Stress and the Immune-Brain Connection I

Andrew Heyman, MD MHSA
Medical Director of Integrative Medicine
The George Washington University
Director of Academic Affairs
American Academy of Ant-Aging Medicine

Stress and the Immune-Brain Connection

Andrew Heyman, MD MHSA

The following potential conflict of interest relationships are germane to my presentation.

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N/A

Objectives

- Review physiologic stress response
- Evaluate impact of cortisol on nervous and immune system
- Examine common illnesses in the context of hypocortisol states that mediated disease progression and prognosis
- Review treatment strategies and clinical cases

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.

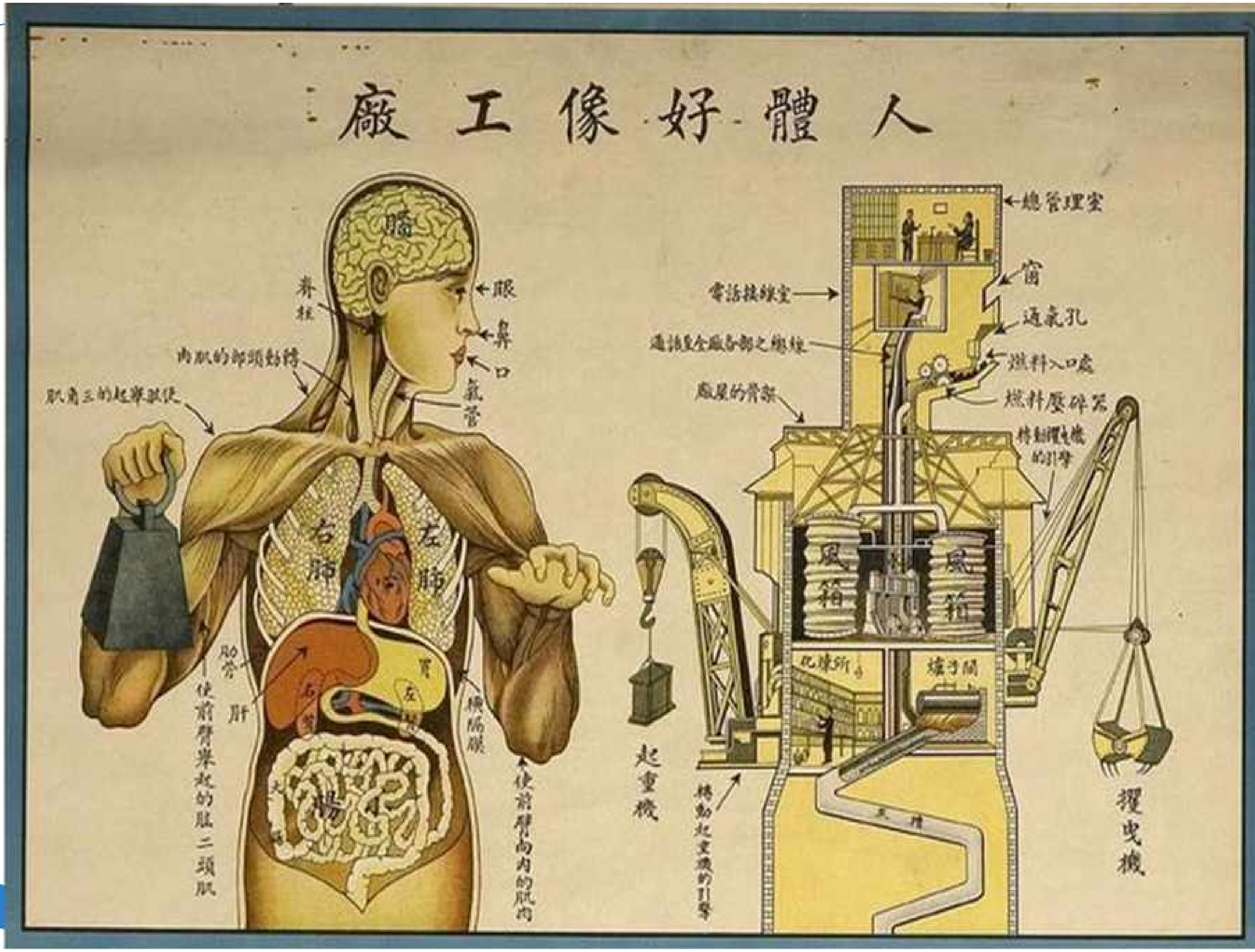
In the measure that we interrelate a greater number of fragments,
the closer we can come to truth, although truth as an absolute is unattainable.

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
右肺
左肺
肝
胃
腸
橫膈膜
起重機
總管理室
窗
通氣孔
燃料入口處
電話接線室
廠屋的骨架
風箱
化驗所

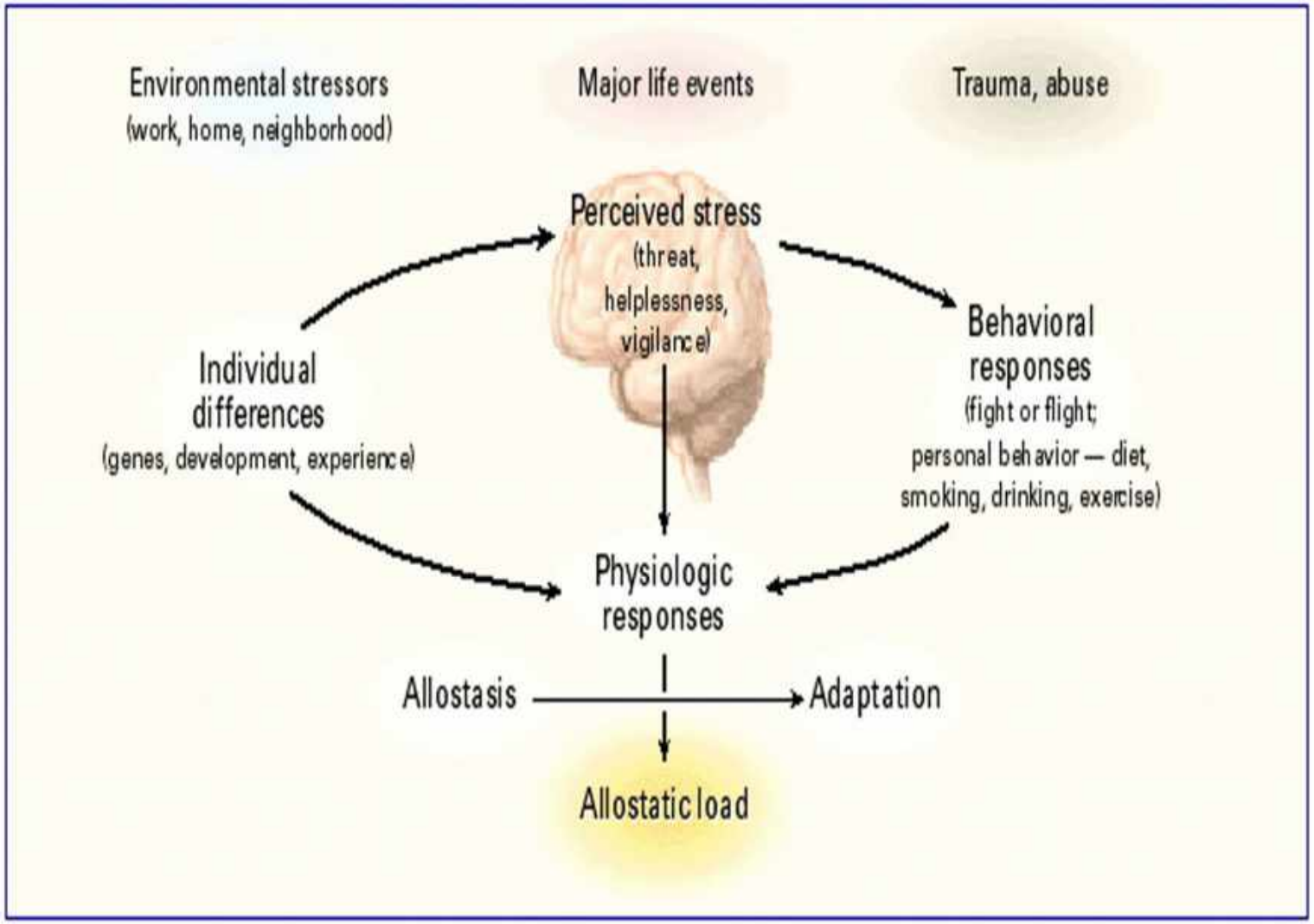
Integrative Physiology

- Examine multiple organ systems simultaneously
- Seeks primary causative factors driving complex biochemical abnormalities
- Utilizes treatment strategies aimed at restoring allostasis and reducing allostatic load
- Emphasizes treatments that improves physiologic function while avoiding risk or harm
- Ecological model of medicine

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



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

Physiologic Stressors

Economic Impact of Stress

A 2004 Report from the American Institute of Stress reported that work place stress had an annual price tag of

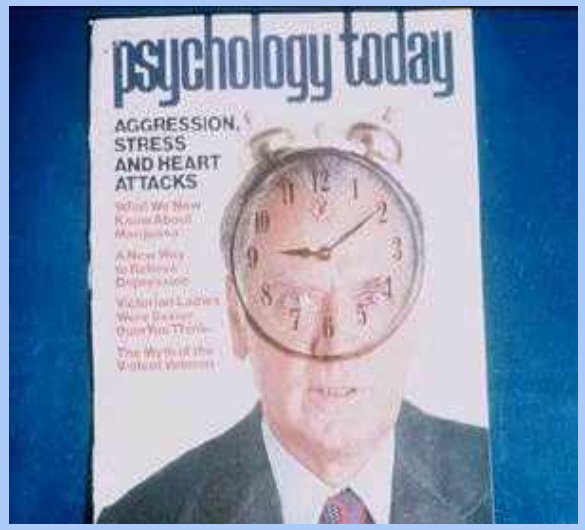
$300 Billion dollars

Economic Impact of Stress

- 19% of absenteeism
- 40% of job turnover
- 10% of costs of prescription drug plans
- 60% of workers' compensation awards

"*What Stress Costs*". Ravi Tangri

Economic Impact of Stress



It has been estimated that 75 to 90% of all visits to primary care physicians are for stress related problems.

Job Stress is the leading source of stress for adults

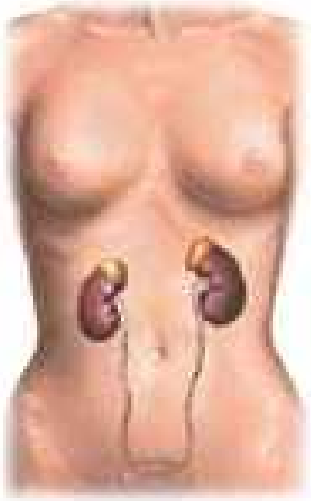
American Institute of Stress

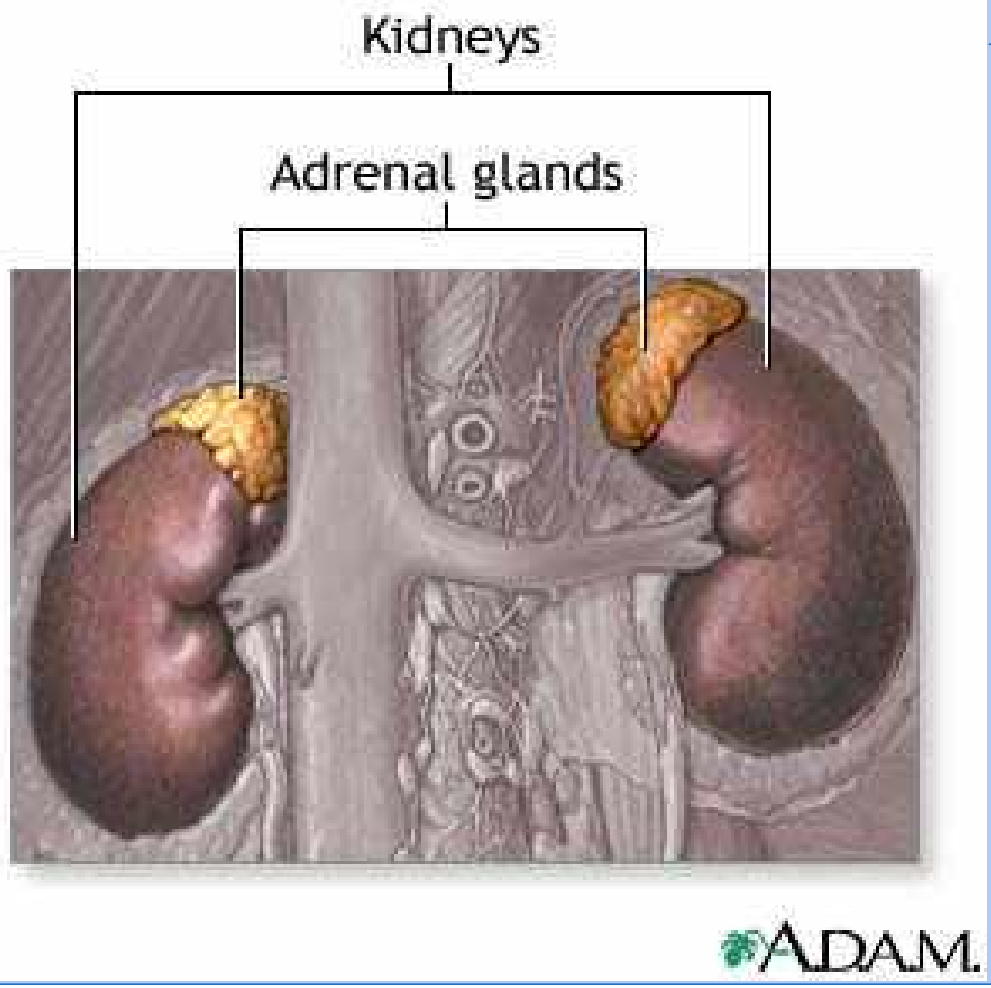
Economic Impact of *Stress*

In the final analysis, we are left with what every "complete" physician eventually learns, namely, that, "Many times it is much more important to know what kind of patient has the disease, than what kind of disease the patient has".

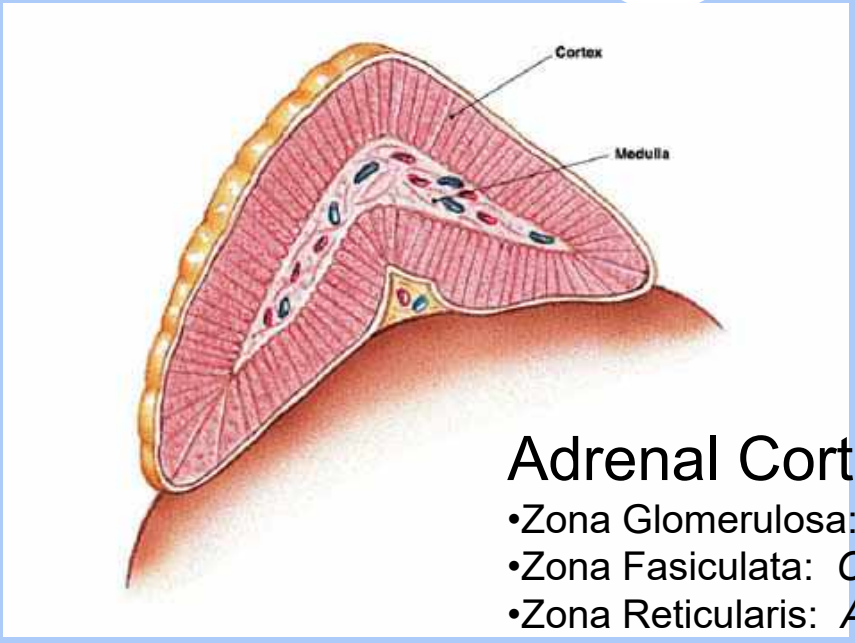
Paul J. Rosch, M.D., F.A.C.P.
President, The American Institute Of Stress
Clinical Professor of Medicine and Psychiatry New York Medical College

Adrenal Glands





Adrenal Gland Anatomy



Adrenal Cortex

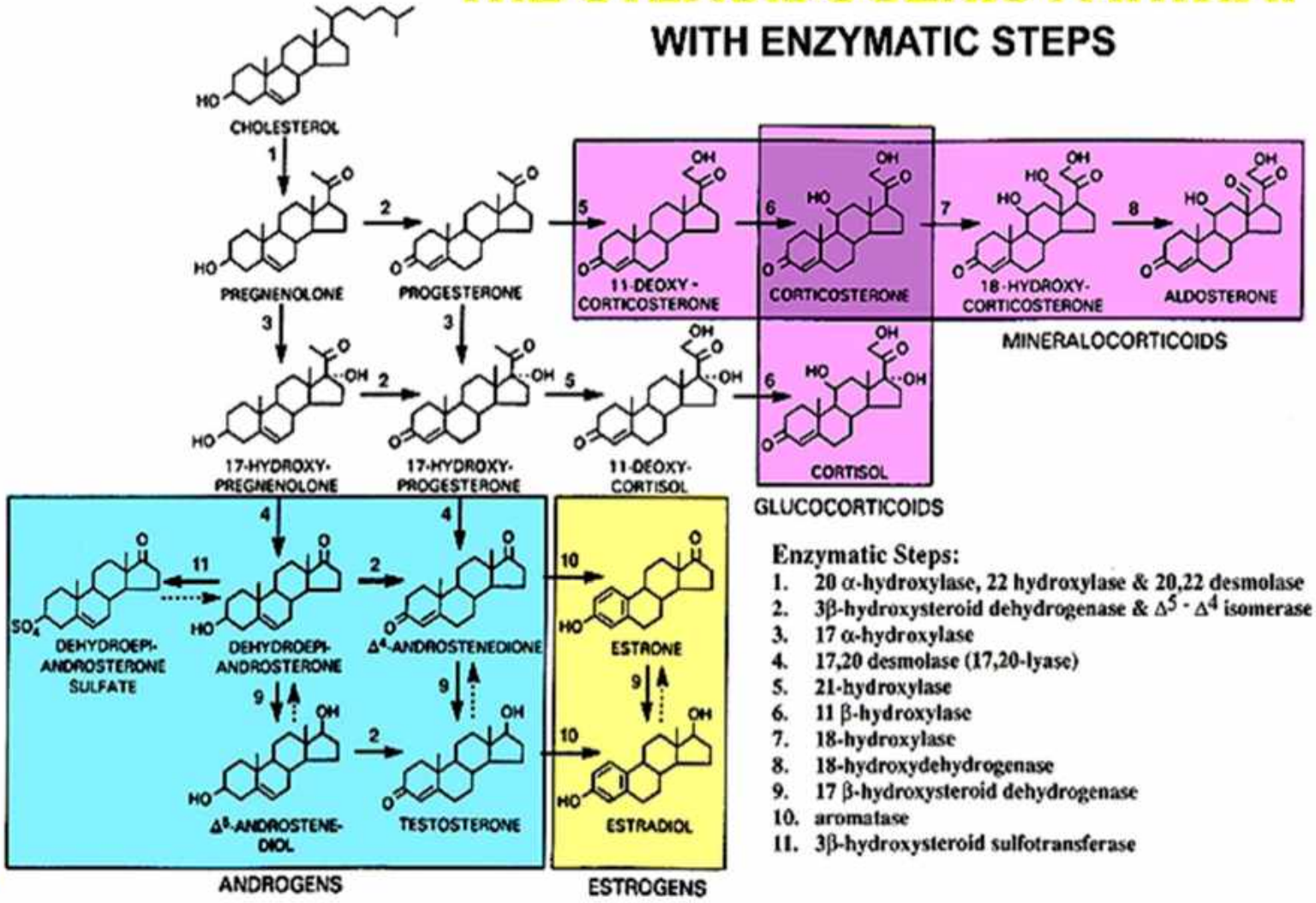
- Zona Glomerulosa: *Aldosterone*
- Zona Fasiculata: *Cortisol*
- Zona Reticularis: *Androgens,Pregnenolone, Progesterone*

Adrenal Medulla

- *Epinephrine (80%)*
- *Norepinephrine (20%)*

THE STEROIDOGENIC PATHWAY

WITH ENZYMATIC STEPS



Enzymatic Steps:

1. 20 α-hydroxylase, 22 hydroxylase & 20,22 desmolase
2. 3β-hydroxysteroid dehydrogenase & Δ^5 - Δ^4 isomerase
3. 17 α-hydroxylase
4. 17,20 desmolase (17,20-lyase)
5. 21-hydroxylase
6. 11 β-hydroxylase
7. 18-hydroxylase
8. 18-hydroxydehydrogenase
9. 17 β-hydroxysteroid dehydrogenase
10. aromatase
11. 3β-hydroxysteroid sulfotransferase

Adrenal Hormone Functions

- Cortisol
  - Produced only in the adrenal glands
  - Regulation of protein, carbohydrate, lipid, and nucleic acid metabolism
  - Elevates blood sugar
  - Elevates blood pressure
  - Increased protein catabolism and inhibition of protein synthesis

Adrenal Hormone Functions

- Cortisol
  - Anti-inflammatory (cytokine suppression)
  - Decreased antibody production
  - Suppresses release of Growth Hormone
  - Bone loss
  - Increases gastric acid production
  - Inhibits production of nucleic acids (except liver RNA)
  - Mobilizes fatty acids

