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New Solutions for Adrenal Health

Stuart White DC, DACBN
Lee Carroll B.Sc.

Your Agenda

- Stress – Historical perspective
- General adaptation syndrome
- Brief review of the stress response and adrenal function
- Cortisol
- Vitamin C
- Hormesis

OXFORD MEDICAL PUBLICATIONS

STUDIES IN DEFICIENCY DISEASE

BY

ROBERT McCARRISON

M.D., D.Sc., Hon. LL.D. (Belf.)

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LONDON

HENRY FROWDE AND HODDER & STOUGHTON

THE *LANCET* BUILDING

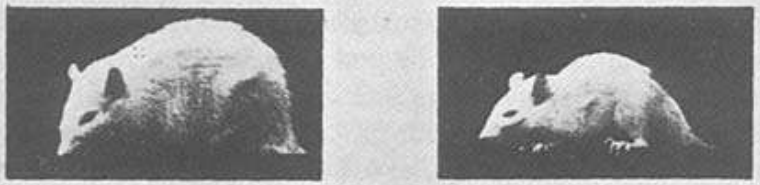
1 & 2 BEDFORD STREET, STRAND, W.C.2

Reproduced by Photo-Lithography
1945
Lee Foundation for Nutritional Research
MILWAUKEE 3, WIS.

SIKH DIET VERSUS DIET OF POORER CLASS EUROPEAN.

The former diet consisted of whole wheat flour chapatties, butter, whole milk, dhal (legume), fresh raw vegetables ad libitum and fresh meat with bone once a week.

The latter diet consisted of white bread and margarine, tinned meat, boiled vegetables, tinned jam, tea and sugar with a little milk.



Two rats of the same age and initial body-weight: the one (left) fed on the Sikh and the other (right) on the poor European diet.

Two rats of the same age and initial body-weight: the one (left) fed on the Sikh and the other (right) on the poor European diet.

Two rats of the same age and initial body-weight: the one (left) fed on the Sikh and the other (right) on the poor European diet.

The rats shown above are representative of 20 in each group. Duration of experiment 187 days. Average initial body-weight both groups 125 grams: average final body-weight: Sikh, 188 gms: poor European, 118 gms. Common diseases in the latter group were pneumonia and gastro-intestinal ailments.

Sir Robert McCarrison MD

"The functional perfection of the adrenal glands is dependent upon the balance of the food and upon the quality and quantity of its vitamins"

"An intimate relationship exists between the adrenal glands and the meta-bolic processes of the animal organism"

"Each vitamin exercises a specific influence on the adrenal glands; the effect of their deprivation on these organs is one of the most outstanding features of deficiency disease"

Stress - Historical Context

- Early research by W B Cannon (1871-1945)
- In 1915 coins the term "fight or flight mechanism" to describe associated changes in adrenal gland secretions
- In 1926 coined the term "homoeostasis" to describe the maintenance of physiological variables within certain ranges eg blood glucose, O_2 tension and core temperature

