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Models and Studies of Aging:

Adaptation to stress: Resilience

Thursday 9/22/2016
9:50-10:10 AM

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References:

Journals of Gerontology: Medical Sciences
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OXFORD

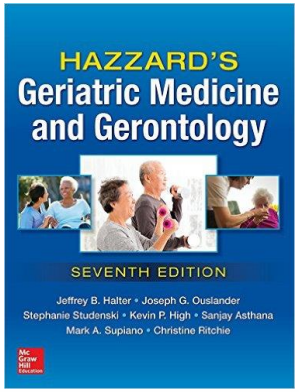
Review

Physical Resilience in Older Adults: Systematic Review and Development of an Emerging Construct

Heather E. Whitson,[1,2,3,4] Wei Duan-Porter,[1,5] Kenneth E. Schmader,[1,2,3] Miriam C. Morey,[1,2,3] Harvey J. Cohen,[1,2,3] and Cathleen S. Colón-Emeric[1,2,3]

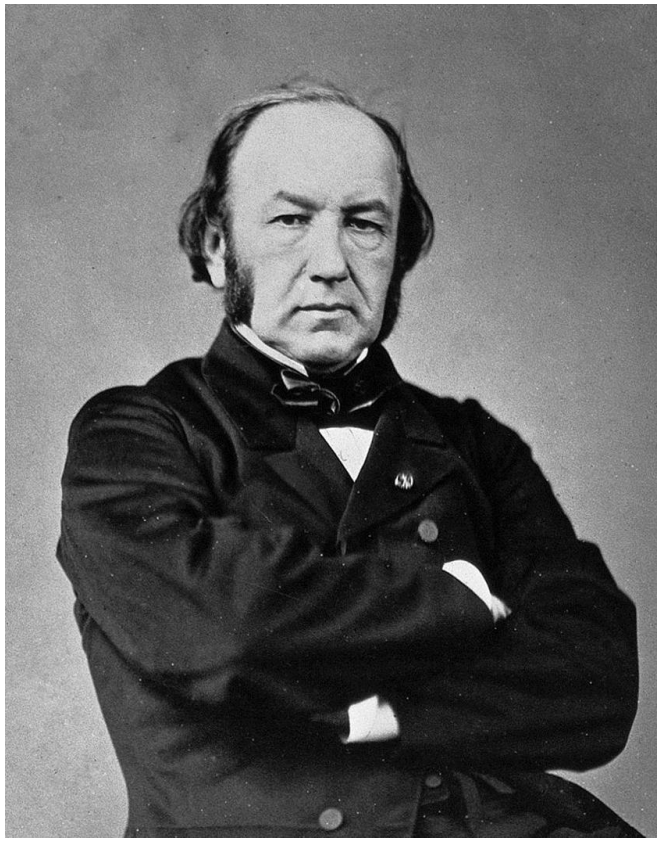
Report: NIA Workshop on Measures of Physiologic Resiliencies and Vulnerabilities in Human Aging

Hadley *et al.* (submitted)



45 Chapter | Aging and Homeostatic Regulation
George A. Kuchel

Constancy of the “milieu intérieur”

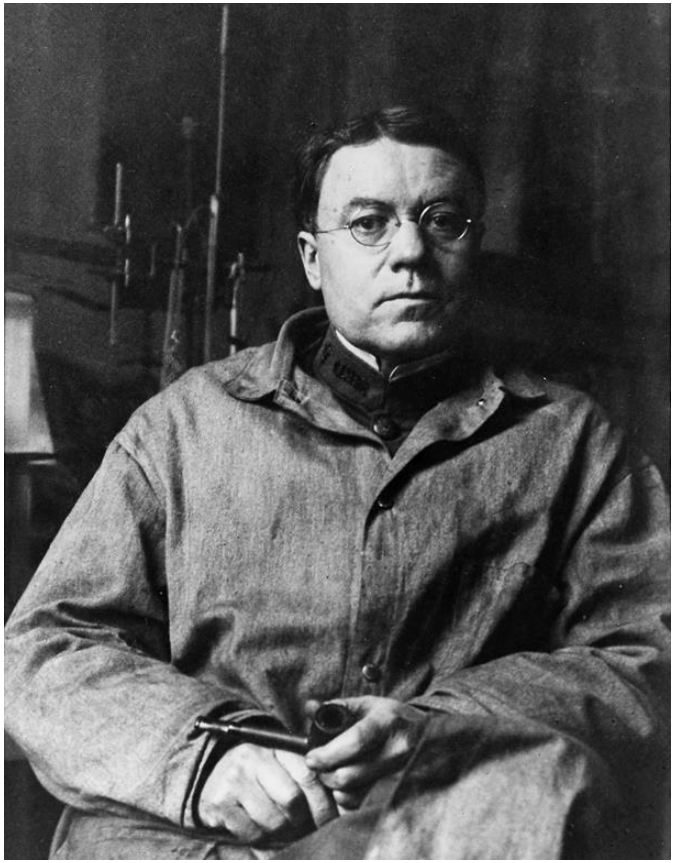


Claude Bernard (1813—1878)

The constancy of the milieu supposes a perfection of the organism such that the external variations are at each instant compensated for and equilibrated….

