Biology and Lived Experience in Health and Disease: A Tribute to Bruce McEwen (1938–2020), a Scientist without Silos

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Bruce McEwen

Bruce McEwen, head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at the Rockefeller University, died suddenly after a brief illness on January 2, 2020. Bruce was a towering figure in neuroscience and an inspiration to many whose interest in the interface between biology and the way we live our lives were influenced by Bruce's research. The usual metrics of scientific accomplishment and respect from peers are present in every way in Bruce's career. Consider for a moment that he published nearly 1,400 papers that garnered over 130,000 citations; that he was recognized with many prestigious awards and prizes,

including the Pasarow Neuropsychiatry Award, the Ipsen Foundation Neuroplasticity and Endocrine Regulation Prizes, the Scolnick Prize in Neuroscience from the McGovern Institute of MIT, and the William James Lifetime Achievement Award for Basic Research presented in honor of the 25th Anniversary of the American Psychological Society; and that he was also an elected member of the National Academy of Sciences, the National Academy of Medicine, and the American Academy of Arts and Sciences.

Imagine for a moment that this prodigious scientific output was less impressive than the impact that Bruce had on the science of many students and fellows who trained in his laboratory, and on the approach to science of so many individuals whose careers intersected with his. It is because of these intersections that Bruce's work has had so many unexpected ramifications. Although he is best known for his basic science studies on how stress hormones reshape neural circuits and brain structures, McEwen's work has had profound implications for public health and clinical medicine, impacting conditions from normal aging to neurodegenerative disease, depression, and PTSD. Today, Bruce's research and clear, concise writing is notable for its continuing relevance to discussions about social justice, and the profound impact that

discrimination and economic and social disadvantage has on both health and disease.

Bruce McEwen grew up in the college town of Ann Arbor, Michigan. He attended Oberlin College where he majored in chemistry before moving to Rockefeller University to pursue a PhD in cell biology. In 1966, Bruce joined the faculty at Rockefeller in the laboratory of Neal Miller. Bruce early on showed a penchant, sustained over his career, for research ideas that strayed far from those of the Miller lab, ultimately culminating in the self-described label of “molecular sociologist” that Bruce used to signal his interest in how cell and molecular biology could be integrated with the social sciences.

The McEwen lab is best known for its landmark research unraveling the biology of stress. The first step in what would be a lifelong commitment to stress research was Bruce’s discovery of corticosteroid receptors in the brain [1], a finding that made it possible to understand how a person’s experience of stress outside in the environment could be expressed as disturbances inside in the body. The elegant studies in Bruce’s lab of stress and glucocorticoid receptor signaling were amplified by the brilliant work of his trainees and collaborators, including Robert Sapolsky and Michael Meaney. Further, adult neurogenesis, originally discovered in the adult mammalian brain by Altman and Das [2] and then suppressed [3], was rediscovered in the dentate gyrus of the hippocampus [4–5] in the context of studies of neuron cell death and in the actions of adrenal steroids and excitatory amino acids in relation to stress. Together with these and other scientists, McEwen promoted the hypothesis that the brain was not fixed in its connectivity, but instead, that the adult brain was adaptive, dynamic, and capable of evolving in the face of environmental challenge.

Over time, Bruce McEwen became the champion for a deep biological understanding for how stress increases the risk of disease and response to treatment. Until his field-defining papers on stress and disease, few seriously considered the adverse effects of stress to be anything more than pop psychology. Bruce changed that view through his science and his papers in clinical journals (NEJM, JAMA, and others) that helped physicians understand the pathways linking stress to an array of chronic diseases. This work led to a collaboration between Bruce and Eliot Stellar to expand on the concept of allostasis, first introduced by Sterling and Eyer [6], and then to introduce the concept of allostatic load that described the role of stress mediators on adaptation to chronic stress and the long-term consequences to physiological stability and health.