Goldstein DS, Kopin IL. *Stress* 2007; **10**(2): 109-120

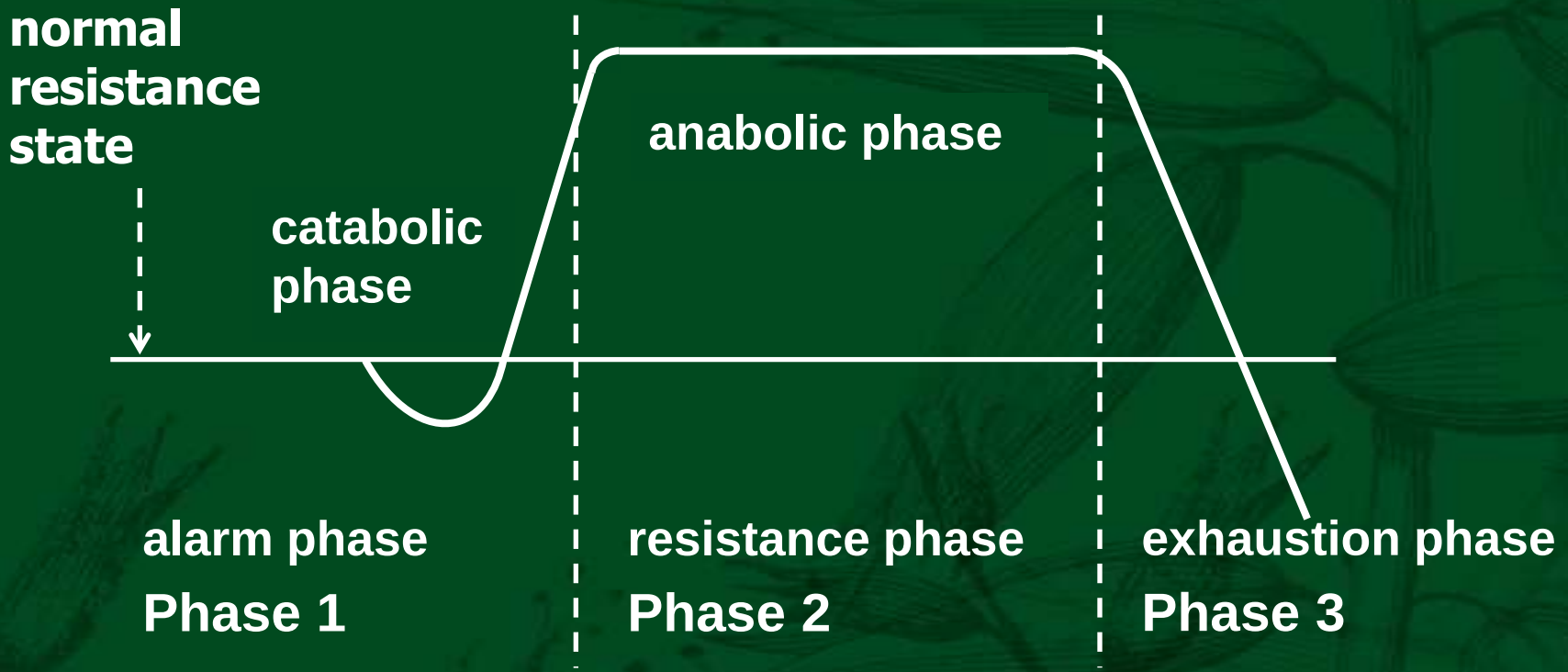
Stress - Historical Context

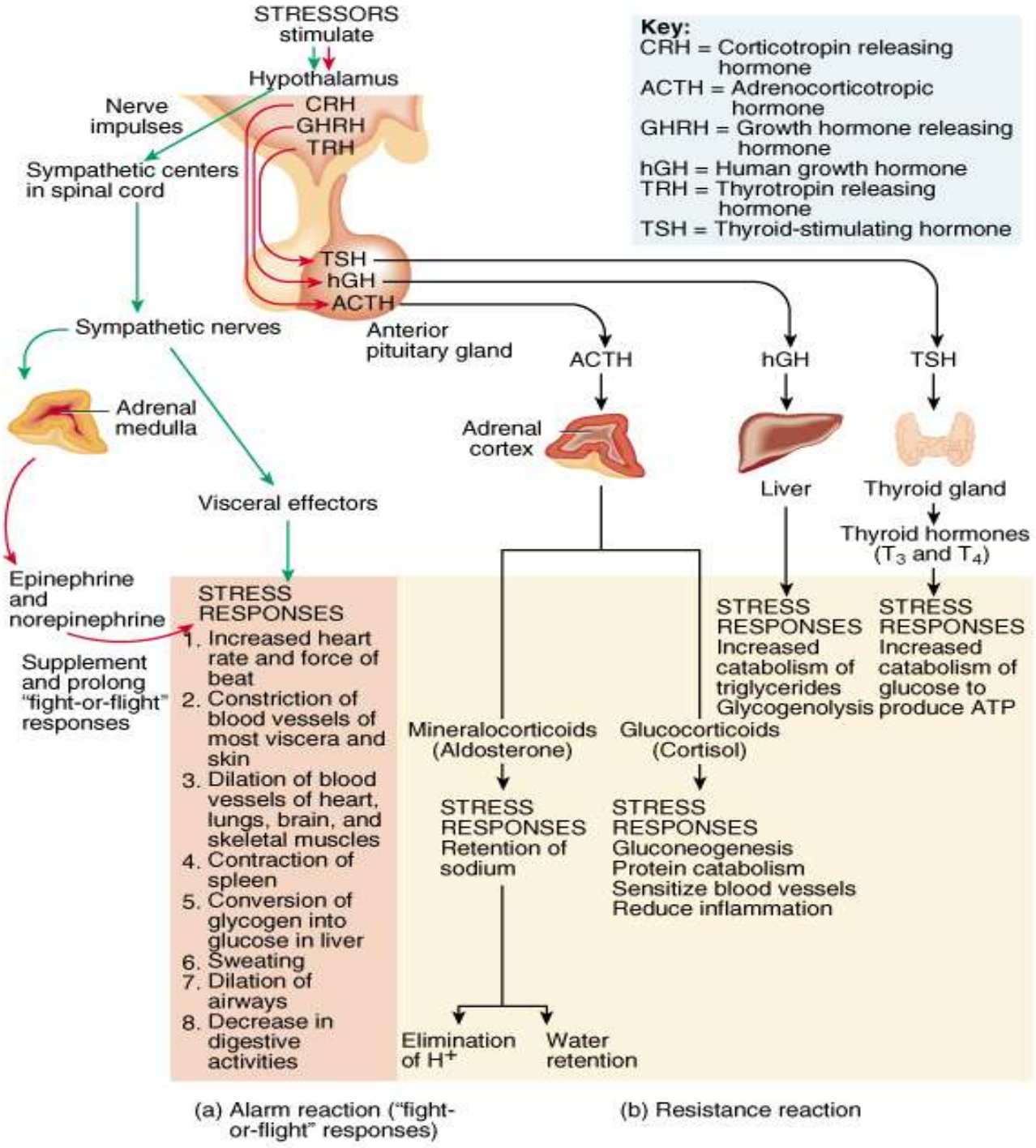
- Cannon's work was then extended by Hans Selye (1907-1982)
- Observed that the same characteristics and physiological responses occurred in rats subjected to a variety of intense stimuli
  - adrenal enlargement, thymus and spleen atrophy and GIT ulcers
- Termed the series of responses the General Adaption Syndrome (GAS)