The stability of the internal environment is the condition for free and independent life

Aging and Homeostasis



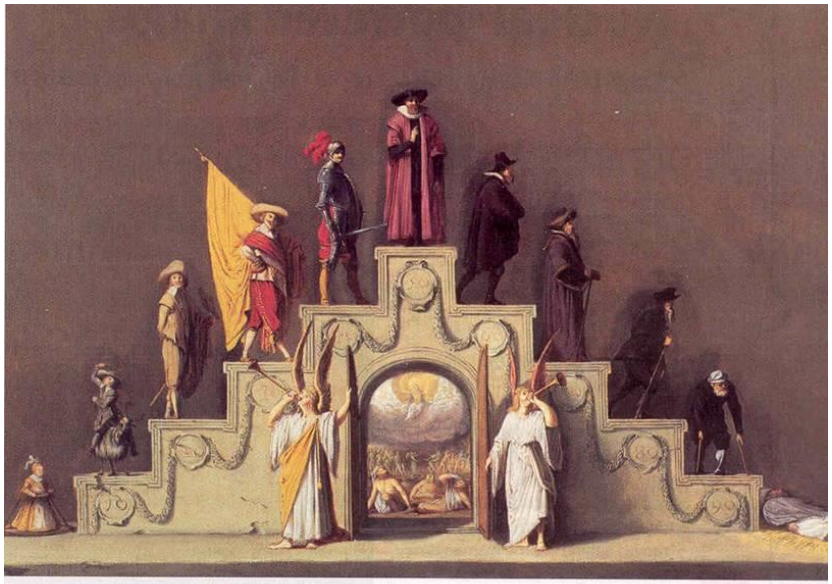
Walter Bradford Cannon (1871–1945)

Besides more or less obvious physical changes in old age, physiological investigation may reveal increasing limitation of the effectiveness of homeostatic devices which keep the bodily conditions stable

Agenda:

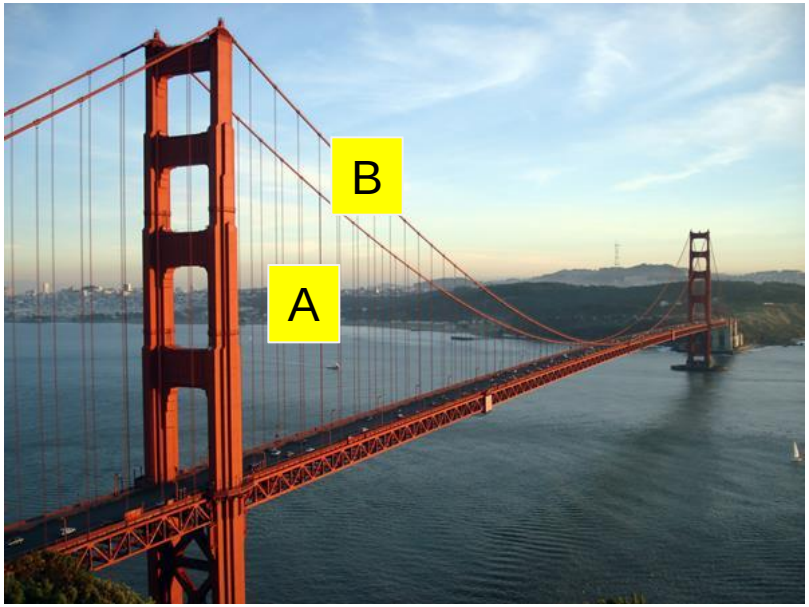
- Multifactorial complexity of aging trajectories and disease behavior
- Homeostasis and Homeostatic Dysregulation:
  - Concepts and Terms
  - Impact of Aging on Specific Challenges
- Resilience:
  - Definition(s)
  - Recent workshops and conferences
  - Concepts related to resilience
  - Factors influencing resiliencies in aging
  - Considerations for animal and human studies
- Resilience and Precision Medicine

Multifactorial complexity of aging trajectories and disease behavior in old age



The downward path: a seventeenth-century view of a man's progression through life.

Frailty as a vulnerability and as a defined phenotype



Fried Frailty Phenotype
1.Weight loss
2.Sense of exhaustion
3.Poor grip strength
4.Slow walking speed
5.Poor physical activity

Sarcopenic Obesity
1.Obesity
2.Poor physical performance
3.Low muscle mass
4.Poor muscle quality

Resiliency and Aging:
It's a tough world out there

Dictionary Definitions of Resiliency
(Mirriam-Webster)

1. The ability to become strong, healthy or successful again after something bad happens

2. The ability of something to return to its original shape after it has been pulled, stretched, pressed, bent, etc.

Scientific Approaches to Resiliency

1. Established interest in role of psychosocial factors on resilience to age-related social and behavioral stressors

2. Focus of August 2015 NIA workshop of resiliencies to physical stressors

Resiliency: Must Consider the System, the Stressor, the Response and the Outcome

Homeostenosis represents a diminished capacity to respond to varied homeostatic stressors:

- Elevated or lowered ambient temperature
- Elevated or lowered serum glucose
- Fluid depletion or fluid overload
- Orthostasis
- Loss of neural networks (disease, receptor blockade)
- Sepsis
- Trauma
- Bedrest
- Hip Fracture
- Chemotherapeutic agents

Taking it All Apart

- What are some of the key physiologic features of homeostatic dysregulation of aging?
- What are the physiologic features of resilience?
- Is it possible to identify shared or common physiologic motifs that emerge in response to different stressors and across different systems?

