

ALLOSTATIX

The History, Measurements, and Integration of
Allostasis and Allostatic Load

Topics

- Historical Overview of Allostasis and Allostatic Load
- Measurement of Allostatic Load
- Allostatic Load in the Medical Community and General Population

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The concept of allostasis builds from scientific research beginning in the 1860s with Bernard's concept of "milieu interieur."

- 1860: **Dr. Claude Bernard** – “Father of Physiology”
 - 19th Century French Physiologist and Medical Scientist
 - Chair of physiology at the Sorbonne
- **“Milieu Interieur”** – The Environment Within
 - Living organism exists in an aqueous internal environment which bathes all tissues and provides a medium for the elementary exchange of nutrients and waste
 - Related total body health to the purity of the fluid environment in which the body cells exist
 - Underlying principle of what would later be known as “homeostasis”

Later in 1932, Dr. Cannon’s definition of “homeostasis” and the “fight or flight” response established normal “reference ranges” or set-points within the body.

- 1932: **Walter Cannon, MD, ScD** – “Homeostasis”
 - Harvard University Medical School
 - 1915 coined term **“fight or flight”** as body’s response to threats
- Coined the term **homeostasis**:
 - Perfectly balanced body chemistry
 - Does not mean “fixed” or “non-changing”, but a relatively consistent, complex, well-coordinated and usually stable condition
 - Does not occur by chance, but results from **organized self-government**
- Homeostasis today: Established the importance of **“set points”** or normal **reference ranges** for any physiological parameter

In 1936, Dr. Hans Selye began investigating the body's response to stress and the **General Adaptation Syndrome**.

- 1936: **Dr. Hans Selye**--“The Einstein of Medicine”
 - Vienna-born physician and endocrinologist
 - Attended Johns Hopkins on a Rockefeller Foundation scholarship; studied stress at McGill University and University of Montreal
 - Wrote 30 books and more than 1,500 articles on stress and related problems
- Demonstrated the existence of stress
 - Investigated the pituitary gland and the role of **glucocorticoids** in the **body's non-specific stress response** of “looking sick”
 - Examined the influence of stress on people's ability to cope with and adapt to the pressures of injury and disease
- Conceptualized the physiology of stress as having two components: a set of responses which he called the **General Adaptation Syndrome**, and the development of a **pathological state** from **ongoing, unrelieved stress**

Dr. Philip S. Hench, a former student of Dr. Selye, won the Nobel Prize for his 1948 discovery of the hormone later named “Cortisone.”

- 1948: **Dr. Philip S. Hench—Nobel Prize for “Cortisone”**
 - 1920 doctorate in medicine from the University of Pittsburg
 - Specialist in arthritic disease
 - 1923 Fellow at Mayo Foundation; 1926 Head of Mayo Dept of Rheumatic Diseases; 1935-47 Professor of Medicine at Mayo Foundation
- Successfully applied an adrenal hormone (later named **“Cortisone”**) in the treatment of rheumatoid arthritis at The Mayo Clinic
 - Investigated the favorable effects of steroids on the alleviation of pain in arthritic patients.
- Won the Nobel Prize in 1950 for discoveries concerning hormones of the adrenal cortex, their structure and biological effects.

Scientific medical studies continued through the 1940s, 50s, and 60s, building upon each other to further understand the body's response to stress and glucocorticoids.

- **1948: Rome and Braceland**
 - Reviewed the psychiatric effects of glucocorticoids
 - Described four categories of psychiatric responses to steroids, ranging from improved sense of well-being to clinically psychotic.

- **1952: Selwyn Brody, MD and Clark et. Al.**
 - Further investigated glucocorticoids and individual responses
 - Concluded reactions to glucocorticoids reflected an extreme version of a patient's usual stress reaction

In the late 1960s, Bruce McEwen began his pioneering work in what would later (1988) be named “allostasis” and “allostatic load.”

- **1968: Dr. Bruce McEwen**
 - Ph.D. in Cell Biology in 1964 from The Rockefeller University
 - Alfred E. Mirsky Professor and Head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at The Rockefeller University
 - Member of the U.S. National Academy of Sciences, The Institute of Medicine, the American Academy of Arts and Sciences, and a Fellow of the New York Academy of Sciences
- Early research concluded high levels of stress impair memory.
 - Discovered adrenal steroid receptors in the hippocampus
 - Researched the hippocampus and concentration of glucocorticoids

Then in 1988, the actual term “allostasis” —achieving stability through change—is defined by Peter Sterling and Joseph Eyer.

