Stress and the Body

ANDREW HEYMAN, MD MHSA
Director of Academic Affairs
American Academy of Anti-Aging Medicine
Medical Director, Integrative Medicine
The George Washington University

A human being is much more than the sum of blood, bone, and viscera.
In the same way, each fragment of truth in itself is a lie; therefore, the accumulation
Of unintegrated scientific facts does not protect us against ignorance.

In the measure that we interrelate a greater number of fragments,
the closer we can come to truth, although truth as an absolute is unattainable.

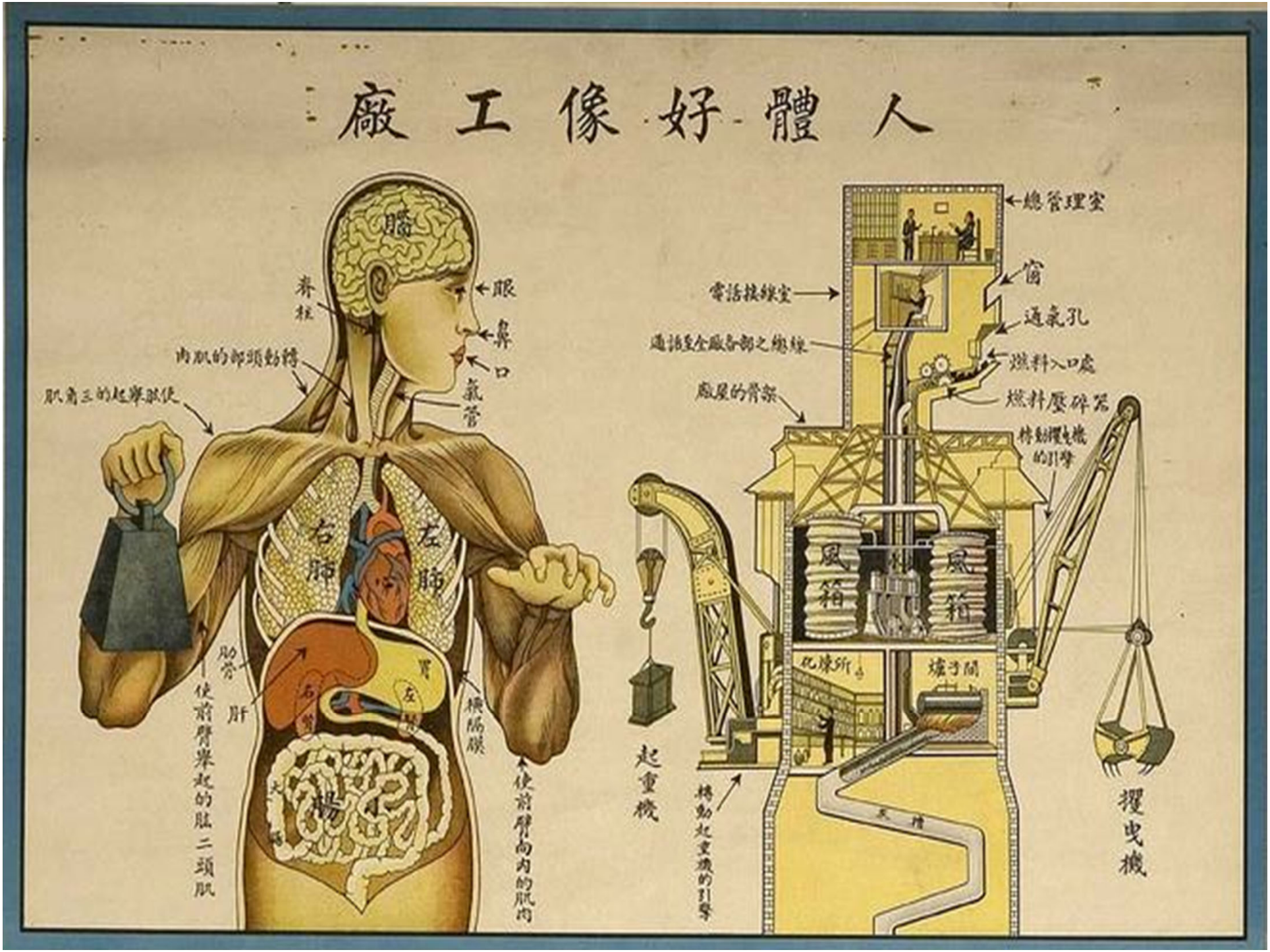
Fuad Lechin
Bertha van der Dijs

Tibetan Medicine

His eyes are closed as he feels for the pulse. In a moment he has found the spot, and for the next half hour he remains thus, suspended above the patient like some exotic golden bird with folded wings, holding the pulse of the woman beneath his fingers, cradling her hand in his. All the power of the man seems to be drawn down into this one purpose…And I know that I, who have palpated a hundred thousand pulses, have not felt a single one.

- Richard Selzer "The Healing Arts"

人體好像工廠


腦
眼
鼻
口
氣管
脊柱
肩肌的部頭動轉
使肱舉起的三角肌
右肺
左肺
胃
肝
膈膜
使前臂向內的肌肉
使前臂舉起的肱二頭肌
大腸
小腸
總管理室
窗
電話接線室
通氣孔
通話室全廠各部之總線
燃料入口處
廠屋的骨架
燃料壓碎器
轉動攪煤機的引擎
風箱
風箱
化驗所
爐子間
起重機
轉動起重機的引擎
攪煤機

Definition of *Stress*

"Stress is a state of threatened homeostasis that is re-established by a complex repertoire of physiologic and behavioral adaptive responses of the organism…."

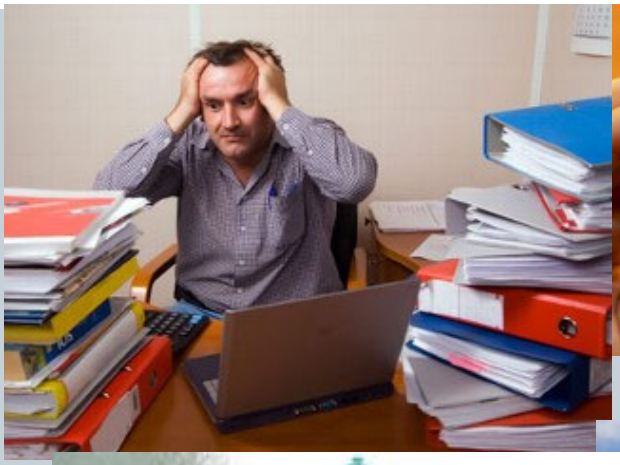
Chrousos et al. *Sleep Med Clin*. 2007; 2(2):125-145.

