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Commentary

The path traveled and the path ahead for the allostatic framework: A rejoinder on the framework's importance and the need for further work related to theory, data, and measurement

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Abstract

Ideas related to the newly introduced allostatic framework have caught on in the scientific community, and not without good reason. This short report highlights what we have gained from the framework by discussing the term "allostasis" in comparison to "homeostasis" and "homeostatic mechanisms," and by outlining key ideas behind the phrase "allostatic load." In terms of how allostatic theory can be strengthened, this piece delves into the need for the theory to be clearer about what is meant by load that is "cumulative" and the need to incorporate results from research work on hormesis demonstrating the salutary, not damaging, effects of a moderate amount of stress. Lastly, some space in the rejoinder is devoted to how we can better operationalize the allostatic load construct and how new waves of biomarker-containing surveys are poised to collect yet more physiological information and are now more comprehensively measuring, in what is surely a difficult task, stress over the life course.

Keywords: Stress; Homeostasis; Allostasis; Allostatic load (AL); Neuroendocrine biomarkers

First introduced in 1988, allostatic load (AL) and related concepts have caught on in the scientific community such that, to borrow a term from Richard Dawkins, they might well be considered successful "idea-memes" (Dawkins, 2006). As evidence consider that in the PubMed/MEDLINE database in 1993, only one article could be retrieved through a search of "allostasis" or "allostatic load." By 2000, the number of retrievals reached 8, and by 2006 the number of retrievals reached 34 (Fig. 1).

In my opinion, the popularity of the allostatic framework witnessed to date is largely justified, but that, as indicated in commentaries by McDade (2008) and Loucks, Juster, and Pruessner (2008), much work still remains to further advance research integrating biological, psychological, and sociodemographic approaches. To help in this end, I would like to structure this rejoinder by addressing the following questions. First, what are the key aspects of the allostatic framework, how have they advanced our knowledge, and what have they focused or refocused our attention on? Second, what aspects of allostatic theory are in need of refining or are challenged by the stress literature? Third, how can we accurately measure stress over the life course? Fourth and lastly, what are issues related to the collection and analysis of biomarkers that we need to address?

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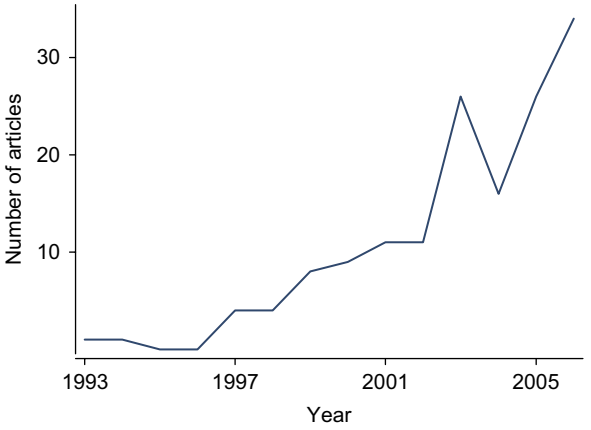

Fig. 1. Number of retrieved articles from the PubMed/MEDLINE database using the search terms "allostasis" and "allostatic load." (The literature search for years 2005 and earlier was conducted on February 7, 2007 and the literature search for year 2006 was conducted on June 14, 2007. The figure was created by this author).

Taking up the first question, the allostatic framework presents a number of key ideas (some novel, some not) related to the newly introduced terms "allostasis" and "allostatic load." In shorthand, allostasis can be defined as "stability through change," or the body's dynamic mechanisms that attempt to achieve homeostasis. This shorthand definition of allostasis has mainly served to clarify confusion related to the word "homeostasis." Before allostatic theory was introduced and seriously considered, homeostasis could often be misunderstood as both the process the body undergoes in order to achieve a steady-state (or equilibrium) and the steady-state itself. As an illustration, consider a couple of passages from the introductory biology textbook assigned to me as a Berkeley undergraduate. A paragraph on page 791 begins, "Today, Bernard's 'constant internal milieu' is incorporated into the concept of homeostasis, which means 'steady-state'." In contrast, page 6 reads, "Regulatory mechanisms maintain an organism's internal environment within tolerable limits, even though the external environment may fluctuate. This *regulation* is called homeostasis" (Campbell, 1996, italics added). With the introduction of allostatic theory, then, the term allostasis could now refer to the process that attempts to achieve a steady-state, whereas homeostasis could refer to the steady-state itself. As my choice of wording has suggested, because internal and external demands on the body are constantly changing, a true steady-state does not exist and hence can be considered ideal (Timiras & Gersten, 2007).

