

Book review

A theory for curing the diseases of modernity

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What Is Health? Allostasis and the Evolution of Human Design

Peter Sterling

(The MIT Press, Cambridge, MA; 2020)

ISBN: 978-0-262-04330-4

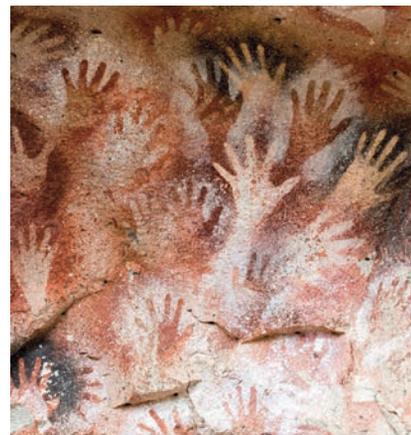
Strange times are these in which we live when old and young are taught falsehoods in school, and the person that dares to tell the truth is called at once a lunatic and fool. Plato

In his recent brilliant revisionist history *The Fate of Rome*, Kyle Harper states at the end of the prologue, “the Romans built an interconnected, urbanized empire on the fringes of the tropics, with tendrils creeping across the known world. In an unintended conspiracy with nature, the Romans created a disease ecology that unleashed the latent power of pathogen evolution [...] Here is an account of how one of history’s most conspicuous civilizations found its dominion over nature less certain than it ever dreamed” [1]. These lines about ancient Rome will resonate for any reader of this review in 2020 as we grapple with the current world pandemic. Most recent evidence suggests that SARS-CoV-2, the coronavirus that causes COVID-19, came from bats in the Yunnan province in China [2]. The exact circumstances that led to the virus getting from a bat to a human remain to be determined, but it is undeniable that the core cause is, like all zoonoses, either encroachment of human civilization on wildlife habitats or the mingling of other animal species with humans. In comparison with Rome, the tendrils of the modern world extend farther and faster, and now the virus is everywhere.

In the last six months, a vast biomedical research-industrial complex has been brought to bear on the virus, with hopes for the

development of an effective anti-viral or vaccine in record time. Indeed, this is where reductionist modern medicine tends to excel, bringing its impressive knowledge and techniques to fight an infectious pathogen and its effects on the body: in this case, the fields of immunology, virology, and pulmonology/critical care. In parallel, sophisticated mathematical modeling has sought to predict and control the spread of the virus. This partnership between biology and epidemiology is medicine’s success story, arguably its best recurring motif. Indeed, in August of this year it was officially declared that the World Health Organization African Region was free of wild polio virus. And in October the Nobel Prize for Physiology and Medicine was awarded for the discovery of the Hepatitis C virus, a discovery that has led to the development of ever more effective anti-viral treatments against what is a leading infectious cause worldwide of cirrhosis and liver cancer. It remains to be seen whether SARS-CoV-2 will similarly yield, but if past history is any guide there are reasons for optimism.

There is, however, another story to be told. This is the story about the health characteristics of the people being infected with SARS-CoV-2. What we are seeing is a clash between an ancient family of viruses and the modern industrial world’s diseases of lifestyle, including diabetes, cardiovascular disease, and obesity. These chronic diseases are associated with aging but are also prevalent in people under 65, especially those of lower socioeconomic status. The over-65 age group is the fastest growing segment of the world’s population. It is of great scientific interest that it is people who are both over 65 and suffering from lifestyle diseases who are most vulnerable to COVID-19 [3]. The showdown between a virus and the ailments of a hyper-connected but politically fragmented modern world is attracting increasing commentary, with a recent article referring to it as a ‘complexity crisis’ [4]. A lifestyle disease by definition is non-communicable; it is not caused by a pathogen but by civilization, i.e. poor diet, addiction, and sedentary living. SARS-CoV-2 has X-rayed



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the health of the modern world and exposed a latent vulnerability: it is lacking in robustness. The reasons for this are attributable to both synchronic network effects and diachronic historical, political, and economic trends; reasons that go well beyond the scope of this review. But regardless of the origin story behind the sorry state of the health of large swathes of the world’s population, the question is what does science say we should do about it? How do we treat diseases of modern civilization and aging? The Western medical establishment’s answer was, and largely still is, to bring the mono-causal and mono-therapeutic framework that has done well for acute infectious disease and force it onto non-infectious chronic disease. In essence, solve these diseases one molecule (or pathway) and one drug at a time. This has not gone according to plan. Of course, a person reading this will object and reach for their favorite counterexample, but exceptions do not prove the rule. In an article titled ‘What happens when underperforming big ideas in research become entrenched?’, Michael Joyner and colleagues raised hackles when they argued that far too much research money has been spent on this reductionist mindset with not much to show for it [5]. They state, “the biomedical research community

has pursued a narrative positing that a combination of ever-deeper knowledge of subcellular biology, especially genetics, coupled with information technology will lead to transformative improvements in health care and human health". It is not a stretch to believe that one reason for the attractiveness of this narrative is that microbes yielded to it and so genes will do so also.