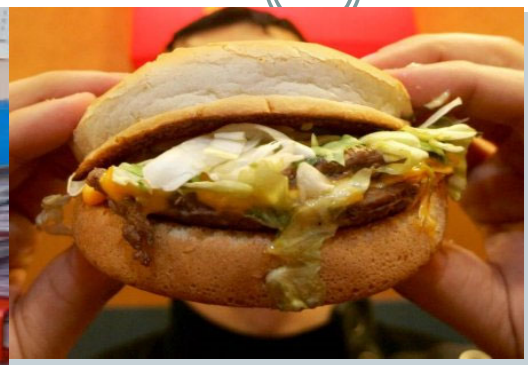
Stress

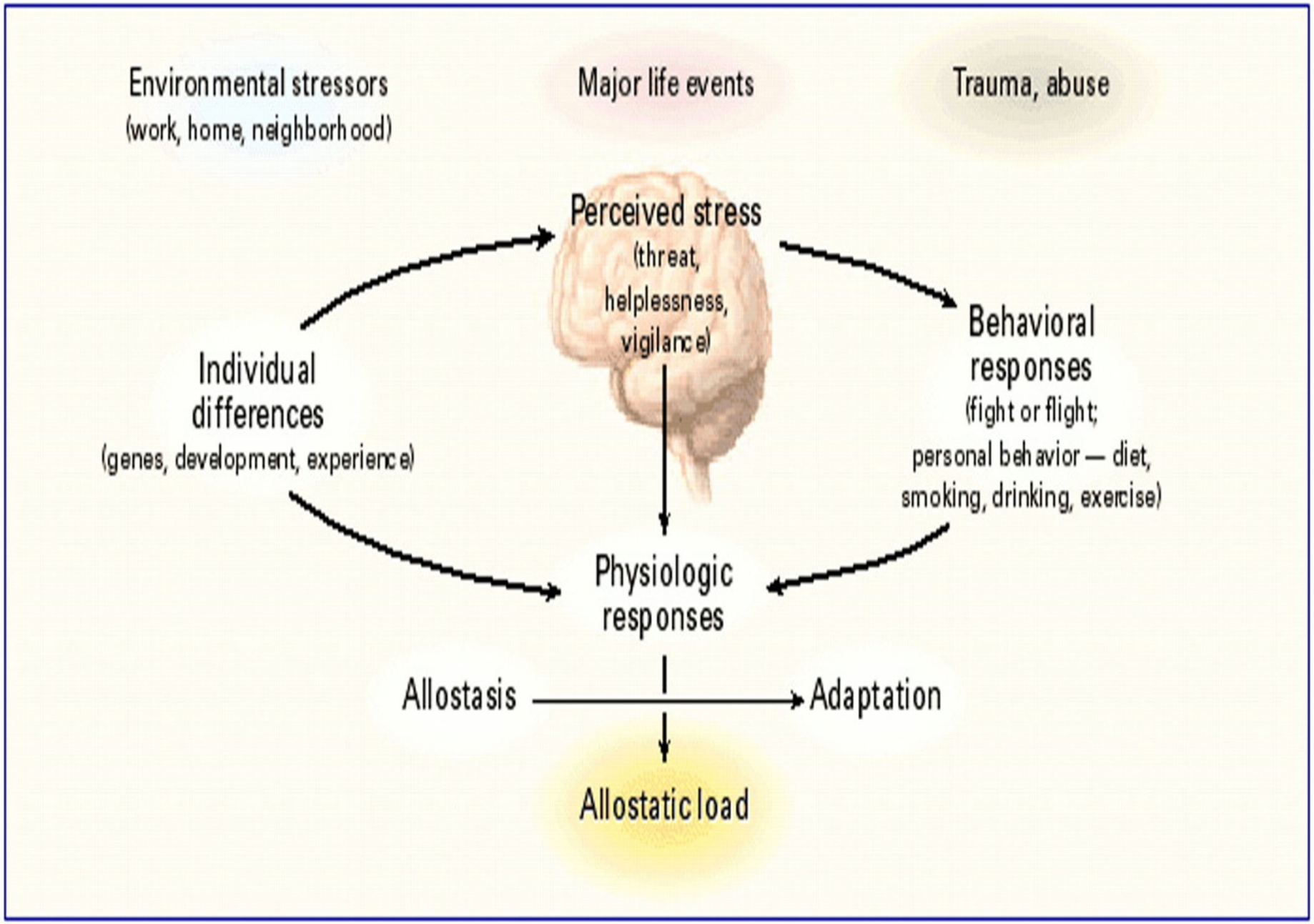
- ***Allostasis*** - the ability to achieve stability through change — is critical to survival.
- Stress system - protect the body by responding to internal and external stress.
  - Autonomic nervous system
  - Hypothalamic–pituitary–adrenal (HPA) axis
  - Cardiovascular and metabolic systems
  - Immune systems
- ***Allostatic load*** - the price of accommodation to stress, (wear and tear) that results from chronic overactivity or underactivity of allostatic systems.

Bruce S. McEwen, Ph.D. Protective and Damaging Effects of Stress Mediators. NEJM. Jan 2008: Volume 338:171-179

