

## Allostatic Load and its Utilization in Clinical Practice

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### Definitions<sup>1</sup>

- **Allostasis:** The ongoing adaptive efforts of the body to maintain stability (homeostasis) in response to stressors
- **Allostatic Load:** The physiological wear and tear on the body that results from ongoing adaptive efforts to maintain stability (homeostasis) in response to stressors.

### Introduction

Based on considerable evidence implicating allostatic (over)load in the mechanisms by which psychosocial factors influence health risks,<sup>2,3,4</sup> we believe that it is critical to develop a clinical assessment tool to identify those (often subclinical) changes in physiology that increase the risk of adverse outcomes. In children<sup>5</sup> and young adults, measurable allostatic load could be an early warning sign of accumulating health risks; making early changes in lifestyle choices and health behaviors could dramatically alter a patient's lifetime risk. Identifying markers of subclinical changes is especially important in older adults. Many older men and women experience gradual declines in physical and cognitive abilities even in the absence of a clinically diagnosable disease. Measures of allostatic load can help identify those older adults who are at increased risk for such declines, and can help the clinician select appropriate interventions with which to lower the patient's risk profile.<sup>6</sup>

Typical HRAs (health risk assessments), which often include questions from the SF-36 (perhaps the most widely used survey of functional health and well-being), do not do a good job of predicting future health problems; in fact, Sacks' article on the reliability of the health hazard appraisal explains that only 15% of participants studied gave consistent answers at baseline and follow up, giving little accuracy to what is likely to happen to an individual's health in the future.<sup>27</sup> More than 20 years ago, a group of noted scientists from UCLA, Rockefeller University, Princeton, and the University of Wisconsin began a decades-long study of the application of allostatic load to predicting future health. Thousands of individuals were followed for many years as they developed diseases or died. The subjects were between 18 and 70 years of age at the start of the studies. Many peer-reviewed research papers have been published from these data, illustrating the clear efficacy of using allostatic load as a reliable measure of future health, notably:

- Reduction in allostatic load in older adults is associated with lower all-cause mortality risk: MacArthur studies of successful aging (T.E. Seeman, A.S. Karlamangla, B.H. Singer - 2006)
- Calcified Coronary Artery Plaque Measurement with Cardiac CT in Population-based Studies: Standardized Protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) Study (J. Jeffrey Carr, MD, MSCE, et al. – 2005)
- Cumulative biological risk and socio-economic differences in mortality: MacArthur studies of successful aging (T.E. Seeman, E. Crimmings, M.H. Huang, B. Singer, A. Bucur, T. Gruenewald, L.F. Berkman, D.B. Rueben - 2004)

Other research teams from around the world have taken the concept of allostatic load and used it to study individual health, including Australia's Flinders University Study on environmental and psychological stress and allostatic load<sup>24</sup>, the Swedish National Institute for Working Life's study on how work life influences public health<sup>25</sup> and England's Whitehall Study discussing stress responsivity and socioeconomic status as a mechanism for increased cardiovascular risk<sup>26</sup>.

The outcome of all these studies has been to demonstrate that allostatic load, a measure which combines blood and biometric tests from multiple body systems, is a significantly better predictor of health risks than the HRAs and individual tests typically used at the time of annual physical exams.<sup>4, 6</sup>

## **Objectives**

The primary objective of this paper is to serve as a reference for clinicians (physicians and other health professionals) on the concept and utilization of allostatic load in clinical practice. After reading this document, you will:

1. Be able to define allostasis and allostatic load and describe their use in assessing the effects of stress on patient health.
2. Understand how the allostatic load diagnostic test is created from individual blood and biometric test results.
3. Be able to identify and proactively manage those patients whose allostatic load score is elevated, before the cumulative effects of stress lead to severe disease onset.
4. Have an identifiable source for obtaining an allostatic load test.