The case of psychiatric disorders is instructive in this regard. There has been no real change in the neurotransmitters targeted for almost 50 years, but nevertheless Big Pharma has made billions from slight modifications to old drugs that for the most part have not imparted greater effectiveness. In a recent article surveying the history of psychopharmacology [6], the authors state, "Psychiatry and American culture have been particularly seduced by the technological solutions promised by a magic bullet that will simultaneously cure madness and provide simple explanations for the inexplicable. Psychopharmacological solutions have been especially compelling during the past 50 years since they require far fewer questions of how America cares for those unable to care for themselves." This magic-bullet approach extends to chronic conditions in general, when in reality what is needed is a renewed focus on prevention, lifestyle modification, and long-term multi-disciplinary care.

What seems to be lacking is an alternative scientific conceptual framework that would at the very least complement the idea that all diseases should be treated as honorary infectious diseases with a clear target. What would an alternative to the 'let's find a gene for it' approach look like? That word: *alternative*. For most members of the medical research establishment, the word is treated like a bad smell; it is widely assumed to imply non-scientific ideas that play to people's ignorance and fears, and it means distrust of doctors and the rejection of science. The fact that Big Pharma and scientific publications frequently indulge in hype and exaggerated claims is considered somehow different. The truth is, however, that resistance is

futile: the \$4 trillion wellness industry is here and it is going to have to be faced, the good and the bad. What is required is an acknowledgment by the medical establishment that there is a need for pluralism in the ideas and approaches used to promote health. More specifically, there needs to be an understanding that top-down approaches, which focus, for example, on reduction of stress and despair, more hours of sleep, better diets, and increased physical exercise, are scientifically legitimate and should not play second fiddle to the search for genetics-based pharmacological solutions. The sooner a broader scientific framework, which recognizes the integrative as well as the componential, is brought to bear on 'The New Medicine' and is taught in medical schools, the sooner sense can be separated from nonsense.

This brings us to Peter Sterling's *What Is Health?* This book is a challenge to review because, although it is only 177 pages long, it contains multitudes and addresses concerns that radiate from the biological into the sociological and the political. It is a very important book because it does indeed seek, and largely succeeds, to provide a scientific justification for top-down approaches to health. Peter Sterling is a Professor of Neuroscience at the University of Pennsylvania and has done seminal studies on the neural circuitry of the retina. More broadly, he has been interested in discovering principles of engineering design and optimality in structures in the nervous system from neurons to brains, always viewed in the light of evolution. His book on this topic, *Principles of Neural Design* [7], co-authored with Simon Laughlin, is already a classic (and was reviewed in these pages [8]). In parallel to a successful scientific career, Peter Sterling is also a life-long political activist. For example, he was arrested in Mississippi in 1961 as a Freedom Rider. This is relevant as research now suggests that racism itself is an independent stressor with an impact on health, and this plays right into the main theory of the book that was originally as Sterling says "hatched from the top down: from society to cells". The book can initially appear

paradoxical in so much that Sterling — as a scientist — is very interested in and is an expert on fine-grained cellular and neuronal details, but he then uses this bottom-up knowledge to make the top-down case for health-related interventions at the level of the whole organism.

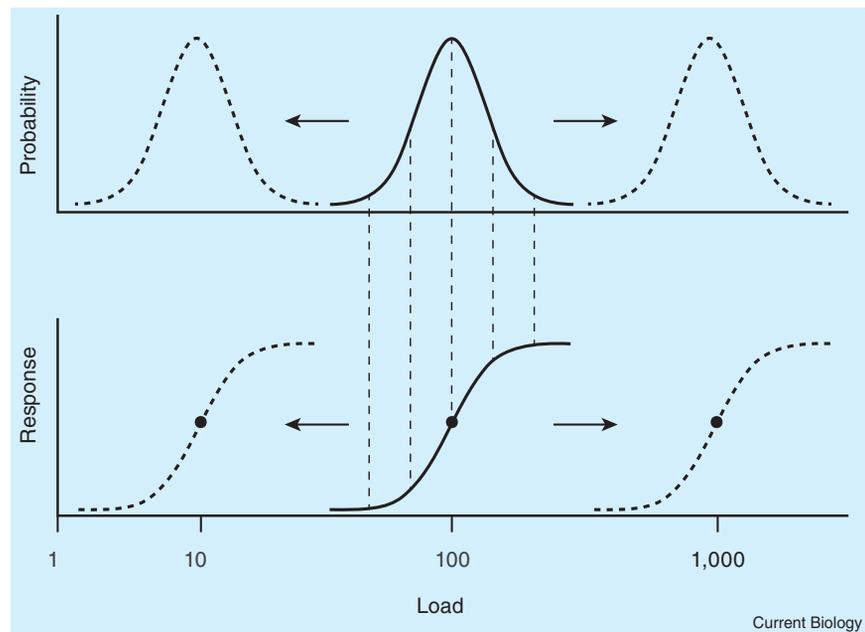
The overarching concept is that of allostasis (Greek for stability through change), which is contrasted with homeostasis, and can be defined as brain-centered prediction of upcoming needs, such as food, body temperature, and shelter. This prediction is accomplished by adjusting physiology and behavior to prevent errors that would otherwise require homeostatic correction. Such proactive over reactive regulation requires a brain. Through neural and endocrine signaling, the brain can send signals to the whole body to coordinate and adaptively regulate the set points of multiple component systems. Accordingly, the story of allostasis centers on the emergence and evolution of an increasingly large and complex brain that allowed ever longer predictive time horizons and habitat flexibility.

