. 5 (May 2020): 365–67. https://doi.org/10.1176/appi.ajp.2020.20030305.
Kaplan, Sherrie H., Sheldon Greenfield, and John E. Ware. "Assessing the Effects of Physician-Patient Interactions on the Outcomes of Chronic Disease." *Medical Care* 27, no. 3 (1989): S110–27.
Kearney, David J., Kelly McDermott, Carol Malte, Michelle Martinez, and Tracy L. Simpson. "Effects of Participation in a Mindfulness Program for Veterans with Posttraumatic Stress Disorder: A Randomized Controlled Pilot Study." *Journal of Clinical Psychology* 69, no. 1 (January 2013): 14–27. https://doi.org/10.1002/jclp.21911.
Khoury, Bassam, Manoj Sharma, Sarah E. Rush, and Claude Fournier. "Mindfulness-Based Stress Reduction for Healthy Individuals: A Meta-Analysis." *Journal of Psychosomatic Research* 78, no. 6 (June 2015): 519–28. https://doi.org/10.1016/j.jpsychores.2015.03.009.
Lehrner, Amy, and Rachel Yehuda. "Cultural Trauma and Epigenetic Inheritance." *Development and Psychopathology* 30, no. 5 (December 2018): 1763–77. https://doi.org/10.1017/S0954579418001153.
Lengacher, Cecile A., Richard R. Reich, Carly L. Paterson, Melissa Shelton, Steve Shivers, Sophia Ramesar, Michelle L. Pleasant, et al. "A Large Randomized Trial: Effects of Mindfulness-Based Stress Reduction (MBSR) for Breast Cancer (BC) Survivors on Salivary Cortisol and IL-6." *Biological Research for Nursing* 21, no. 1 (January 2019): 39–49. https://doi.org/10.1177/1099800418789777.
Levine, Glenn N., Richard A. Lange, C. Noel Bairey-Merz, Richard J. Davidson, Kenneth Jamerson, Puja K. Mehta, Erin D. Michos, et al. "Meditation and Cardiovascular Risk Reduction." *Journal of the American Heart Association* 6, no. 10 (September 28, 2017): e002218. https://doi.org/10.1161/JAHA.117.002218.
Lush, Elizabeth, Paul Salmon, Andrea Floyd, Jamie L. Studts, Inka Weissbecker, and Sandra E. Sephton. "Mindfulness Meditation for Symptom Reduction in Fibromyalgia: Psychophysiological Correlates." *Journal of Clinical Psychology in Medical Settings* 16, no. 2 (June 2009): 200–207. https://doi.org/10.1007/s10880-009-9153-z.
Magazine, Smithsonian, and Greg Daugherty. "The Brief History of 'Americanitis.'" Smithsonian Magazine. Accessed October 25, 2021. https://www.smithsonianmag.com/history/brief-history-americanitis-180954739/.
Maizes, Victoria, David Rakel, and Catherine Niemiec. "Integrative Medicine and Patient-Centered Care." *EXPLORE* 5, no. 5 (September 2009): 277–89. https://doi.org/10.1016/j.explore.2009.06.008.
Mano, Tadaaki, Satoshi Iwase, and Shinobu Toma. "Microneurography as a Tool in Clinical Neurophysiology to Investigate Peripheral Neural Traffic in Humans." *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 117, no. 11 (November 2006): 2357–84. https://doi.org/10.1016/j.clinph.2006.06.002.

Marengoni, Alessandra, and Graziano Onder. “Guidelines, Polypharmacy, and Drug-Drug Interactions in Patients with Multimorbidity.” *BMJ* 350 (March 11, 2015): h1059. https://doi.org/10.1136/bmj.h1059.

Mays, Vickie M., Robert-Paul Juster, Timothy J. Williamson, Teresa E. Seeman, and Susan D. Cochran. “Chronic Physiologic Effects of Stress among Lesbian, Gay, and Bisexual Adults: Results from the National Health and Nutrition Examination Survey.” *Psychosomatic Medicine* 80, no. 6 (2018): 551–63. https://doi.org/10.1097/PSY.0000000000000600.

McGowan, Patrick O, and Stephen G Matthews. “Prenatal Stress, Glucocorticoids, and Developmental Programming of the Stress Response.” *Endocrinology* 159, no. 1 (January 1, 2018): 69–82. https://doi.org/10.1210/en.2017-00896.

Mcinnis, Craig, and Patrick Griffin. “Training and Youth Affairs CONTENTS Development of the Course Experience Questionnaire (CEQ),” n.d.