## Emergence of Stress as a Recognized Factor in Health

“The groundwork for understanding the physiology of mind-body interactions was established by pioneering studies in the 1930s by Walter Cannon, and in the 1950s by Walter Hess and by Hans Selye that led to an understanding of the fight-or-flight response.”<sup>7</sup> The work of Hans Selye advanced our understanding of stress from a description of purely physical influences to encompass the biologic sphere. His final definition, as cited by Szabo,<sup>8</sup> became: “Stress is the nonspecific response of the body to any demand made upon it.” In the same article, Szabo also wrote that “Selye’s last main contribution to the stress concept was the recognition that, despite our different psychological and cerebral reactions, both negative and positive stressors (i.e., distress and eustress) elicit virtually identical corticoid/catecholamine responses.” Even more specifically, he wrote that “different stressors elicit different patterns of activation of the sympathetic, nervous, and adrenomedullary hormonal systems.” As both scientists and clinicians know, activation of those systems eventually involves the entire mind/body of the patient.

Later in his career, Selye distinguished distress from eustress: “...the fact that eustress causes much less damage than distress graphically demonstrates that it is ‘how you take it’ that determines, ultimately, whether you can adapt successfully to change.”<sup>9</sup>

### ***Chronic vs. Acute Stress***

The word stress has acquired so many different connotations over the years, describing external events as well as internal reactions, that it has been difficult to use it in a precise, scientific manner and to describe the differences between acute and chronic stress. Bruce McEwen, a neuroscientist at Rockefeller University who has a considerable body of work in this field, suggested the term *allostasis*, as opposed to homeostasis, to describe the physiological response of the body in the face of a challenge. Allostasis is thought to occur primarily via acute and chronic changes in the stress response system (involving the hypothalamic-pituitary-adrenal or HPA axis and the immune, autonomic, cardiovascular, and metabolic systems). Chronic dysregulation of the HPA axis, the autonomic nervous system, and the immune system contributes to chronic alterations in metabolism and inflammation, which then interact with other influences (e.g., nutrition and/or genetics) to cascade into specific diseases such as the metabolic syndrome, hypertension, cardiovascular disease, depression, and cancer.

Acute stress induces changes that are generally thought to be essential and adaptive, while chronic stress is thought to exact a higher physiological price, creating what Bruce McEwen coined as an *allostatic load*, defined as the long-term effect of the physiological response to stress. Robert Sapolsky, a former student of McEwen’s and an established researcher on stress, explains the difference between acute stress and chronic stress in his book *Why Zebras Don’t*

*Get Ulcers*: “Unlike us, the zebra has an episode of stress only when the lion is in pursuit; otherwise, he is physiologically calm.” Chronic stress (which most people experience) and its cumulative effects comprise allostatic load. “Allostatic load does not always denote a failure of the body’s efforts to cope with change or emergency. We can create it for ourselves by living in a way that makes for internal imbalance.”<sup>10</sup> Some examples of self-generated stress are not getting enough sleep, eating an unhealthy diet, and not getting enough exercise.

### ***Health Effects of Stress and Allostatic Load***

Increased stress has been associated with many health conditions that are widely discussed in the medical literature. Some of the most familiar include cardiovascular disease, gastrointestinal disease, and hormone dysfunctions, all of which have active, ongoing explorations that continue to produce interesting introducing data. The interesting characteristic of allostatic load, however, is that “...whereas singular physiological markers of adaptation to environmental demands (e.g., blood pressure) are modestly linked to various disease endpoints (e.g., coronary heart disease), the combined effect of singular physiological changes across multiple biological systems captured by allostatic load is substantially more predictive of disease outcomes.”<sup>11</sup>

From a biomarker perspective, the proinflammatory cytokine IL-6 has been shown to be one mediator of stress-induced illness. A study of the daily burdens of Alzheimer caregivers reported elevated IL-6 levels.<sup>12</sup> Chronic stress also raises cortisol levels,<sup>13</sup> which have been shown to damage the brain.<sup>14</sup>