- 1988: **Peter Sterling, Ph.D. and Joseph Eyer—Defined allostasis**
 - Peter Sterling—Ph.D. in Biology , Western Reserve University; Professor of Neuroscience, University of Pennsylvania, School of Medicine
 - Joseph Eyer—Department of Biology, University of Pennsylvania
- **Defined the concept of allostasis**
 - “Achieving stability through change” in order to provide a logical structure for understanding the ever-shifting integrated biobehavioral, endocrinological and physiological systems of the body that promote adaptation and drive natural selection
 - Concluded **any set point will change in response to environmental demands** (e.g., poverty or cardiovascular disease)
 - Examined the relationship between stress and health

During the 1980s and 1990s, Bruce McEwen introduced the concept of allostatic load and how to measure it.

- **Bruce McEwen—Father of allostatic load**
- Defined **allostatic load**: “The price the body pays over long periods of time for adapting to challenges.”
- Created an **index to measure** allostatic load
 - Based on the number of key indicators which fell in the upper- or lower-most quartile of the population distribution
 - Applied the index to the health outcomes of participants in the MacArthur Study of Successful Aging
- **Proved the allostatic load index predicted decline in cognitive and physical functioning.**
- Continues to conduct and publish research, concentrating on the role of hormones, cell changes, brain coordination, and body function in response to stress.

Research and continued publications validate the predictive relationship between allostatic load and cognitive and physical functioning.

- **1993:** Stress and the individual: Mechanisms leading to disease. Arch Int Med 153: 2093-3101. B.S.McEwen, E.Stellar.
- **1998:** Protective and damaging effects of stress mediators. New England Journal of Medicine 338: 171-179. B.S.McEwen
- **2001:** Allostatic load as a marker of cumulative biological risk. Proc Natl Acad Sci 2001;98(8):4770-4775. Seeman TE, McEwen BS, Rowe JW, Singer BH
- **2004:** Allostasis, Homeostasis, and the Costs of Physiological Adaptation. Cambridge University Press. Edited by J.Schulkin
- **2006:** The detrimental effects of allostasis: allostatic load as a measure of cumulative stress. J Physiol Anthropol: Jan; 25(1): 133-45. J.Stewart.
- **2006:** Predicting mortality from clinical and nonclinical biomarkers. Journal of Gerontology 2006; 61A(10), 1070-1074. Goldman, N, Turra CM, Gleib DA, Seplaki CL, Lin Y, Weinstein M.

Topics

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- Measurement of Allostatic Load