Impact of aging on resilience: handling a glucose challenge

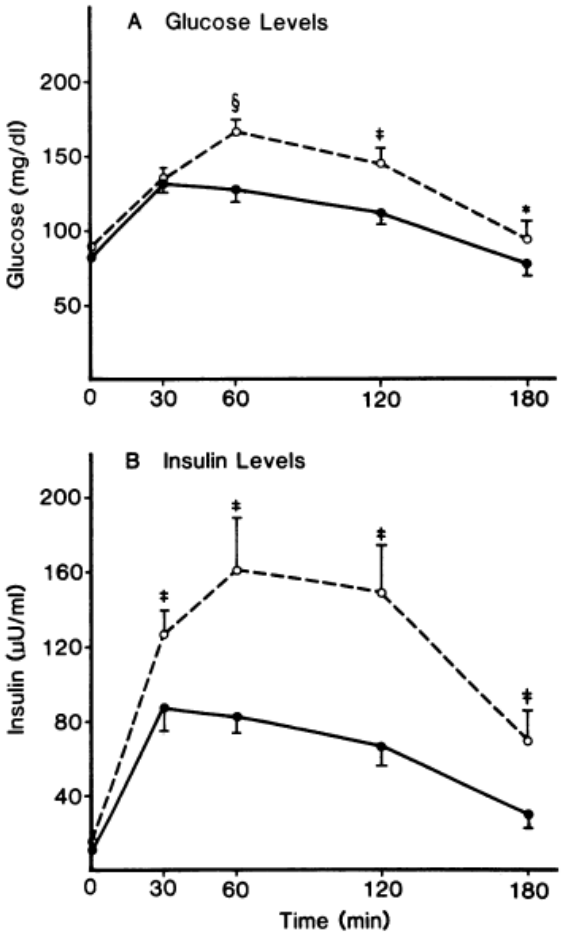


FIGURE 1 (A) Glucose levels during the oral glucose tolerance tests in nonelderly (●) and elderly (○) subjects. (B) Insulin levels during the oral glucose tolerance tests in nonelderly (●) and elderly (○) subjects. Results are plotted as mean±SEM.
* $P < 0.01$.
‡ $P < 0.005$.
§ $P < 0.001$.

Fink *et al.* JCI 1983

Impact of aging on resilience: orthostasis

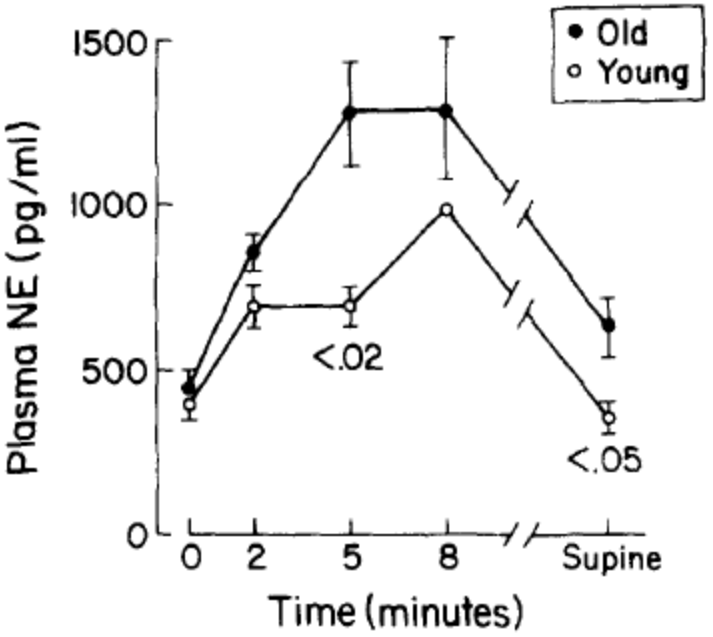


Fig. 1. Effect of standing and supine recovery on plasma NE in young and old subjects. Data are plotted as mean ± SE for 6 young and 11 elderly subjects, except at 8 min when values represent mean of 2 young and 6 elderly. Supine recovery value was obtained after 15 min. Statistical significance refers to comparisons between young and old.