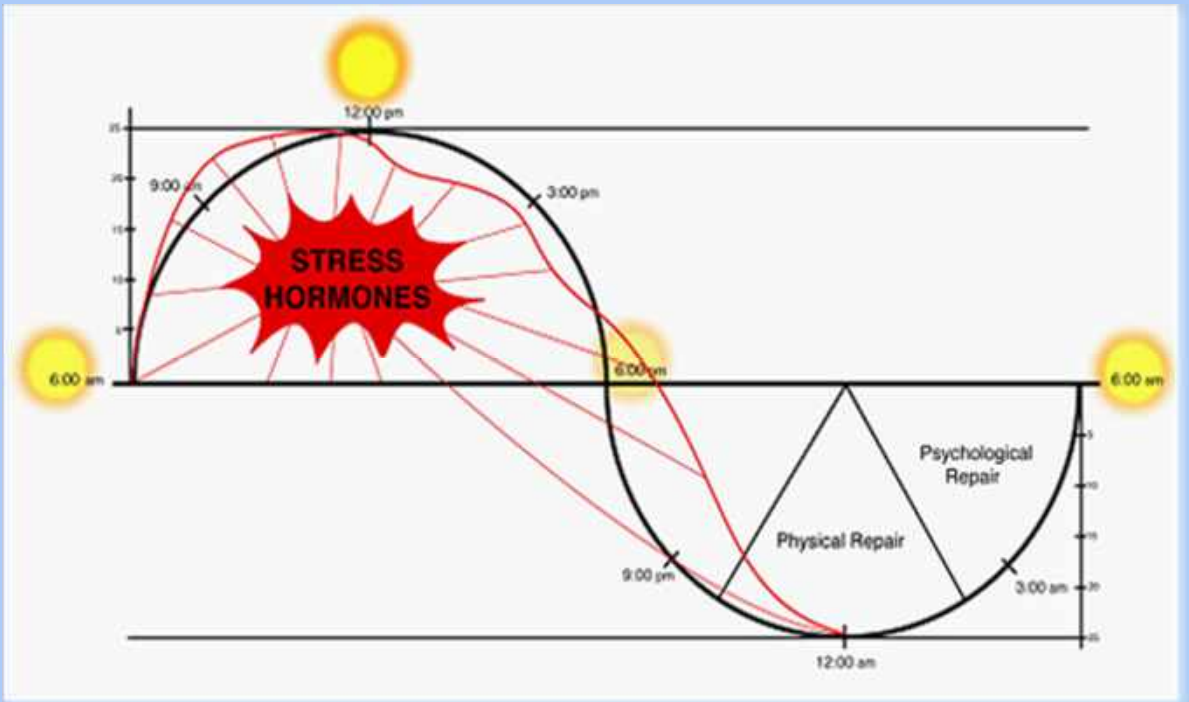
Adrenal Hormone Functions

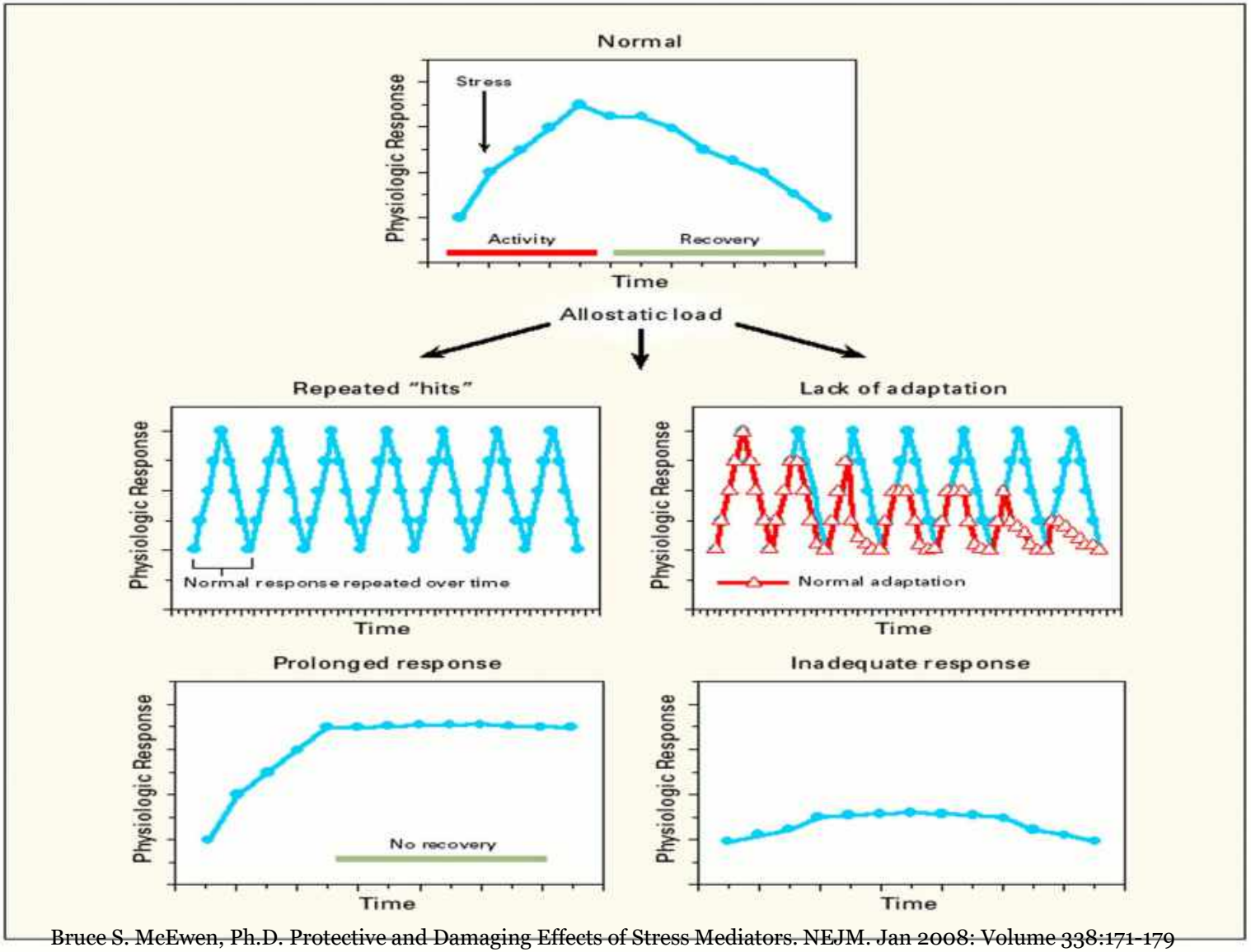
- Dehydroepiandrosterone (DHEA)
  - Precursor to sex hormones
  - Most abundant hormone produced by adrenal cortex
  - Activates endothelial nitric oxide synthase
  - Directly binds to NMDA and GABA receptors in the brain
  - Lowers cortisol

Adrenal Hormone Functions

- Dehydroepiandrosterone (DHEA)
  - Anti-atherogenic
  - Lowers triglycerides
  - Improves insulin sensitivity
  - Promotes sense of well being
  - Neuroprotective
  - Maintains tissue strength and repair
  - Direct action on immune cells
  - Promotes bone growth

Normal Diurnal Hormone Release





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

Definition of *Allostatic Load*

- The wear and tear of the body and brain resulting from chronic over activity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge.

- Allostatic load results when the HPA axis is either overworked or fails to shut off after stressful events or when normal compensatory systems over react.

McEwen et al. *Ann NY Acad Sci*. 1998;840:33-44
Fries et al. *Psychoneuroendocrinology*. 2005;30(10):1010-1016

Evolution of Hypocortisolism: Beyond Adrenal Fatigue

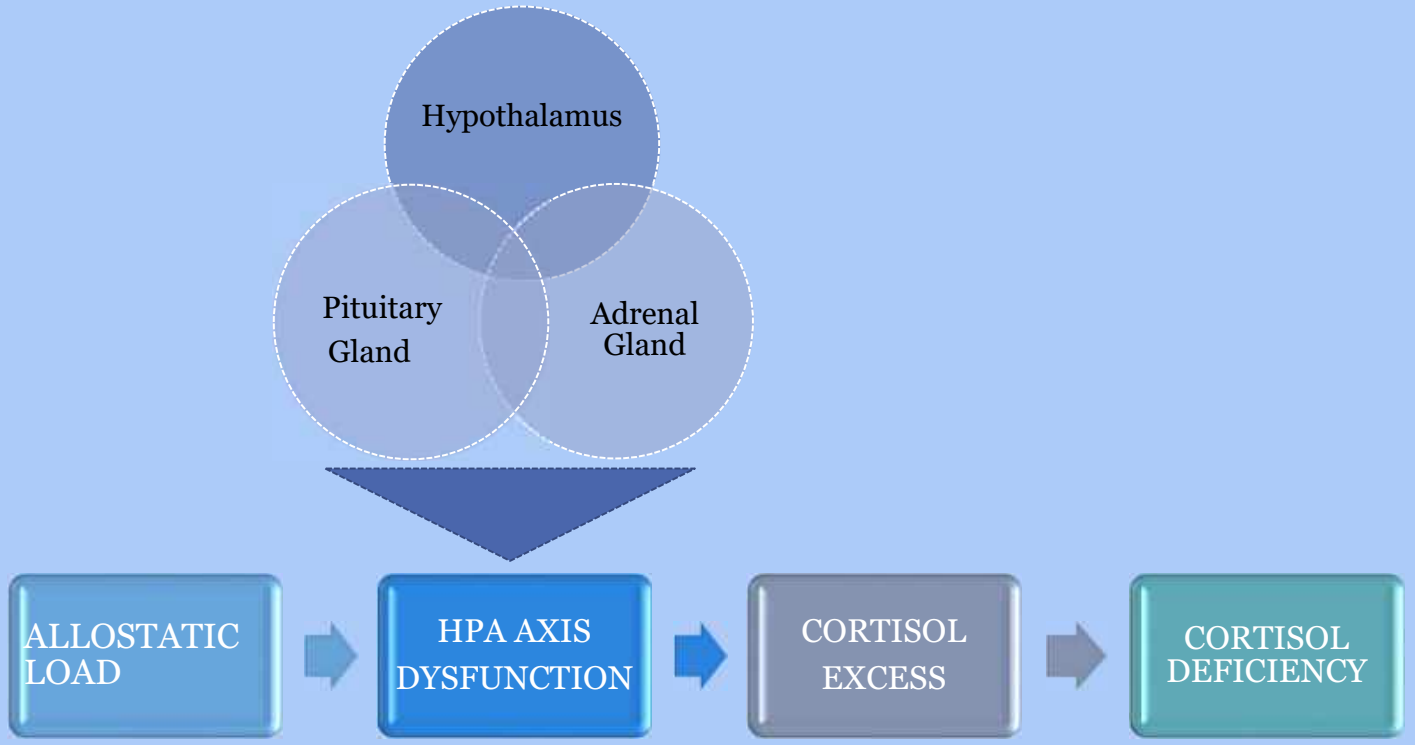


Table 1 – States associated with hyperactivation or hypoactivation of the HPA axis

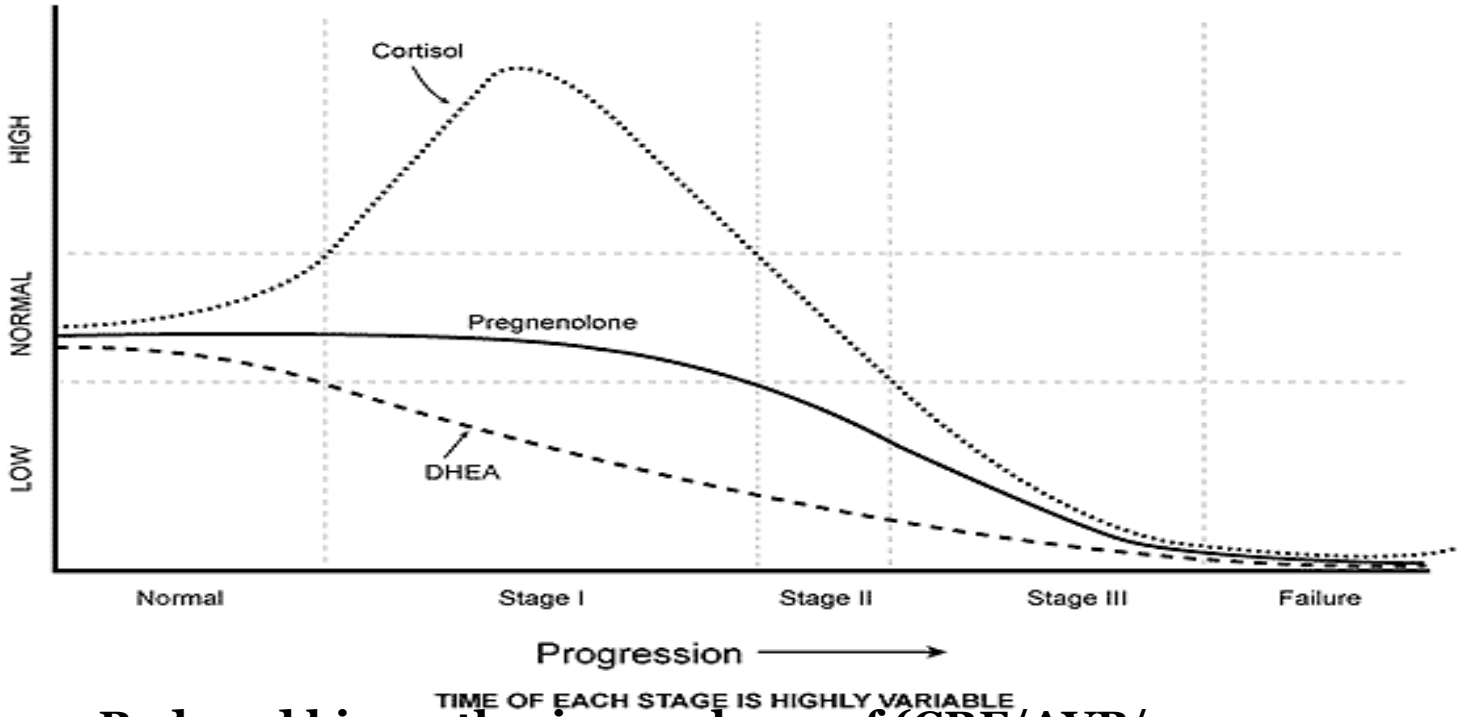
Increased HPA axis activity	Decreased HPA axis activity	Disrupted HPA axis activity
Severe chronic disease		Cushing syndrome
Melancholic depression	Atypical depression	
Anorexia nervosa	Seasonal depression	Glucocorticoid deficiency
Obsessive–compulsive disorder	Chronic fatigue syndrome	Glucocorticoid 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		

Central Mechanisms of Stress Induced Hypocortisolism

- Reduced biosynthesis of releasing factors or hormones
  - Hypothalamus
  - Pituitary
  - Adrenal gland
- Decreased or Increased target receptor sensitivity
- Hippocampal atrophy
- Hypersecretion of secretagogue with down-regulation of target receptors

Mechanisms of Stress Induced Hypocortisolism

- Reduced adrenocortical sensitivity and reactivity
- Adrenal gland atrophy
- Reduced tissue sensitivity to glucocorticoids



- **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**

Factors Mediating Development and Severity of Stress Dysfunction

- Stressor characteristics
  - Duration
  - Severity
  - Exposure to previous chronic stressors
- Individual coping mechanisms
- Genetics
- Gender (female > male)

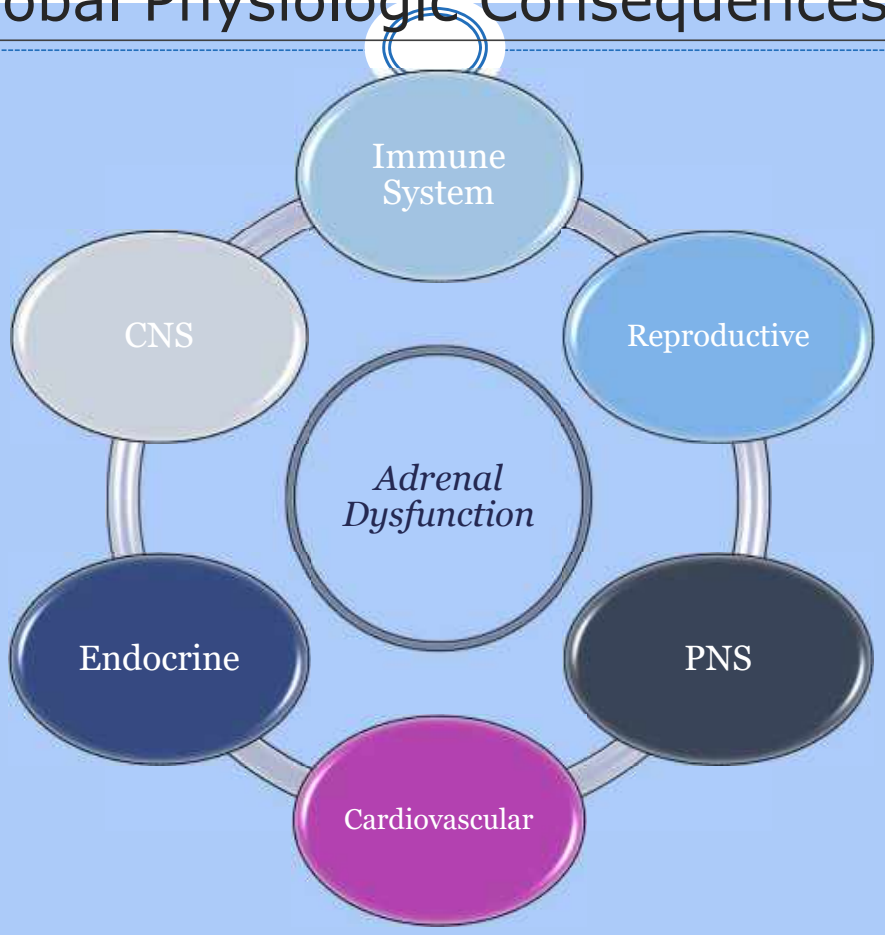
Factors Mediating Development of Stress Dysfunction

- Developmental factors
  - Prenatal stress
  - Childhood stress
- Personality
  - Low self esteem
  - High external control
  - Introversion

Hypocortisolism

Physiological Consequences

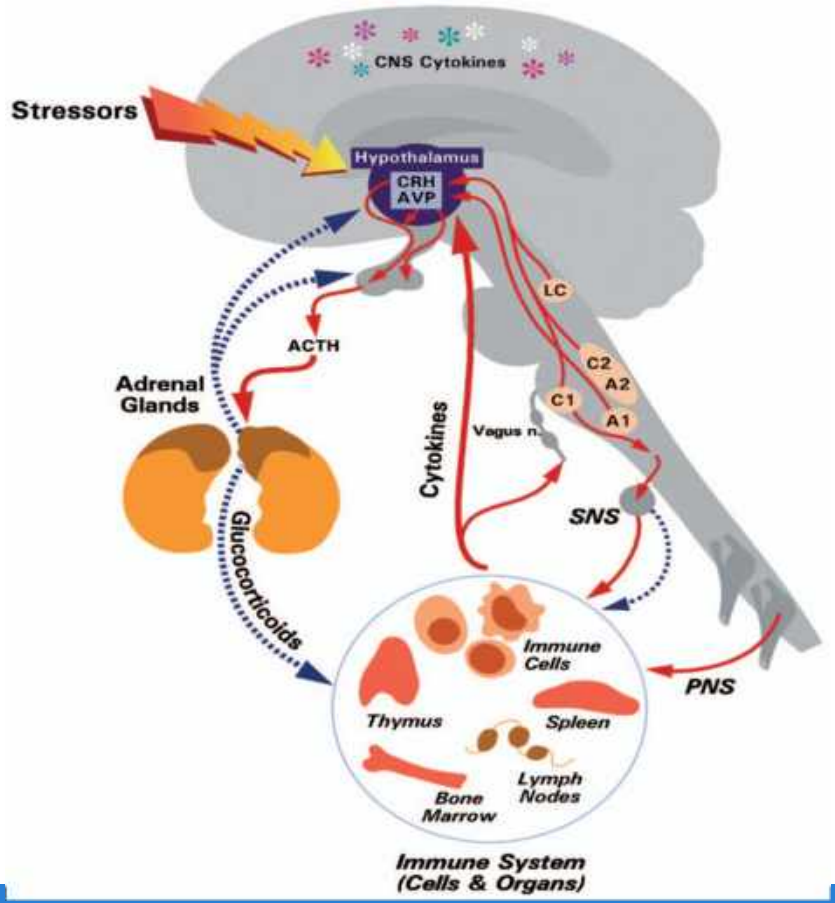
Hypocortisolism: Global Physiologic Consequences



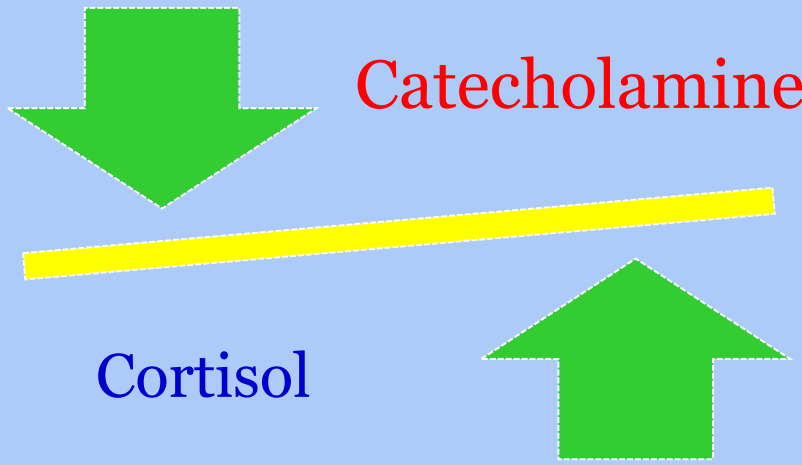
Immune System Dysfunction

- Inadequate immune cell trafficking
- Inability to defend against pathogens
- Inadequate leukocyte trafficking
- Elevations of immune mediators (esp. hypocortisol states)
  - Interleukins (IL-6 and 10) and TNFa
  - Prostaglandins
  - Lymphocytes
  - Natural killer cells
  - ANA antibodies
  - Thyroid antibodies