The magnitude of Bruce’s accomplishments in developing the concept of allostatic load and its relevance to clinical medicine is evident in the systematic review of allostatic load and its impact on health by Guidi and colleagues in this issue of the journal [7]. In summarizing the state of knowledge for allostatic load and overload, the authors included 267 original publications in their review. McEwen’s contributions are prominent in the review, and many of the other papers cited his work. The authors’ conclusion that allostatic load and overload is associated with poorer health outcomes would have been acknowledged by McEwen, whose own research reinforced these findings.

Bruce was more than a great scientist; he was a great person. He projected a personal modesty that was all the more remarkable for its authenticity. Bruce was also more generous with his time and expertise than anyone could possibly expect. Both at the Rockefeller where he hosted so many visiting students and colleagues, and at labs around the world where he was hosted by others, Bruce unfailingly critiqued, encouraged, and inspired everyone with whom he came into contact. In the following sections, we describe Bruce’s scientific accomplishments, his extraordinary development of Sterling and Eyer’s [6] concept of allostasis and the notion of allostatic load, and the impact of his work on the larger world community.

Scientific Accomplishments

Bruce McEwen’s well-supported view that an integrated consideration of the brain – especially brain plasticity – and the body was essential for understanding how features of the social and physical environment influenced the maintenance and enhancement of good health as well as vulnerability to disease was put forth at the culmination of a complex research career with many profound contributions along the way. No summary of Bruce’s remarkable discoveries would be adequate without briefly indicating who the people were that provided the motivation and pointed questions that led this remarkable mind to some amazing accomplishments.

When Bruce was still an undergraduate at Oberlin, he worked during the summer between his junior and senior years in the laboratory of Irving Fritz in the department of physiology at University of Michigan. This led to Bruce’s first publication [8] on the role of carnitine in facilitating fatty acid oxidation by mitochondria. Carnitine plays a critical role in energy production. It transports long-chain fatty acids into the mitochondria so they can be oxidized (“burned”) to produce energy.

Because of his experience with Irving Fritz, Bruce was fascinated by oxidative metabolism and oxidative phosphorylation by mitochondria, and he joined the laboratory of Alfred Mirsky and Vincent Allfrey at Rockefeller University to study the question of how the cell nucleus obtains the adenosine triphosphate to make ribonucleic acid. What he found in his PhD thesis research is that there is another terminal oxidase, most probably in the nuclear envelope, that is less sensitive to carbon monoxide than the cytochrome c of the mitochondria [9–12].

After a brief post-PhD period at University of Minnesota, Bruce returned to Rockefeller as a faculty member in 1966 and remained there for the rest of his life. There it was the influence of Mirsky and Allfrey that led him to study steroid hormone receptors in the brain. He was also heavily influenced by his new laboratory head, Neal Miller, whose interest in and development of “behavioral medicine” led Bruce to the topic of stress and stress hormones. There followed in 1968 what turned out to be a very surprising and monumental discovery; namely, that of adrenal steroid receptors in the hippocampus [1]. This ultimately led to the realization that circulating hormones of the gonads, adrenal cortex, thyroid gland, and also of the metabolic system affect many – if not most – areas of the brain, including those involved in higher cognitive function [13].

The big surprise was, indeed, the discovery of cell nuclear receptor sites for glucocorticoids in the hippocampus not only of rodents but also monkeys, with extension to other species [1, 14, 15]. This finding was a major part of the motivation for Bruce to study brain functions above the hypothalamus and, in particular, to the function of the hippocampus – a brain region important for memory and other aspects of behavioral regulation [16]. An important review paper on this entire area was published by Bruce and colleagues in 2012 [17].

In parallel with Bruce’s discovery of adrenal steroid receptors in the hippocampus, he and Bernice Grafstein published the first characterization of the rapid axonal transport of newly synthesized proteins in particulate material in the goldfish optic nerve and followed this with papers characterizing components of that transported material [18].