Young *et al.* Metabolism 1980

Impact of aging on resilience: cold pressor test

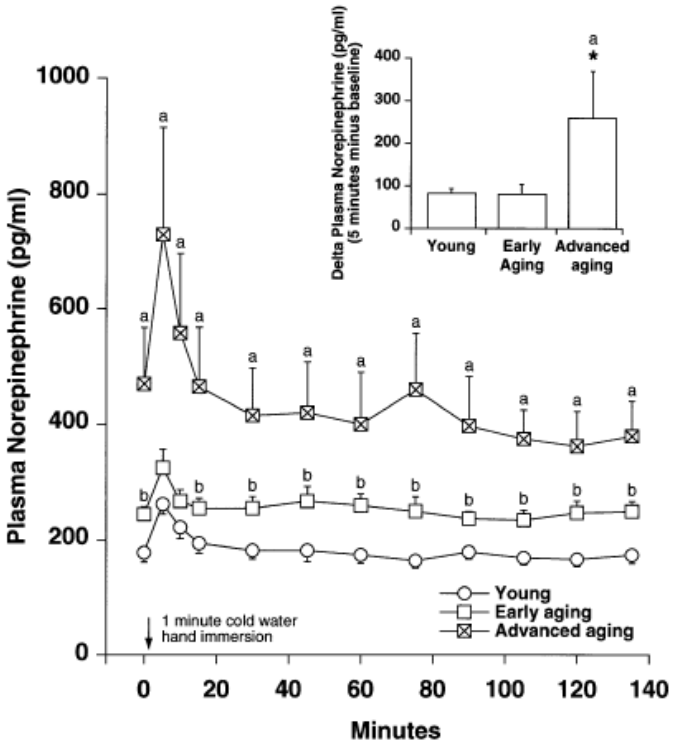
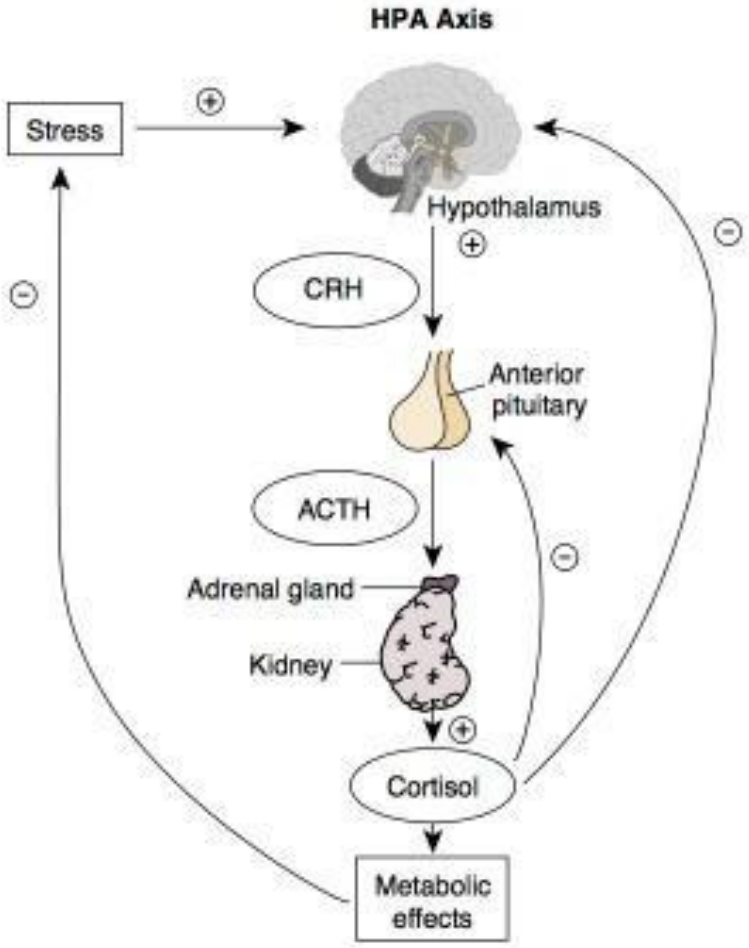


Fig. 1. Plasma norepinephrine levels (pg/ml) in young (Y; open circles, n = 19), early aging (EA; open boxes, n = 28), and advanced aging (AA; crossed boxes, n = 8) subjects before and after cold pressor test (1 min cold water hand immersion beginning at arrow). Bars show SEM. Letters show differences between groups at the same time point (a = AA > Y, EA; b = EA > Y; all comparisons $p < 0.05$ by Newman Keuls post-hoc tests).