To be clear, allostasis is not merely a relabeling of what others have previously called the "homeostatic mechanisms." Indeed, when Sterling and Eyer (1988) first introduced the concept of allostasis they took pains to distinguish it from the concept of homeostasis. For instance, they stressed that instead of the homeostatic emphasis on optimal, fixed setpoints, the allostatic framework emphasizes that different challenges or states (e.g., sleeping, awakening, eating, and exercising) require continuously readjusted and flexible setpoints. The allostatic regulatory system, moreover, is conceived of far more broadly than is the homeostatic one. For example, the allostatic framework emphasizes the preminent role of the brain in perceiving psychological and physical threats and in orchestrating holistic (in contrast to local feedback) responses. Further, the allostatic regulatory system can learn from previous experience and anticipate future challenges. For instance, one could be planning a hiking trip to the Grand Canyon and could recall how hot it was the last time one went. Thinking ahead and making sure to bring sunscreen, a hat, and a lot of water for the upcoming trip constitutes an allostatic response, and so too does sweating (a way for the body to cool down) during the hike itself.

In addition to allostasis, the allostatic framework has usefully brought us the concept of AL, which includes the following ideas: (1) the body's response to challenges can carry a physiological toll and that this toll is cumulative, (2) this toll (or load) can negatively influence a wide variety of health outcomes, (2) these outcomes operate through or are a result of dysregulation of multiple physiological systems, including the neuroendocrine, immune, metabolic, and cardiovascular systems, (3) load accumulates throughout the life course, and (4) load does not represent poor health per se, but is a predisease indicator. Condensed into one sentence, AL could be defined as "the cumulative, multisystem physiological dysregulation that results from exposure to challenges over the life course and that places individuals at greater risk for poor health." The main contribution of the term AL, then, is to offer a succinct phrase to represent an important set of ideas, albeit ideas that were already present in various literatures. Although others may disagree (Dallman, 2003; Day, 2005), I find this to be a useful contribution.

I now will turn to a more detailed discussion of the aspects of allostatic theory that are in need of refining or are challenged by the stress literature. To begin with, it seems to me that some refining of the theory needs to be made in reference to the idea that AL builds up over the life course. For instance, although it has been recognized that prenatal events are important in the accumulation of AL postnatally (e.g., in predisposing the organism to overreact physiologically and behaviorally to events throughout life), from a theoretical standpoint I think it still remains unclear whether AL starts to accumulate at birth or perhaps even before then as the Barker hypothesis might suggest (Phillips & Jones, 2006).

Another area in which AL theory could be refined is to clarify what is meant by load that is "cumulative." As I understand it, one can think of load accumulating much like adding coins to one end of a scale which can only become heavier and heavier. Perhaps there is a way to retard the speed at which new coins are added (e.g., through diet and/or exercise), but there is no doubt about the scale's increasing burden. If AL is indeed cumulative, does this mean that load for any particular system (e.g., the metabolic or immune) is cumulative, or that load in reference to the entire construct (i.e., all the different systems put together) is cumulative? Also, over what time period is load thought to be cumulative? Is it cumulative, say, over the last few weeks or the last few years? Certainly the cumulative aspect of AL theory cannot be applied in its strictest sense to every single biomarker that makes up the construct since markers like blood pressure, cholesterol, and BMI can head toward lower risk values in a matter of days and weeks.

Even more challenging to allostatic theory is the idea of hormesis or eustress, in which a moderate amount of stress can be good for an organism. An increasing body of research indicates that various types of mild stress (e.g., dietary restriction, exposure to heat, physical and mental exercise, and social stimulation) in humans and non-human animals is beneficial at the molecular, cellular, and perhaps other levels (Hayes, 2007; Piper & Partridge, 2007). To take but one example from this work in non-humans, an experiment using white rats found that compared to those fed *ad libitum*, the rats whose diet was restricted experienced a nearly doubling of their lifespans (Piper & Partridge, 2007). This sort of research suggests that a fruitful direction for future analysis involving the allostatic framework is to focus on both the ways in which stress may harm or damage the body and the ways in which the body is capable of resisting, recovering from, or even benefiting from the impact of various insults.

I now turn to question three posed toward the beginning of this piece which asked how to accurately measure stress over the life course. I am in full agreement with Loucks, Juster, and Pruessner that the battery of questions measuring stress ought to be tested for reliability and validity and tap dimensions of stress related to severity and duration. Also, as mentioned in the discussion section of my article appearing in this issue, surveys striving to measure stress ought to include raw life events that we as researchers think are likely to be stressors in addition to measures of subjective interpretations of potential stressors. To the extent possible, as McDade points out, we should also strive for both standardized and culturally informed measures. Allow me to quickly add that the Social Environment and Biomarkers of Aging Study (SEBAS) has been funded for another wave of data collection in Taiwan and in addition to its original set of stress-related questions, it now asks about daily hassles (e.g., argument with anyone since yesterday), major life events (e.g., job change, major illness, and death of a family member) in the past year, traumas (e.g., being beaten and homicide or suicide of a family member) at any time in one's life, and perceived stress (e.g., difficulty coping with events and feelings of loss of control) over the past month.

The expanded set of stress indicators in SEBAS II strikes me as quite thorough, but it seems that even the best survey instrument will face great difficulties in accurately measuring stress in its entirety and complexity over such a long and varied period of time as the "life course." How, for example, can we fully capture myriad events such as being psychologically bullied in middle school, growing up with a father who battled alcoholism, being gay or being a part of some other minority group, or working for a dreadful boss some years ago? Moreover, if we are to take the life course approach seriously, we need to consider in our analysis prenatal insults (perhaps proxied by low birth weight) and early postnatal life events (such as handling and maternal care) that might influence the way in which we react to later challenges. As if this task were not difficult enough, it also would be wise to account for the possibility that stressors during very early at older ages are more deleterious than those during other, more robust years.