Acute stress prepares the organism for a short-term emergency, but prolonged or chronic stress impairs health through a complex array of physiologic functions initiated by the release in the hypothalamus of corticotrophin releasing factor (CRF). CRF triggers the release of adrenocorticotrophic hormone (ACTH) from the pituitary, which in turn causes the release of cortisol from the adrenal cortex. Cortisol helps maintain blood glucose levels, but chronic stress or chronic administration of pharmacological cortisol preparations causes insulin resistance, hypertension, redistribution of fat in the body, and decreased protein synthesis.<sup>15</sup> Furthermore, the immune system is weakened through a decrease in the production of blood cells, antibodies, and gamma globulins, but also through inhibition of proinflammatory interleukins (IL-1, 2, and 6), tumor necrosis factor, and gamma interferon. This shift in resources from ongoing maintenance and repair of the organism to all-out defense is understandable when fleeing the lion, but harmful when chronic.<sup>16</sup>

The effects of allostatic load established to date are multiple, and extend to every age group. In a study involving 1,189 men and women, aged 70-79 years at outset, participants were assessed with respect to allostatic load, cognitive functioning, and physical functioning.<sup>17</sup>

Participants with the highest allostatic load performed most poorly with respect to cognitive and physical functioning and, on seven-year follow up, higher baseline allostatic load scores predicted greater loss in cognitive and physical functioning. Specifically, persistent elevated levels of cortisol are toxic to hippocampal neurons, and lead to neuronal atrophy or death and loss of memory.

In addition, prolonged HPA axis activation in infancy and childhood takes its toll,<sup>18</sup> inhibiting the production of growth hormone and somatomedin C. This impairment can contribute to a “failure to thrive,” in which caloric intake does not promote weight gain. Early loss of a parent and physical or sexual abuse at any age increase the risk of major depression and PTSD, both of which have been correlated with a high allostatic load and increased illness.<sup>19,20</sup> Both of these disorders also carry a large cardiovascular and metabolic risk, in addition to neural implications.

### ***Determinants of Individual Responses to Stress***

Although chronic and cumulative stress increases the chance of illness, genetic, psychological, and social factors also play important modifying roles. For example, Sapolsky conducted a series of experiments with rats in which a second rat receives the same electric shock as the first.<sup>16</sup> He found that not all rats of the same strain suffered the same degree of ill effects from the same stress. The second rat did not develop an ulcer if there were mechanisms that helped the rat “cope,” such as: a warning before the shock, a companion rat it likes, a piece of wood it can gnaw on, or a lever it could press that it thinks would reduce the shock. Sapolsky translated these studies to humans, observing that stress-related illness is less likely to happen if:

- we have an outlet for our frustration
- we have “a hobby” for diversion
- we have predictive information
- we have a real or imagined sense of control
- we can interpret a stress favorably, and/or
- we have social connectedness<sup>16</sup>

Thus, more important than the amount of stress is one’s reaction to it and that reaction is influenced by many factors. Oakley Ray describes four classes of coping skills that improve one’s ability to handle stress.<sup>21</sup> The first step is knowledge. “With knowledge or information, comes an empowerment, a belief that the world is understandable, controllable and friendly.” The second coping skill he describes is inner resources: the “beliefs, assumptions, and predictions” one learns growing up, including whether life is seen positively or negatively. The third skill is social support. “In general, the larger the social support system is, the lower the mortality rate.” Lastly, the fourth class of coping skill is spirituality. Drawing from a 1995 study by Oxman, Freeman, and Mancheimer, Ray explains that “those who were ill and did not

participate in spiritual group activities were four times more likely to die than those who did.” All of these elements correlate back to Sapolsky’s list in a very substantive way.

In this brief summary, we have touched on some of the psychosocial factors that influence health through the interconnected information systems of the mind, the endocrine system, the nervous system, and the immune system. The possibility that the signs and symptoms exhibited by patients may be initiated (triggered) and/or influenced (mediated) by psychosocial experiences should not be discounted. Research validates the importance of paying particular attention to stress, loss, attitude, knowledge, beliefs, social support, and spirituality, as they all have a direct impact on health.