The first three chapters of the book span three billion years and tell an evolutionary story of increasing organismal complexity that Sterling calls 'embodied information', from single-celled eukaryotes to multicellular worms to mammals. An emphasis in these chapters is that the specialized systems that evolved are near or essentially optimal, for example, the mitochondrial electron-transport chain. As will be seen shortly, this is important for health because these 'deep' cell biological and physiological mechanisms have been optimized and locked in to the vertebrate lineage for over half a billion years and therefore are stubbornly resistant to attempts to change them, with unforeseen consequences likely to occur if they are interfered with in isolation, as drugs often do. The reason for this relates to perhaps the most important principle in the book, being the ubiquitous ability of any biological system, from receptors to behaviors, to optimally adapt its response capacity to the anticipated/ change distribution of its inputs or

expected loads (see diagram). The implication is that, when background loads get very large, rather than just parametrically changing the response along the original sigmoid, which is what happens with small changes, the whole sigmoid shifts. This is optimal because it centers the part of the sigmoid with greatest slope on the mean of the new distribution so as to maximize its sensitivity. This adaptive response forms the basis of Sterling's account of the diseases of modernity (and what to do about them).

Chapter 4 outlines the evolution of the brain in the genus *homo*, with increases in its size being accompanied by greatly expanded computational capacity. This is thought to have been driven by a self-reinforcing loop between changes in the brain and new behaviors that externalized bodily functions, such as digestion through the invention of cooking and thermoregulation with clothing. All of this culminated in egalitarian foraging societies. Chapter 5 titled 'What went wrong?' is essentially Sterling's account of *homo sapien's* fall from this hunter-gatherer Garden of Eden. He states, "what foragers do *not* suffer is hypertension, obesity, type 2 diabetes, or cardio-reno-cerebro-vascular disease". It is right here that the book really begins to engage with its theme. To reach this point has taken us nearly four billion years and four chapters to show that we humans are a layer cake of evolutionary optimizations: bacterial metabolism, eukaryotic cell biology, a worm's bilaterian body plan, and primate cortex.

It all started to go wrong, at least in the USA, after World War II and has been getting worse ever since. People are succumbing to 'deaths of despair' (a term taken from Nobel Laureates Anne Case and Angus Deaton [9]). As Sterling states, "we are drug-addicted, obese, and compulsively gambling and shopping. We are sleep-deprived, anxious, fearful, and depressed". The cause of this massive attack of ennui is our neural Achilles' heel, the dopaminergic reward system; for Sterling, modern society has induced a chronic dopamine deficit. The dopamine system, one of the most investigated areas in current neuroscience, provides transient



Response capacity adapts to changes in predicted load: "Every system encounters some particular distribution of loads (upper, bold). The effector responds (lower, bold) by matching its most sensitive region (dot) to the most probable load. When the distribution of loads changes (upper, dashed), the effector anticipates by shifting its response curve (lower, dashed) to match the new distribution. This diagram applies to every process and structure across scales." Figure and legend text from *What Is Health?* by Peter Sterling; figure originally adapted from [13].

bursts of dopamine whenever a pleasant surprise is experienced (a reward prediction error) and has been in place since the time of our bilaterian worm ancestor 500 million years ago. The critical point is that these bursts should be sparing: a lion has days when it catches no prey, a hunter-gatherer may have lean days. The temple of Apollo at Delphi bore the inscription 'nothing in excess'. For ancient philosophers, "health was seen to flow from observing moderation — in exercise, in study, and in diet" [10]. It is important, however, to have a steady stream of small satisfactions in life because the dopamine bursts are transient and so pleasures are not stored. The foraging life provides such small surprises based on the person's own efforts and skills. Modernity, in contrast, did two things: first, life became dreary and depleted of small self-attributed pleasures. Sterling states, "we evolved to explore the planet, but now multitudes are confined to punch a ticket, scan an item, or sit in cubicles and stare at screens. These activities are unrewarding, and so we despair."