The Immune System and Stress



SNS Hyperactivity



Loss of negative feedback from cortisol results in a rise in catecholamine production and sympathetic overdrive

Central Nervous System

- Prolonged hypercortisolism leads to degeneration of the:
  - Hippocampus – memory
  - Hypothalamus – CFS, FM, Depression, PTSD
  - Pre-Frontal Cortex – executive decision making
  - Amygdala – emotional stability
- fMRI Pathologic changes seen, some irreversible despite treatment
- Effects remain after hypocortisolism has developed

Cardioendocrine System

- Accelerated progression of atherosclerosis, risk of MI and CHF
- Elevated inflammatory markers
  - PAI-1
  - Fibrinogen
  - HS-CRP
- Endothelial dysfunction and hypertension
- Enhancement of insulin resistance and hyperglycemia

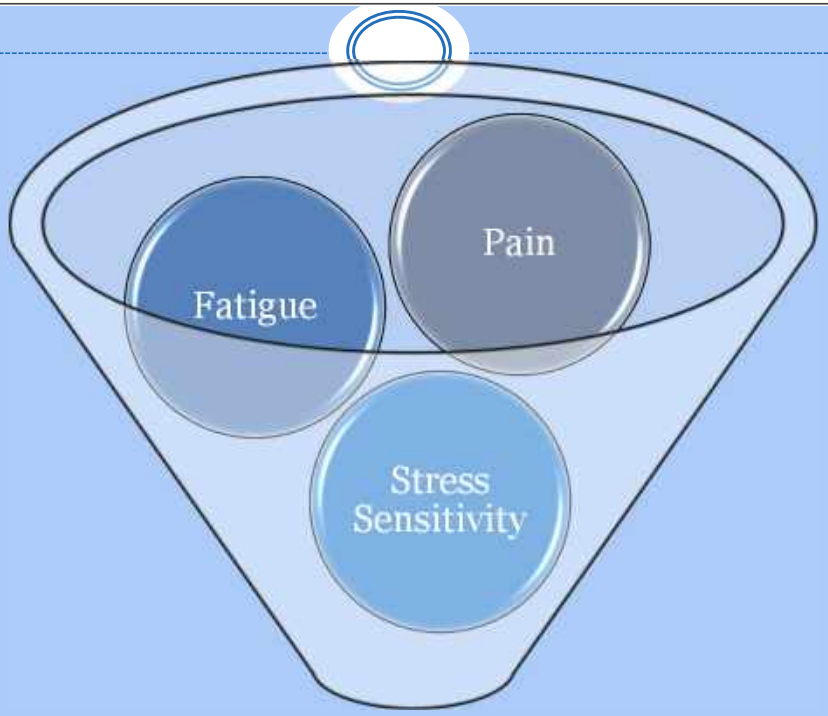
Hypocortisolism
Clinical Consequences

Physical Effects of Chronic Stress

1992

2000

Symptom Triad of Hypocortisolism



Chronic Fatigue Syndrome
Fibromyalgia
PTSD

Disease States Associated with Hypocortisolism

- Asthma/Atopy/Allergies
- Malignancies
- Cardiovascular disease
- Chronic pain syndromes
- Autoimmune diseases
- Irritable bowel syndrome
- Sleep Disorders
- Neurological Disorders

Disease States Associated with Hypocortisolism

- Chronic fatigue syndrome
- Fibromyalgia
- Mood disorders
  - Post-traumatic stress disorder
  - Depression
  - Anxiety
  - Bipolar disorder
  - Schizophrenia
  - Eating disorders

Chronic Fatigue Syndrome

- Numerous studies confirm the presence of
  - low cortisol
  - blunted cortisol responses to stimulation testing
  - Abnormal diurnal cortisol release patterns
- Studies have shown improvement in symptoms with administration of low dose hydrocortisone treatment

Cardiovascular Disease

- CARDIA Study 2006
  - 718 black and white middle-aged men
  - 6 salivary cortisol samples and coronary calcium scoring throughout one full day
  - Persons with cortisol slope scores in the flattest quartile had a greater likelihood of any coronary calcium than did those in the remaining quartiles adjusted for sex-race group, age, smoking, treatment for diabetes, systolic blood pressure, triglycerides, average cortisol, and educational attainment.

Physical Effects of Chronic Stress

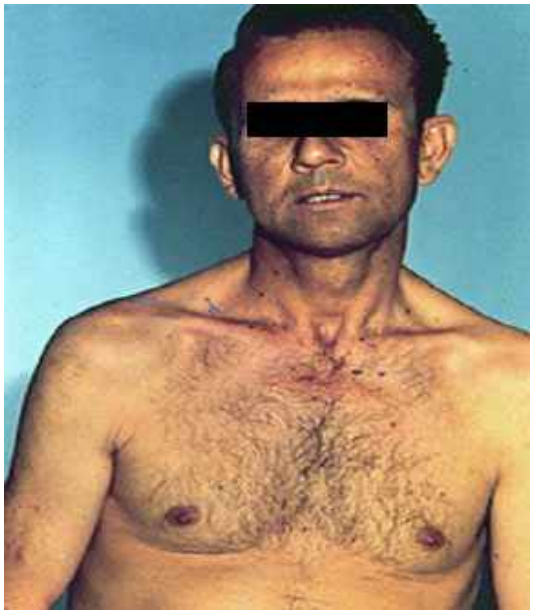
2000

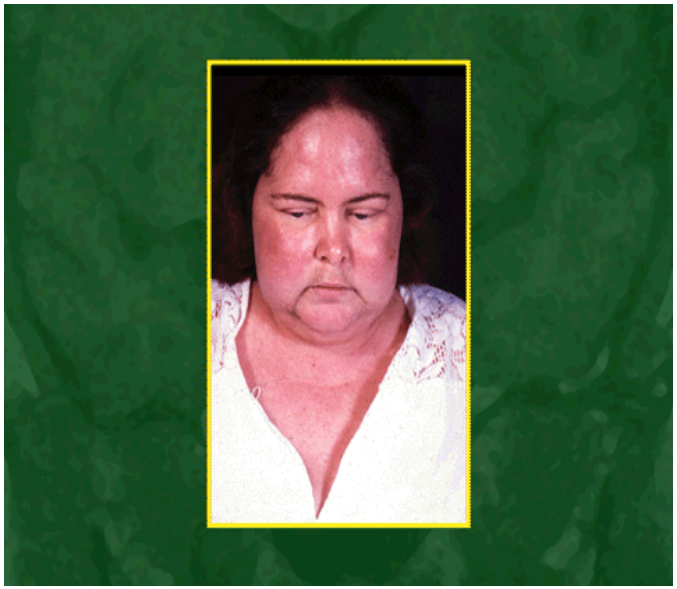
2008

Hypocortisolism

Diagnosis

Traditional medical testing is designed to diagnose *DISEASE*





After it is already present

Diagnostic Assays

- **Serum Cortisol**
  - Must been done under controlled situations
  - One morning reading not useful in gauging overall adrenal function
  - Results can be highly variable (Cortisol Binding Globulin)
  - Numerous studies confirm the use of lab reported normal baseline or stimulated cortisol levels cannot be used to accurately rule out hypocortisolism.

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

- **Serum Cortisol**
  - Immunoassays *overestimate* serum cortisol levels by an average of *70%* resulting in misclassification of *44-56%* of patients.
  - Degree of overestimation of some assays
    - Bayer Advia Centuar: 35%
    - Abbott TDx: 79%
    - DPC Immulite 2000: 95%

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

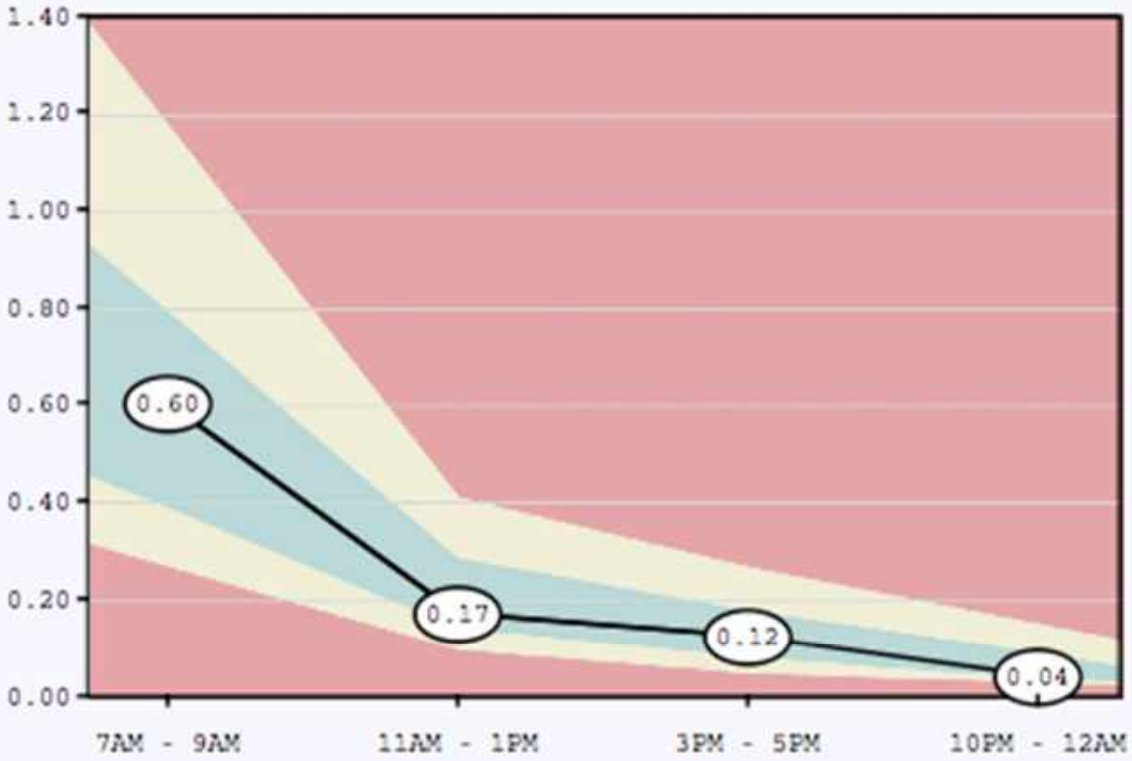
Diagnostic Assays

- **Salivary Cortisol**
  - Endocrine Society Clinical Practice Guidelines (May, 2008) recommend the use of midnight salivary cortisol testing as an appropriate screening test for Cushing's Disease.
  - Salivary cortisol measurements
    - Practical and accurate
    - Useful in determining intermittent changes in cortisol secretion over long periods of time
    - Non-invasive
    - Stress-free
    - Real-time

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:

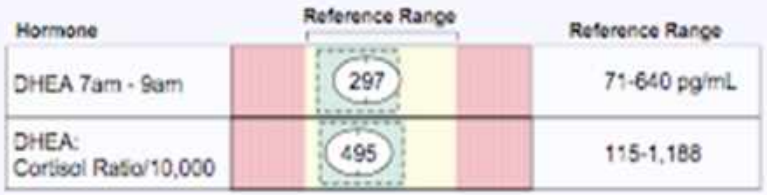
0.10-0.41 mcg/dL

3PM - 5PM:

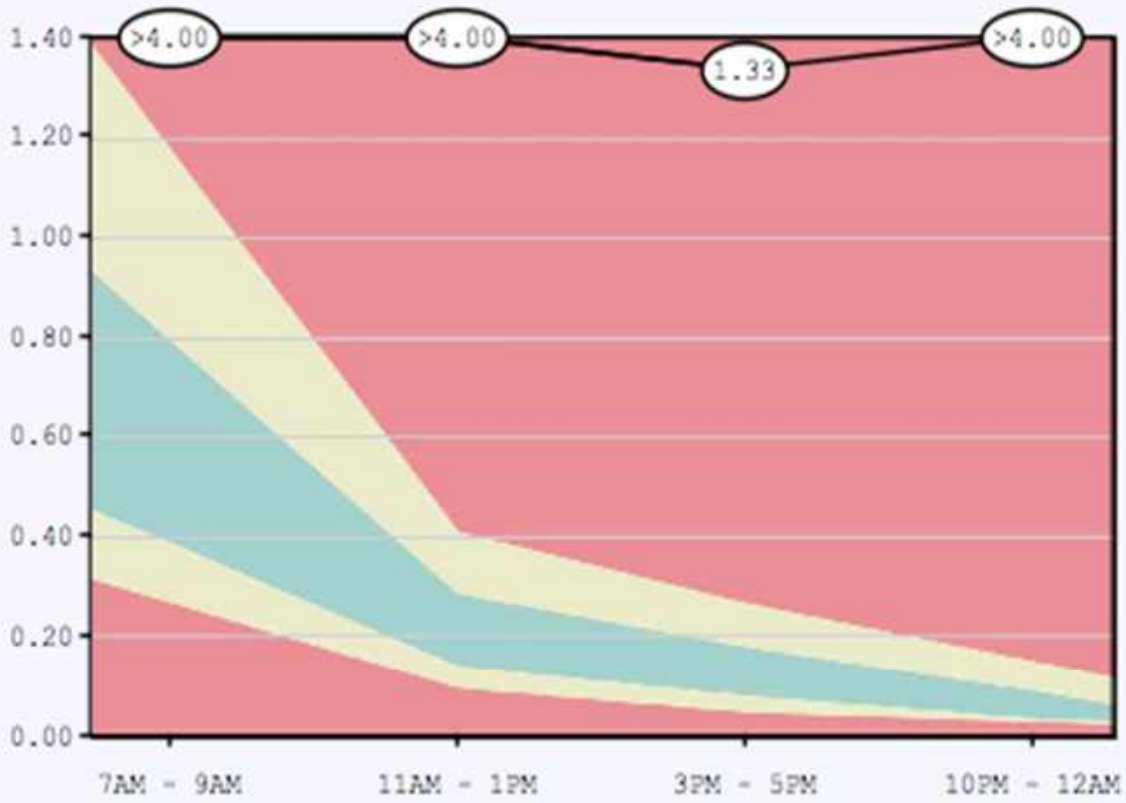
0.05-0.27 mcg/dL

10PM - 12AM:

0.03-0.14 mcg/dL



Salivary Cortisol and DHEA



Cortisol •

Reference Range

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11AM - 1PM:

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3PM - 5PM:

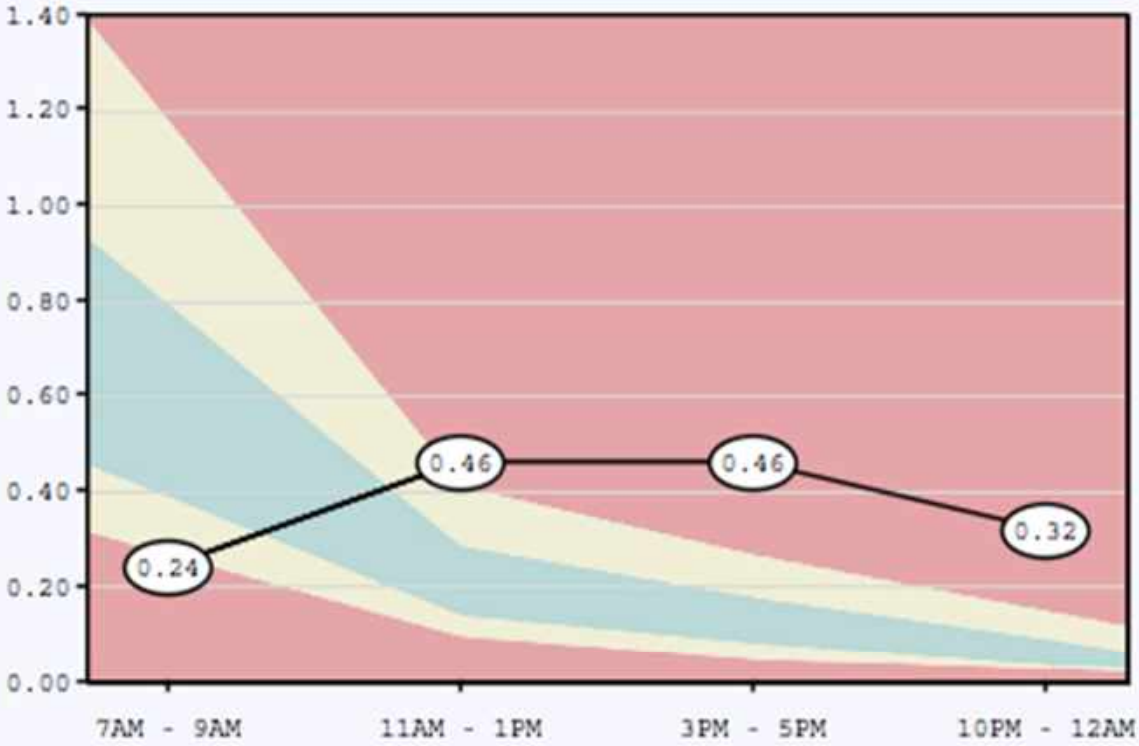
0.05-0.27 mcg/dL

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•

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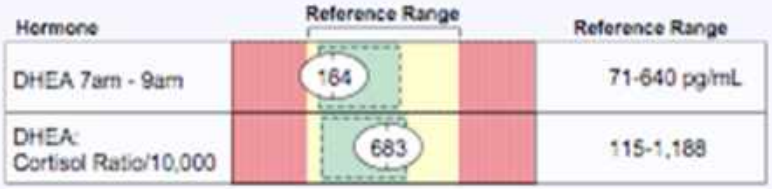


Salivary Cortisol and DHEA

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

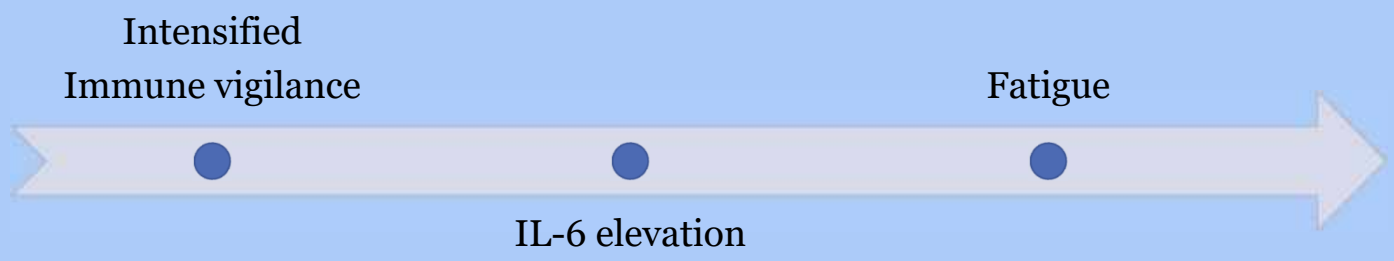
10PM - 12AM:

0.03-0.50 mcg/dL

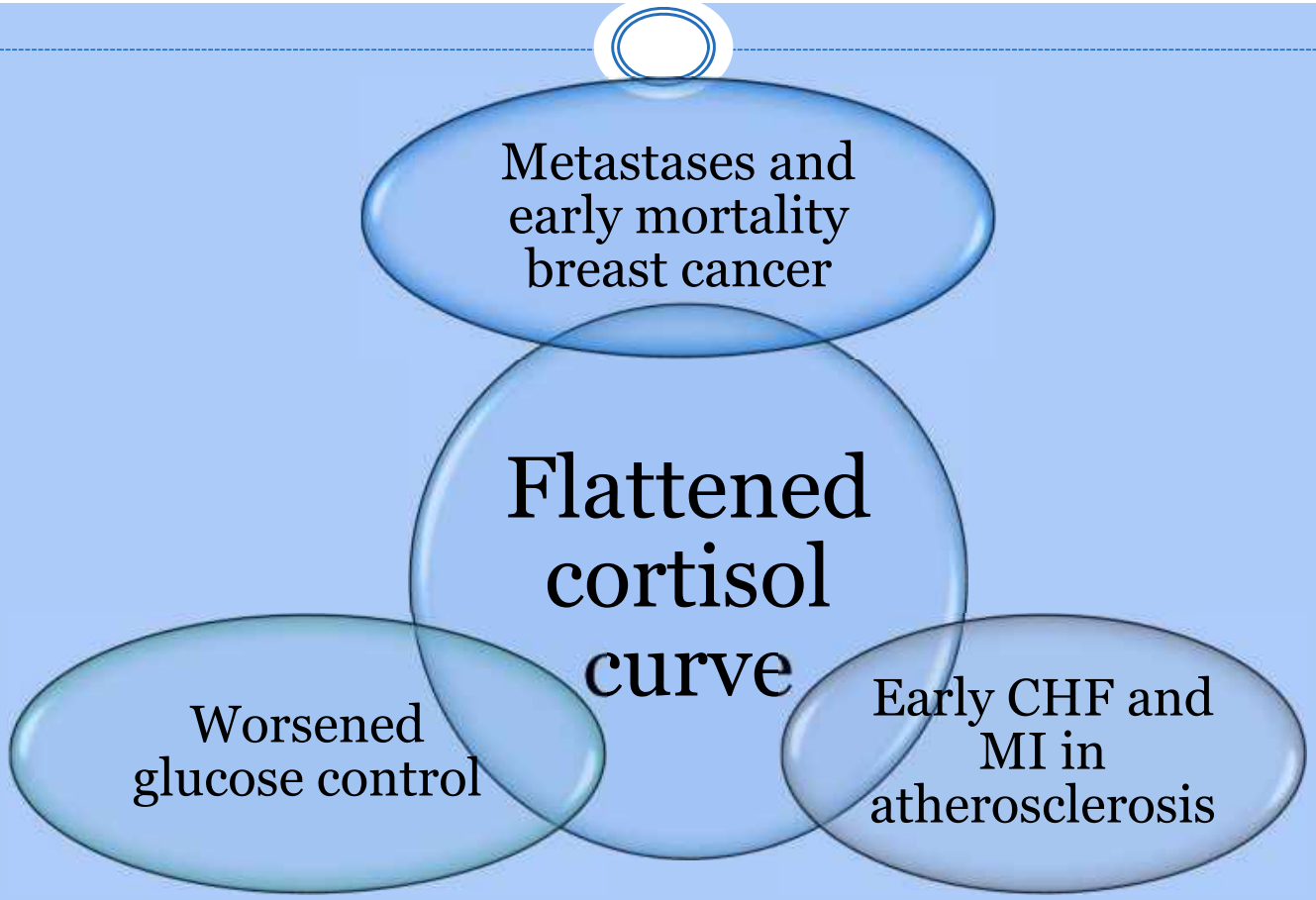
Hormone	Reference Range	Reference Range
DHEA 7am - 9am	72	14-277 pg/mL
DHEA / Cortisol Ratio x 10,000	277	35-435