Physiologic Stressors







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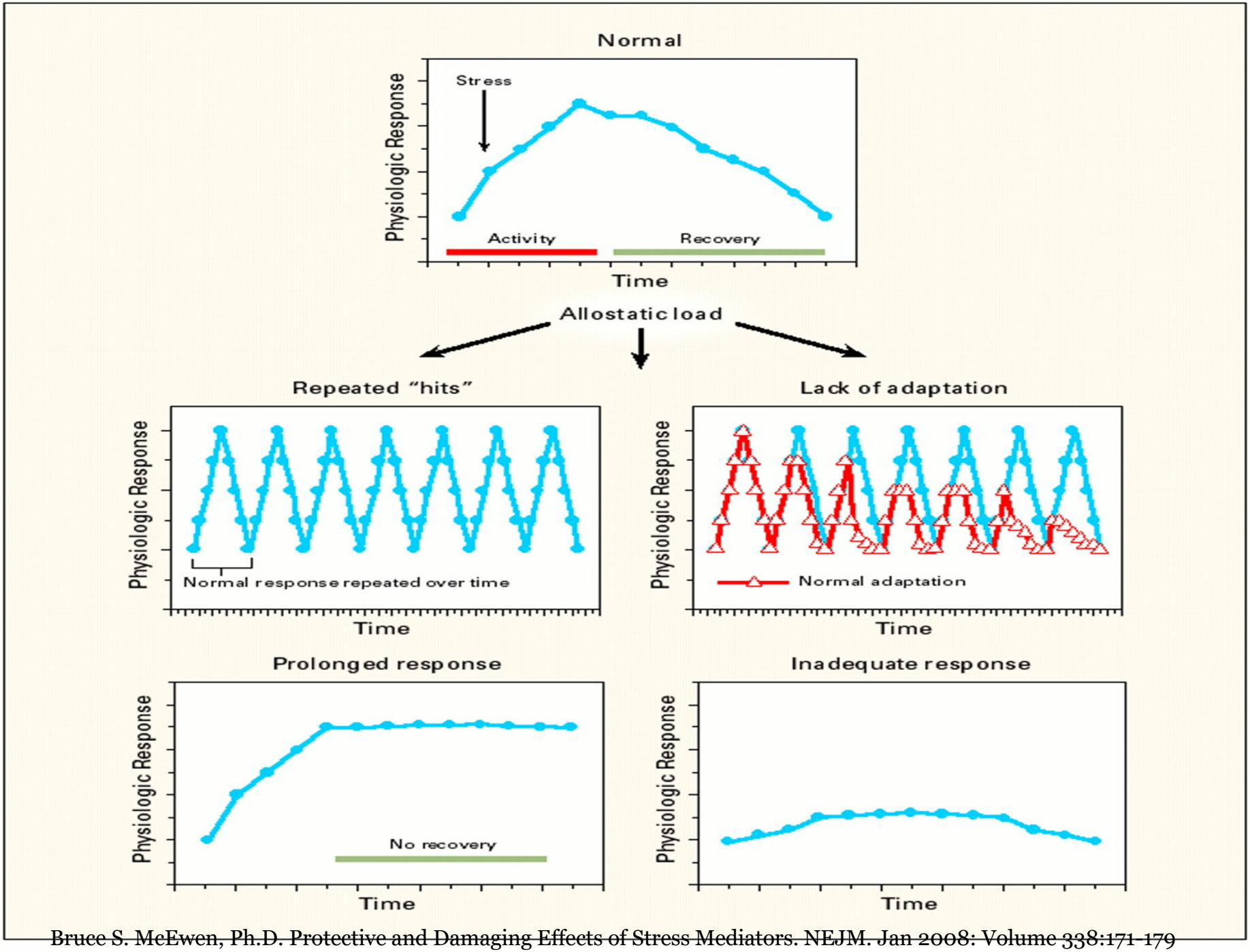
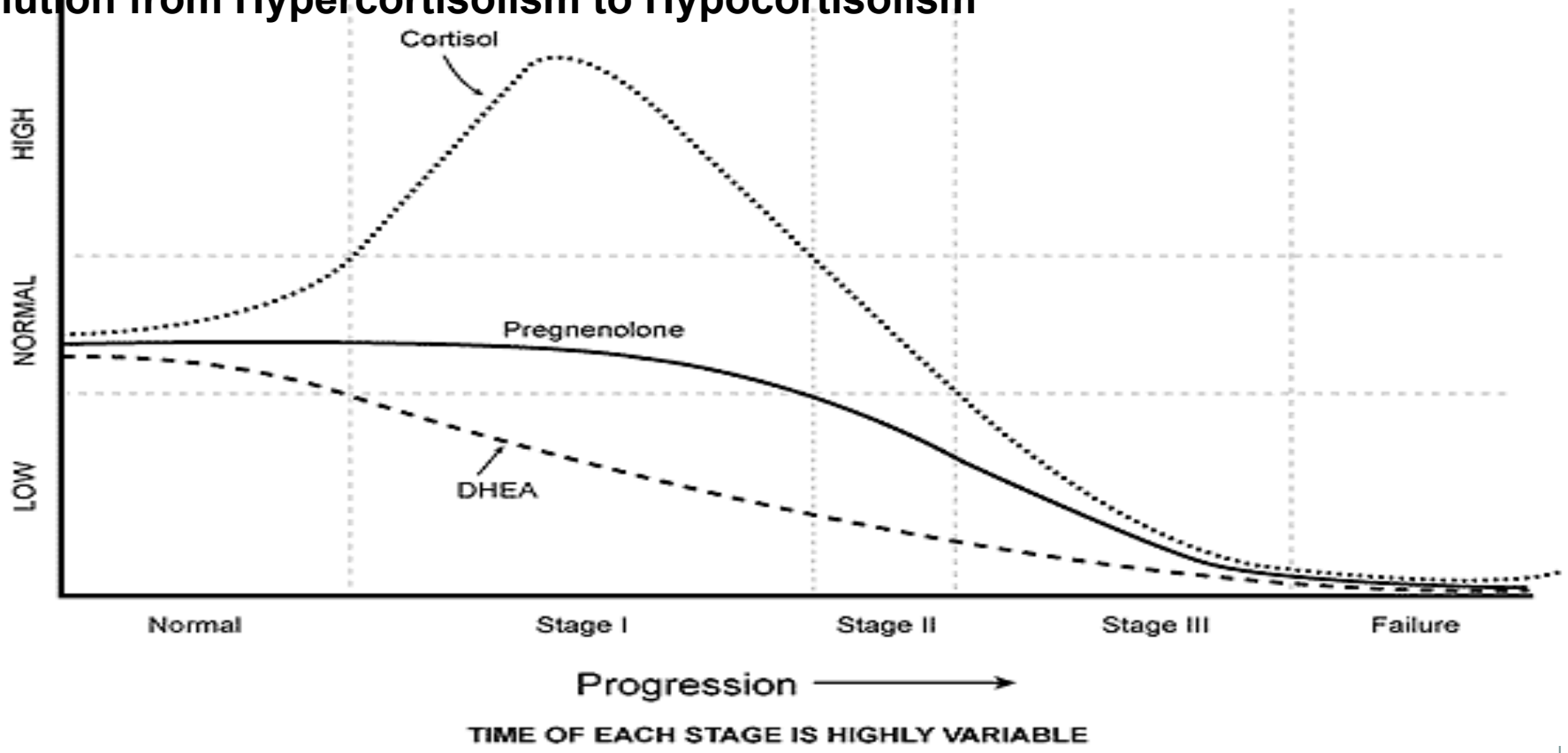


Bruce S. McEwen, Ph.D. Protective and Damaging Effects of Stress Mediators. NEJM. Jan 2008: Volume 338:171-179

Table 1 – States associated with hyperactivation or hypoactivation of the HPA axis

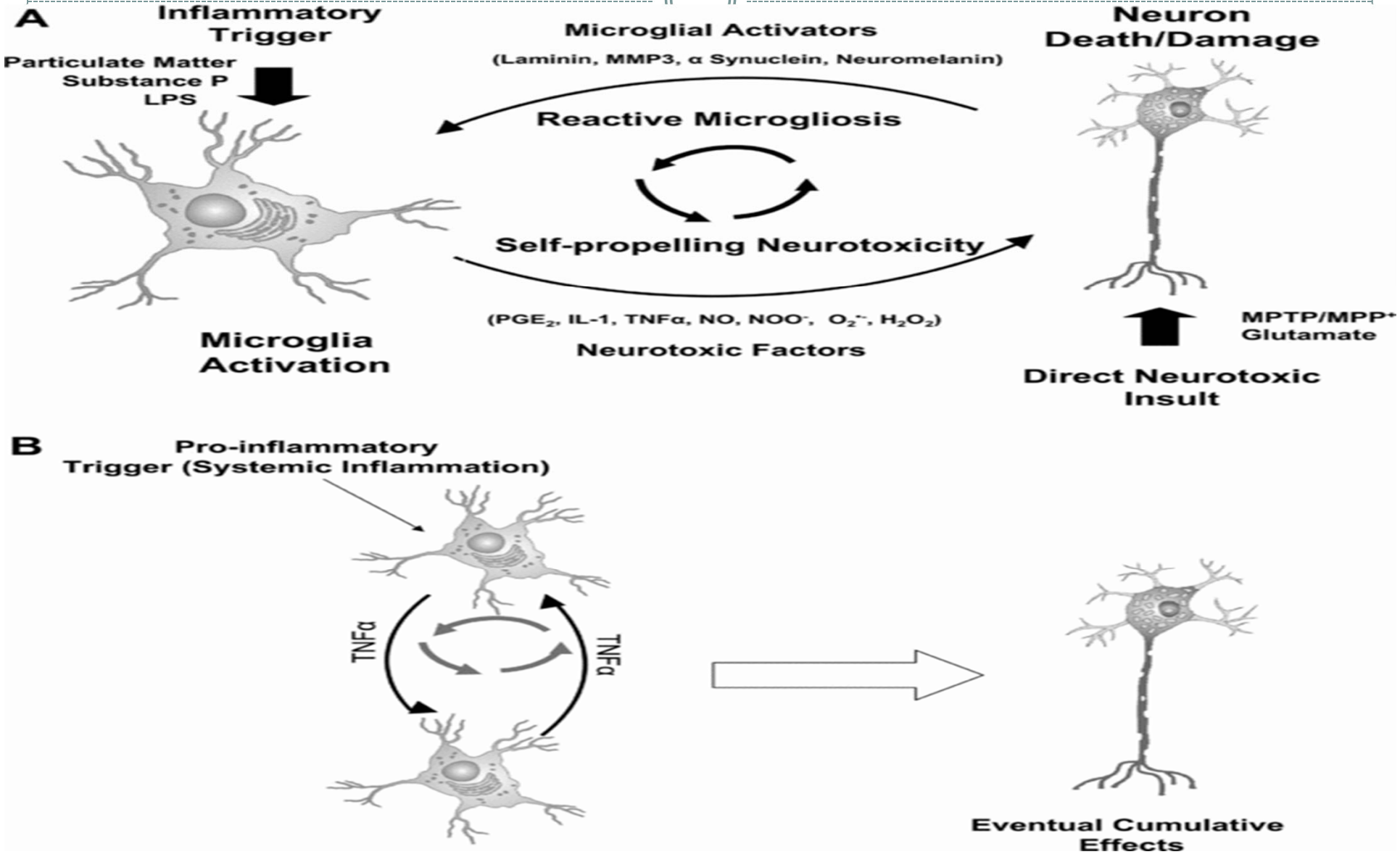
Increased HPA axis activity	Decreased HPA axis activity	Disrupted HPA axis activity
Severe chronic disease		Cushing syndrome
Melancholic depression	Atypical depression	
Anorexia nervosa	Seasonal depression	Glucocorticoid deficiency
Obsessive–compulsive disorder	Chronic fatigue syndrome	Glucocorticoid resistance
	Fibromyalgia	
Panic disorder	Hypothyroidism	
Chronic excessive	Adrenal suppression	
Exercise		
Malnutrition	Post glucocorticoid therapy	
Diabetes mellitus Hyperthyroidism	Post stress	
	Nicotine withdrawal	
Central obesity	Postpartum	
	Menopause	
Childhood sexual	Rheumatoid arthritis	
Abuse		
Pregnancy		