In addition to pointing out the challenges of stress measurement, I can only offer what may be perhaps a naïve suggestion in terms of a relevant survey question related to AL. Namely, since AL is supposed to represent cumulative costs in adapting to challenges over the entire life course, why not ask survey participants a question along the following lines: "Over your entire life (including the very earliest years of childhood that you can remember) up until now, how much stress would you say you've experienced? Very much … Some … Very little." Another version of this question could be stated in terms of stress experienced relative to peers. Such global questions related to stress over the life course could complement more specific questions as outlined earlier. The preceeding question suggestions make sense to me because I have yet to see such questions in a study of AL and because global, subjective questions related to other phenomena have proved powerfully predictive. Take, for example, the questions which ask about subjective interpretations of perceived social support (Krause, 2001) and subjective interpretations of overall health (Idler & Benyamini, 1997).

Let me now discuss issues surrounding which biomarkers to use as part of the AL construct and how to measure and score the biomarkers. First, which biomarkers should we measure? Outside of the neuroendocrine ones, I do not feel fully qualified to discuss which markers are more or less promising, but I agree with other researchers who think that the future is likely to hold an embarrassment of riches in terms of physiological information to analyze (Freese, Li, & Wade, 2003; National Research Council, 2000). A looming challenge seems to be, then, how to rigorously and parsimoniously make use of a wide array of health indicators. We should be guided in this effort by our understanding of biology and of what contributes to poor health and by our openness to contrasting in a thorough and systematic way different approaches at biomarker measurement and analysis.

As far as the neuroendocrine markers are concerned, I part company with Loucks, Juster, and Pruessner over their pessimism about the value of continuing to analyze dehydroepiandrosterone sulfate (DHEAS). Although the initial enthusiasm over DHEAS as a star marker has waned, not enough longitudinal studies and studies in non-Western contexts have been carried out to form a strong opinion about the marker one way or the other. At the very least, evidence from the SEBAS links stressful insults over the life course to riskier DHEAS levels (Gersten, Boyce, & Timiras, 2007) and supports the view that DHEAS is a marker predictive of worse health (Glei & Goldman, 2006; Goldman & Glei, in press).

A whole host of issues surround how exactly to measure biomarkers in the field. Important considerations include making efficient use of limited study resources and obtaining valuable information from study participants while at the same time limiting the burden they must shoulder in providing it. For example, as Loucks, Juster, and Pruessner suggest, it would be preferable to have daily urinary samples in addition to nightly ones. While this may be the case in the abstract, attempts at collection of 24-h urinary samples in pilot tests of the MacArthur studies yielded more participant refusals and less complete collection (Crimmins & Seeman, 2000). The latest wave of SEBAS, in another example, attempted to collect a number of salivary cortisol measures over the day in addition to urinary measures. However, because of the difficulty in getting respondents to adhere to the salivary cortisol collection protocol (probably in part due to the illiteracy rate in this population), collection of salivary samples eventually were abandoned (Dana Glei, personal communication, May 9, 2007; Noreen Goldman, personal communication, June 4, 2007). Nevertheless, newer methods of data collection and analysis should result in reduced participant burden and more biological material to analyze. Dried blood spots, as a case in point, is a method where the blood produced from a single finger prick can be analyzed for levels of tens of different markers (McDade, Williams, & Snodgrass, in press).

Another area of complexity regarding the operationalization of AL is how to score multiple markers in a meaningful way. Early AL studies used an "elevated risk zone" approach in which an index was created for respondents who earned one point for each biomarker that was considered to be at a risky level. This level was determined by whether biomarker values were either above or below certain cutpoints, with cutpoints determined by distribution percentiles in the population under study. This early approach has been extended in a number of ways, including by defining high-risk for a number of markers to be at both ends (i.e., both high and low values) of the population distribution. I think that this "Goldilocks" approach makes

some amount of sense since, for instance, we know that a BMI over 25 or under 18.5 is risky. As regards the neuroendocrine markers, I agree with Loucks, Juster, and Pruessner that there is good evidence to think that both high and low levels of cortisol pose risk. Although the bulk of research conducted to date leads me to be skeptical of the merits of the two-tailed approach for the other neuroendocrine markers, such an approach may be worth experimenting with since so much is still unknown about them.

To close, I would like to mention that in some ways biomarkers have been incorporated into social surveys for decades. Height and weight, for instance, were collected by the British Association for the Advancement of Science during the reign of Queen Victoria. But biomarkers that are now being collected in social surveys are novel in their ability to possibly explain the biological mechanisms underlying important associations between, say, SES and health and social deprivation and health. Hopefully, social surveys containing biomarkers will allow us to further pinpoint the mechanisms causing ill health, mechanisms upon which we can successfully intervene through behavioral and medicinal means.

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