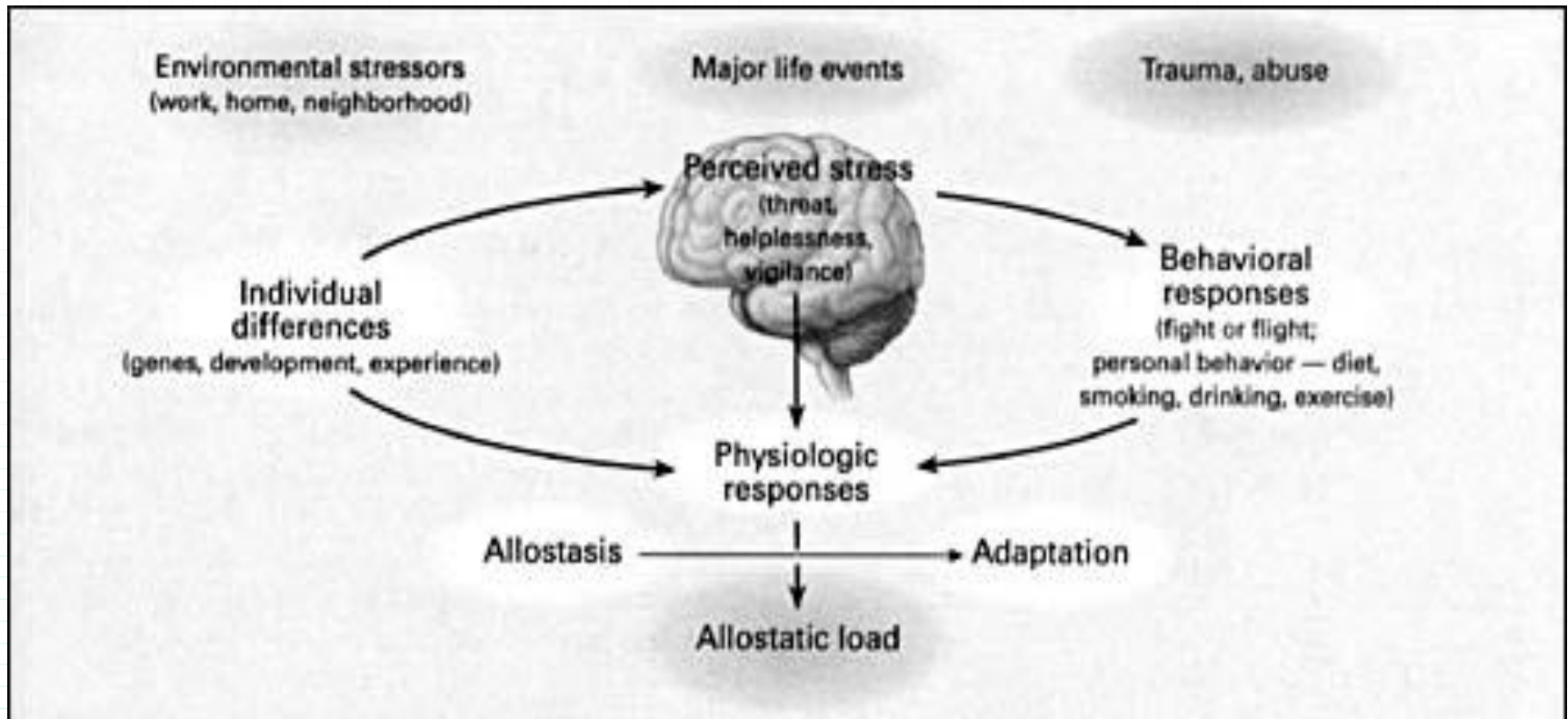
- Allostatic Load in the Medical Community and General Population

The index McEwen developed to measure allostatic load reflects information on levels of physiologic activity across a range of important regulatory systems.

--Operational Measurements of Allostatic Load--

- Hypothalamic-pituitary-adrenal (HPA) Nervous System
- Autonomic Nervous System
- Cardiovascular System
- Metabolic Processes
- Inflammatory System

These systems all have a role in the cause and effect relationship that is triggered when the brain perceives stress.

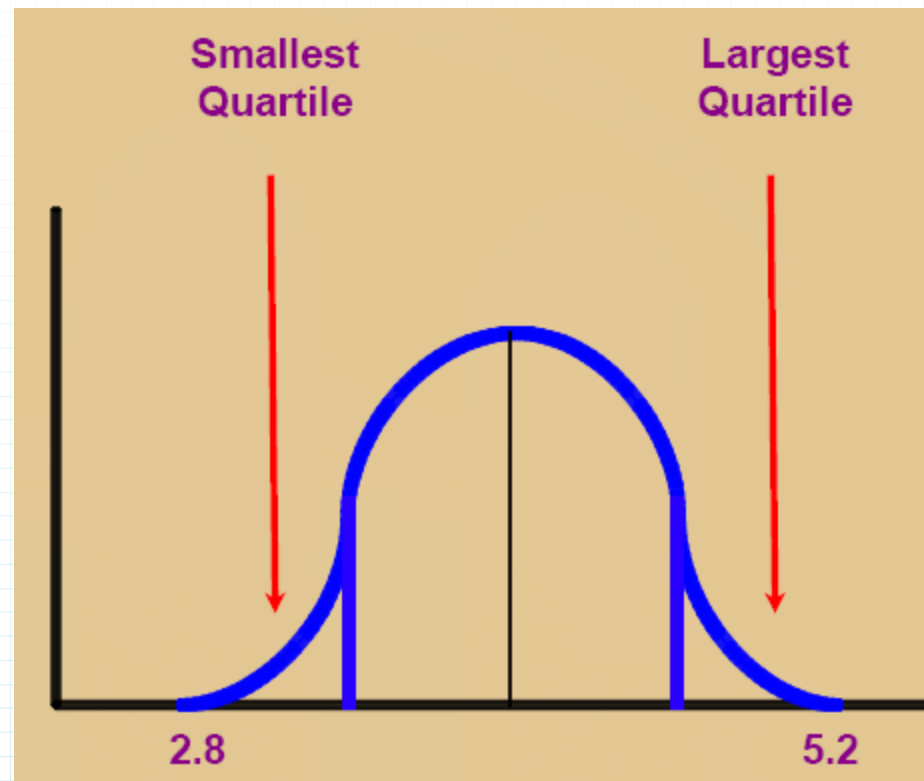


The MacArthur Study of Successful Aging* calculated allostatic load by measuring primary mediators and secondary outcomes.