Evolution from Hypercortisolism to Hypocortisolism

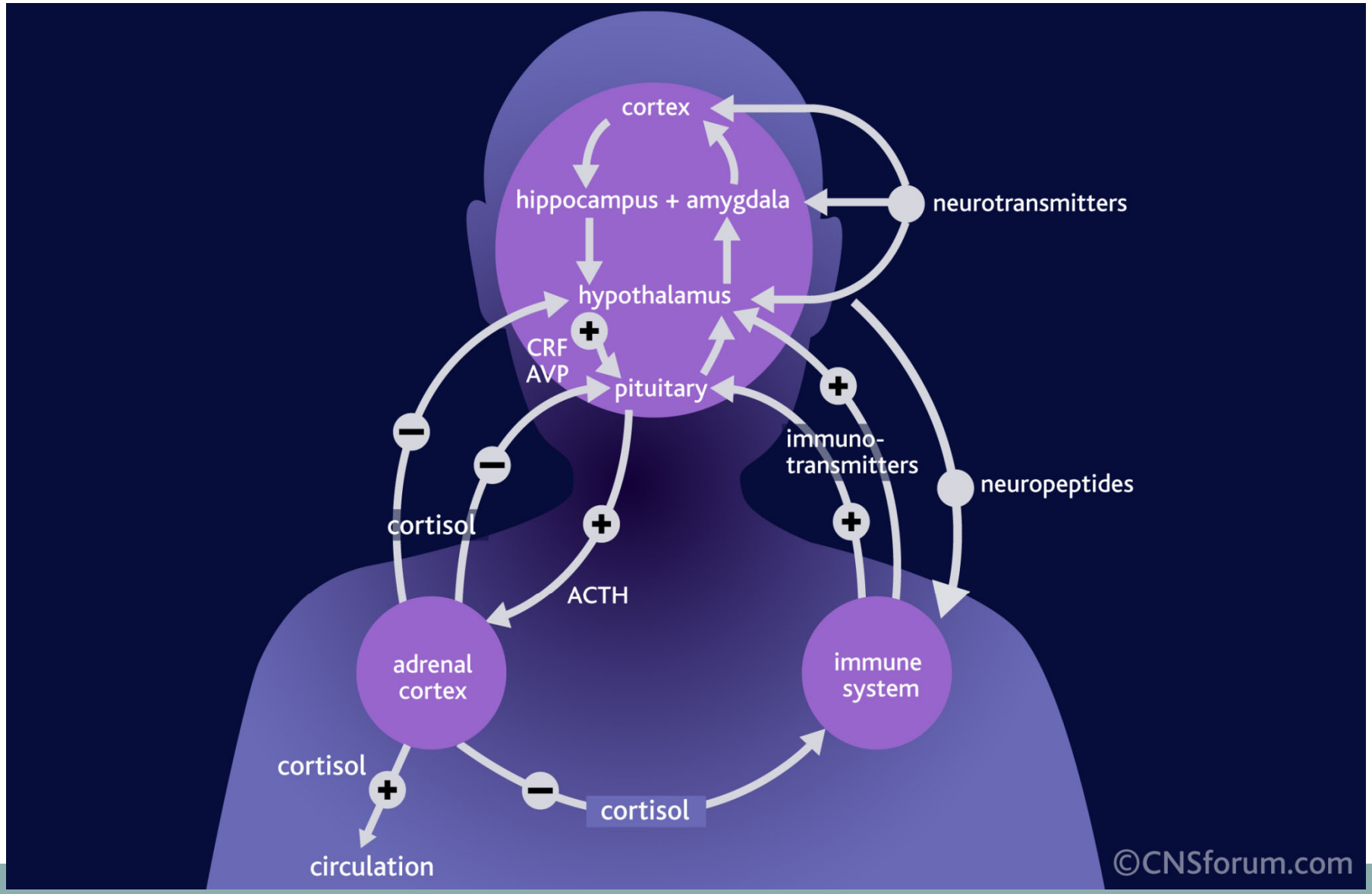


- **Reduced biosynthesis or release of (CRF/AVP/ ACTH/Cort)**
- **Hypersecretion of secretagogue with down-regulation of target receptors**
- **Enhanced sensitivity to the negative feedback of cortisol**
- **Decreased availability of free cortisol**
- **Reduced effects of cortisol on the target tissue**

Neuroinflammation: Microglial Cells



The HPA Axis


cortex
hippocampus + amygdala
neurotransmitters
hypothalamus
CRF
AVP
pituitary
immuno-
transmitters
neuropeptides
cortisol
ACTH
adrenal
cortex
immune
system
cortisol
cortisol
circulation
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Cortisol and the Hippocampus

- Repeated stress affects brain function, especially hippocampus.
  - Hippocampus alterations in both structure and function have been identified in long term stress
  - Volume loss demonstrated in PTSD, depression, cushing' s syndrome
- High concentrations of cortisol and NMDA receptors.
- Participates in verbal memory and memory context
  - Damage may exacerbate stress by preventing access to the information needed to decide that a situation is not a threat
- Regulates the stress response and acts to inhibit the response of the HPA axis to stress