Diagnostic Assays:
Salivary Cortisol Patterns Matter

- Flattening of the cortisol curve
  - Most predictive of adrenal dysfunction
  - Most well studied
  - Hypocortisolism induces:



Diagnostic Assays:
Salivary Cortisol Patterns Matter



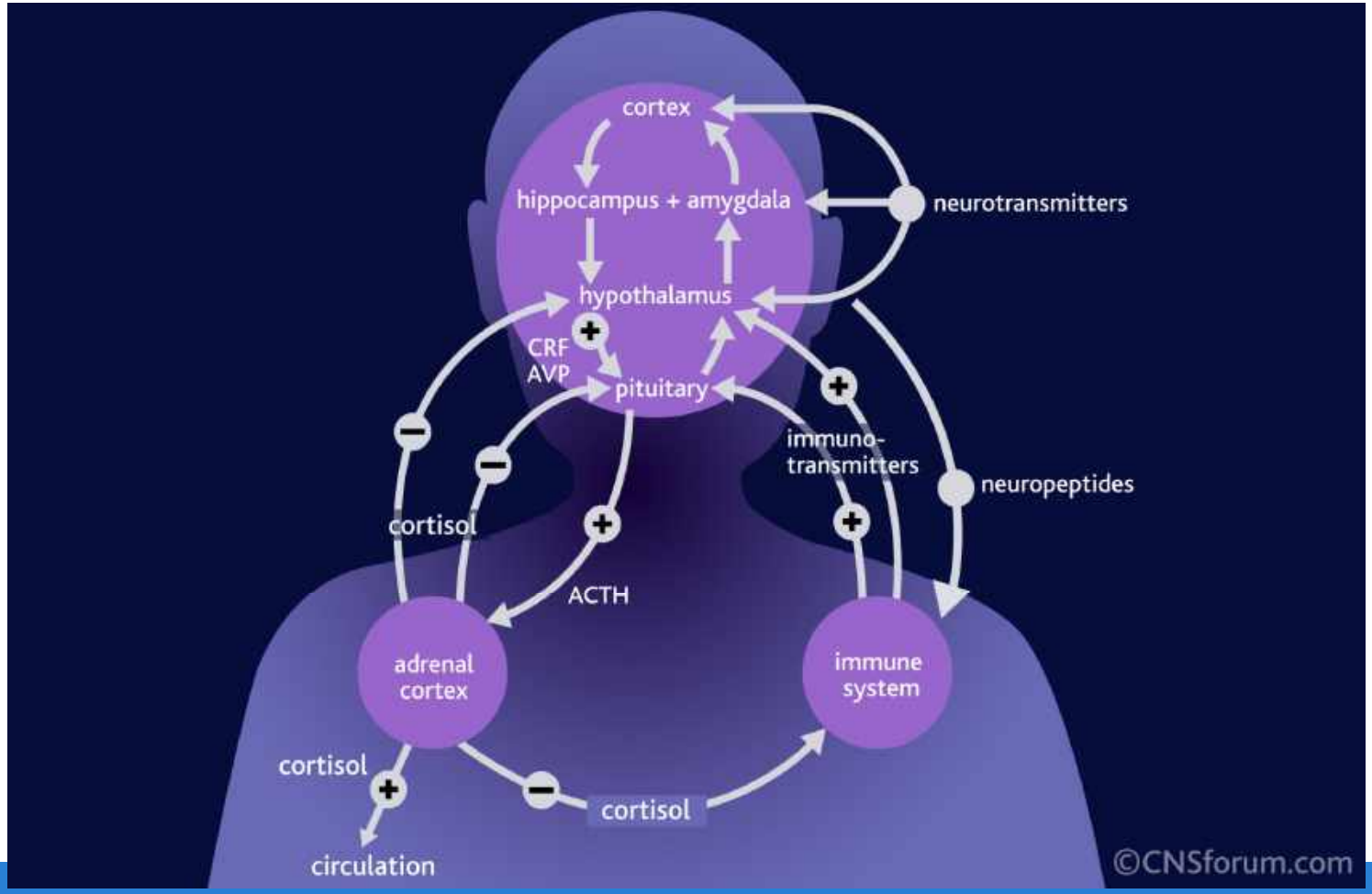
Stress and the Immune-Brain Connection II

Andrew Heyman, MD MHSA
Program Director of Integrative Medicine
The George Washington University

Objectives

- Review physiologic stress response
- Evaluate impact of cortisol on nervous and immune system
- Examine common illnesses in the context of hypocortisol states that mediated disease progression and prognosis
- Review treatment strategies and clinical cases

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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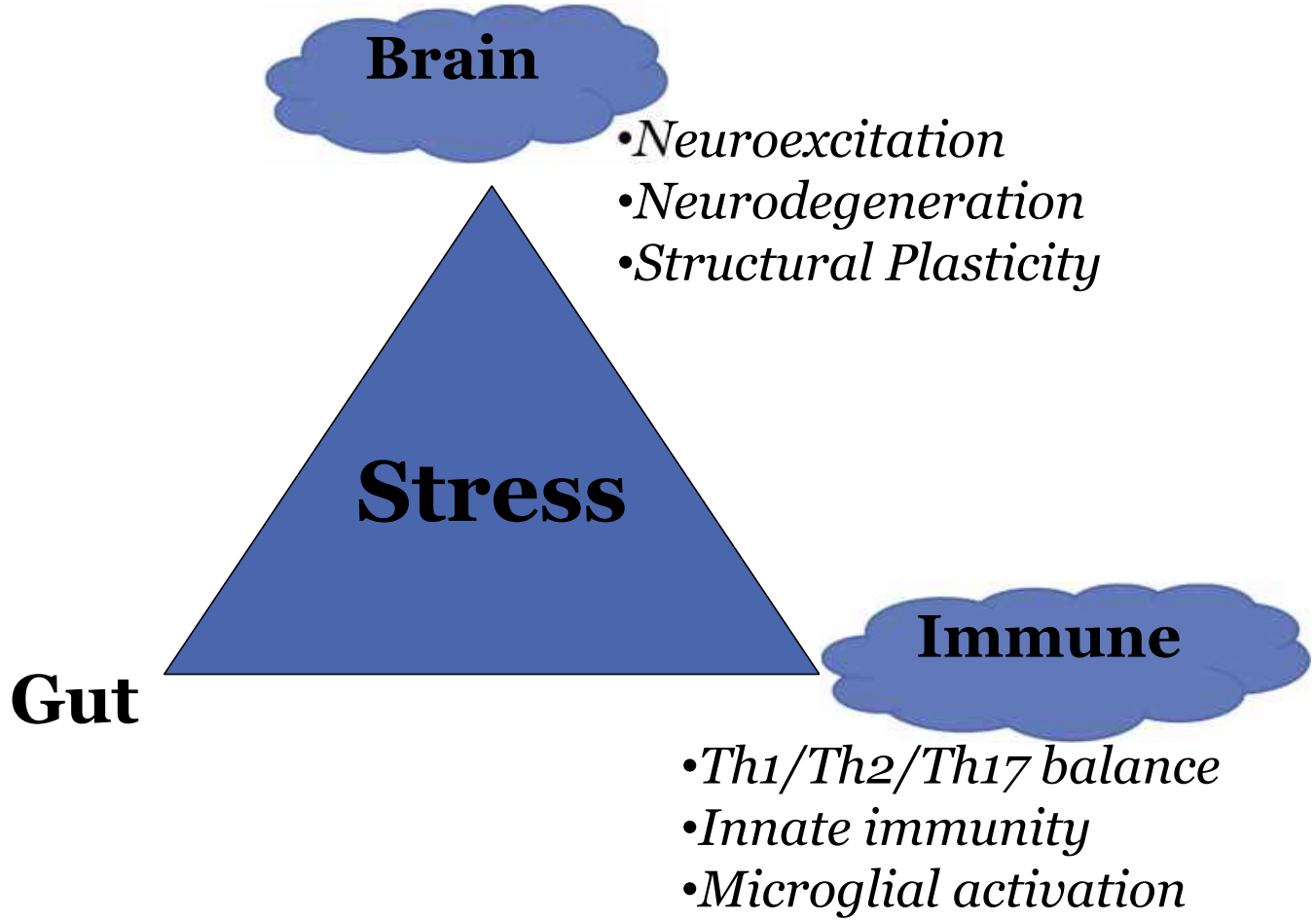

Brain
•Neuroexcitation
•Neurodegeneration
•Structural Plasticity
Stress
Gut
Immune
•Th1/Th2/Th17 balance
•Innate immunity
•Microglial activation

Cortisol and the Hippocampus

- Repeated stress affects brain function, especially hippocampus.
- High concentrations of cortisol and NMDA receptors.
- Participates in verbal memory and memory context
- Impairment decreases the reliability and accuracy of contextual memories.
- 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

Hippocampal Changes in Chronic Stress

- Hippocampus alterations in both structure and function have been identified in long term stress
- Volume loss demonstrated in PTSD, depression, cushing’ s syndrome
- Functional changes include reduction in hippocampal excitability, long-term potentiation and memory.

Dendritic Retraction of Hippocampus

- Induce shrinkage of the apical dendrites of the CA3 and CA1 pyramidal cells and dentate granule cells
- Changes of neuronal morphology likely to contribute to cognitive deficits
- A functional outcome of dendritic retraction is a disturbance of HPA axis regulation, leading to unregulated glucocorticoid release.
- Increased oxidative stress, neuroexcitation, loss of counter-regulatory control

NMDA Receptors

Neurons need to protect themselves from the excitotoxic effect of glutamate by reducing their input surface area.

How Do I Protect the Brain?

European Neuropsychopharmacology (2010) 20, 1–17

ELSEVIER

www.elsevier.com/locate/euroneuro

REVIEW

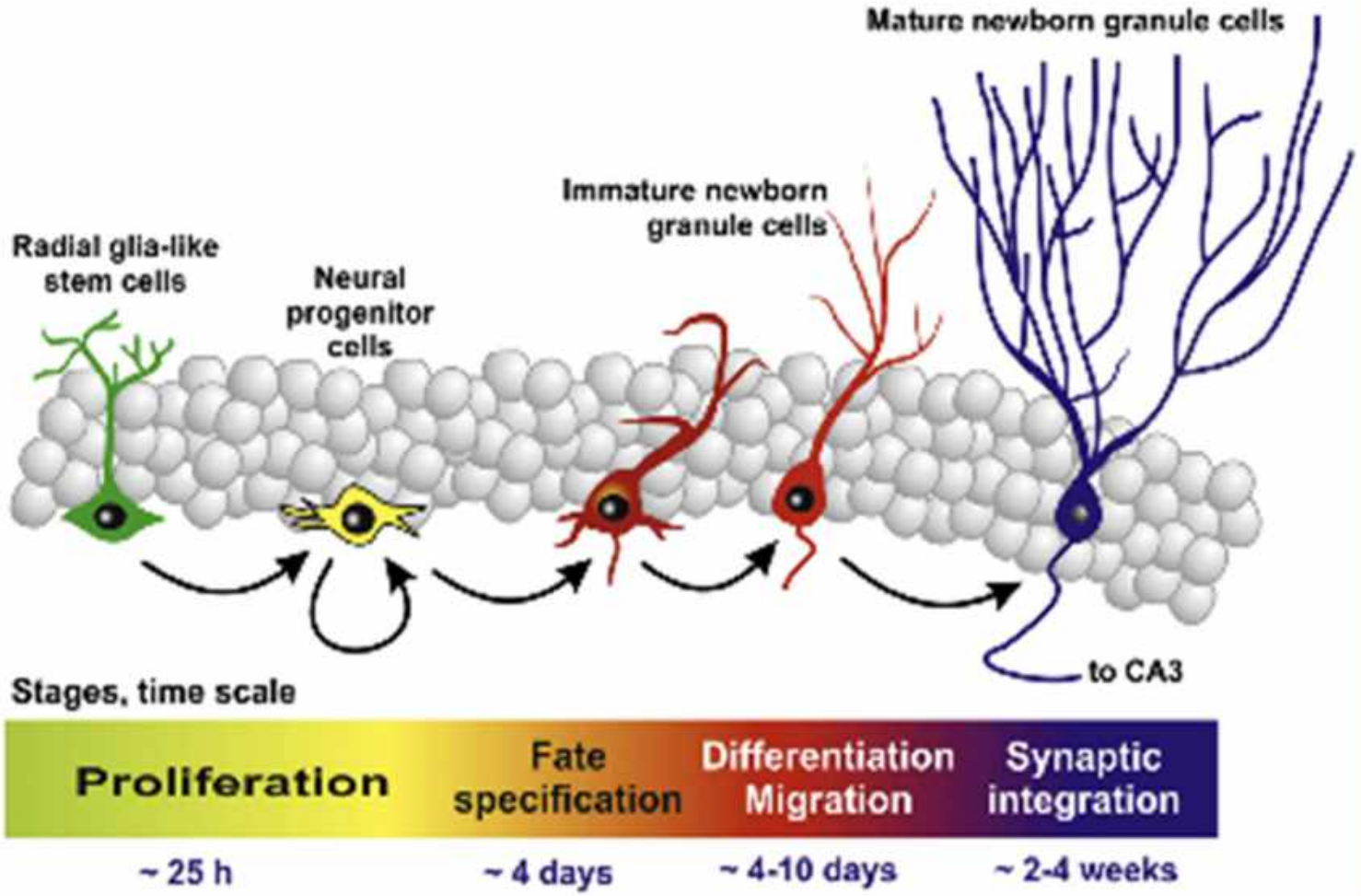
Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: Implications for depression and antidepressant action☆

P.J. Lucassen [a,*], P. Meerlo [b], A.S. Naylor [c,d], A.M. van Dam [e], A.G. Dayer [f], E. Fuchs [g,h], C.A. Oomen [a], B. Czéh [g,i]

Adult Neurogenesis

- Adult neurogenesis refers to the production of new neurons in an adult brain
- Follows a similar complex multi-step process that starts with the proliferation of progenitor cells, followed by their morphological and physiological maturation.
- Ends with a fully functional neuron that is integrated into the pre-existing hippocampal network

Adult Neurogenesis



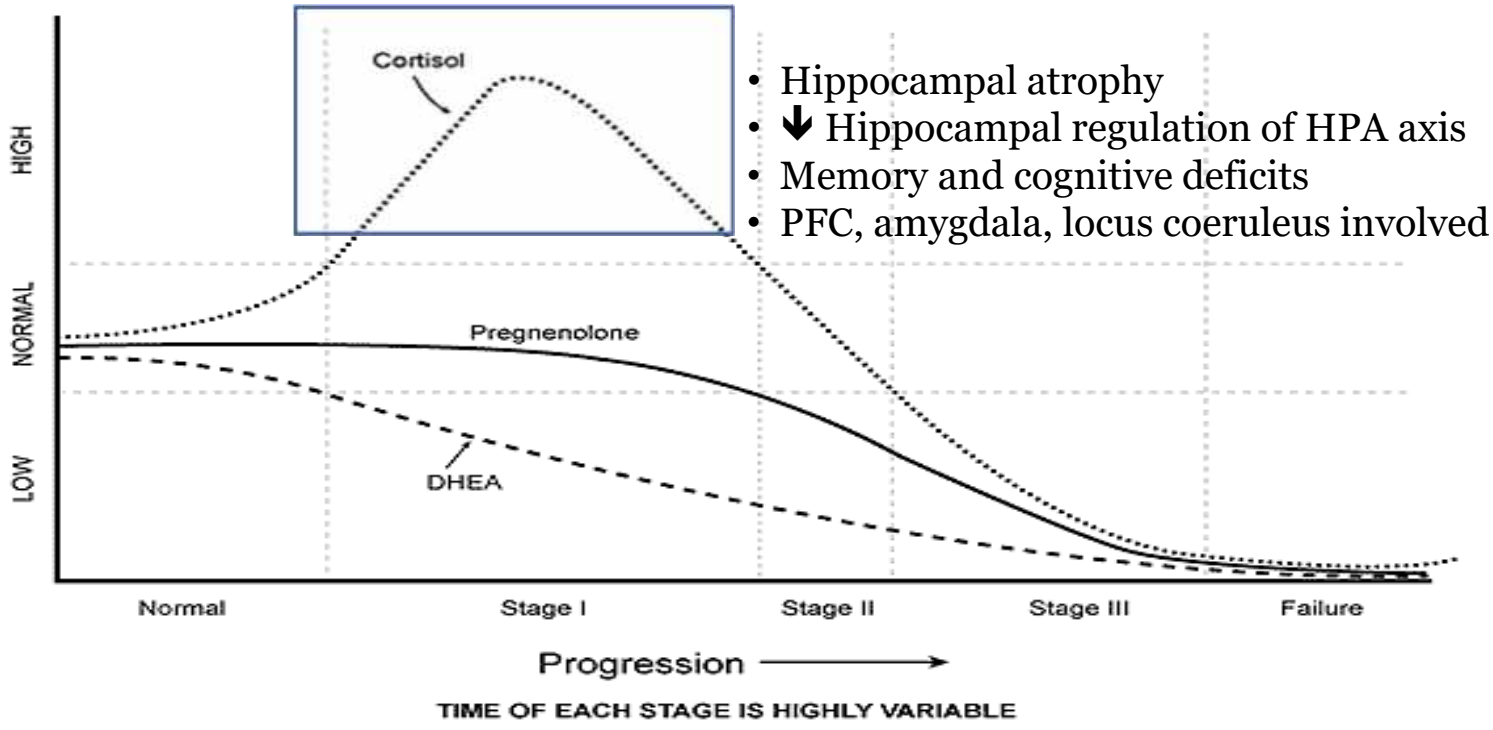
Mediators of Adult Neurogenesis

- Stress and sleep disruption suppress adult neurogenesis
- Stress interferes with all stages of neuronal renewal, and inhibits both proliferation and survival.
- **Glucocorticoid** and **NMDA** receptors have been identified on progenitor cells.
- *Lasting inhibition of AN* occurs after an initial stressor, despite later normalization of cortisol.