Pascualy *et al.* Neurobiology of Aging 1999

Impact of aging on resilience: HPA axis responses



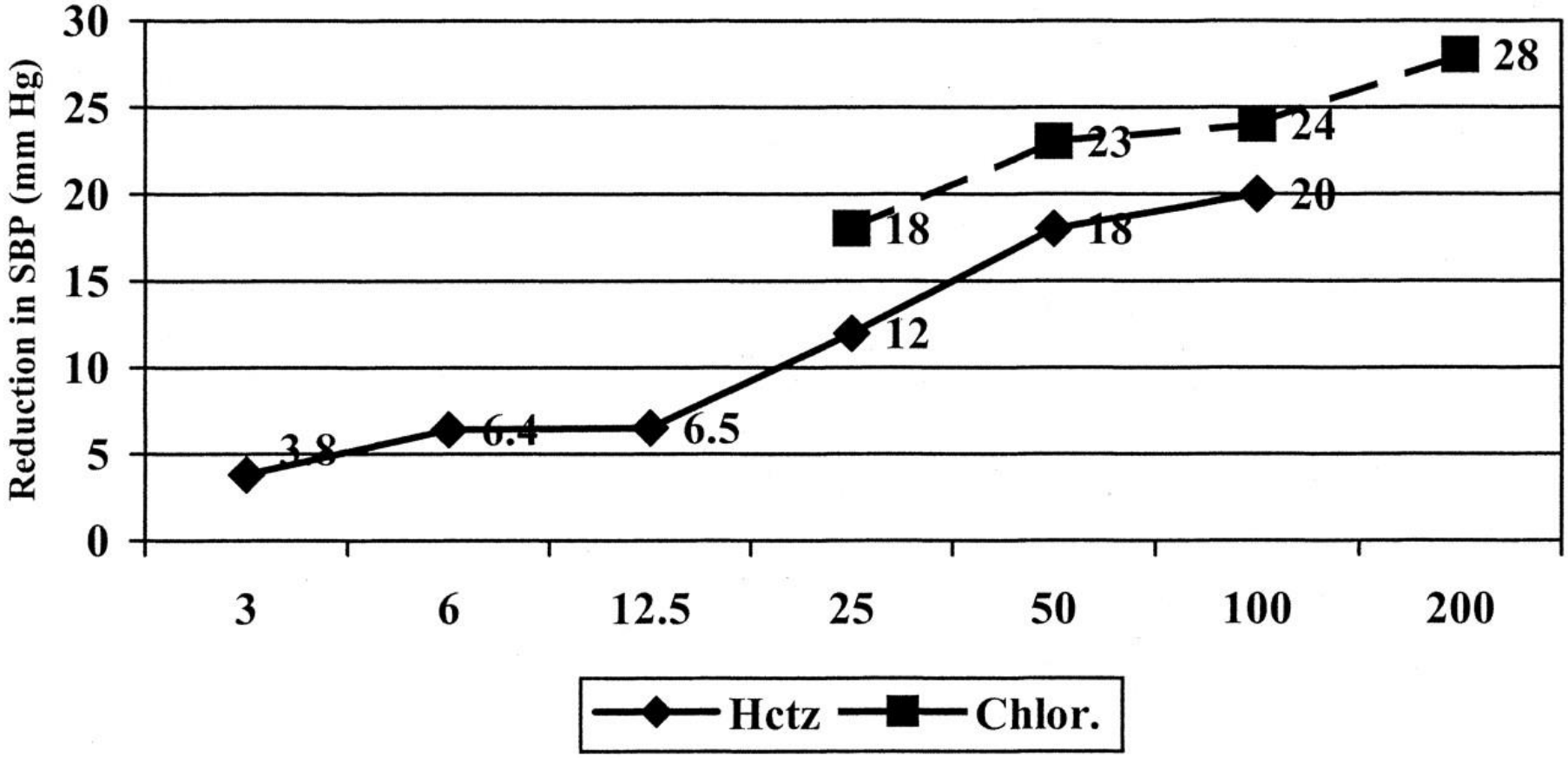
Homeostatic Dysregulation of Aging: Overarching Theme(s)

1. Loss of Physiologic Reserve
2. Enhanced Basal Activity
3. Lower End-Organ Responsiveness
4. Higher Basal Activity
5. Loss of Negative Feedback Inhibition

<u>Shared Features</u>

- Shared across different stressors
  (e.g. emotional stress, orthostasis, oral glucose)
- Shared across different systems (e.g. SNS, HPA, immune-inflammatory pathways)

Overarching Themes in Homeostatic Dysregulation of Aging:
Stressor-Related Considerations: Magnitude of Stressor



Effects of HCTZ and chlorthalidone on SBP as a function of daily dose (mg).

Carter *et al. Hypertension*. 2004;43:4-9

Overarching Themes in Homeostatic Dysregulation of Aging: *Stressor-Related Considerations: Co-existing stressors*