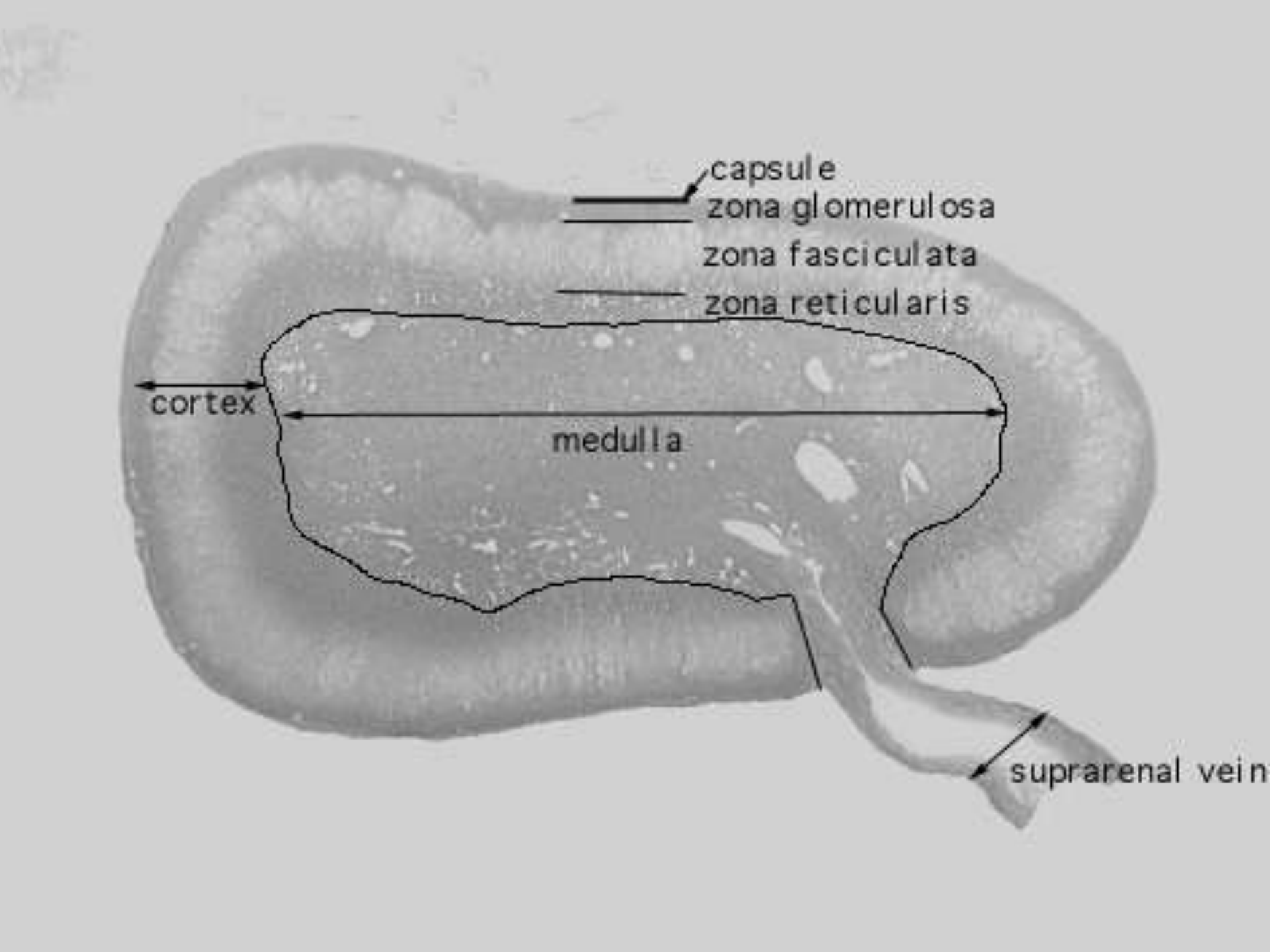
Goldstein DS, Kopin IL. *Stress* 2007; **10**(2): 109-120