Neurodegeneration

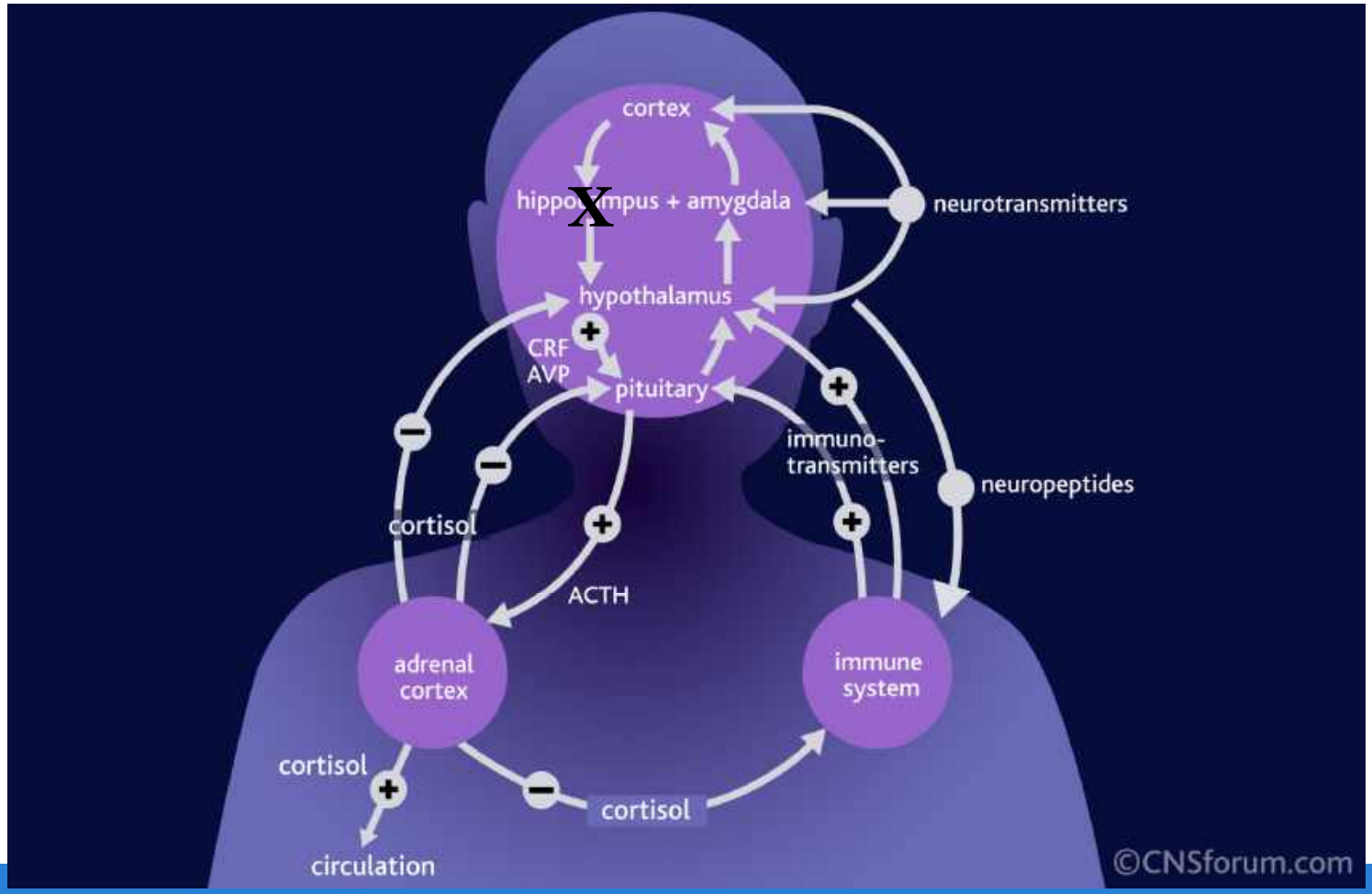
Adult Neurogenesis

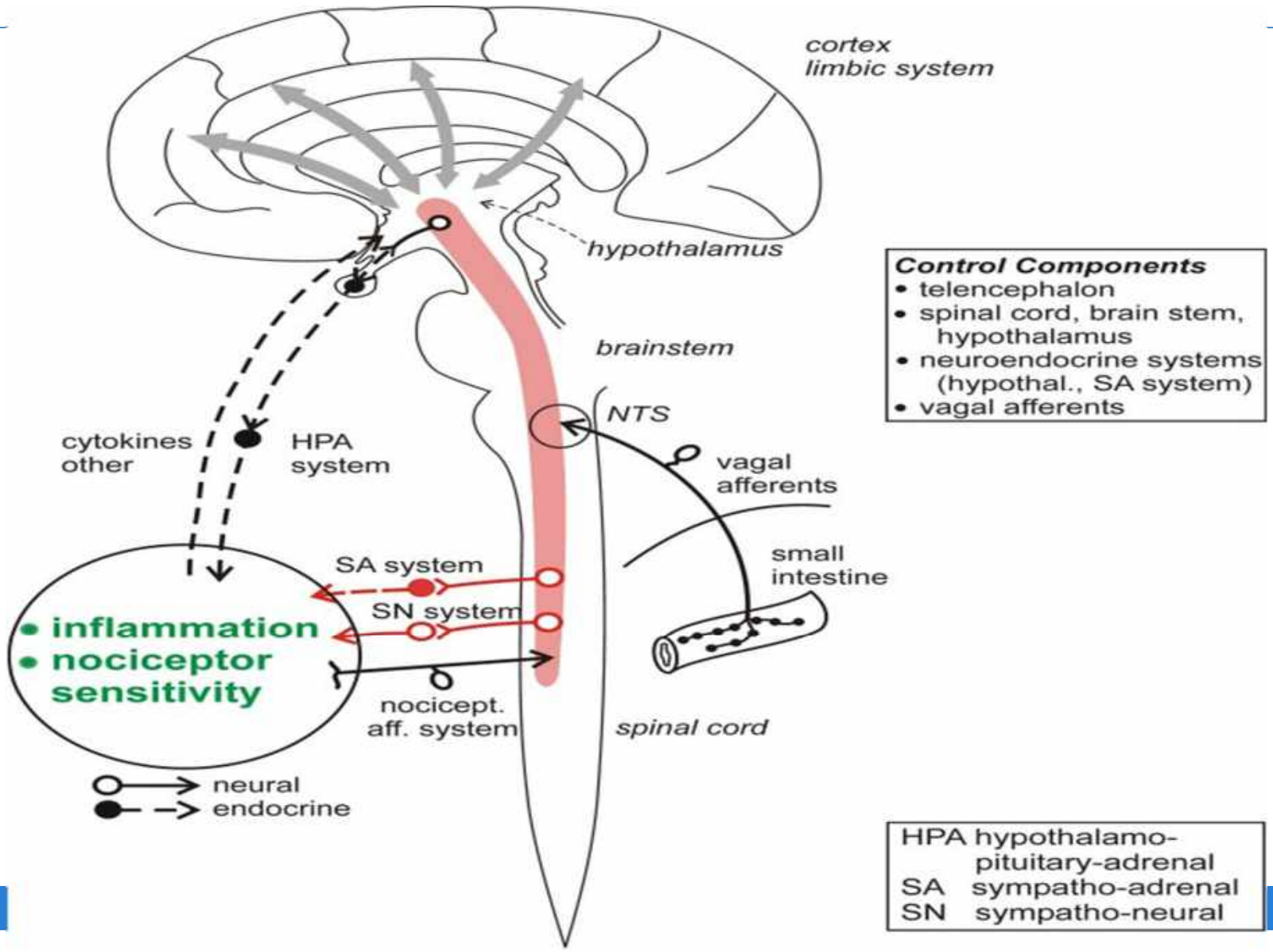
Progression of Stages of Adrenal Exhaustion

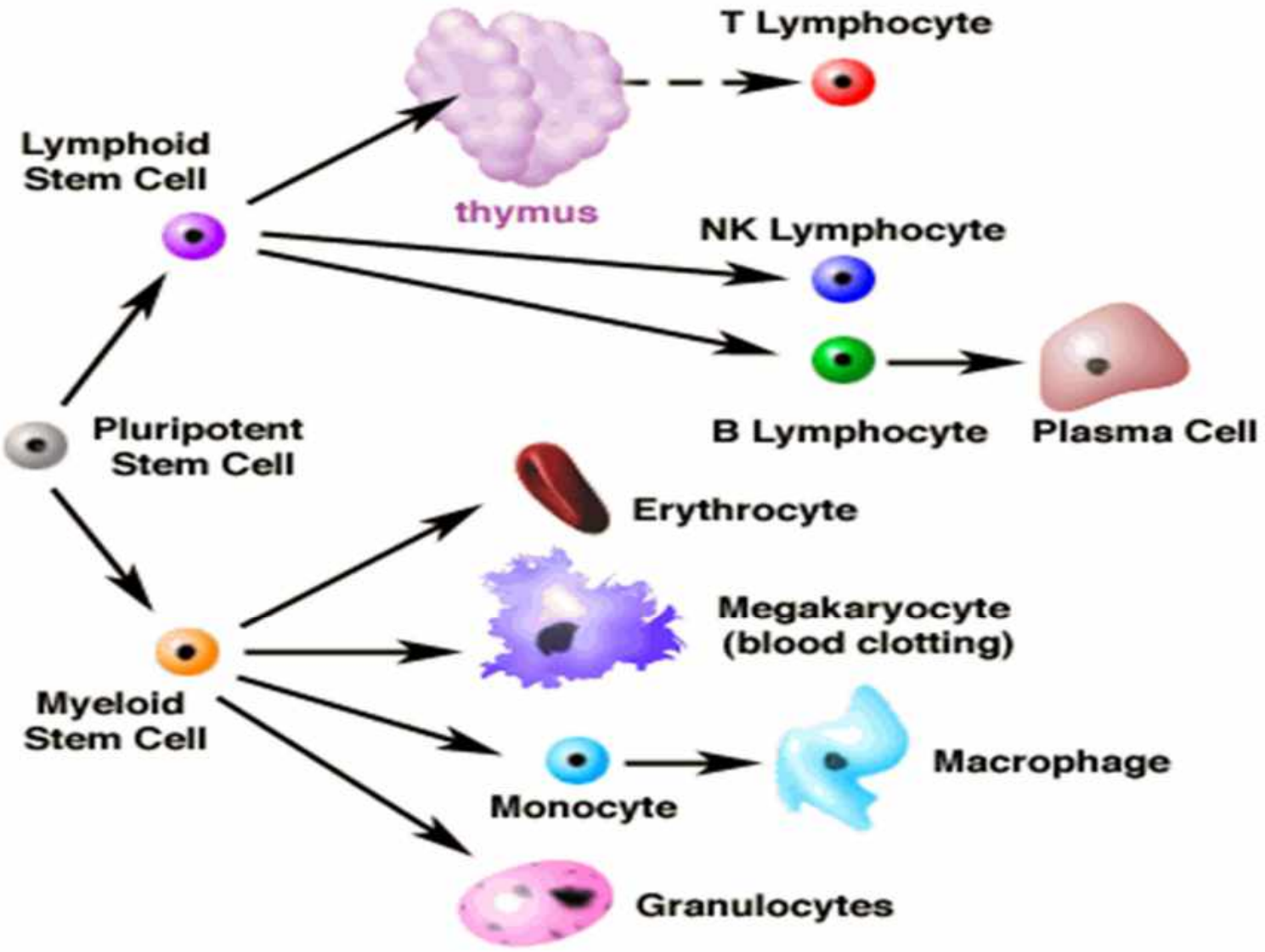


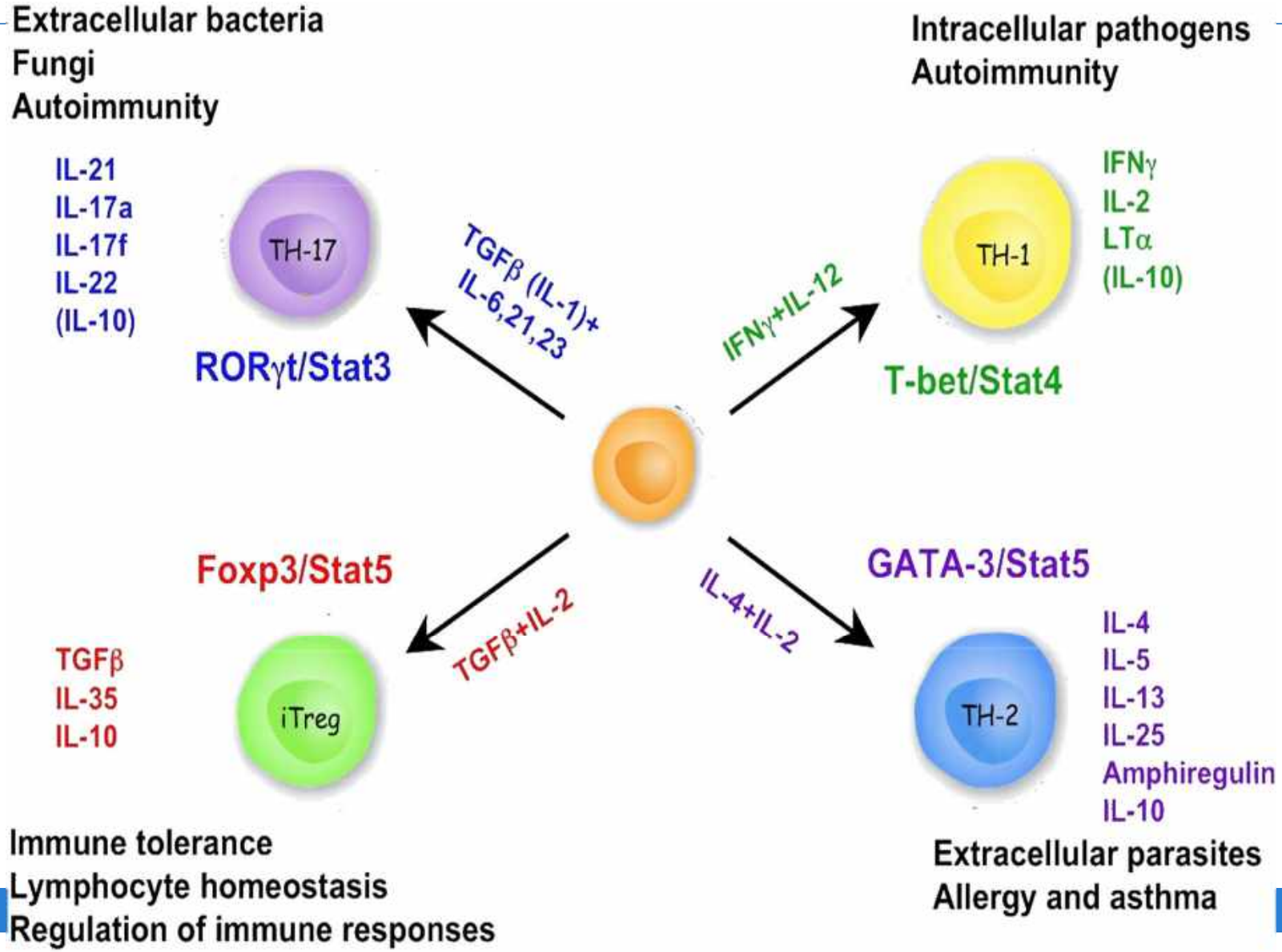
- Hippocampal atrophy
- ↓ Hippocampal regulation of HPA axis
- Memory and cognitive deficits
- PFC, amygdala, locus coeruleus involved

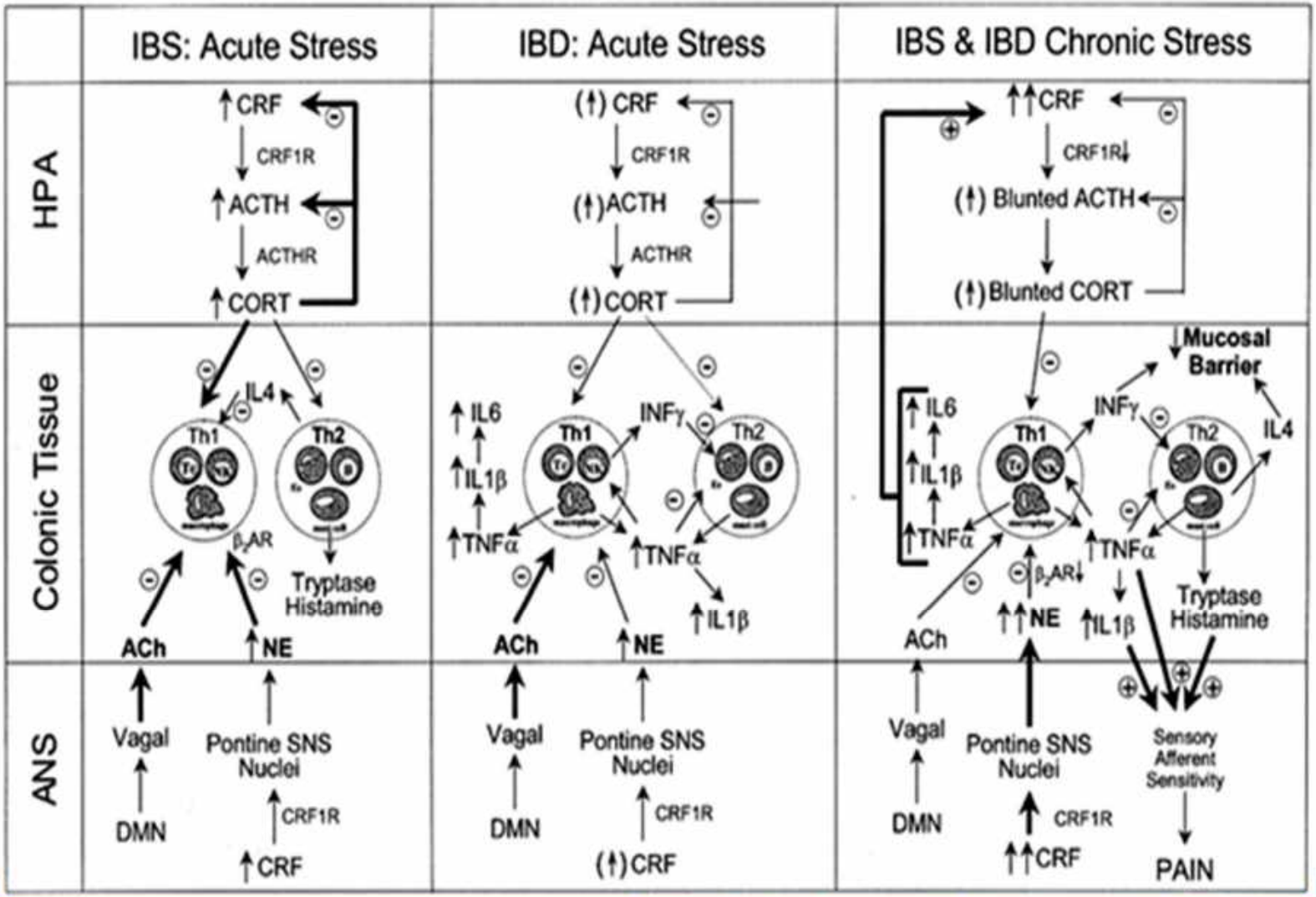
The HPA Axis


cortex
hippocampus + amygdala
neurotransmitters
hypothalamus
CRF
AVP
pituitary
immuno-
transmitters
neuropeptides
cortisol
ACTH
adrenal
cortex
immune
system
cortisol
cortisol
circulation
©CNSforum.com


cortex
limbic system
hypothalamus
brainstem
NTS
vagal
afferents
small
intestine
cytokines
other
HPA
system
SA system
SN system
• inflammation
• nociceptor
sensitivity
nocicept.
aff. system
spinal cord
neural
endocrine
Control Components
• telencephalon
• spinal cord, brain stem, hypothalamus
• neuroendocrine systems (hypothal., SA system)
• vagal afferents
HPA hypothalamo-pituitary-adrenal
SA sympatho-adrenal
SN sympatho-neural


T Lymphocyte
Lymphoid
Stem Cell
thymus
NK Lymphocyte
B Lymphocyte
Plasma Cell
Pluripotent
Stem Cell
Erythrocyte
Megakaryocyte
(blood clotting)
Myeloid
Stem Cell
Monocyte
Macrophage
Granulocytes


Extracellular bacteria
Fungi
Autoimmunity
IL-21
IL-17a
IL-17f
IL-22
(IL-10)
TH-17
RORγt/Stat3
TGFβ (IL-1)+
IL-6,21,23
IFNγ+IL-12
Intracellular pathogens
Autoimmunity
TH-1
IFNγ
IL-2
LTα
(IL-10)
T-bet/Stat4
Foxp3/Stat5
TGFβ+IL-2
TGFβ
IL-35
IL-10
iTreg
IL-4+IL-2
GATA-3/Stat5
TH-2
IL-4
IL-5
IL-13
IL-25
Amphiregulin
IL-10
Immune tolerance
Lymphocyte homeostasis
Regulation of immune responses
Extracellular parasites
Allergy and asthma