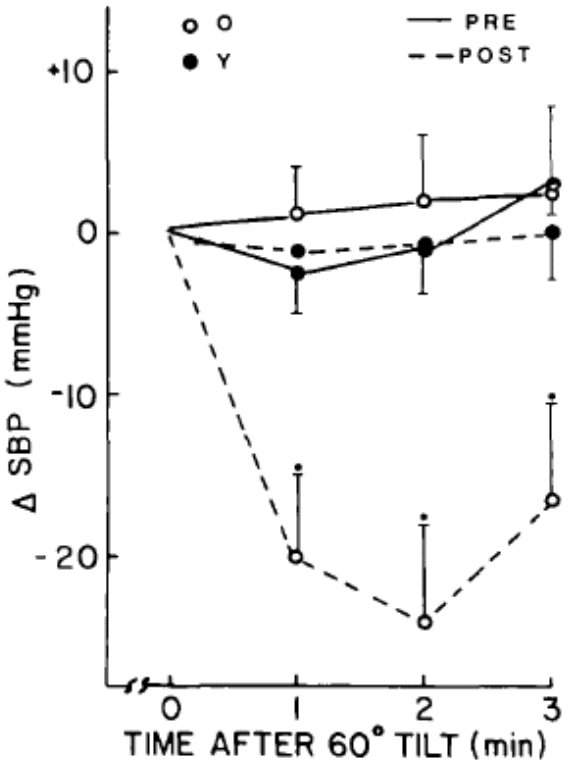
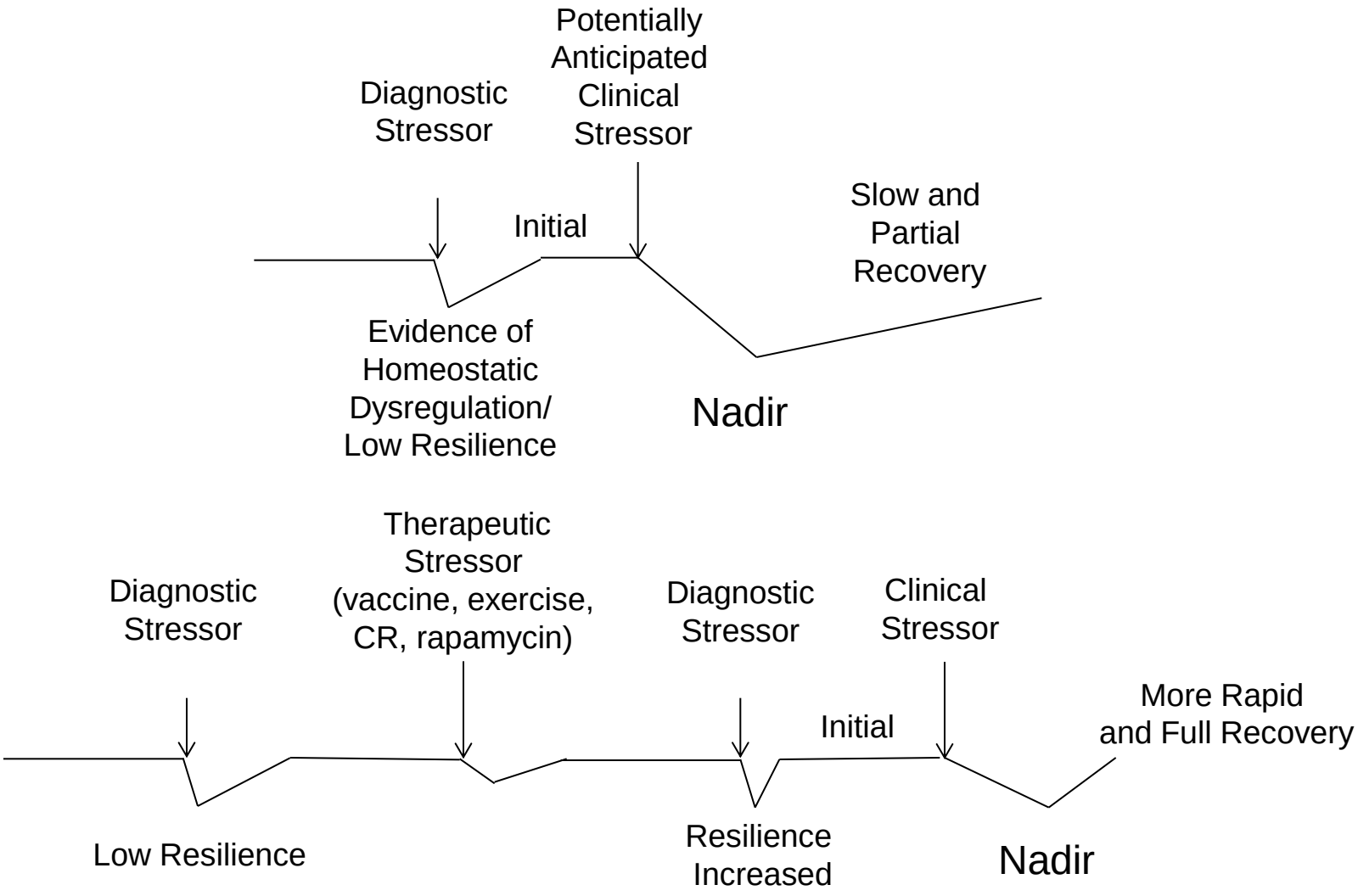


FIGURE 1. *Change in systolic blood pressure (SBP) during 60-degree upright tilt in six young (Y) and six old (O) subjects before (PRE) and after (POST) diuresis. Asterisk indicates significant change from prediuresis values* ($p < 0.02$).