General Adaptation Syndrome

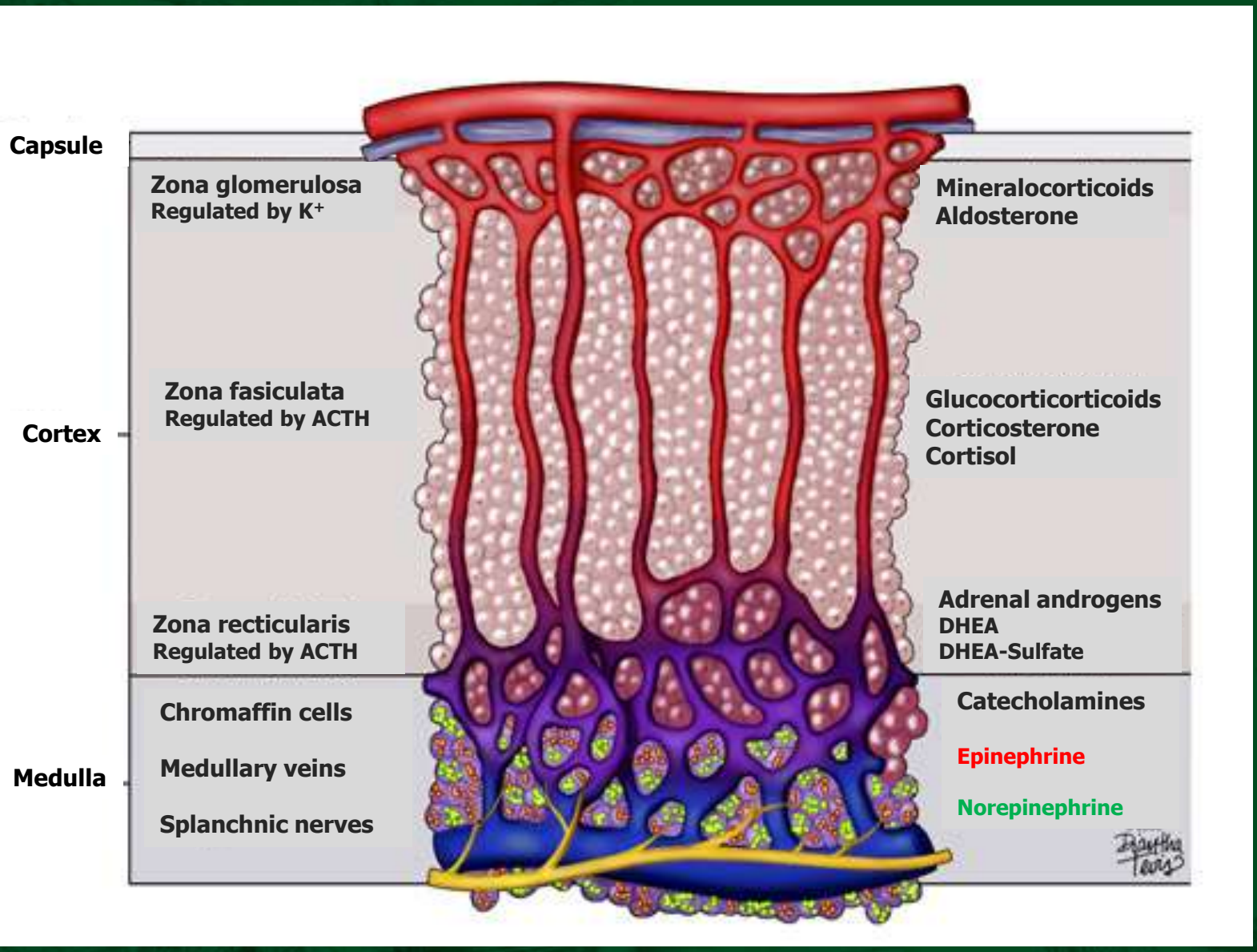
SELYE'S STRESS MODEL




STRESSORS stimulate
Hypothalamus
Nerve impulses
CRH
GHRH
TRH
Sympathetic centers in spinal cord
TSH
hGH
ACTH
Sympathetic nerves
Anterior pituitary gland
ACTH
hGH
TSH
Adrenal medulla
Adrenal cortex
Liver
Thyroid gland
Thyroid hormones (T_3 and T_4)
Visceral effectors
Epinephrine and norepinephrine
Supplement and prolong "fight-or-flight" responses
STRESS RESPONSES
1. Increased heart rate and force of beat
2. Constriction of blood vessels of most viscera and skin
3. Dilation of blood vessels of heart, lungs, brain, and skeletal muscles
4. Contraction of spleen
5. Conversion of glycogen into glucose in liver
6. Sweating
7. Dilation of airways
8. Decrease in digestive activities
STRESS RESPONSES Increased catabolism of triglycerides Glycogenolysis
STRESS RESPONSES Increased catabolism of glucose to produce ATP
Mineralocorticoids (Aldosterone)
Glucocorticoids (Cortisol)
STRESS RESPONSES Retention of sodium
STRESS RESPONSES Gluconeogenesis Protein catabolism Sensitize blood vessels Reduce inflammation
Elimination of H^+
Water retention
Key:
CRH = Corticotropin releasing hormone
ACTH = Adrenocorticotropic hormone
GHRH = Growth hormone releasing hormone
hGH = Human growth hormone
TRH = Thyrotropin releasing hormone
TSH = Thyroid-stimulating hormone
(a) Alarm reaction ("fight-or-flight" responses)
(b) Resistance reaction


capsule
zona glomerulosa
zona fasciculata
zona reticularis
cortex
medulla
suprarenal vein

Adrenal Hormones



Cortisol Physiological Function

- In addition to its role as a stress response hormone, cortisol plays many key roles in almost every physiological system:
  - Central nervous system
  - Activity and direction of energy metabolism
  - Maintenance of a proper cardiovascular tone
  - Activity and quality of immune system and inflammatory responses
  - Growth and reproduction