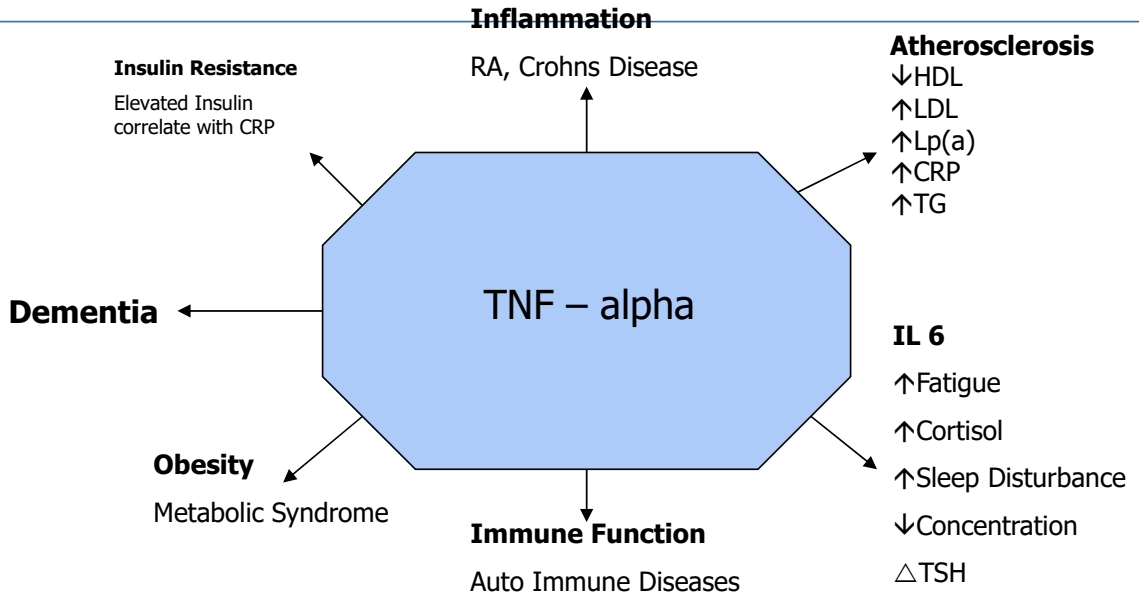


Source: Curr Opin Gastroenterol © 2003 Lippincott Williams & Wilkins

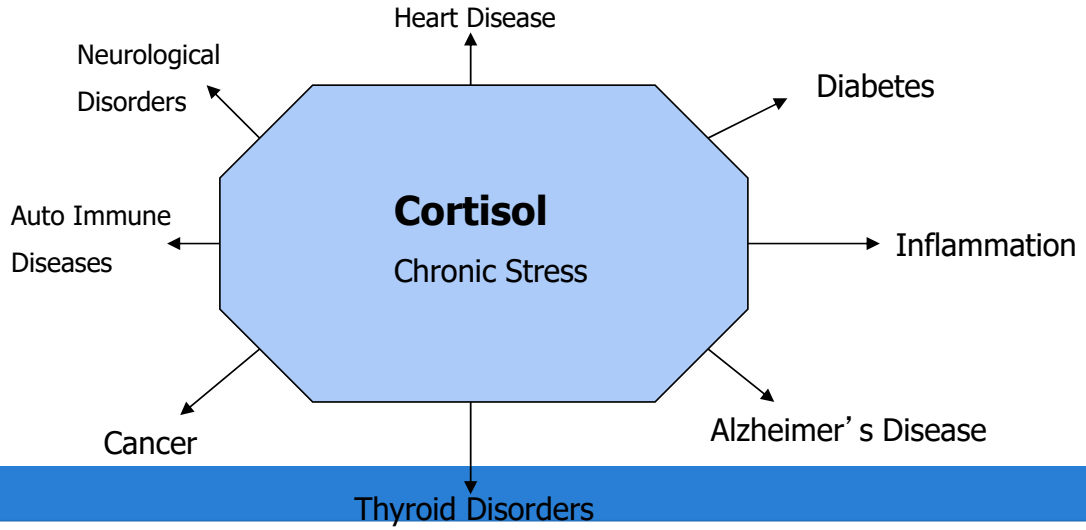
Stress, Immune System and Acquired Immunity

- IBS
  - Stress increases HPA axis, and both branches of the ANS
  - Cortisol, NE, Ach inhibit the mucosal immune system, especially Th1-type responses.
  - Shift toward Th2 cytokine responses (IL-4) that can further inhibit Th1 responses.
- IBD
  - CRF response blunted, leading to diminished Cortisol and NE release.
  - Favor production of Th1 cytokines and proliferation of macrophages, natural killer (NK) cells, and cytotoxic T cells (Tc).
  - TNF stimulates IL-1 (Th1 pathway) and IL-6 (by lymphoid and nonlymphoid tissues).
- Chronic stress
  - Both types shift to Th1 response.
  - TNF-, IL-1, and IL-6 increase to concentrations that stimulate CRF production
  - Both IFN (Th1 cytokine), produced by NK cells in response to TNF, and IL-4 (a Th2 cytokine)

Inflammation Research

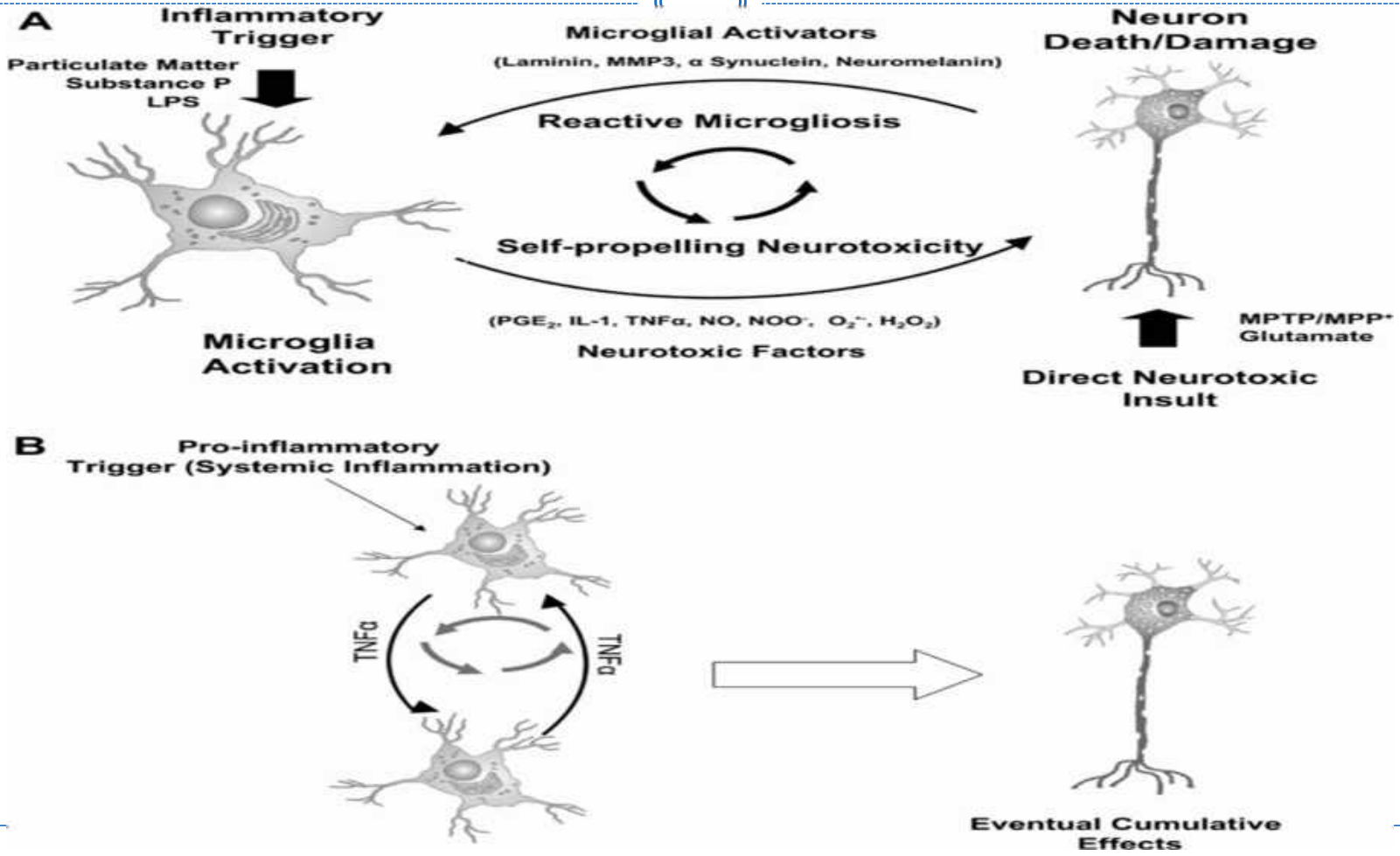


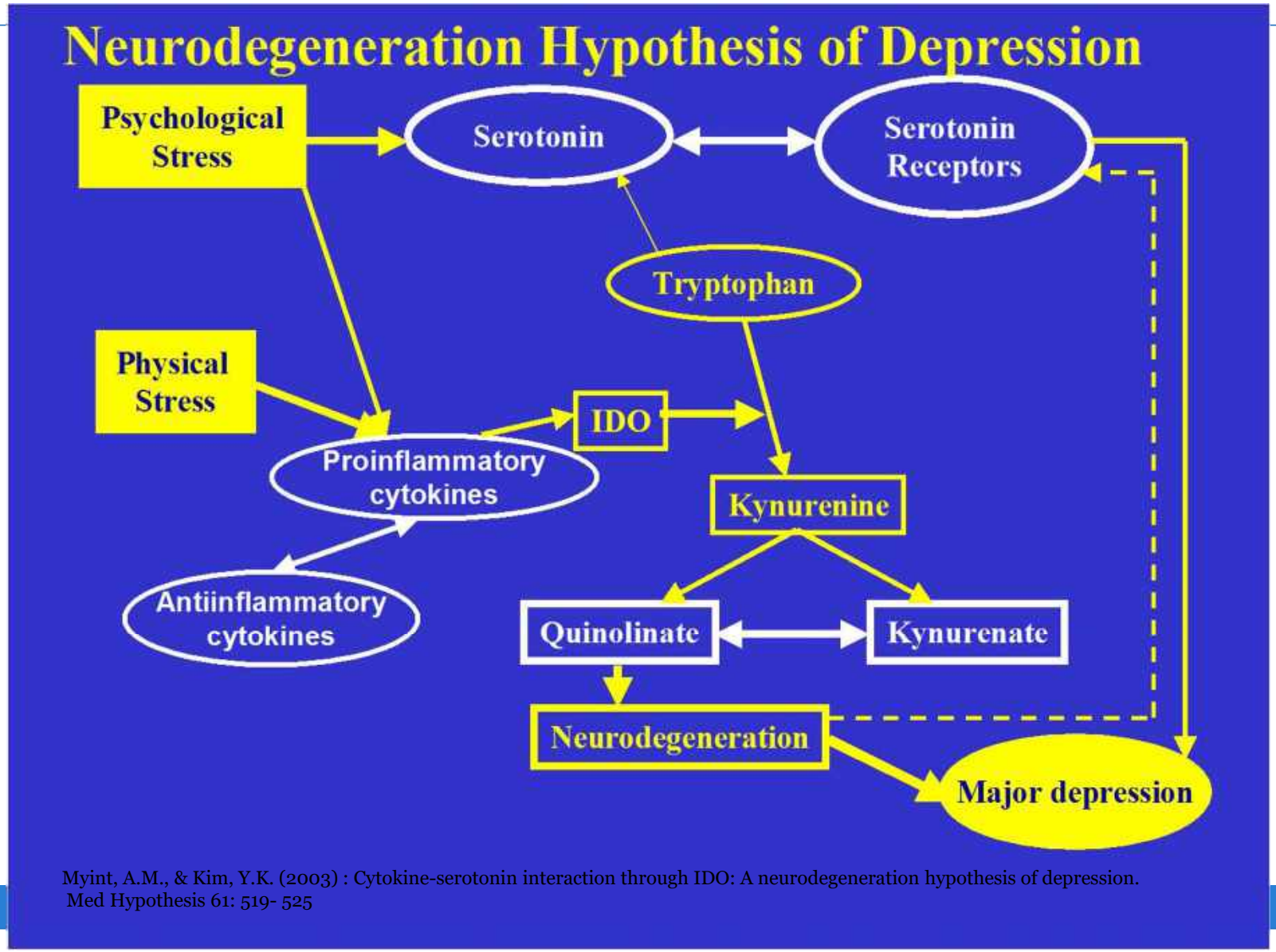
Research Focus



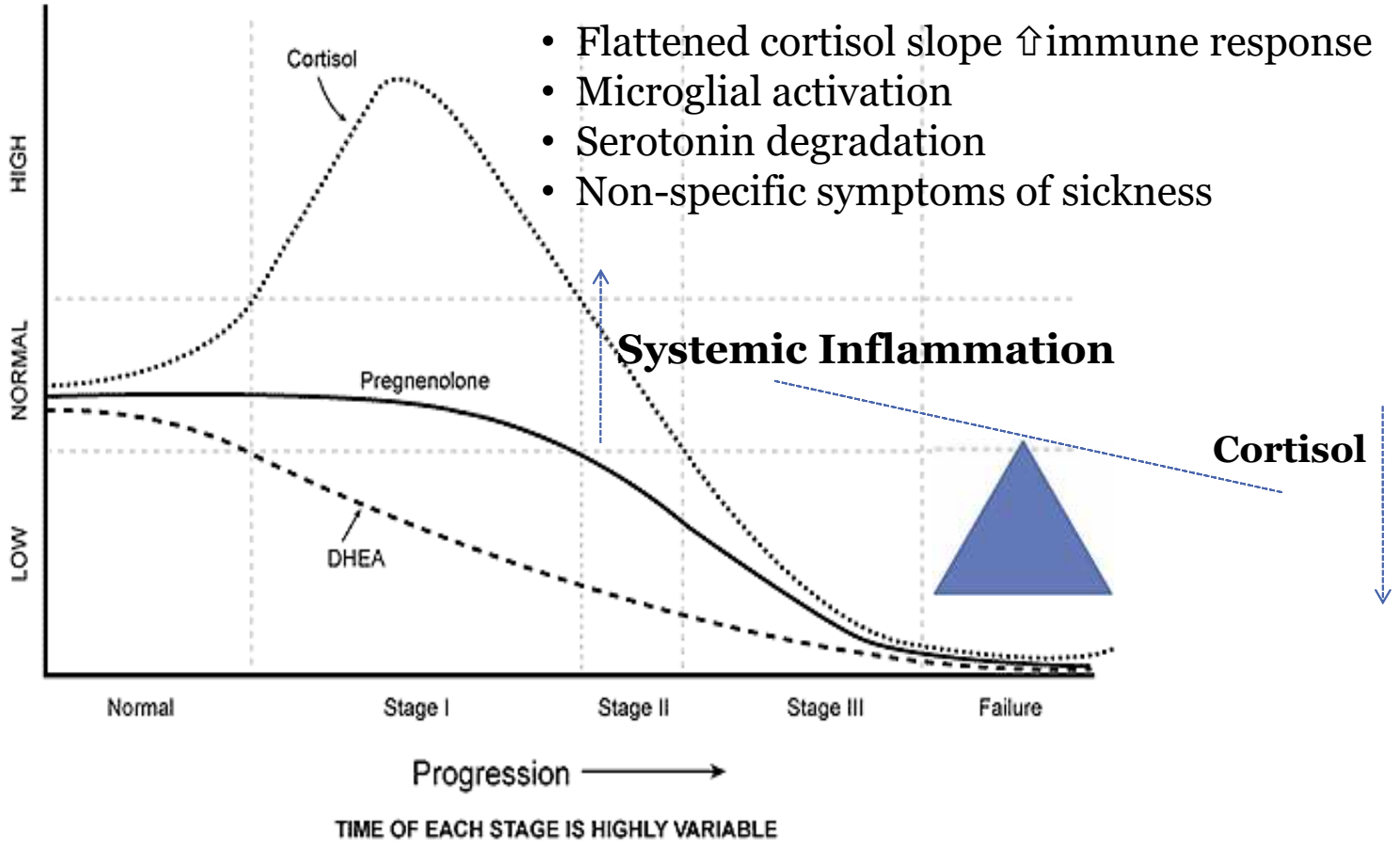
Stress/Anxiety Research

Neuroinflammation: Microglial Cells





Myint, A.M., & Kim, Y.K. (2003) : Cytokine-serotonin interaction through IDO: A neurodegeneration hypothesis of depression. Med Hypothesis 61: 519- 525



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

Systemic Inflammation

Cortisol

A new view on hypocortisolism

Eva Fries, Judith Hesse, Juliane Hellhammer, Dirk H. Hellhammer*

Department for Psychobiology, University of Trier, Johanniterufer 15, 54290 Trier, Germany

Received 18 November 2004; received in revised form 6 April 2005; accepted 6 April 2005

KEYWORDS
Hypocortisolism;
Cortisol;
Allostatic load index;

Summary Low cortisol levels have been observed in patients with different stress-related disorders such as chronic fatigue syndrome, fibromyalgia, and post-traumatic stress disorder. Data suggest that these disorders are characterized by a symptom triad of enhanced stress sensitivity, pain, and fatigue. This overview will

Raison and Miller (2003) assume that prolonged or repeated exposure to immune stimuli might predispose an individual to reduced glucocorticoid signaling as a means of freeing bodily defenses from inhibitory control in the face of an ongoing infectious threat. Thus, an enhanced release of

A new view on hypocortisolism

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may be beneficial for health and survival. Most strikingly, the demonstration of a low allostatic load index in hypocortisolemic subjects suggests that a down-regulation of the HPA axis in chronically stressed subjects protects those subjects against the harmful effects of a high allostatic load index.

Key Points

- Models of Hypocortisolism
  - Developmental Model
  - Immune mediated
- Prolonged cortisol production is neurotoxic
- Reciprocal relationship between immune system and HPA axis

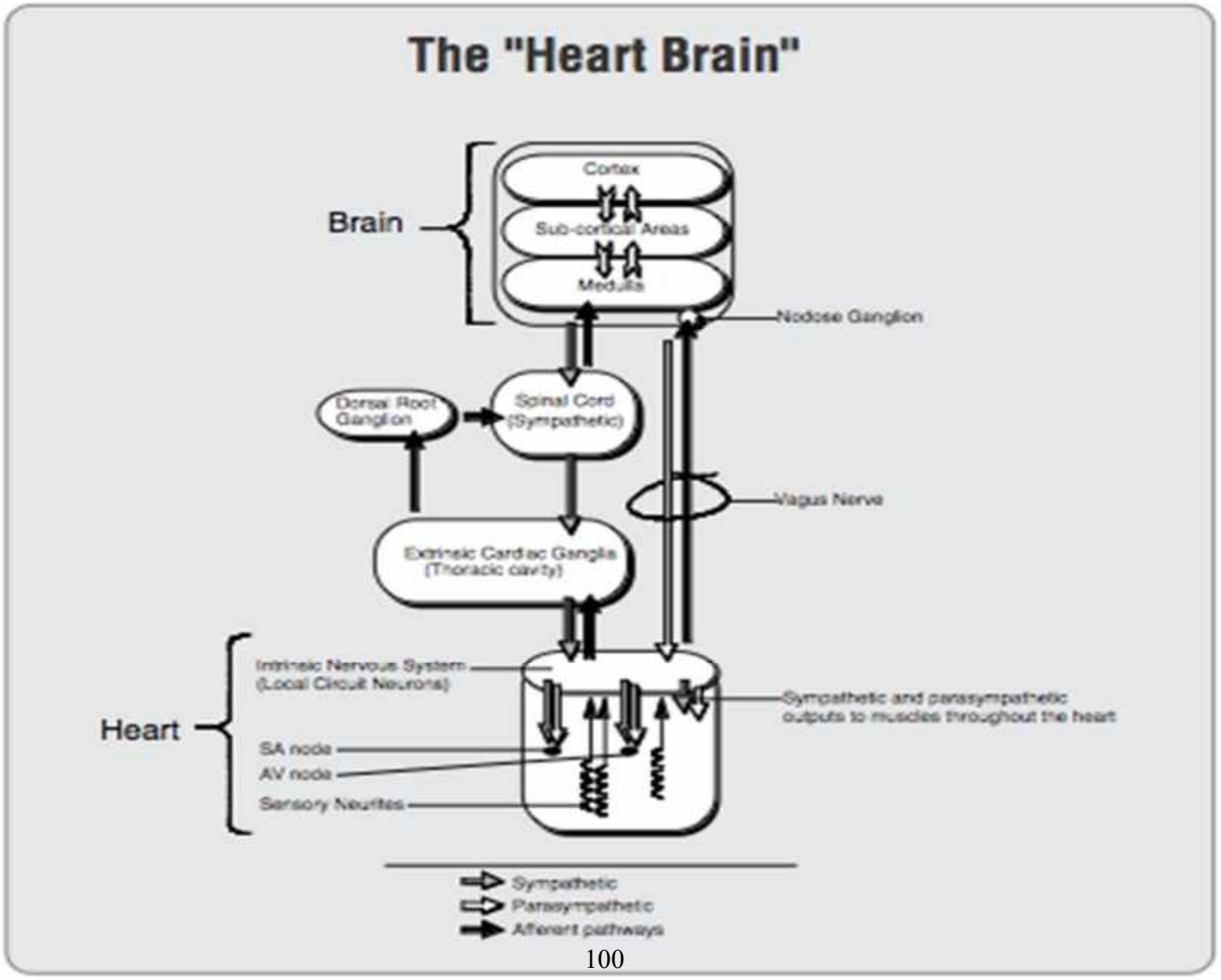
Hypocortisolism may be an adaptive mechanism to liberate the immune system or protect the nervous system

Stress, Emotions and the Heart

- New field of research - neurocardiology
- Demonstrates bidirectional information between CNS and Heart
- Mediated by lung function and peripheral nervous system
- Keys concepts: Resting Heart Rate and Heart Rate Variability