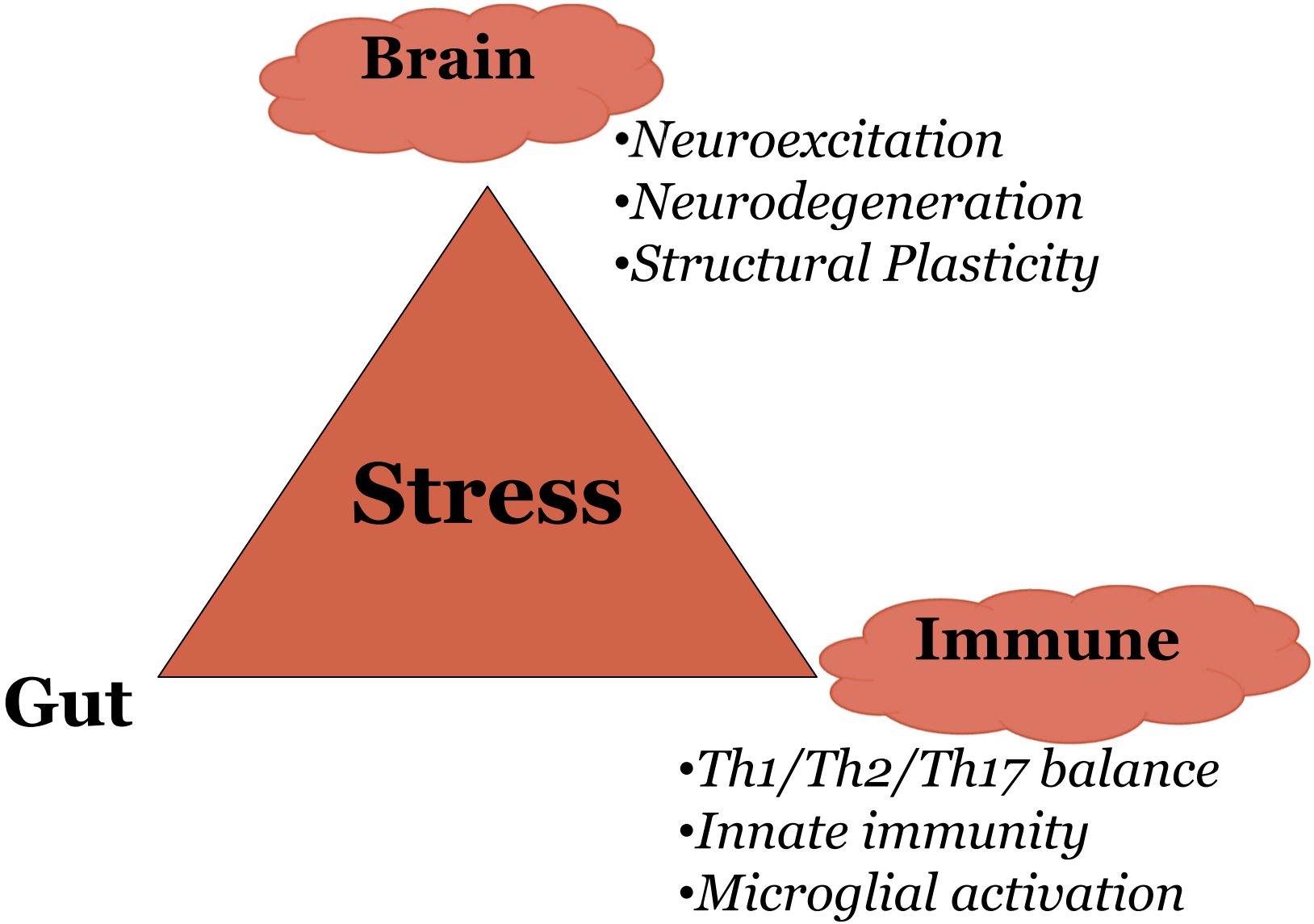
Bruce S. McEwen, Ph.D. Protective and Damaging Effects of Stress Mediators. NEJM. Jan 2008: Volume 338:171-179

Hypocortisolism may be an adaptive mechanism to protect the nervous system

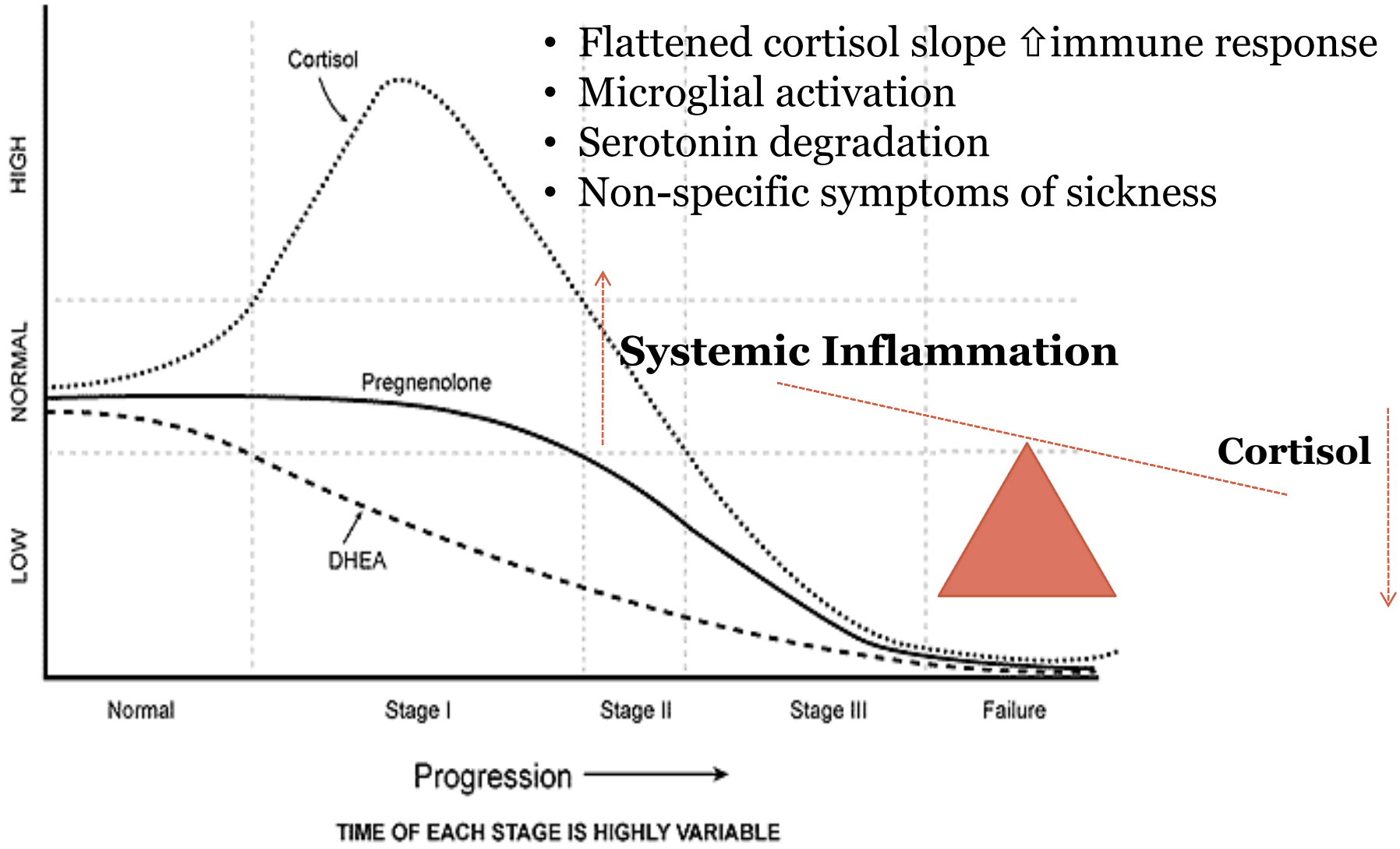
Physical Effects of Chronic Stress

1992

2000


Brain
•Neuroexcitation
•Neurodegeneration
•Structural Plasticity
Stress
Gut
Immune
•Th1/Th2/Th17 balance
•Innate immunity
•Microglial activation

- Flattened cortisol slope ⇧immune response
- Microglial activation
- Serotonin degradation
- Non-specific symptoms of sickness



Diagnostic Assays

- **Serum Cortisol**

"It has been shown that the plasma cortisol immunoassays used by the majority of laboratories, institutions, and studies suffer from considerable inaccuracy and variance and can significantly ***overestimate serum cortisol*** levels when compared to gold standards (GC/MS, HPLC)…

This has lead to controversy, a high degree of misdiagnosis and the misclassification of patients as having normal HPA function despite significant dysfunction or severely underestimating the severity of the dysfunction."