Moving toward a more elaborate and diverse set of ideas, Bruce’s work on adrenal steroid hormone effects on the hippocampus and other limbic system brain areas attracted the attention of Eliot Stellar and his colleagues at University of Pennsylvania. Stellar and McEwen looked at a bigger picture, related to how the brain is the master organ of adaptation to a changing external and internal

environment and an active and malleable participant in those adaptive changes. The 1993 paper by McEwen and Stellar [19] both included consideration of allostasis, but went beyond it, to introduce the notion of allostatic load – meaning the price paid by the body for repeatedly responding to what are perceived as stressful challenges. Allostatic load purports to measure signs of dysregulation of bodily systems. Initial attempts to operationalize the idea of allostatic load [20] have been followed by a large set of papers using essentially the same methodology as put forth in that original publication. At the present time, 27 years after its initial conceptual formulation, allostatic load remains to be operationalized in a manner that builds directly on its complex biological basis. Here is a research challenge waiting for a new generation of investigators.

During the last decade of his life, Bruce described himself as a molecular sociologist. This description reflected his broad view of brain-body interaction, and especially took account of a holistic view of behavior from the societal level to the fundamental molecular biological level. Partially this description was fostered in Bruce by his collaboration with his brother, Craig, a professor of sociology at Bowdoin College. Bruce summed up his views of what is important for neuroscience and medicine looking ahead: “Because hormones influence so many aspects of brain structure and function and because hormone secretion is governed by the cognitive and emotional brain acting through the hypothalamus, the role of brain plasticity must be considered in understanding how the social and physical environment ‘gets under the skin’ to affect brain and body resilience and positive aspects of health, on the one hand, and vulnerability to disease, on the other.” This perspective clarifies why an operationalization of the idea of allostatic load is such a subtle and difficult problem. The challenge ahead in this area is both interesting and difficult.

In the next section, we elaborate on Bruce’s development of the concept of allostatic load and illustrate its central role in his scientific worldview.

Bruce McEwen and Allostatic Load

McEwen and Stellar [19] provided a novel and groundbreaking perspective on the profound and multifaceted ways in which adaptation to stress over one’s life-course impacts on trajectories of health and well-being. Their discussion of the importance of incorporating a multi-systems view of the array of crucial physiological regula-

tory systems that contribute to patterns of morbidity, disability, and mortality represented a significant shift away from more traditional discussions of the individual roles of different biological parameters as “risk factors” for disease and other health outcomes. As they presciently stated, “This article presents a new formulation of the relationship between stress and the processes leading to disease. It emphasizes the hidden cost of chronic stress to the body over long time periods, which act as a predisposing factor for the effects of acute, stressful life events. It also presents a model showing how individual differences in the susceptibility to stress are tied to individual behavioral responses to environmental challenges that are coupled to physiologic and pathophysiologic responses.” “This new formulation emphasizes the cascading relationships, beginning early in life, between environmental factors and genetic predispositions that lead to large individual differences in susceptibility to stress and, in some cases, to disease” [19].

Bruce went on to contribute many insightful and important additions to the theoretical and empirical literature on allostatic load. Among his most highly cited papers was a 1998 article in *NEJM* in which he delineated the theoretical model underlying the concept of allostatic load and its relationship to life-course experiences with acute and chronic stress. As he noted in that article, “acute stress (in the sense of ‘fight or flight’ or major life events) and chronic stress (the cumulative load of minor, day-to-day stresses) can both have long-term consequences... Two factors largely determine individual responses to potentially stressful situations: the way a person perceives a situation, and a person’s general state of physical health, which is determined not only by genetic factors but also by behavioral and lifestyle choices. Whether one perceives a situation as a threat, either psychological or physical, is crucial in determining the behavioral response – whether it is fleeing, fighting, or cowering in fear – and the physiologic response – calmness or heart palpitations and elevated cortisol levels” [21, p. 171]. As Bruce went on to discuss, over the course of time, each of us seeks to adapt and respond to the various situations we confront in our daily lives and our major physiological regulatory systems participate in this effort at adaptation. As Bruce so succinctly wrote, “the price of this accommodation to stress can be allostatic load, which is the wear and tear that results from chronic overactivity or underactivity of allostatic systems” [21].