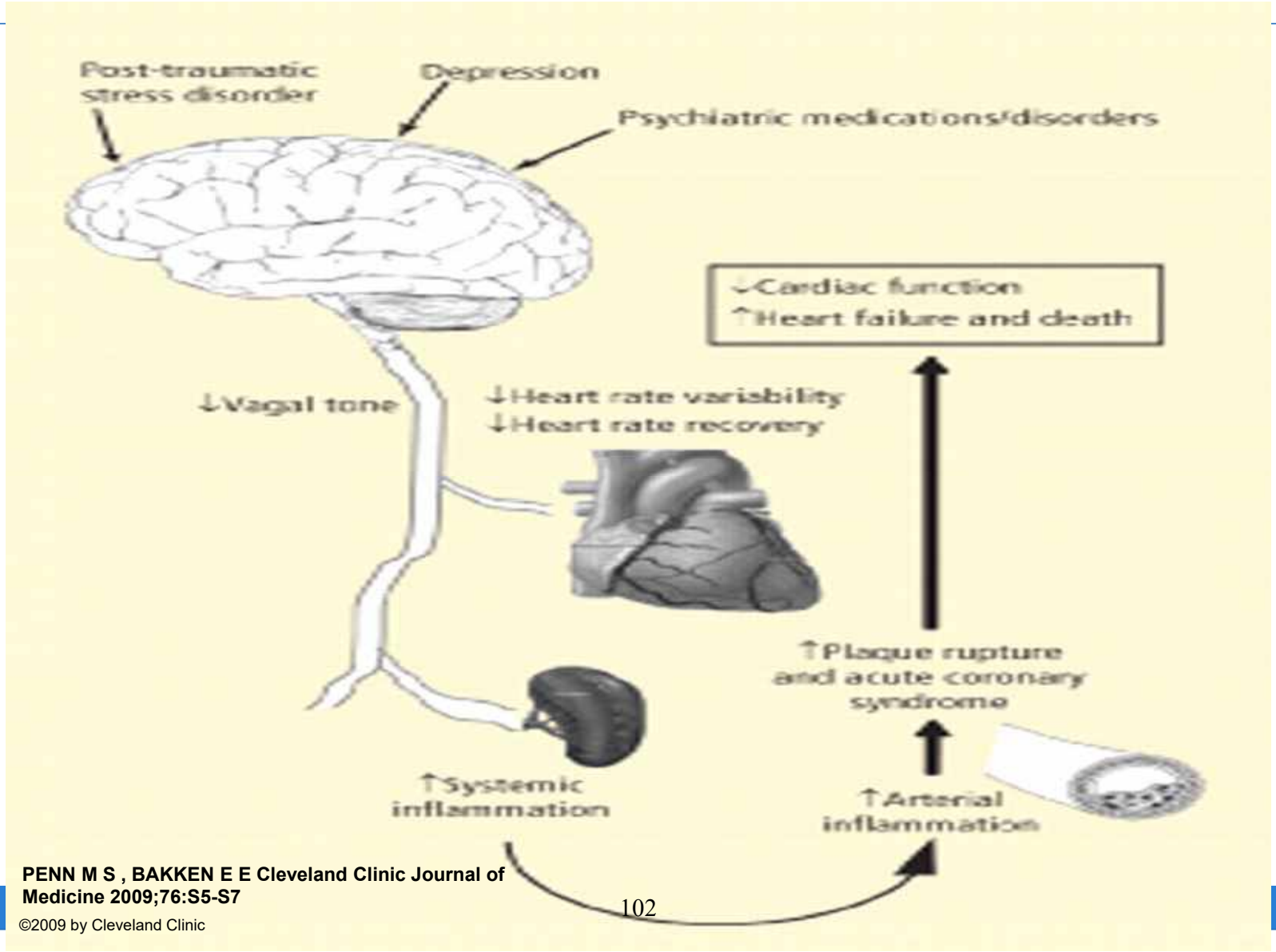
The heart communicates with the brain and body in four ways:

- *Neurological communication* (nervous system)
- *Biophysical communication* (pulse wave)
- *Biochemical communication* (hormones)
- *Energetic communication* (electromagnetic fields)


The "Heart Brain"
Brain
Cortex
Sub-cortical Areas
Medulla
Nodose Ganglion
Dorsal Root Ganglion
Spinal Cord (Sympathetic)
Vagus Nerve
Extrinsic Cardiac Ganglia (Thoracic cavity)
Heart
Intrinsic Nervous System (Local Circuit Neurons)
Sympathetic and parasympathetic outputs to muscles throughout the heart
SA node
AV node
Sensory Neurites
Sympathetic
Parasympathetic
Afferent pathways

Sympathetic Overdrive

- Imbalance between sympathetic and parasympathetic nervous systems
- Direct innervation of sinus node
- Increased SNS due to affective disorders, chronic stress, neuroinflammation
- Leads to elevation in resting heart rate (RHR)



PENN M S , BAKKEN E E Cleveland Clinic Journal of Medicine 2009;76:S5-S7

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Mood and Heart Disease

- Up to 60% of patients with an acute coronary event experience symptoms of depression within the 12 months following the event
- Depression following acute MI doubles risk of mortality in the months following the acute event.
- Just having symptoms of depression at various times in the course of CHD doubles the risk of death, and that clinical depression is associated with an even higher risk.

- *Separate studies showed that the risk of developing heart disease is significantly increased for people who impulsively vent their anger as well as for those who tend to repress angry feelings.*

A. Siegman et al. J Behav Med. 1998; 21(4)
D. Carroll et al. J Epidemiol Comm Health. 1998; Sept.

Mood and Heart Disease

- Depression linked to:
  - reduced adherence to treatment regimens
  - increased prevalence of smoking and diabetes
  - platelet dysfunction and coagulant processes
  - inflammatory processes
  - alterations in HPA axis
  - Autonomic nervous system (ANS) dysfunction
  - increased inflammation and plaque rupture
- Depression ➔ ⇩vagal tone➔ ⇧inflammation and coagulation

Mood and Vagal Tone

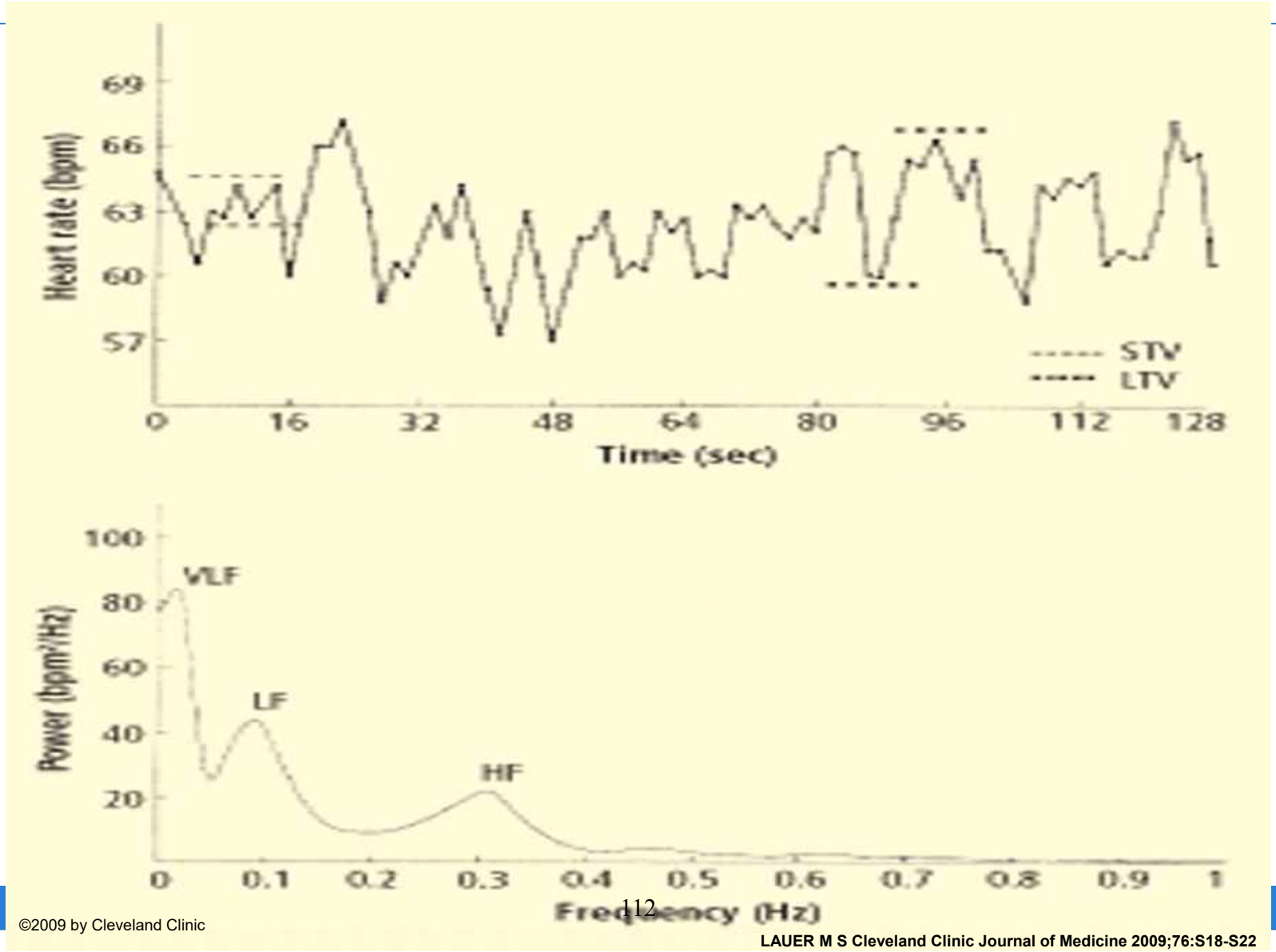
- Increased IL-6 and TNFα
- Increased CRP
- Increased Fibrinogen
- Increased Resting Heart Rate
- Decreased Heart Rate Variability

Resting Heart Rate

- Remarkably strong association between heart rate and survival, an association that transcends species.
- Small mammals that have rapid heart rates have short life expectancies.
- Larger mammals that have slower heart rates have correspondingly higher life expectancies.
- Among nearly all mammals, life expectancy is close to 2 billion heartbeats.
- Investigators have been able to increase survival in animal models by deliberate slowing of heart rate.

Heart Rate Variability

- Even before the ECG, it was known that heart rate normally varies with respiration.
- The heart rate accelerates with inhalation and decelerates with exhalation.
- Physiologic respiratory sinus arrhythmia (RSA) can be demonstrated by plotting heart rate over time in resting supine subjects.



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LAUER M S Cleveland Clinic Journal of Medicine 2009;76:S18-S22

Heart Rate Variability

- Decreased HRV linked to cardiac events and mortality.
- Among healthy elderly subjects enrolled in the Framingham Heart Study, decreased HRV associated with increased major cardiac events.

Decreased Vagal tone and HRV

- Obesity
- Insulin resistance and diabetes
- Hypertension
- Hypercholesterolemia
- Depression and anxiety
- Heart failure
- Peripheral vascular disease

HPA dysregulation and Cancer

Flattened cortisol rhythms in metastatic breast cancer patients

Heather C. Abercrombie[a,*], Janine Giese-Davis[b], Sandra Sephton[c], Elissa S. Epel[d], Julie M. Turner-Cobb[e], David Spiegel[b]

[a]Department of Psychiatry, University of Wisconsin Medical School, 6001 Research Park Blvd., Madison, WI 53719, USA
[b]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305-5718, USA
[c]J.G. Brown Cancer Center, Department of Psychiatry and Behavioural Sciences, University of Louisville School of Medicine, 500 South Preston Street, Room 210, Louisville, KY 40202, USA
[d]Department of Psychiatry, Health Psychology Program, University of California, 3333 California Street, Suite 465, San Francisco, CA 94143, USA
[e]Department of Psychology, University of Bath, Claverton Down, Bath BA2 7AY, UK

Received 19 June 2003; received in revised form 7 November 2003; accepted 8 November 2003

Hypocortisolism, IL-6, and Breast Cancer

Inflammatory responses to psychological stress in fatigued breast cancer survivors: Relationship to glucocorticoids

Julienne E. Bower [a,b,c,*], Patricia A. Ganz [c,d], Najib Aziz [e], Richard Olmstead [a], Michael R. Irwin [a,b], Steve W. Cole [a,f]

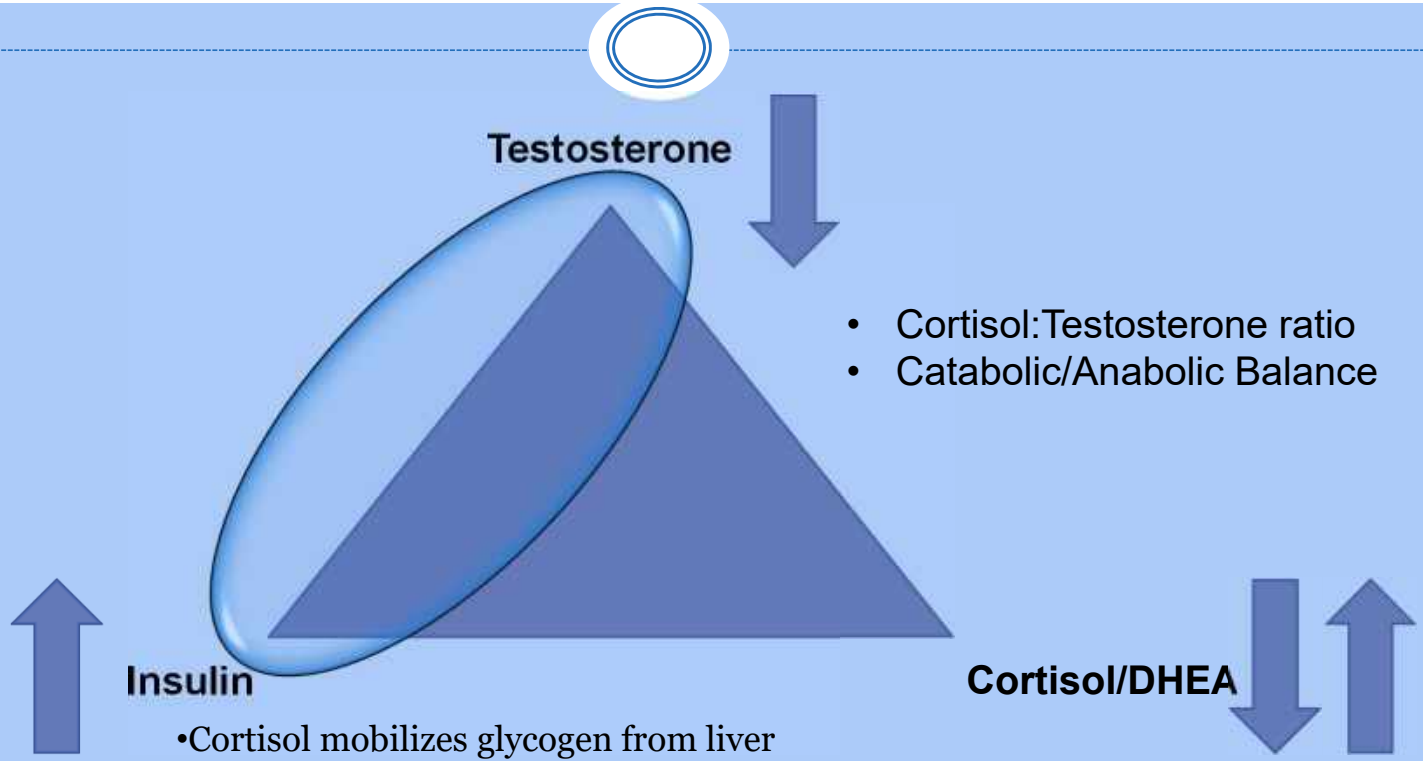
[a] Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience at UCLA, 300 UCLA Medical Plaza, Room 3306, Box 957076 Los Angeles, CA 90095-7076, USA
[b] Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, USA
[c] Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center at UCLA, USA
[d] UCLA Schools of Medicine and Public Health, USA
[e] UCLA Department of Pathology and Laboratory Medicine, USA
[f] UCLA Department of Medicine, USA

Received 15 December 2005; received in revised form 4 August 2006; accepted 6 August 2006
Available online 27 September 2006

Abstract

Fatigue is a common problem following cancer treatment and our previous studies suggest that a chronic inflammatory process might contribute to cancer-related fatigue. However, immune responses to challenge have not yet been evaluated among individuals with can-

To Make Matters Worse: Multiple Hormonal Shifts



- Cortisol:Testosterone ratio
- Catabolic/Anabolic Balance

•Cortisol mobilizes glycogen from liver
•Cortisol decreases insulin sensitivity
•Cortisol increases TNF alpha directly

Journal of Internal Medicine 2003; **254**: 386–390

A 5-year follow-up study of disease incidence in men with an abnormal hormone pattern

R. ROSMOND[1], S. WALLERIUS[1], P. WANGER[2], L. MARTIN[2], G. HOLM[1] & P. BJÖRNTORP[1]
From the [1]Cardiovascular Institute, Sahlgrenska University Hospital, Göteborg; and [2]Department of Clinical Sciences, Huddinge University Hospital, Huddinge; Sweden

Abstract. Rosmond R, Wallerius S, Wanger P, Martin L, Holm G, Björntorp P (The Cardiovascular Institute, Sahlgrenska University Hospital, Göteborg; and Huddinge University Hospital, Huddinge; Sweden). A 5-year follow-up study of disease incidence in men with an abnormal hormone pattern. *J Intern Med* 2003; **254**: 386–390.

Objectives. Previous studies have suggested that abnormal levels of cortisol and testosterone might increase the risk of serious somatic diseases. To test this hypothesis, we conducted a 5-year follow-up study in middle-aged men.

Methods. A population-based cohort study conducted in 1995 amongst 141 Swedish men born in 1944, in whom a clinical examination supplemented by medical history aimed to disclose the presence of cardiovascular disease (CVD) (myocardial infarction, angina pectoris, stroke), type 2 diabetes and hypertension were performed at baseline and at follow-up in the year 2000. In addition, salivary cortisol levels were measured repeatedly over the day. Serum testosterone baseline data, an algorithm was constructed, which classified the secretion pattern of cortisol and testosterone from each individual as being normal or abnormal.

Results. By the end of follow-up, men with an abnormal hormone secretion pattern ($n = 73$) had elevated mean arterial pressure ($P = 0.003$), fasting insulin ($P = 0.009$) and insulin : glucose ratio ($P = 0.005$) compared with men with a normal secretion pattern ($n = 68$). Body mass index, waist circumference, and waist : hip ratio were significantly elevated in both groups. However, the 5-year incidence of CVD, type 2 diabetes, and hypertension were significantly higher ($P < 0.001$) in men with an abnormal neuroendocrine secretory pattern compared to men with a normal pattern.

Conclusions. These data suggest that an abnormal neuroendocrine secretory pattern is prospectively associated with an increased incidence of cardiovascular-related events and type 2 diabetes.

Keywords: blood pressure, cardiovascular disease, cortisol, diabetes, men, prospective, testosterone.

Cortisol, Testosterone, and Coronary Heart Disease

Prospective Evidence From the Caerphilly Study

George Davey Smith, DSc; Yoav Ben-Shlomo, BSc, MBBS, MRCP, FFPHM, PhD; Andrew Beswick, BSc; John Yarnell, MBChB, DPH, MSCM, MD, MFPHM (Ire), FFPHM; Stafford Lightman, MBChB, PhD, FMedSci; Peter Elwood, DSc, MD, FRCP, FFPHM

Background—There is a popular belief that chronic stress causes heart disease through psychoneuroendocrine mechanisms. We have examined whether an elevated circulating cortisol-to-testosterone ratio increases the risk of ischemic heart disease.

Methods and Results—We undertook a prospective cohort study of 2512 men aged 45 to 59 years between 1979 and 1983 from Caerphilly, South Wales, with a mean follow-up of 16.5 years. Subjects underwent a clinical examination, and morning fasting blood samples were taken for analysis of cortisol levels, testosterone levels, and other cardiovascular risk factors. The ratio of cortisol to testosterone showed weak associations with potential confounding factors but strong positive associations with components of the insulin resistance syndrome ($P<0.001$). A positive linear trend was seen across quintiles of cortisol:testosterone ratio for incident ischemic heart disease (age-adjusted OR per z score change in ratio 1.22, 95% CI 1.07 to 1.38, $P=0.003$). This was markedly attenuated after adjustment for components of the insulin resistance syndrome (age-adjusted OR per z score change in ratio 1.10, 95% CI 0.96 to 1.25, $P=0.18$). There was no association between the cortisol:testosterone ratio and other causes of death (age-adjusted hazard ratio 0.99, 95% CI 0.88 to 1.11, $P=0.81$).