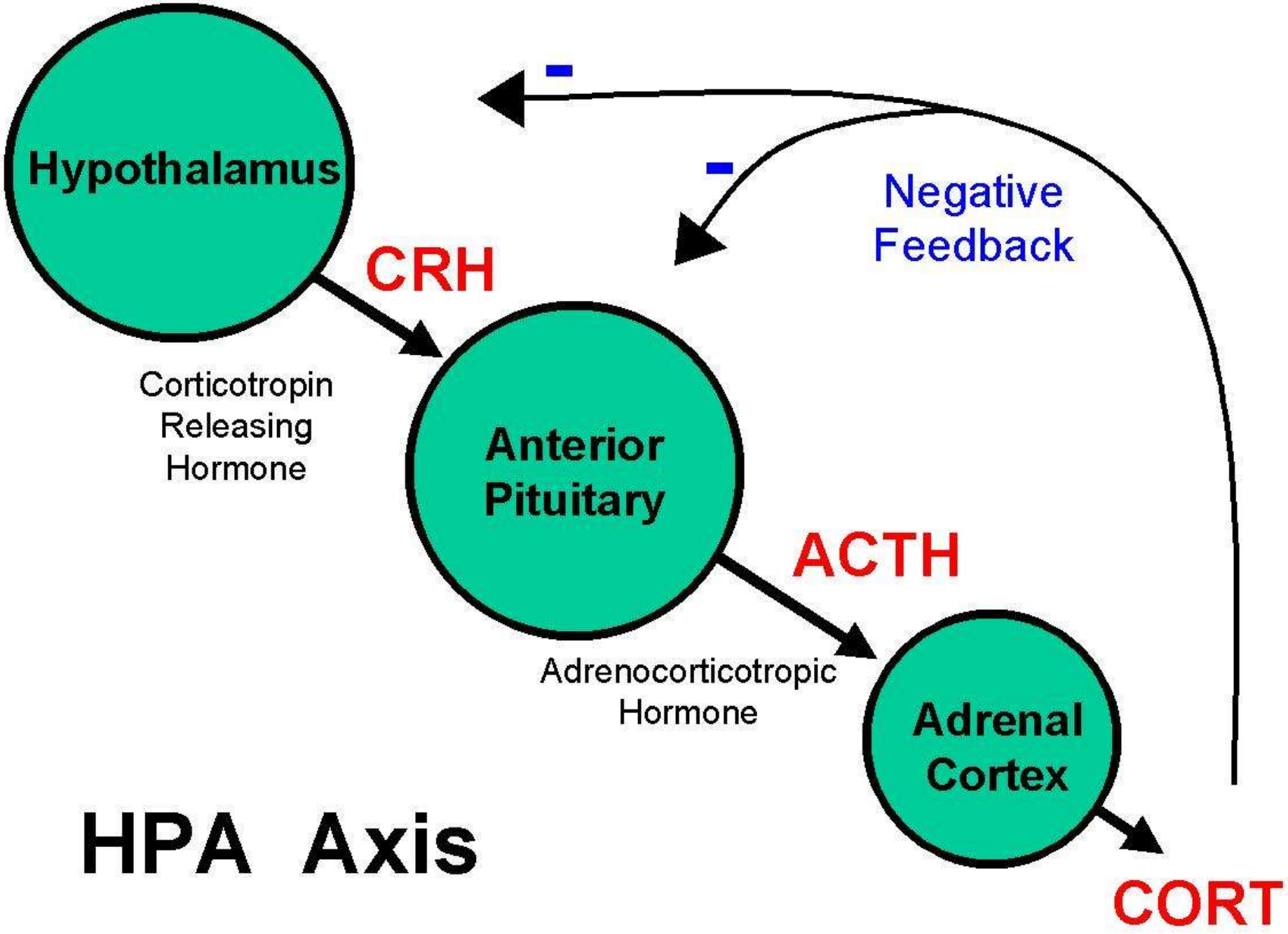
Chrousos, GP, and Kino, T, Glucocorticoid Signaling in the Cell: Expanding Clinical Implications to Complex Human Behavioral and Somatic Disorders *Ann N Y Acad Sci. 2009 October ; 1179: 153–166*

Cortisol Pathophysiology

Glucocorticoids are heavily involved in human pathophysiology and influence life expectancy