What became more striking over time were the ways in which this basic neuroscientist, whose initial research focused on investigation of fundamental physiological

mechanisms of stress in classic animal models, expanded his focus to include an ever-widening consideration and attention to social, psychological, behavioral, and macro-level environmental influences on human population health. His writings expanded to include in-depth discussion of the significant roles of social, economic, and other factors in differential life-course trajectories of human health, including collaborations with his brother Craig, a sociologist, discussing the roles of social structure, inter-generational poverty, and childhood adversity in generating toxic stress and consequent negative health outcomes [22]. This is only one of numerous such articles that Bruce contributed to the literature on human health. In so doing, Bruce exhibited a unique ability to integrate his knowledge and expertise in basic neuroscience with equally important expertise in the significant impacts of broader social and societal factors on population-level trends in health. His work over the later years of his stellar career resulted in a unique body of writing that served importantly to enrich development and understanding of the concept of allostatic load and its role as a crucial index of life-course-relative experiences with the damaging and protective roles of our multiple physiological regulatory systems.

McEwen, Science, and Social Justice

Bruce McEwen died just as the novel coronavirus, SARS-CoV-2, was poised to cause a worldwide epidemic. Now, 10 months later the United States has experienced 9.5 million officially reported cases of Covid-19 and more than 250,000 Americans have died from the disease. Covid-19 spares no group of people, but certain groups are targeted more than others. For instance, Covid-19 is more likely to kill the very old than the young, and those with comorbidities such as hypertension and diabetes than those without comorbidities.

But as the disease was spreading throughout the US, an astonishing disparity became apparent. In Louisiana, African Americans accounted for 33% of the population but 70% of the Covid-19 deaths. In Michigan where blacks constitute 14% of the population, they accounted for 40% of the deaths. Similar disparities were reported in Chicago, New York, and then other communities around the country.

The finding of racial disparities in deaths from Covid-19 was so surprising to many Americans that it earned headlines in major American newspapers. Yet few physicians or social scientists were surprised by these findings.

Although comorbidities are more common among African Americans, most appreciate that the real reason for the disproportional burden of disease in minority communities is attributable to decades of racial segregation, inadequate access to healthcare, and the extreme economic inequity in America. As Camara Phyllis Jones, the former President of the American Public Health Association stated, “there is nothing different biologically about race. It is the conditions of our lives.”

Bruce McEwen, as much as anyone who tried to understand how the body functions, illuminated the rich and still poorly understood interplay between biology and the lived experience (biography) of individuals. Bruce was a leading scientist in the field of stress biology. Here, Bruce’s willingness to ignore disciplinary boundaries and to work in the fields of psychology and anthropology was critical to his success in providing fresh insights into the role that economic and social disadvantage played in contributing to the risk of disease and the response to treatment. Bruce argued that for the individual, an external challenge is something that is first perceived by the brain, which then communicates with the neuroendocrine system, the immune system, the sympathetic and parasympathetic nervous systems, and others. Excessive psychological challenge, especially severe psychological trauma or repeated stress can lead to physiological damage that manifests as diseases of diverse types – e.g., cardiovascular diseases. Indeed, a growing body of research has linked the excess hypertension in African Americans that affects their recovery from Covid-19 to just such repeated stress, including the pervasive effects of discrimination.

Science is often presented to the public as an objective process, indifferent to the opinions of scientists who car-

ry out the research or affected by the social injustice that occurs in the world that we study. Yet, the truth is that scientists make decision after decision in their research that is tied closely to their values. In choosing to study the interplay between biography and biology, Bruce McEwen lived his values. His research will continue to serve as a model for all those who envision science as an engine for progress towards a more just and equitable world.

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Author Contributions

Dr. Seeman contributed to the manuscript in equal parts to the other authors. She was responsible for outlining Dr. McEwen’s work relating to allostatic load. Dr. Horwitz contributed to the manuscript in equal parts to the other authors. He was responsible for the Introduction, the concluding section, and for integrating the sections. Dr. Singer contributed to the manuscript in equal parts to the other authors. He was specifically responsible for the section on Dr. McEwen’s scientific contributions.

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