Mollayeva, Tatyana, Pravheen Thurairajah, Kirsteen Burton, Shirin Mollayeva, Colin M. Shapiro, and Angela Colantonio. “The Pittsburgh Sleep Quality Index as a Screening Tool for Sleep Dysfunction in Clinical and Non-Clinical Samples: A Systematic Review and Meta-Analysis.” *Sleep Medicine Reviews* 25 (February 2016): 52–73. https://doi.org/10.1016/j.smrv.2015.01.009.

Momeni, Javad, Abdollah Omidi, Fariba Raygan, and Hossein Akbari. “The Effects of Mindfulness-Based Stress Reduction on Cardiac Patients’ Blood Pressure, Perceived Stress, and Anger: A Single-Blind Randomized Controlled Trial.” *Journal of the American Society of Hypertension* 10, no. 10 (October 1, 2016): 763–71. https://doi.org/10.1016/j.jash.2016.07.007.

Monica, 1776 Main Street Santa, and California 90401-3208. “Stress Accumulates in Marginalized Communities, Generation After Generation,” July 8, 2020. https://www.rand.org/blog/rand-review/2020/07/stress-accumulates-in-marginalized-communities.html.

National Institutes of Health (NIH). “National Center for Complementary and Integrative Health (NCCIH),” July 10, 2015. https://www.nih.gov/about-nih/what-we-do/nih-almanac/national-center-complementary-integrative-health-nccih.

Omidi, Abdollah, Abolfazl Mohammadi, Fatemeh Zargar, and Hossein Akbari. “Efficacy of Mindfulness-Based Stress Reduction on Mood States of Veterans with Post-Traumatic Stress Disorder.” *Archives of Trauma Research* 1, no. 4 (2013): 151–54. https://doi.org/10.5812/atr.8226.

Pace, Thaddeus W. W., Lobsang Tenzin Negi, Daniel D. Adame, Steven P. Cole, Teresa I. Sivilli, Timothy D. Brown, Michael J. Issa, and Charles L. Raison. “Effect of Compassion Meditation on Neuroendocrine, Innate Immune and Behavioral Responses to Psychosocial Stress.” *Psychoneuroendocrinology* 34, no. 1 (January 2009): 87–98. https://doi.org/10.1016/j.psyneuen.2008.08.011.

Polusny, Melissa A., Christopher R. Erbes, Paul Thuras, Amy Moran, Greg J. Lamberty, Rose C. Collins, John L. Rodman, and Kelvin O. Lim. “Mindfulness-Based Stress Reduction for Posttraumatic Stress Disorder Among Veterans: A Randomized Clinical Trial.” *JAMA* 314, no. 5 (August 4, 2015): 456–65. https://doi.org/10.1001/jama.2015.8361.

Public, Institute of Medicine (US) Committee on the Use of Complementary and Alternative Medicine by the American. *Integration of CAM and Conventional Medicine*.