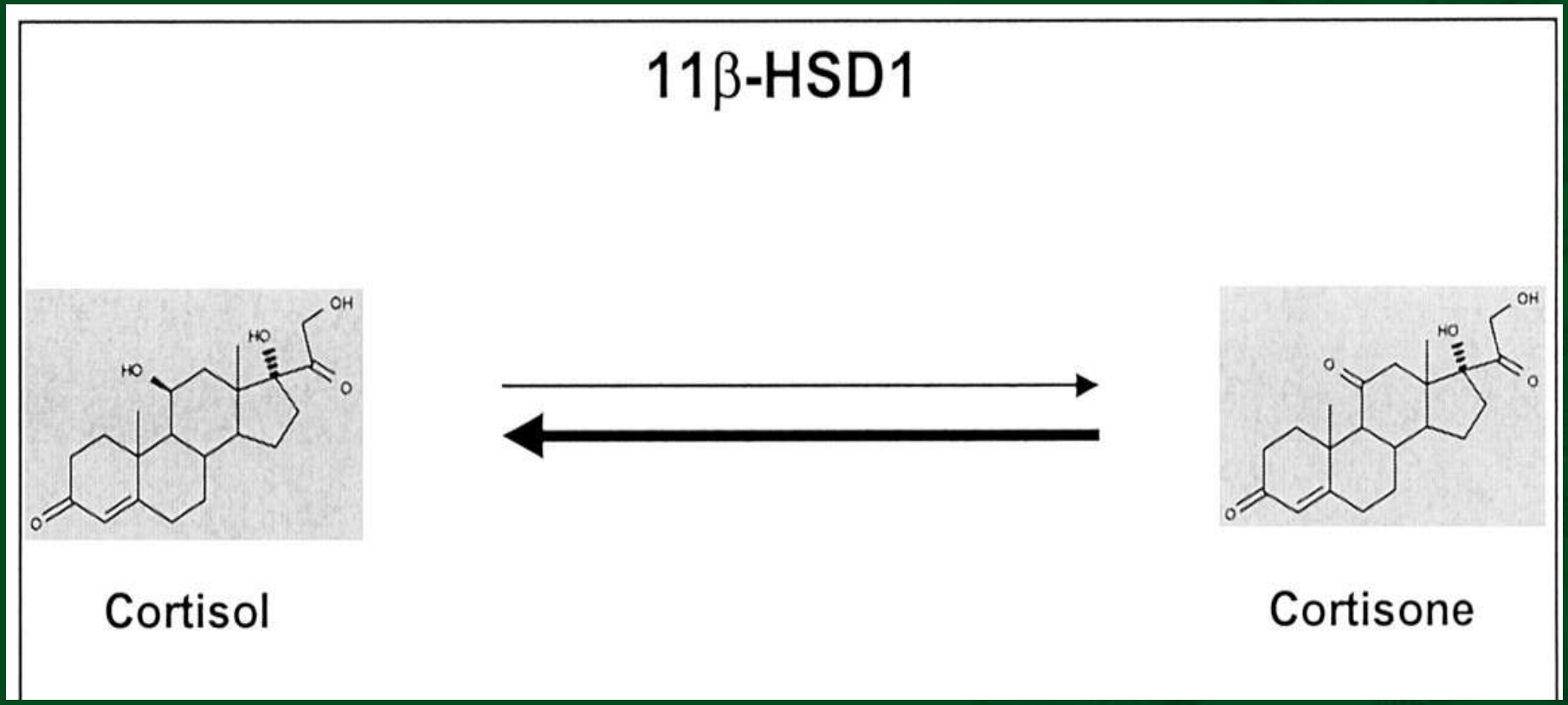
- Anxiety
- Depression
- Insomnia
- Chronic pain and fatigue syndromes
- Obesity
- Metabolic syndrome
- Essential hypertension
- T2 Diabetes
- Atherosclerosis with its cardiovascular sequelae
- Osteoporosis
- Autoimmune disease
- Inflammatory and allergic disorders
- Sickness syndrome

Chrousos, GP, and Kino, T, Glucocorticoid Signaling in the Cell: Expanding Clinical Implications to Complex Human Behavioral and Somatic Disorders *Ann N Y Acad Sci.* *2009 October ; 1179: 153–166*


Hypothalamus
CRH
Corticotropin
Releasing
Hormone
Anterior
Pituitary
ACTH
Adrenocorticotropic
Hormone
Adrenal
Cortex
CORT
Negative
Feedback
HPA Axis