Conclusions—This is the first population-based prospective study that has found a specific association between cortisol:testosterone ratio and incident ischemic heart disease, apparently mediated through the insulin resistance syndrome. Whether this reflects the effects of chronic stress, behavioral factors, or genetic influences remains to be determined. (***Circulation***. **2005;112:332-340.**)

Key Words: heart diseases ■ hormones ■ stress

Multiple Factors: Stress Immune Brain Connection

- *Cortisol*
- *NMDA excitation*
- *Reduced neuroplasticity*
- *SNS/PNS imbalance*
- *Th1/Th2 imbalance*
- *Microglial activation*
- *IL-6, TNFα*
- *Gut permeability*
- *IDO elevation*
- *Heart Rate Variability*

Natural Compounds for Support for Stress

- Vitamin C
- B Vitamins
- Calcium
- Magnesium
- Zinc, selenium, copper
- Sodium
- Manganese
- 5-HTP
- Phellodendron/Magnolia
- Phellodendron/Ziziphys
- Valerian
- L-theanine
- Sterolins
- Ginseng
- Rhodiola
- Ashwagandha
- Rg3
- Nicotinamide Riboside
- Phosphorylated Serine
- Holy Basil
- Glandulars

Magnesium

- Participates in 300 enzymatic reactions in the body
- 50% stored in bones, 50% intracellular, trace amounts in blood.
- Serum measures less accurate than intracellular Mg (Alon, 2006)
- Occurs in 13.5 to 47.7% among NIDDM patients
- Contributing factors include:
  - Poor diet
  - Autonomic dysfunction
  - Altered insulin metabolism
- Also linked to:
  - CAD
  - HTN
  - Arryhthmias
  - DM retinopathy, neuropathy, nephropathy
    - Pham, 2007

Functions of Magnesium

- Muscle relaxant-Ca channel blocker
- ↓ platelet aggregation
- Thins the blood
- Blocks Ca uptake
- Relaxes blood vessels
- Improves cardiac contractibility which ↑ oxygenation of the heart

Magnesium Repletion

- Studies are mixed for Hypertensiom, IR, and DM with treatment by magnesium
- Many, but not all patients will have a mild lowering of blood pressure
- More recently, in patients with low measured Mg and DM, treatment did produce significant improvements in glucose control. (Guerrero-Romero, 2005)

Magnesium Repletion

300 to 800 mg/day

Better absorbed forms:

Magnesium citrate

Magnesium glycinate

Magnesium taurate

Magnesium malate

Magnesium carbonate and oxide not effective at repleting magnesium status

Phellodendron/Magnolia

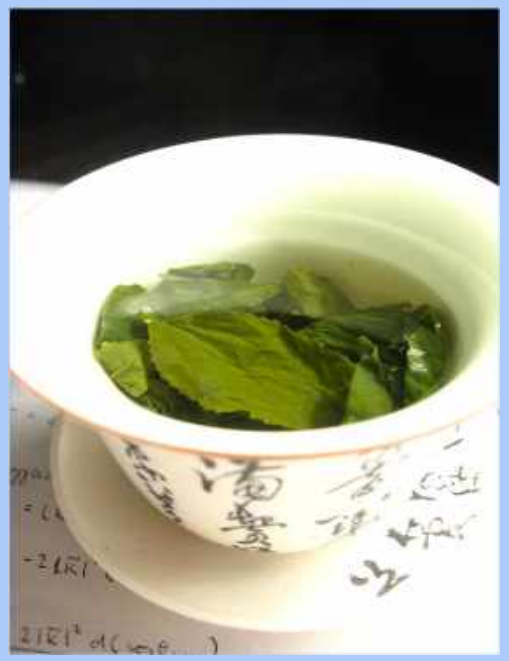
- Combination of magnolia amd phellodendron
- Anti-anxiety and anti-stress properties similar benzodiazapenes, yet non-sedating
- Anti-depressant properties
- Has been shown to normalize high cortisol and DHEA levels
- Low side-effect profile
- Dosage: 1 capsule TID

Phellodendron/Magnolia

- Open Study
  - 200 mg TID for two weeks
  - 50 subjects
  - 227% increase in salivary DHEA
  - 37% reduction in morning salivary cortisol
- RCT (Kalman, 2008)
  - 40 subjects, 6 week trial
  - Improvement in anxiety symptoms
  - No change in cortisol levels

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

Plant Sterolins

- Patented blend of plant sterols and sterolins in a clinically proven ratio of 100:1
- Natural pine source
- Used in Germany for over 30 years

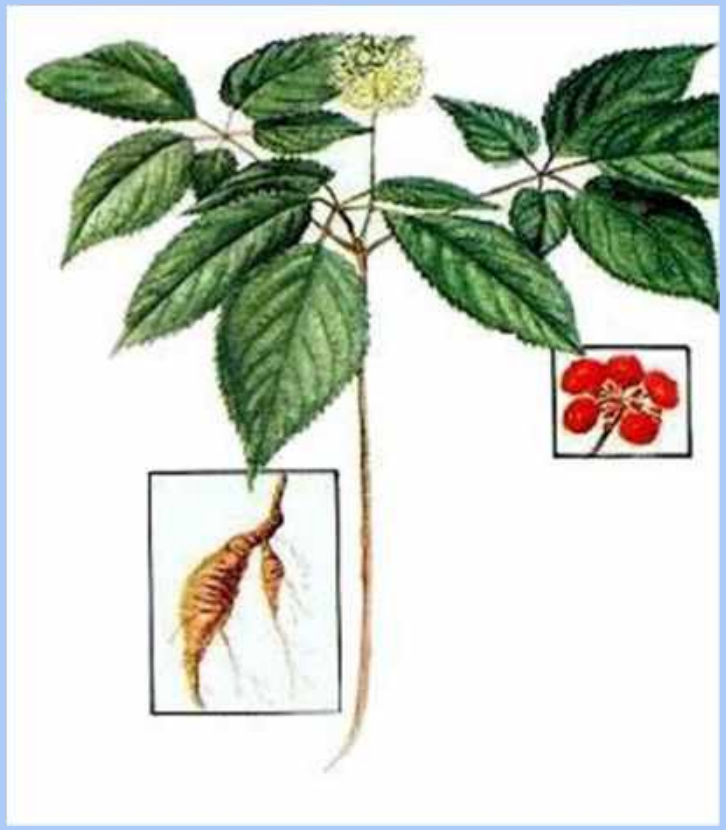
Plant Sterolins

- Immune modulating activity
- Moducare targets the regulatory CD4 helper cells which tell the immune system when to be more active or when to switch off to prevent damage to healthy tissues
- Moducare enhances Natural Killer (NK) cell activity
- Moducare balances TH1 and TH2 cells

Bouic P, et al. Int J Sports Med 1999 May:20(4):258-62

Eleutherococcus senticosus (Siberian Ginseng)

- Eleuthero is sold in the United States as 'Siberian Ginseng'
- The plant is a spiny-stemmed shrub found in northeast Asia and Japan
- Prescribed for medicinal use in France, Germany, Russia, and China.
- The part used - dried roots and root bark.



Eleutherococcus: Traditional Uses

- Adaptogen
- Normalizing blood pressure
- Atherosclerosis
- Pyelonephritis
- Rheumatic heart disease
- Neuroses
- Insomnia
- Alzheimer's disease
- Attention deficit-hyperactivity disorder (ADHD)

Eleutherococcus: Traditional Uses

- Chronic fatigue syndrome
- Diabetes
- Fibromyalgia
- Rheumatoid arthritis
- Influenza, chronic bronchitis
- Reducing toxicity of chemotherapy
- Herpes simplex type II infections
- Preventing colds and flu.

Eleutherococcus: Active Constituents

- Eleutherosides A-M.
- Ciwujianosides (minor saponins)
- Eleutherans (polysaccharides)
- Beta sitosterol
- Isofraxidin (a coumarin derivative)
- Syringin
- Lignans

Eleutherococcus: Mechanism of Action

- Adaptogen
  - Harmless to the host
  - General, nonspecific, effect
  - Increases resistance to a variety of physical, chemical, or biological stressors
  - Acts as a general stabilizer/normalize
- Immunomodulatory effects.
  - Increases natural killer cells
  - Inhibits replication of RNA viruses
  - Induced and enhanced IL- 1 and IL-6

Eleutherococcus: Mechanism of Action

- Anti-inflammatory and neuroprotective effects.
- Prevents bone resorption during experimental, steroid-induced osteoporosis
- Protection against experimentally-induced fulminant hepatic failure
- Radioprotection of the hematopoietic system in mice exposed to lethal radiation
- Inhibition of histamine release from rat peritoneal cells, and inhibition of systemic anaphylaxis in rats.
- Increases the concentration of biogenic amines (noradrenalin and dopamine) in the rat brain.
- Induces apoptosis in human stomach cancer KATO III cells.

Eleutherococcus and Endurance

- Runners given either 2 mL (n=34) or 4 mL (n=33) of the extract 30 minutes before participating in a 10-kilometer race. (Halstead, 1984)
  - Completed the race in an average time of 48.7 minutes and 45 minutes, respectively, compared to 52.6 minutes for the control group.
- Nine endurance cyclists, 1,200 mg of a crude extract was taken daily for seven days prior to a simulated 10kilometer time trial.
  - Supplementation did not significantly alter the physiological responses of the athletes . (Esbach, 2000)

Eleutherococcus and Chronic Stress

- In a double-blind study, 45 healthy volunteers (Fachinetti, 2002)
  - Received two vials of Eleutherococcus senticosus or placebo for 30 days.
  - Patients subject to the Stroop Colour-Word to assess stress response, along with heart rate, and systolic and diastolic blood pressure, before and after treatment.
- Treatment group - 40-percent reduction in heart rate response to the Stroop CW stressor.
- In females - accounted for a 60 percent reduction in systolic blood pressure response to the cognitive challenge test.

Eleutherococcus and Immune System

- Siberian ginseng extract, standardized to contain eleutheroside 0.3% (Elagen), orally seems to reduce the frequency, severity, and duration of herpes simplex type II infections.
- Combination product containing Siberian ginseng plus andrographis orally significantly improves symptoms of the common cold when started within 72 hours of symptom onset.
  - Some symptoms improve after 2 days of treatment.
  - Typically takes 4-5 days of treatment before maximal relief

Eleutherococcus Dosing

- Common cold (Kan Jang, Swedish Herbal Institute) 400 mg three times daily.
- For herpes simplex type II infections 400 mg/day

Eleutherococcus Cautions

- Use with caution in individuals on hypoglycemic/ cardiac or hypo/hypertensive medications (may alter effects of these medications
- Should not be taken in high doses during acute phases of infection, especially when accompanied by a high fever
- Reports of hypertension, insomnia, irritability, anxiety and tachycardia in rare instances

Eleutherococcus Cautions

- False elevation/depression with measured digoxin therapy

Source: S. McRae, "Elevated Serum Digoxin Levels in a Patient Taking Digoxin and Siberian Ginseng," CMAJ 155(3) (Aug1996) : 293-95.

Rhodiola Rosea (Rhodiola)

- Plant in the Crassulaceae family that grows in cold regions of the world
- Also known as goldenor ‘arctic’ root, has been used for centuries to cope with the cold Siberian climate.

Rhodiola: Traditional Uses

- Energy
- Stamina
- Mood
- Sexual function
- Arrhythmias
- Hyperlipidemia
- Cancer
- Diabetes
- Cold and flu

Rhodiola: Mechanism of Action

- Contains over 30 compounds including phenlyethanoids, phenylpropanoids, flavonoids, cyanoglycosides, monoterpenes, and triterpenes.
- Salidroside and rosavin is thought to be responsible for many of the stimulant or "adaptogenic" effects of roseroot

Rhodiola rosea

- “Second generation” plant adaptogen- similar to the effects of ginseng
- Studied and used in Russia for over 30 years to combat stress
- Used to enhance physical and mental performance of athletes and cosmonauts

Rhodiola rosea

- Initial studies revealed cardioprotective benefits due to antiarrhythmia effect and protection against reperfusion injury
- Limits adrenergic effects on heart during stress
- Reduces catecholamines during alarm phase of stress and after intense exercise
- May influence levels of monoamines and beta-endorphins

Rhodiola rosea

- RCT, cross over trial
- 56 male and female night shift physicians treated for (3) two week periods
- 20% improvement in Fatigue Index (mental performance, short-term memory, calculation, concentration
  - Darbinyan, 2000

Rhodiola rosea

- Extract should contain minimum 2.5% rosavin and 1% salidroside
- Dose 150-200 mg daily
- No known drug interactions or side effects.

Withania Somnifera (Ashwagandha)

- Ashwagandha is Sanskrit horse smell.
- In Ayurvedic, Indian, and Unani medicine, is described as "Indian ginseng”.
- Used in traditional African medicine.

Ashwagandha: Traditional Uses

- Arthritis
- Anxiety
- Insomnia
- Tumors
- Stress
- Infertility
- Fibromyalgia

Ashwagandha

- Reported to have tonic or adaptogenic effects similar to panax ginseng

  A. Grandhi, et al., "A Comparative Pharmacological Investigation of Ashwagandha and Ginseng," J Ethnopharmaco 44(3) (Dec1994) : 131-35.

- Prevented myelosuppression in mice treated with three immunosuppressive drugs

  M. Ziauddin, et al., "Studies on the Immunomodulatory Effects of Ashwagandha," J Ethnopharmacol 50(2) (Feb1996) : 69-76.

Ashwagandha

- Standardized to 1.5% withanolides per dose
- Dosage: 450mg (standardized extract) two to three times a day
- No known toxicity
- Do not use in pregnancy due to potential abortifacient effects
- Use with caution with narcotics, anxiolytics, and sedatives

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

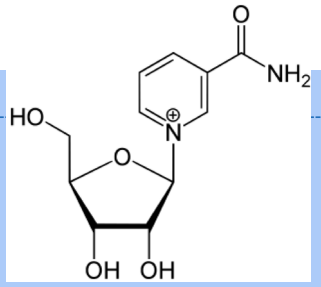
- Decrease oxidative iNOS, increase macrophage scavenger receptor type A
- Reduce inflammatory cytokine expression and significantly reduce the expression of TNF-alpha in activated microglia.
- Increases survival rate of neurons exposed to TNF-alpha.
- Attenuates NMDA receptor-mediated currents and NMDA-induced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

Nicotinamide riboside (NR)



- Form of vitamin B3 (niacin) found mainly in cow's milk
- NR improves NAD^+ levels in conjunction with nicotinic acid and tryptophan
- NAD+ is a rate-limiting co-substrate for sirtuin enzymes
- Laboratory studies report NR may improve Alzheimer's Disease cognitive function and synaptic plasticity
- Neuroprotective activity – Brain Food!!!

- Yang SJ, Choi JM, Kim L, et al. Nicotinamide improves glucose metabolism and affects the hepatic NAD-sirtuin pathway in a rodent model of obesity and type 2 diabetes. J Nutr Biochem. 2014;25(1):66-72.
-Bieganowski P, Brenner C. Discoveries of nicotinamide riboside as a nutrient and conserved NRK genes establish a Preiss-Handler independent route to NAD+ in fungi and humans. Cells. 117;495-502.
- Belenky P, Bogan KL, Brenner C. NAD+ metabolism in health and disease. Trends Biochem Sci. 2007;32(1):12-9.

Nicotinamide Riboside

- Most common oral dosage of nicotinamide riboside - 250 – 500 mg daily
- Orally available commercial product containing nicotinamide riboside is Niagen™, manufactured by Chromadex, Inc., Irvine, CA.
- May also be used intranasally and/or sublingually

Conclusion

- Hypocortisolism has diagnostic and prognostic value
- Stress system tightly integrated with nervous system (CNS and PNS) and immune system
- Flattened cortisol curve may be adaptive mechanism
- Clinical strategy to address low cortisol should include:
  - Seek primary or causative factors
  - Address nervous system and immune system in treatment plan
  - Avoid over-emphasis on supportive adrenal treatments only

Now What?

- Classic presentation
  - Fatigue
  - Under significant prolonged stress or acute stressful events
  - Complains of fatigue, weight gain, sleep disturbance, low mood
- Evaluation
  - Standard – biometrics, BP, depression, alcohol, preventive screening
  - Additional
    - Hormones – insulin, testosterone, ***cortisol***, estrogen, thyroid panels
    - Nutrients – Vitamin D, RBC magnesium, B vitamins, COQ10
    - CM/Immune MComp, CBC, hsCRP, lipids, homocysteine, ferritin, Uric Acid

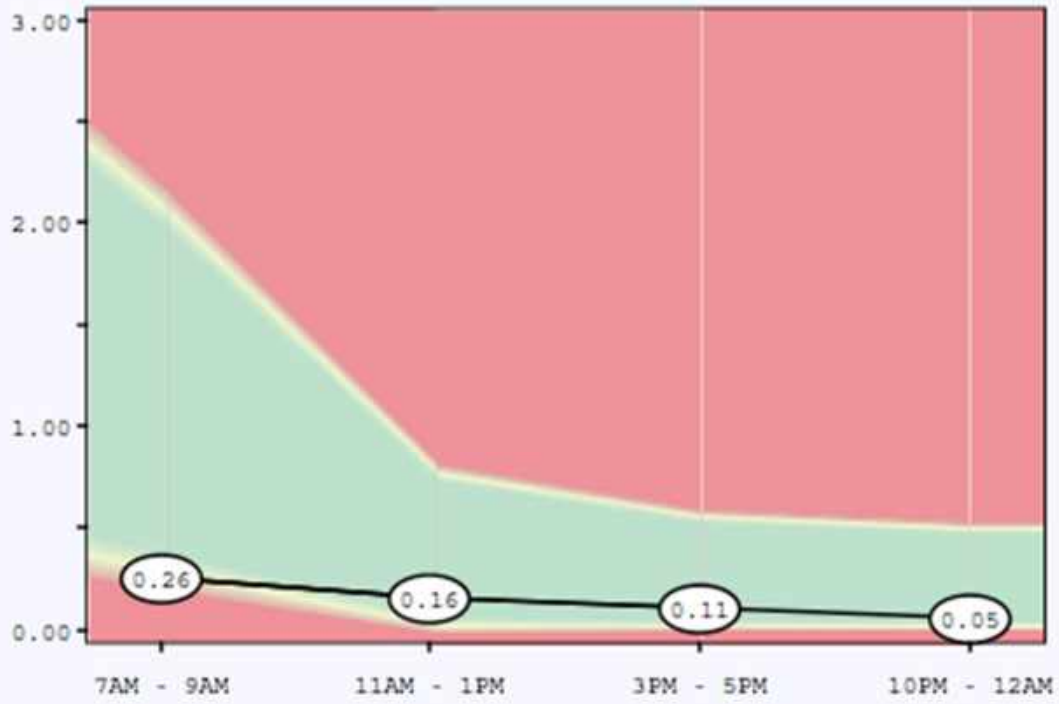
Case

- 15 year old female with 3 year history of Postural Orthstatic Tachycardia Syndrome (POTS)
- Complained of pre-syncope with standing, generalized fatigue and muscle aches
- + Bloating and constipation
- Failed conventional medication
- No other significant medical history
- No medications, surgeries or allergies
- Competitive swimmer, unremarkable social history

Laboratory Values

- CBC and Comprehensive Metabolic Panel Normal
- HS-CRP – 3
- D 52
- RBC Mg 5.1
- Ferritin 420

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

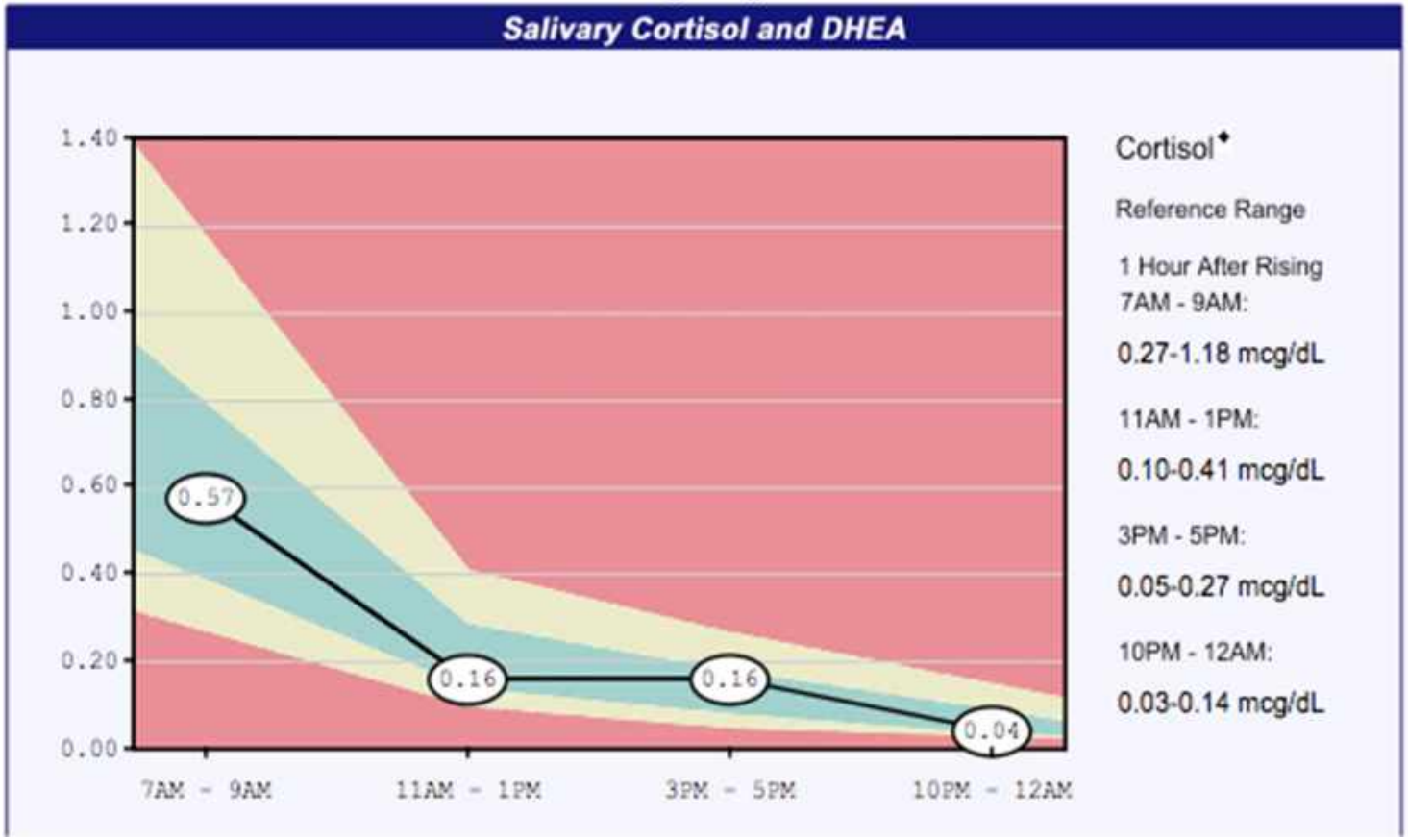
Follow Up Laboratory Values

- Mycoplasma pneumonia IgM – 2250 (nl<760)
- EBV IgM – 1.1 (nl<1.0)

Treatment Plan

- Valtrex and azithromycin
- Probiotic
- 5HTP 200 mg qhs
- Rg3/NR 2 mg/ml 2 sprays per nostril BID
- Plant Sterolins 2 c qam, 1 c qpm x 60 days
- L-theanine 400 mg BID

Post-treatment



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Thank You

ANDREW HEYMAN, MD MHSA
ahheyman@gwu.edu
aheyman@mmimedicine.com