Shannon *et al. Hypertension*. 1986

Overarching Themes in Homeostatic Dysregulation of Aging: *Response-Related Considerations*

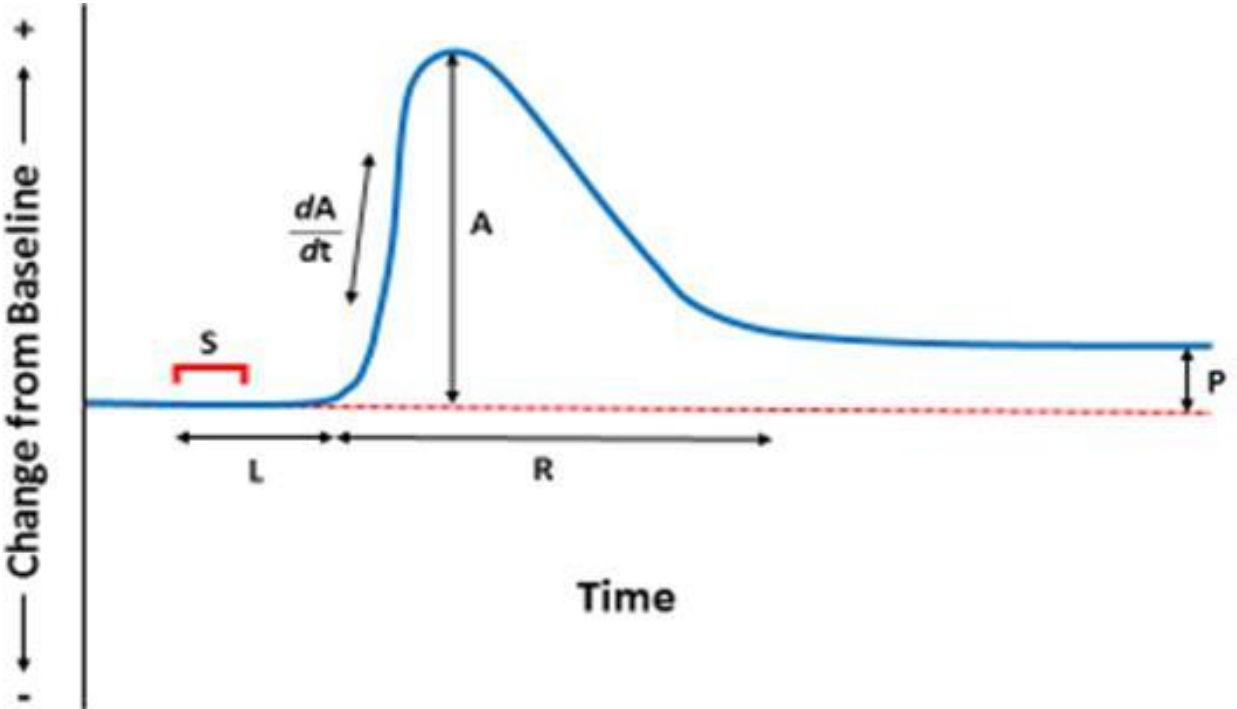


Pulling It All Together

- No cell, organ or system works in isolation from other cells, organs and systems
- Complex inter-relationships exist at all these levels mediated by shared molecules, proximal risk factors, and distal outcomes with bidirectional feedback loops
- Emergence permits larger entities or patterns to arise through interactions among smaller or simpler entities that themselves do not exhibit such properties
- This defines our uniqueness as humans and as individuals
- Systems-based perspectives are key to understanding and predicting resilience in old age

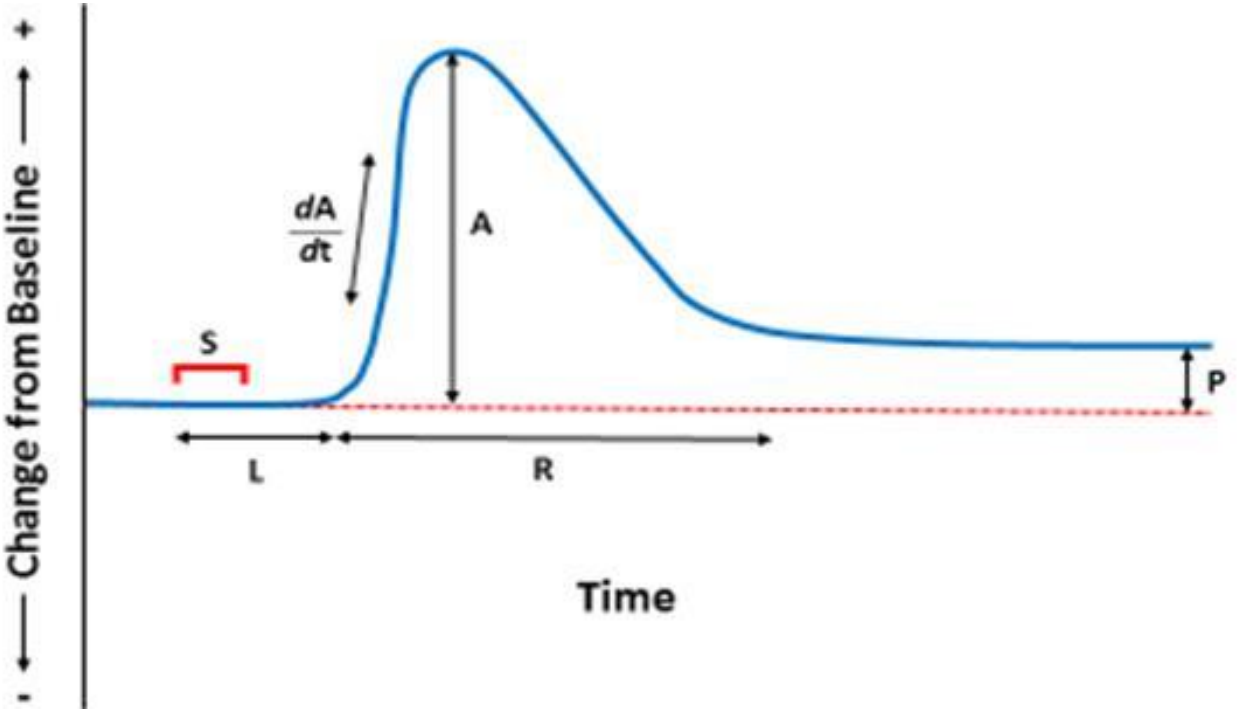
What it will take to really move forward:

- Need to address variability
- Not just at baseline, but also when challenged
- Need to address ability to maintain or regain normal homeostasis when challenged by a stressor
- NIA Workshop, "*Measures of Physiologic Resiliencies and Vulnerabilities in Human Aging*" August 26-27, 2015



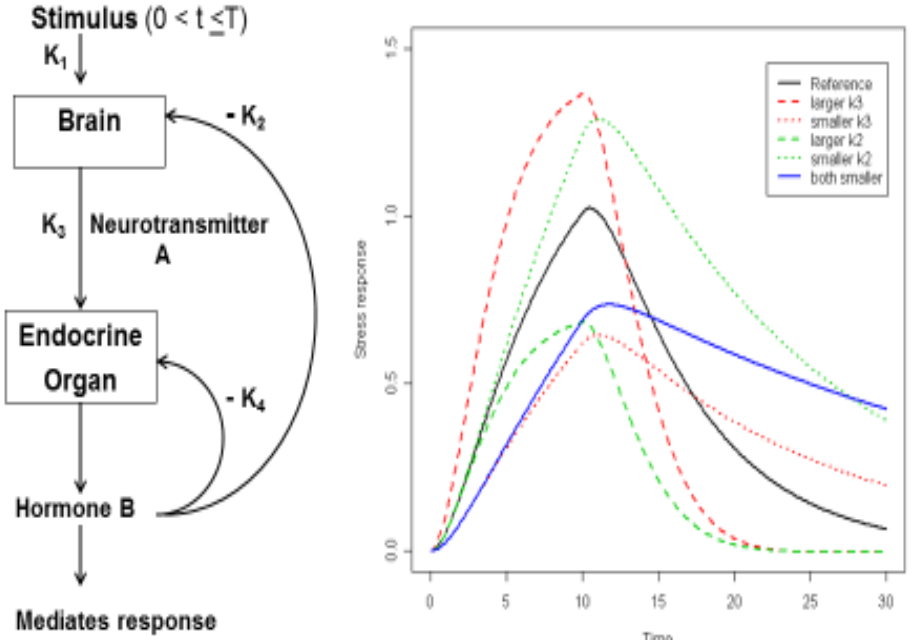
Lack of resilience in aging when:

- Unable to maintain core body temperature in face of elevated or lowered ambient temperature (hyper- or hypothermia)
- Unable to handle oral glucose load (poor OGT)
- Changes are often exagerated with delayed return to baseline



Lack of resilience in aging when:

- Declines in negative feedback result in a system being less resilient with exagerated responses and delays in return to baseline
- Examples include decreased ability of cortisol to dampen its own release and diminished ability of inflammatory responses to shut off



Dynamical Responses to Stressors Source: Varadhan *et al.* MAD 2008

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Examples of Clinically Relevant Resilience:

- Avoid fall on uneven or slippery surface surface
- Avoid syncope on standing
- Recover physical function after bedrest
- Avoid delirium following anasthesia and surgery
- Permit rapid and effective wound healing
- Avoid or rapidly recover from influenza infection
- Avoid bone marrow toxicity of chemotherapeutic agents

Final Messages Regarding Resilience:

- Resilience is not merely the absence or converse of frailty
- Do not fear but embrace complexity and increased variability with aging
- Studies of dynamic responses to stressors often offer insights into aging that would not be observed when studying individuals under “ideal” basal conditions
- Such dynamic studies may uncover additional variability between older individuals in their response capacities
- Added inter-individual variability in responses to stressors may offer novel insights and predictive capacities in terms of risk of future resilient responses ….and clinical outcomes