Holtorf KH. *J Chr Fatigue Syn.* 2008; 14(3):1-14

Diagnostic Assays

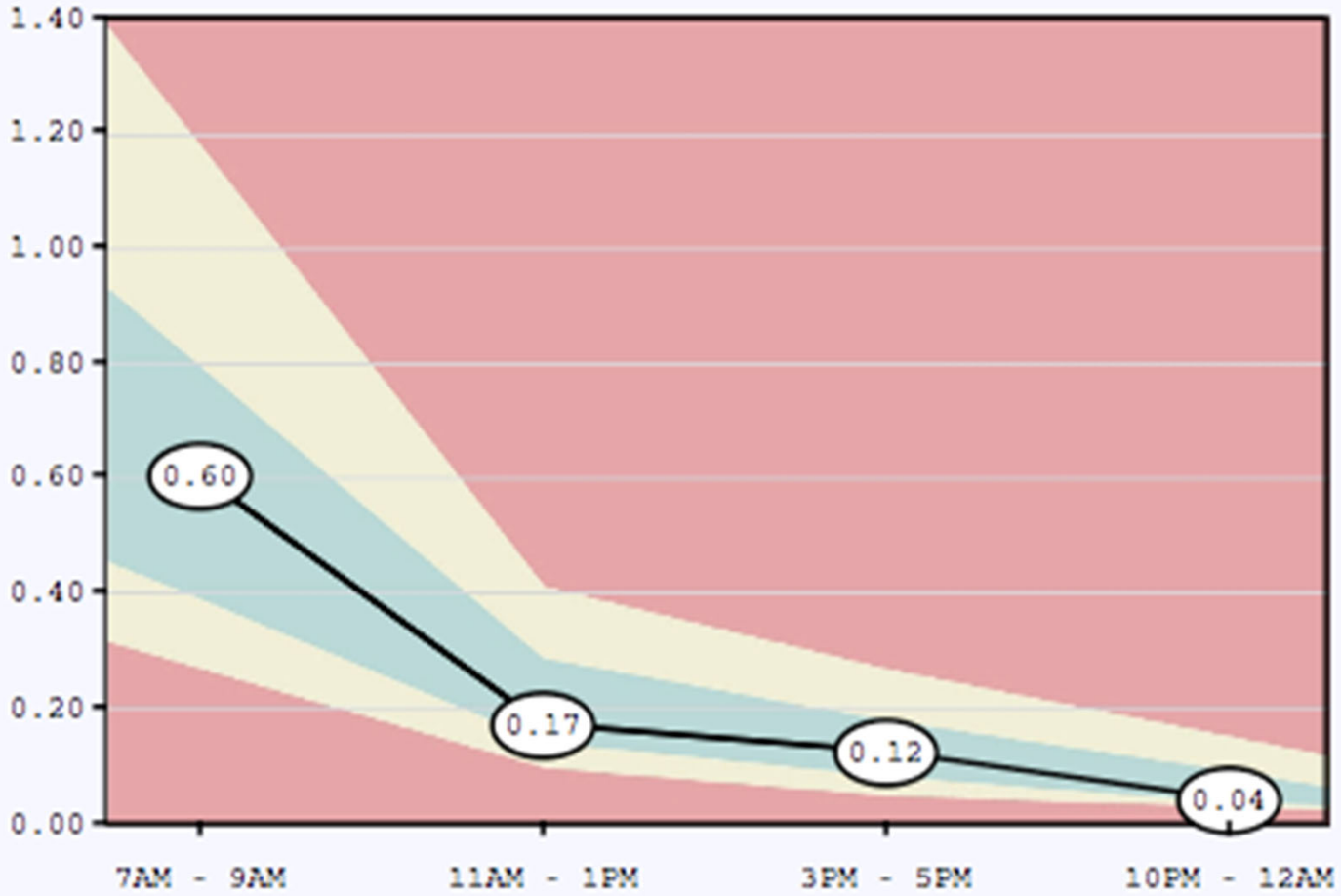
- **Salivary Cortisol**
  - Useful tool in assessing both baseline and post-stimulation levels of cortisol
  - "Salivary testing offers a noninvasive, stress free alternative to plasma and serum testing of hormones. Although saliva has not yet become a mainstream sample source for hormone analysis, it has proven to be reliable and, in some cases, even superior to other body fluids".

    Clin Chem. 2008;54(11):1759-69

Diagnostic Assays: Salivary Cortisol Patterns Matter

- Common abnormal patterns
  - Elevated
  - Depressed
  - Mixed

Salivary Cortisol and DHEA



Cortisol ♦

Reference Range

1 Hour After Rising
7AM - 9AM:

0.27-1.18 mcg/dL

11AM - 1PM:

0.10-0.41 mcg/dL

3PM - 5PM:

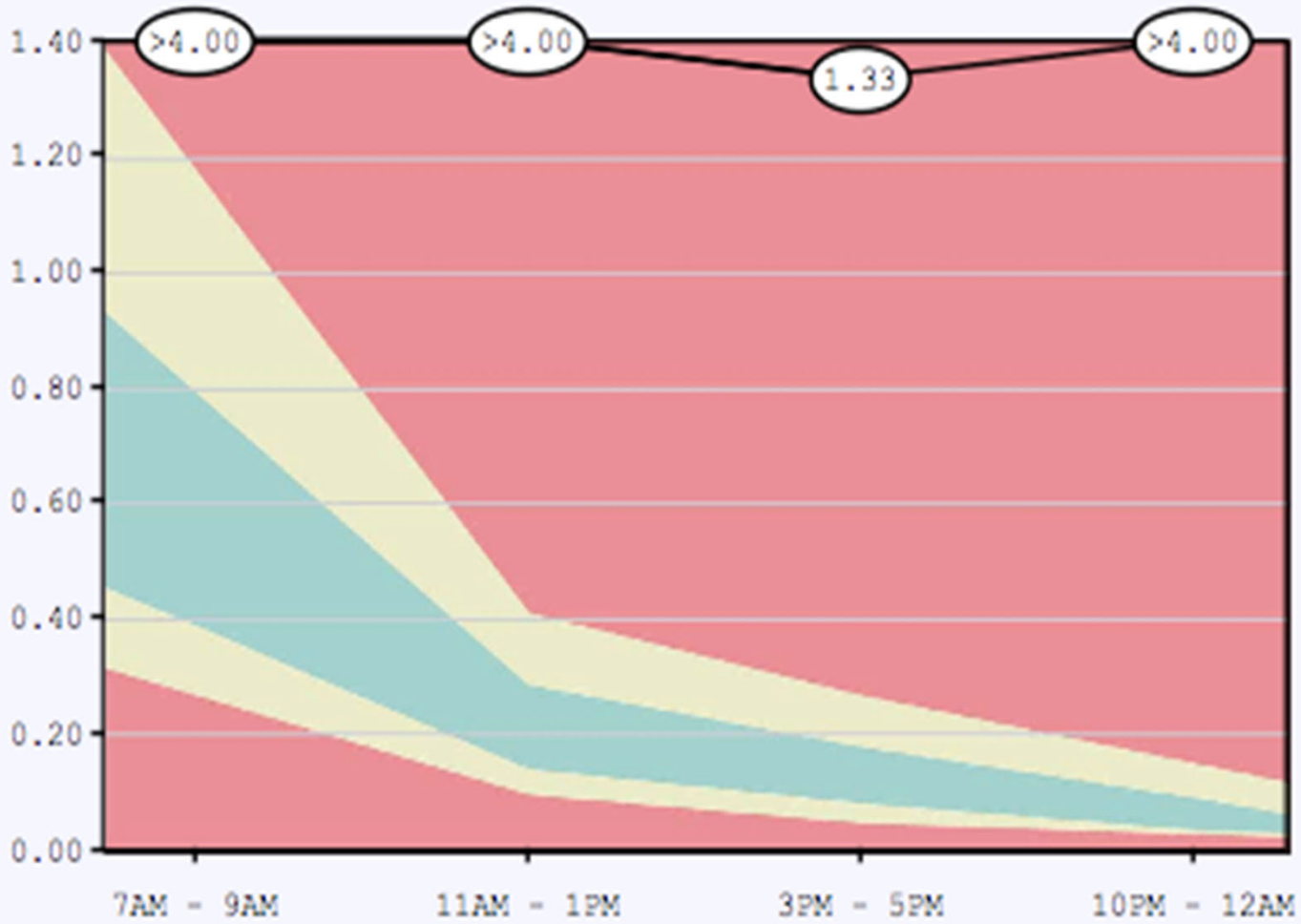
0.05-0.27 mcg/dL

10PM - 12AM:

0.03-0.14 mcg/dL

Hormone	Reference Range	Reference Range
DHEA 7am - 9am	297	71-640 pg/mL
DHEA: Cortisol Ratio/10,000	495	115-1,188

Salivary Cortisol and DHEA



Cortisol ◆

Reference Range

1 Hour After Rising
7AM - 9AM:

0.27-1.18 mcg/dL

11AM - 1PM:

0.10-0.41 mcg/dL

3PM - 5PM:

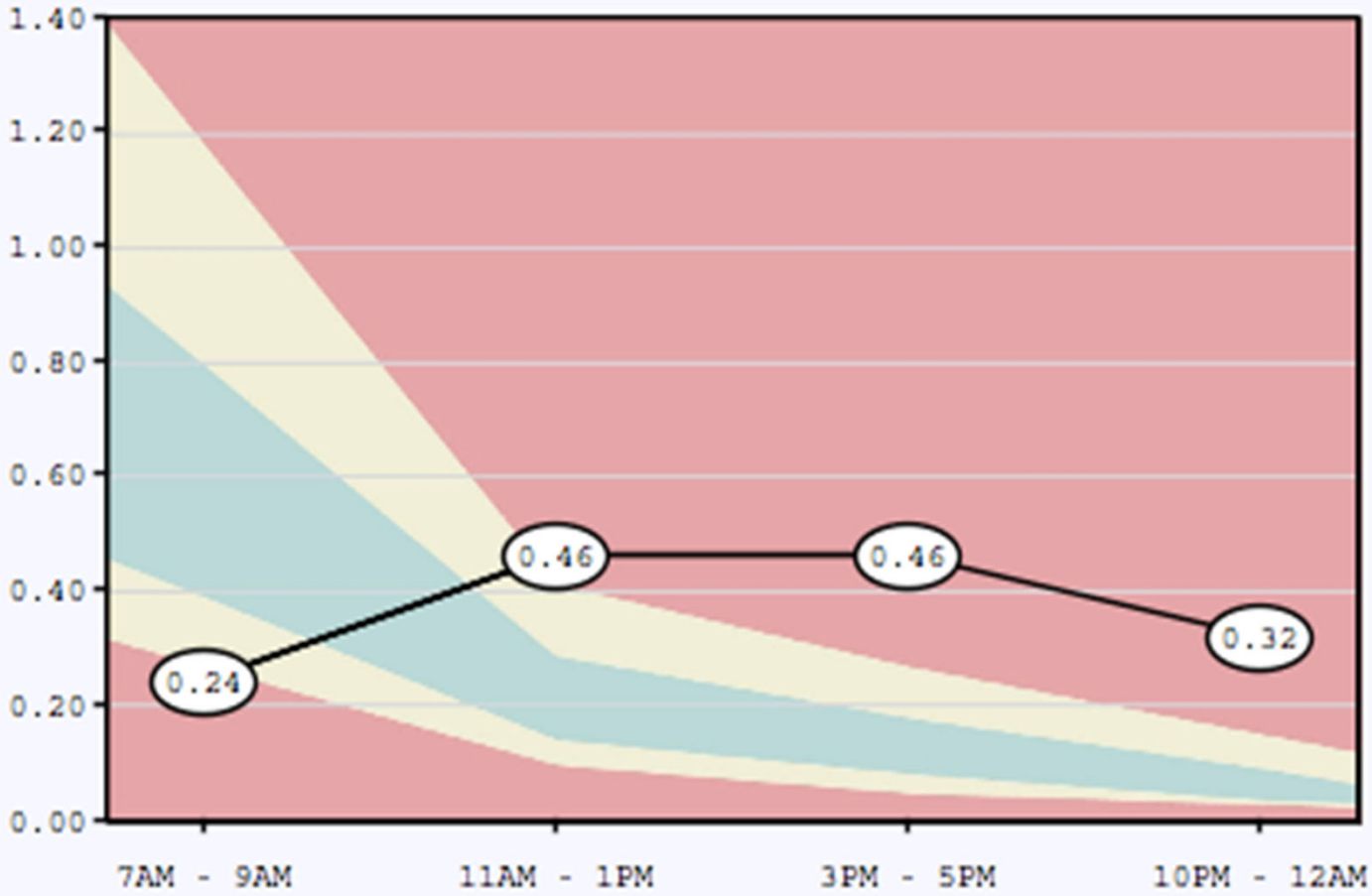
0.05-0.27 mcg/dL

10PM - 12AM:

0.03-0.14 mcg/dL

Hormone	Reference Range	Reference Range
DHEA 7am - 9am	191	71-640 pg/mL
DHEA: Cortisol Ratio/10,000	NR	115-1,188

Salivary Cortisol and DHEA



Cortisol

Reference Range

1 Hour After Rising
7AM - 9AM:

0.27-1.18 mcg/dL

11AM - 1PM:

0.10-0.41 mcg/dL

3PM - 5PM:

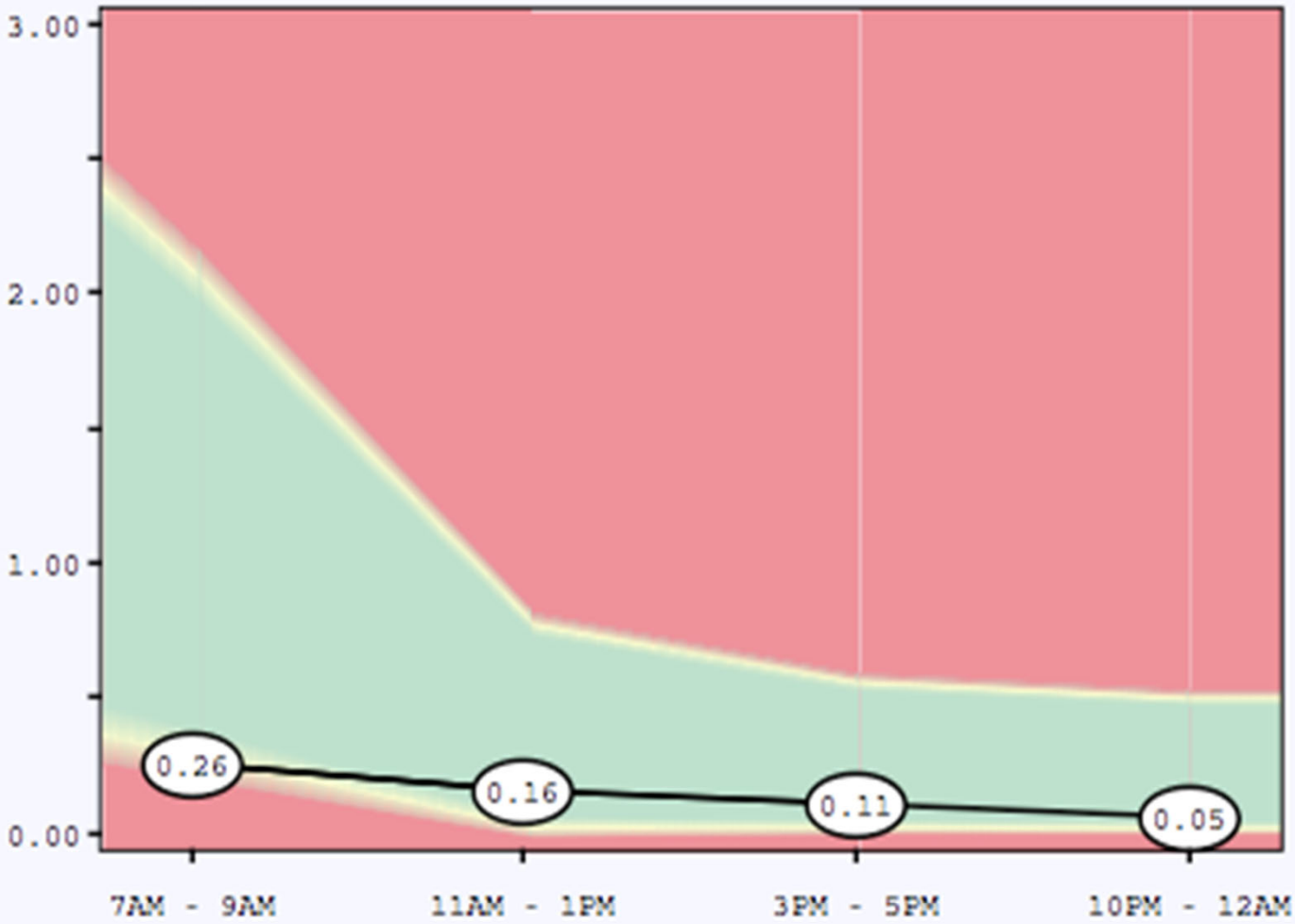
0.05-0.27 mcg/dL

10PM - 12AM:

0.03-0.14 mcg/dL

Hormone	Reference Range	Reference Range
DHEA 7am - 9am	164	71-640 pg/mL
DHEA: Cortisol Ratio/10,000	683	115-1,188

Salivary Cortisol and DHEA



Cortisol ◆

Reference Range

1 Hour After Rising
7AM - 9AM:

0.27-2.06 mcg/dL

11AM - 1PM:

0.03-0.77 mcg/dL

3PM - 5PM:

0.03-0.56 mcg/dL

10PM - 12AM:

0.03-0.50 mcg/dL

Hormone	Reference Range	Reference Range
DHEA 7am - 9am	72	14-277 pg/mL
DHEA / Cortisol Ratio x 10,000	277	35-435

How Do I Protect the Brain?

Magnolia/Phellodendron

- Anti-anxiety and anti-stress properties similar benzodiazapenes, yet non-sedating
- Anti-depressant properties
- Has been shown to normalize high cortisol and DHEA levels
- Low side-effect profile
- Dosage: 1 capsule TID

L-theanine

- Green tea contains 1% to 3% theanine
- Theanine has historically been used for it's relaxing and anti-anxiety effects

L-theanine

- Analog of glutamate
- Demonstrates a protective effect on neuroexcitotoxicity by decreasing ischemic neuronal death in the forebrains of animal models.
- Antagonistic effects on glutamate and N-methyl-D-aspartate (NMDA) receptors
- Reduces norepinephrine levels and decreases systolic and diastolic blood pressure
- Suppresses the stimulatory effects of caffeine

L-Theanine

- An amino acid found in green tea - acts antagonistically against the stimulatory effects of caffeine in the tea on the nervous system.
- Increases GABA (gamma-amino-butyric acid), and reduces restlessness, insomnia, and other disruptive conditions.
- Increases levels of dopamine and improves mental awareness.
- Increases alpha waves (meditative state)

L-Theanine

- Non- sedating
- Dosage - 50-200 mg 2-4 times/day
- No toxicity or reported side effects
- There are no dietary limits on L-theanine intake by the Japan Food Additive Association.
- Maximum daily dose– 1200 mg daily

Rg3

- Rg3 is in a class of triterpene saponins called ginsenosides.
- Supports healthy neurotransmitter function in the brain
- Decreases excitotoxic and oxidative stress-induced neuronal cell damage, leading to enhanced memory effects.
- Decrease both microglial activated inflammation and neuronal cell apoptosis in neurodegenerative conditions, like Parkinson's and Alzheimer's diseases.

Joo SS, Yoo YM, Ahn BW, Nam SY, Kim YB, Hwang KW, Lee do I. Prevention of inflammation-mediated neurotoxicity by Rg3 and its role in microglial activation. Biol Pharm Bull. 2008 Jul;31(7):1392-6.

Rg3

- Decrease oxidative iNOS, increase macrophage scavenger receptor type A
- Reduce inflammatory cytokine expression and significantly reduce the expression of TNF-alpha in activated microglia.
- Increases survival rate of neurons exposed to TNF-alpha.
- Attenuates NMDA receptor-mediated currents and NMDA-induced neurotoxicity

Joo SS, Yoo YM, Ahn BW, Nam SY, Kim YB, Hwang KW, Lee do I. Prevention of inflammation-mediated neurotoxicity by Rg3 and its role in microglial activation. Biol Pharm Bull. 2008 Jul;31(7):1392-6.

Rg3

- Dose – 5 mg BID, on empty stomach
- Taken as 3 months on, 2 weeks off cycle
- Use product for 4 weeks before beneficial effects can be expected
- Slight anticoagulant properties

Conclusion

- Stress response tightly integrated with nervous system, endocrine, cardiovascular, and immune systems
- Flattened cortisol curve may be adaptive mechanism despite metabolic and clinical implications
- Clinical strategy to mitigate stress:
  - Seek primary or causative factors
  - Behavioral and lifestyle interventions
  - Appropriate selection of natural products and medications

Thank You

ANDREW HEYMAN, MD MHSA