Primary Mediators	Secondary Outcomes
Cortisol (overnight)	Waist-to-Hip Ratio
Catecholamines	Blood Pressure (systolic and diastolic)
DHEA-S	Hemoglobin
	CRP, Fibrinogen, and Albumin
	Total and HDL Cholesterol

*Longitudinal, community-based study of relatively high-functioning men and women aged 70-79 years.

An allostatic load score was calculated for each individual based on the number of outcomes in the smallest or largest quartiles.



The MacArthur Studies of Successful Aging showed the overall summary measure of allostatic load significantly predicts risk for major health outcomes, including mortality.

Strong association between allostatic load score and

- (1) Poor cognitive and physical functioning
- (2) Onset or incident of cardiovascular disease
- (3) All-cause mortality

Study details on the following page.

(Con't) The MacArthur Studies of Successful Aging showed the overall summary measure of allostatic load significantly predicts risk for major health outcomes, including mortality.

MacArthur Study Findings:

- Higher allostatic load scores were associated with poorer cognitive and physical functioning and predicted larger decrements in cognitive and physical functioning as well as being associated with an increased risk for the incidence of cardiovascular disease, independent of sociodemographic and health status risk factors (Seeman et al. 1997)
- Higher baseline allostatic load scores were associated with significantly increased risk for 7-year mortality as well as declines in cognitive and physical functioning (Seeman et al. 2001).
- The summary measure of allostatic load reflecting activity across multiple physiological systems had strong associations with both short-term (2.5 year) and long-term (7.5 year) physical and cognitive functional declines using canonical correlation analyses (Karlamanjla et al. 2002).
- Allostatic load provided independent explanatory power, over and above a measure of doctor-diagnosed disease (Seeman et al. 2004).
- Allostatic load measure based on recursive partitioning techniques was associated with a high-risk of mortality over a 12-year period (Gruenewald et al. 2006).

Findings from other researchers and longitudinal studies continue to support allostatic load as a predictive measure of physical functioning, disease onset, and mortality.

Additional Research Findings:

- Higher levels of allostatic load were observed in individuals with higher levels of ischaemic heart disease and periodontal disease (Sabbah et al. 2008).
- In a national sample (NHANES III), across ages 20-90, allostatic load was associated with poorer physical functioning, which remains statistically significant after controlling for age and gender. Similarly, allostatic load was associated with a 1.2 times greater odds of having cardiovascular disease after controlling for age and gender (Crimmins et al. 2006).
- A study of national sample of Taiwanese persons aged 54 years or older found that allostatic load was significantly associated with 3-year mortality. Inclusion of neuroendocrine and immune biomarkers into the allostatic load measure had better explanatory and discriminatory power than the one with just clinical measures, suggesting that the nonclinical measures provide additional warning signs of deteriorating health above and beyond what can be learned from standard clinical measures (Goldman et al. 2006).

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Today, leading medical schools are integrating allostasis and allostatic load into their curriculums and continuing education programs.

University	Course	Instructor
Denver University <i>Medical School Curriculum</i>	Psychophysiology <i>Lecture: Stress & Physical Health</i>	Iris Mauss, Ph.D.
Tufts University <i>Medical School Curriculum</i>	Epidemiology and Biostatistics <i>Lecture: Determinants of Health</i>	Richard Glickman-Simon, M.D.
Harvard University <i>CME Workshop</i>	Clinical Training in Mind/Body Health <i>Lecture: Science & Background</i>	Herb Benson, M.D and Peg Baim, M.S.
Stanford University <i>Pre-Med Curriculum</i>	Living Well With Stress: A Guide for Thriving	Kelly McGonigal, Ph.D.
Princeton University <i>CME Workshop</i>	Workshop on Allostasis & Allostatic Load	Bruce McEwen, Ph.D.

Worldwide, scientific and medical researchers continue to research allostasis and allostatic load.