The late David Graeber describes such lives in his wonderful book *Bullshit Jobs* [11]. Fascinatingly, Graeber speculated that people trapped in such jobs are more likely to suffer clinical depression and other mental illnesses. I wonder if Graeber knew of Sterling's book before his untimely death.

The second thing modernity did was to find external rewards — large and small — to compensate for boredom and stress-induced dopamine deficits. An example of small ones would be 'likes' on Facebook or Instagram. He states that these small pleasures are inferior to those attributable to one's own skills — they are like the difference between pornography and real sex. He also notes that real skills, sex included, require more physical effort, which is itself beneficial. The real issue, however, is that modernity has brought in a plague of health-threatening addictions. Most importantly, addictions should not be judged morally nor viewed as diseases or evidence for something being broken. Instead, they should be seen as an unavoidable consequence

of big external rewards pushing the dopamine system beyond the range for which it was optimized. This is why the earlier diagram is so critical: the large load (reward) pushes the curve rightward, and this means that a larger reward is needed for the same dopaminergic response. This adaptive capacity can then snowball with the new response in the brain sending predictive signals to the rest of the body in anticipation of these larger rewards. In a knock-on effect, these recipient systems also undergo adaptive responses. So, for example, desire for large amounts of high-calorie food reward (super-sizing) is accompanied by adaptation of satiety signals and insulin receptors; the result is morbid obesity. This is the book's repeating story of modern unhealthiness: moving a physiological parameter beyond its characteristic operating range for long periods of time, and thereby shifting its predictive adaptive signals. The story applies to other chronic conditions, such as hypertension and type 2 diabetes.

What is the solution? The answer comes via an answer to another question that is the title of the book: what is health? Sterling defines it "as the capacity to respond optimally to fluctuations in demand". To be honest, this is a bit cursory and unsatisfactory, striving perhaps for excessive compression. Nevertheless, the implication of this allostasis — derived definition, harking back to the beginning of this review — is that top-down system-level interventions should be favored over low-level pharmacotherapies. This is because a drug tries to correct the value of a specific parameter: "A drug blocks some part of the circuit to force the parameter back toward the standard range. But, since the drug doesn't change the prediction, the circuit still anticipates the high demand and uses its remaining components to compensate. This calls for another drug to block another component, eliciting another compensation, and so on." Basically, billions of years of evolution have led to robust and recalcitrant back-up mechanisms in low-level systems. This is why, Sterling says, we must instead treat individuals holistically rather than as clusters of lab values. This

requires a return to what Sterling calls 'moral therapy', which refers back to late eighteenth- and nineteenth-century mental asylums in the USA that were conceived as therapeutic communities that created the best possible environments for people, with well-lit rooms, farm work, good food, and educational lectures. These were phased out, however, and by the 20th century had been replaced by neuroleptics and lobotomies. Now we have Prozac.

The ideal of therapeutic communities as a solution for the diseases of modernity may strike readers as hokey and new agey, but they would be mistaken. It is to the great credit of this book that they will stand corrected in a rigorous way: slow weaning off of big external rewards and substituting them for varied internal small ones is an approach based on both argument and evidence. That chronic illnesses could benefit from some of the philosophy of Alcoholics Anonymous, for example, sounds odd but shouldn't. The burden of chronic disease would be greatly reduced if modern societies were able to reduce meaningless and/or low-paying jobs, distribute affordable nutritious food, and provide locations for physical exercise. Sterling is not suggesting that we return to being foragers in the countryside but to somehow simulate it. The mainstream medical establishment urgently needs to become a lot more interested in systems-level and complexity-based thinking and in long-term behavioral change, and at least partially wean itself off its magic-bullet fixation. Peter Sterling has written an instant classic. The one major criticism that I have of the book is that the benefits of top-down approaches are all viewed through the single lens of an adaptive shifting sigmoid. There is far more going on in disease than this one mechanism. A much-broader perspective couched in the framework of complexity science and non-linearly interacting networked systems is needed. Indeed, several others have also argued against the homeostasis-based single-parameter approach in medicine, but they are not mentioned in the book. As just one example, Tim Buchman refers

to inter-connected systems in the body as 'the community of the self' [12]. He describes multi-organ failure (a major cause of death from COVID-19) as related to uncoupling between previously cooperative organ systems. Thus, the interventions that Sterling prescribes for a healthy life are fundamental, but while the health mechanism/definition he uses throughout is useful it is also narrow. There are other smaller details one could quibble with as one reads, but these pale in comparison with the originality, ambition, scholarlyness, and sheer heart of the book. Every medical student (and medical administrator) should be made to read it.

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