Complementary and Alternative Medicine in the United States. National Academies Press (US), 2005. https://www.ncbi.nlm.nih.gov/books/NBK83807/.
"Racial and Ethnic Disparities in Heart Disease," n.d., 2.
Rakel, David, and Susan K. Golant. *The Compassionate Connection: The Healing Power of Empathy and Mindful Listening*. First edition. New York: W.W. Norton & Company, 2018.
Reveiz, Ludovic, Hernando G Gaitán, and Luis Gabriel Cuervo. "Enemas during Labour." *The Cochrane Database of Systematic Reviews* 2013, no. 7 (July 22, 2013): CD000330. https://doi.org/10.1002/14651858.CD000330.pub4.
Rossello, Xavier, Stuart J. Pocock, and Desmond G. Julian. "Long-Term Use of Cardiovascular Drugs." *Journal of the American College of Cardiology* 66, no. 11 (September 15, 2015): 1273–85. https://doi.org/10.1016/j.jacc.2015.07.018.
Sabri, Bushra, and Douglas A. Granger. "Gender-Based Violence and Trauma in Marginalized Populations of Women: Role of Biological Embedding and Toxic Stress." *Health Care for Women International* 39, no. 9 (September 2, 2018): 1038–55. https://doi.org/10.1080/07399332.2018.1491046.
Scifres, Christina M., Jay D. Iams, Mark Klebanoff, and George A. Macones. "Meta-Analysis versus Large Clinical Trials: Which Should Guide Our Management?" *American Journal of Obstetrics and Gynecology* 200, no. 5 (May 2009): 484.e1-484.e5. https://doi.org/10.1016/j.ajog.2008.09.873.
Seligman, Hilary K., and Dean Schillinger. "Hunger and Socioeconomic Disparities in Chronic Disease." *New England Journal of Medicine* 363, no. 1 (July 2010): 6–9. https://doi.org/10.1056/NEJMp1000072.
Seves, Bregje L., Femke Hoekstra, Jorrit W. A. Schoenmakers, Pim Brandenbarg, Trynke Hoekstra, Florentina J. Hettinga, Rienk Dekker, Lucas H. V. van der Woude, and Cees P. van der Schans. "Test-Retest Reliability and Concurrent Validity of the Adapted Short QUestionnaire to ASsess Health-Enhancing Physical Activity (Adapted-SQUASH) in Adults with Disabilities." *Journal of Sports Sciences* 39, no. 8 (April 2021): 875–86. https://doi.org/10.1080/02640414.2020.1850983.
Sexton, Anne. "The Poet of Ignorance." *The Paris Review*. Accessed December 15, 2021. https://www.theparisreview.org/poetry/3912/the-poet-of-ignorance-anne-sexton.
Soliman, Mary, and Justin Bilszta. "Teaching Complementary and Alternative Medicine in Undergraduate Medical Education: A Scoping Review." *International Journal of Medical Education* 12 (July 27, 2021): 140–49. https://doi.org/10.5116/ijme.60e2.f3ed.
Song, Yeoungsuk, and Ruth Lindquist. "Effects of Mindfulness-Based Stress Reduction on Depression, Anxiety, Stress and Mindfulness in Korean Nursing Students." *Nurse Education Today* 35, no. 1 (January 2015): 86–90. https://doi.org/10.1016/j.nedt.2014.06.010.
Stegenga, Jacob. *Care and Cure: An Introduction to Philosophy of Medicine*. Chicago: The University of Chicago Press, 2018.
Steptoe, Andrew, and Mika Kivimäki. "Stress and Cardiovascular Disease." *Nature Reviews Cardiology* 9, no. 6 (June 2012): 360–70. https://doi.org/10.1038/nrcardio.2012.45.
Stossel, Thomas P. "The Discovery of Statins." *Cell* 134, no. 6 (September 19, 2008): 903–5. https://doi.org/10.1016/j.cell.2008.09.008.
"Stress in America™ 2020: A National Mental Health Crisis." Accessed March 29, 2021. https://www.apa.org/news/press/releases/stress/2020/report-october.

Sugimoto, Michelle A., Lirlândia P. Sousa, Vanessa Pinho, Mauro Perretti, and Mauro M. Teixeira. "Resolution of Inflammation: What Controls Its Onset?" *Frontiers in Immunology* 7 (April 26, 2016): 160. https://doi.org/10.3389/fimmu.2016.00160.

GovTrack.us. "Text of H.R. 3839 (102nd): Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations … (Passed Congress Version)." Accessed March 1, 2022. https://www.govtrack.us/congress/bills/102/hr3839/text.

NobelPrize.org. "The Nobel Prize in Physiology or Medicine 1949." Accessed December 15, 2021. https://www.nobelprize.org/prizes/medicine/1949/hess/lecture/.

Thompson, Frances E., Douglas Midthune, Lisa Kahle, and Kevin W. Dodd. "Development and Evaluation of the National Cancer Institute's Dietary Screener Questionnaire Scoring Algorithms." *The Journal of Nutrition* 147, no. 6 (June 2017): 1226–33. https://doi.org/10.3945/jn.116.246058.

Tsuei, Julia J. "Eastern and Western Approaches to Medicine." *Western Journal of Medicine* 128, no. 6 (June 1978): 551–57.

Wallace, Robert Keith. "Physiological Effects of Transcendental Meditation." *Science* 167, no. 3926 (March 27, 1970): 1751–54. https://doi.org/10.1126/science.167.3926.1751.

Warren, Kimberly R., Teodor T. Postolache, Maureen E. Groer, Omar Pinjari, Deanna L. Kelly, and Mark A. Reynolds. "Role of Chronic Stress and Depression in Periodontal Diseases." *Periodontology 2000* 64, no. 1 (2014): 127–38. https://doi.org/10.1111/prd.12036.

Waxenbaum, Joshua A., Vamsi Reddy, and Matthew Varacallo. "Anatomy, Autonomic Nervous System." In *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2021. http://www.ncbi.nlm.nih.gov/books/NBK539845/.

"Welcome to the Office of Budget." Accessed March 1, 2022. https://officeofbudget.od.nih.gov/.

Zimerman, Ariel L. "Evidence-Based Medicine: A Short History of a Modern Medical Movement." *AMA Journal of Ethics* 15, no. 1 (January 1, 2013): 71–76. https://doi.org/10.1001/virtualmentor.2013.15.1.mhst1-1301.