Examples Include:

UCLA

- Teresa E. Seeman
- Arun S. Karlamangla
- Tara L. Gruenewald

Princeton University

- Burton H. Singer
- Christopher L. Seplaki
- Noreen Goldman

McGill University

- Sonia Lupien

University of Southern CA

- Eileen Crimmins

Georgetown University

- Jay Schulkin

Rockefeller University

- Bruce McEwen

University of Wisconsin-Madison

- Carol D. Ryff

Stockholm University

- Petra Linfors

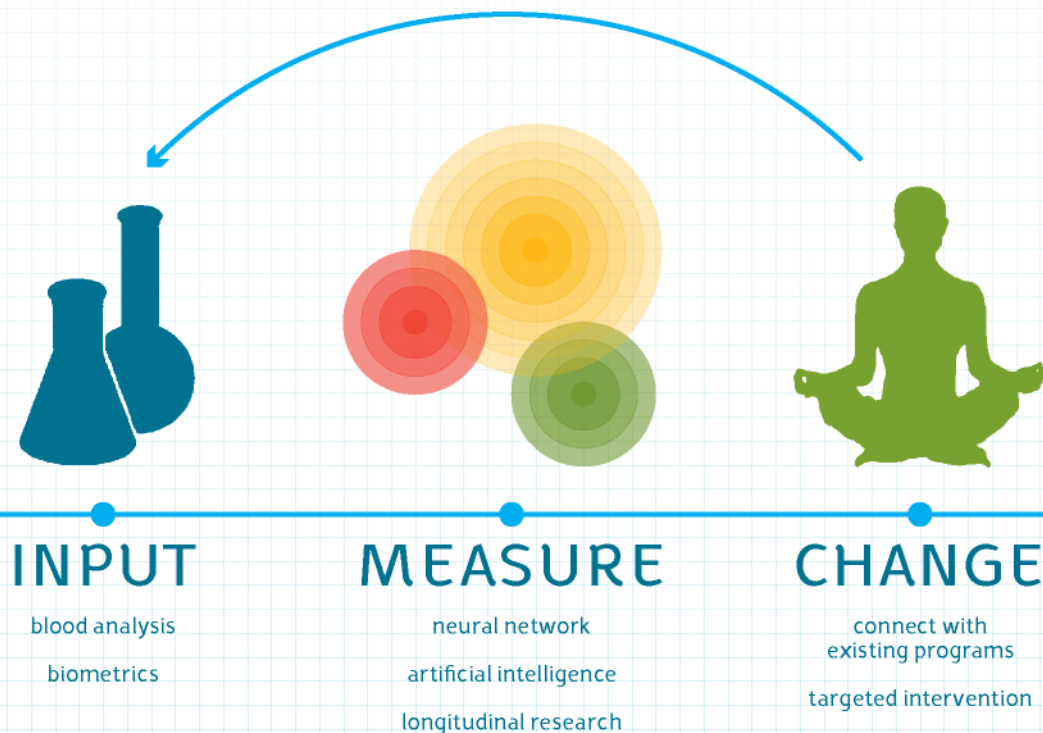
University College London

- W. Sabbah

Stanford University

- Robert M. Sapolsky

Allostatix, LLC introduced the Allostatix Risk Prediction System (ARPS™) to the general population as a predictor of future wellness, to motivate proactive behavior change, and to improve future health status.



Appendix

- Crimmins EM, Johnston ML, Hayward M, Seeman T. Chapter 7. Age Difference in Allostatic Load: An Index of Frailty. In Zeng Yi et al. (eds.), *Longer Life and Healthy Aging*, Netherlands: Springer 2006.
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- Gruenewald TL, Seman TE, Ryff CD, Karlamangla AS, Singer BH. Combinations of biomarkers predictive of later life mortality. *Proc Natl Acad Sci* 2006; 103(38):14158-14163.
- Jaur L, Stoddard S. Chartbook on women and disability in the U.S. Washington DC: US National Institute on Disability and Rehabilitation Research; 1999.
- Karlamangla AS, Singer BH, McEwen BS, Rowe JW, Seeman TE. Allostatic load as a predictor of functional decline: MacArthur studies of successful aging. *Journal of Clinical Epidemiology* 2002;55:696-710.

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- Sabbah W, Watt RG, Sheiham A, Tsakos G. Effects of allostatic load on the social gradient in ischaemic heart disease and periodontal disease: evidence from the Third National Health and Nutrition Examination Survey. *J Epidemiol Community Health* 2008;62:415-420.
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