### **Using Allostatic Load in Clinical Practice**

Clinically, it is important to expand the working concept of stress to include both psychosocial factors (e.g., poverty, abuse, separation, job loss, and cultural context) and the body’s stress response to episodes of, for example, low blood sugar, chronic pain, or food restriction. Once stressors have been identified and explored, the clinician and patient can work together on developing an intervention plan. Lifestyle measures useful for improving stress management include meditation, adequate nutrition and sleep, enhancement of social connectedness, and exercise. An improvement in any one of a patient’s five main areas of lifestyle behaviors will reduce allostatic load over time and diminish the onset of chronic disease and/or illness. It is abundantly clear that each aspect of the bio-psycho-social-spiritual web is interactive and in communication with the other aspects.<sup>22</sup>

Although allostatic load is a subtle phenomenon, assessing it can facilitate diagnosis and treatment. Clinicians can help patients reduce allostatic load by encouraging them to learn behavioral coping skills (stress management) that will enable them to recognize their limitations and teach them to relax.<sup>23</sup> Along with encouraging the development of a strong social support system, the simple steps mentioned above can be confidently recommended to patients even while awaiting the results of further research. Patients can also be reminded about the role of high fat diets and stress in atherosclerosis, the role of risky behaviors such as smoking in cardiovascular disease and cancer, and the beneficial effects of exercise.

Although reductions in allostatic load can be accomplished with standard medical and behavioral approaches, until just recently, there were no clinical mechanisms to quantitatively assess the effects of these approaches on allostatic load. Quite a few research studies have investigated various combinations of the many available biomarkers, but none of these approaches has been converted into a clinical test. Through the identification of targeted biomarkers and the aggregation of those biomarkers into an overall measure of allostatic load,

physicians are now able to assess the level of a person's allostatic load and the changes in that load that occur over time through clinical interventions.

## **Measurements of Allostatic Load**

Available biomarkers for measuring components of allostatic load are extensive and include anthropometric, cardiovascular, metabolic, inflammatory, HPA axis and SNS activity, renal, lung, bone density, immune functioning, and genetic markers.

The existing body of work that has emerged from the McArthur Study focused on the following biomarkers:

- Systolic and diastolic blood pressure, indices of cardiovascular activity.
- Waist-hip ratio, an index of metabolism and adipose tissue deposition.
- Serum HDL and total cholesterol.
- Blood plasma levels of glycosylated hemoglobin, an integrated measure of glucose metabolism over several days time.
- Serum dihydroepiandrosterone sulfate (DHEA-S), a functional HPA axis antagonist.
- Overnight urinary cortisol excretion, an integrated measure of 12-hr HPA axis activity.
- Overnight urinary norepinephrine and epinephrine excretion levels, integrated indices of 12-hr SNS activity.

### ***The Allostatix Load Test™***

Allostatix, LLC has developed the Allostatix Load™ (AL) test and offers it to physicians, organizations and individuals. The AL score is calculated by combining the results of various blood and physiologic tests, chosen to provide information on the functioning of multiple body systems. The physiologic, biophysical, and psychological data collected during longitudinal studies, while different, had considerable overlap. The panel of Allostatix Load Test™ biomarker measurements includes:

- Blood pressure
- Waist-to-hip ratio
- Resting heart rate
- Peak flow
- Total cholesterol
- HDL cholesterol
- Triglycerides
- Fasting glucose
- Hemoglobin A1C
- Fibrinogen
- Homocysteine

- DHEA-S
- Creatinine
- Interleukin-6
- Albumin
- C-reactive protein

Individual test results are combined algorithmically to produce a single score that represents the cumulative impact of stress on the individual at the time of the tests. The algorithm takes into consideration the full range of test results, not just whether the results are within or outside the standard reference ranges, as well as the interactions among the test results from a whole body system perspective.

The Allostatix Load Test™ offers providers, corporations and consumers a comprehensive look at health, giving distinctive inputs and producing specific outputs that deliver an individual risk profile as well as an approach on how to improve someone's health and reduce their Allostatix Load™.

### ***The Research Process Used to Develop the Allostatix Load Test™***

The development of the Allostatix Load Test™ began through review of peer-reviewed research published over the last 25 years. The conclusion from the review was that allostatic load represented the most promising measure of future health found to date because calculating AL requires that multiple body systems be considered simultaneously.

The initial thrust of the development process was to identify existing large published longitudinal databases that followed sizeable populations of individuals through extended periods of their lives, that included the regular collection of extensive biometric and biophysical data, and that identified those who developed chronic diseases and/or died. The MacArthur Study of Successful Aging and the CARDIA databases (see notes about these studies at the end of the paper) were primarily used in developing the Allostatix Load Test™, although NHANES (the National Health and Nutrition Examination Survey, a program of studies designed to assess, through interview and physical examinations, the health and nutritional status of adults and children in the United States) and Framingham data were used in specifying some aspects of the Test algorithms. The ages of the populations studied vary (ages of 18 to 80) as well as the length of follow-up (7 years to 22 years). Teresa Seeman (UCLA), research director for the MacArthur data, and Bruce McEwen (Rockefeller University) served as consultants to the research team. Both hold major research professorships and have published extensively using both the MacArthur and CARDIA data, notably:

- Allostatic Load as a marker of cumulative biological risk: McArthur studies on successful Aging. (T.E. Seeman, B.S. McEwen, J.W. Rowe and B.H. Singer, 2001)
- Allostatic Load as a predictor of functional decline: McArthur studies on successful Aging. (T.E. Seeman, J.W. Rowe, A.S. Karlamangla, 2002)
- Modeling multisystem biological risk in young adults: The Coronary Artery Risk Development in Young Adults Study (T.E. Seeman, T. Gruenewald, A.S. Karlamangla, S. Sidney, K. Lui, B.S. McEwen, J. Schwartz, 2009)

Allostatix, LLC took all the existing MacArthur and CARDIA longitudinal health data, reanalyzed the information to reproduce some of the published results, and then made the decision to use neural network analysis as the primary analysis tool to see whether improved predictions would result. The characteristic of neural networks that we found compelling is that they assume there is a strong interaction (non-linearity) between all of the input variables.<sup>28</sup> Other analytic procedures assume that the variables are at most weakly interactive. In the case of allostatic load, we are using test results as variables. These variables provide information on many multiple different body systems that we know strongly interact. Consequently, we believed that our models would provide a more accurate view of AL, and thus predict health risks better than other approaches. As the results shown below indicate, significant improvement has been made over previously published allostatic load results.

The initial algorithms were based on a unique z-score formulated model that modified the yes/no scoring of previous models and provided a continuous Allostatix Load™ score, predicting future health and the onset of chronic disease. Subsequent algorithms were developed using the neural network analysis. Over a period of three years, approximately 1,100 alternative neural network models were built and tested, ultimately yielding significantly higher predictability of future health and chronic disease than previous models. Different neural network models apply to different age groups, but each of the finalized models provides significant predictability of future health for the individual.

Application of these methods to the MacArthur and CARDIA databases has yielded positive predictive value (PPV), negative predictive value (NPV), receiver operating characteristic (ROC), specificity, and sensitivity values, as shown in the table on the next page:

**Values Associated with the Allostatix Load Scores  
Derived from MacArthur and CARDIA data**

	<b>Predicting Serious Disease Onset</b>	<b>Predicting Mortality</b>
<b>PPV</b>	81%	80%
<b>NPV</b>	79%	88%
<b>Area under the ROC curve</b>	0.83	0.89
<b>Sensitivity</b>	0.93	0.95
<b>Specificity</b>	0.55	0.60

*Comparative Sensitivity Analysis*

A sensitivity analysis, by definition, is the study of how the variation (impact) in the output of a mathematical model can be apportioned, qualitatively or quantitatively. Put another way, it is a technique that produces the parameters that show the “effect” or change in the output. To demonstrate the accuracy and uniqueness of the neural network’s capabilities, we conducted a comparative sensitivity analysis; the results of which are below.

The output from the neural network algorithm provides insight into how individuals can improve their allostatic load most effectively. Our database consists of over 1,100 different networks looking at various disease/mortality outcomes for many different age and demographic groups. Each network uses some, or all, of the 16 biomarker panel discussed in the previous Allostatix Load Test™ section. For each individual, the biomarkers comprising the Allostatix Load Test™ are combined in an optimal way to derive the overall score for that individual. Thus, even though two individuals may have the same overall score from the Neural Network algorithm, the path to developing the score may have been different, suggesting that different interventions may be indicated for each individual. This specificity and sensitivity analysis provides the clinician with detailed information about which of the mediators/systems are the most “out of balance”, allowing them to target the right interventions that will be most effective in improving a person’s Allostatix Load™ score.

For example, one neural network used the MacArthur data and 12 biomarker inputs to predict morbidity and mortality within seven years, with a ROC area under the curve of 0.90. The network provides a score between 0 and 1, which indicates the probability of the outcome such as the onset of chronic disease or death. Illustrated below are the results for two individuals

with similar very high probabilities (score) of having an onset of chronic disease or death (.979 and .981).

Measured Values used in the Network													
ID	Input 1	Input 2	Input 3	Input 4	Input 5	Input 6	Input 7	Input 8	Input 9	Input 10	Input 11	Input 12	Score
226	0.76	75.33	116.67	46.14	20	5.90	4.40	380	3.00	9.32	23.80	100	0.979
526	0.75	88.67	162.00	42.74	97	7.00	6.21	380	4.10	5.18	2.96	390	0.981

The Contributions table (below) is a calculated measure of which variables had the most impact on the total load score for these individuals, with the top three impact variables highlighted in green. Because the source of the allostatic load is different, the most important changes that each individual can make to impact their overall score will also vary.

Contributions												
ID	Input 1	Input 2	Input 3	Input 4	Input 5	Input 6	Input 7	Input 8	Input 9	Input 10	Input 11	Input 12
226	0.01	0.05	2.33	2.95	9.79	2.04	14.03	2.33	100	1.72	0.40	28.76
526	1.36	14.42	0.01	34.61	100	6.31	1.65	23.78	34.20	7.42	58.62	10.08

### Summary

In summary, stress can have wide-ranging effects on emotions, mood, and behavior. Equally important, but often less appreciated, are the cumulative effects of stress on various systems, organs, and tissues all over the body. Reducing allostatic load to a more acceptable level can be accomplished with standard medical and behavioral approaches, using the Allostatix Load Test™ to monitor positive change. The Allostatix Load Test™ sensitivity analysis can indicate where to focus treatments to reduce allostatic load as quickly as possible for the patient. Using the Allostatix Load Test™ as a screening test of cumulative stress can suggest early and proactive lifestyle interventions for patients, as research shows that lowering the impacts of stress on a patient’s physiological systems reduces the likely onset of severe health problems.

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### Major Studies Providing Clinical Data Used to Create the Allostatix Load Test™

#### MacArthur Studies of Successful Aging

- Population: healthy 70-79 year olds
- Sample size used in creating diagnostic test: 1,189
- Period of study: 7 years
- Outcomes tracked: significant disease onset, death

See NIH site for MacArthur Studies details:

<http://www.nia.nih.gov/ResearchInformation/ScientificResources/StudyInfo.htm?id=56>

## **CARDIA Study**

Population: healthy 18-30 year olds  
Sample size used in creating diagnostic test: 1,200  
Period of study: 20 years  
Outcomes tracked: significant disease onset, death

See NIH site for CARDIA Study details:

<http://www.nhlbi.nih.gov/resources/deca/descriptions/cardia.htm>

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## **General Resources on Allostasis and Allostatic Load**

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