Cortisol Pathophysiology

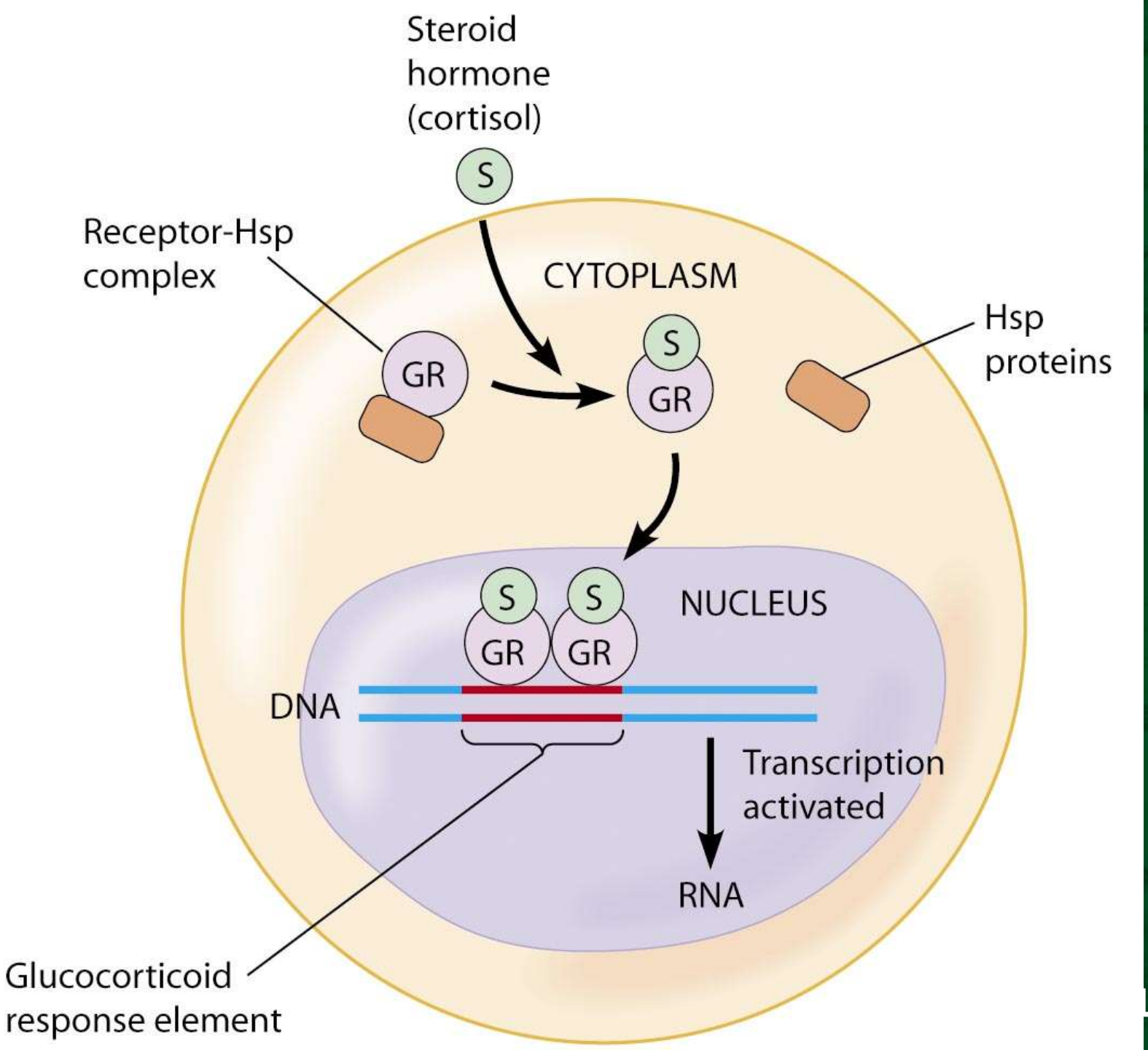
- HPA axis activity or sensitivity
  - hypothalamus and pituitary
- Cortisol activity or sensitivity
  - Receptor based
  - Enzyme based
- Responsiveness of the target tissues to cortisol is highly variable



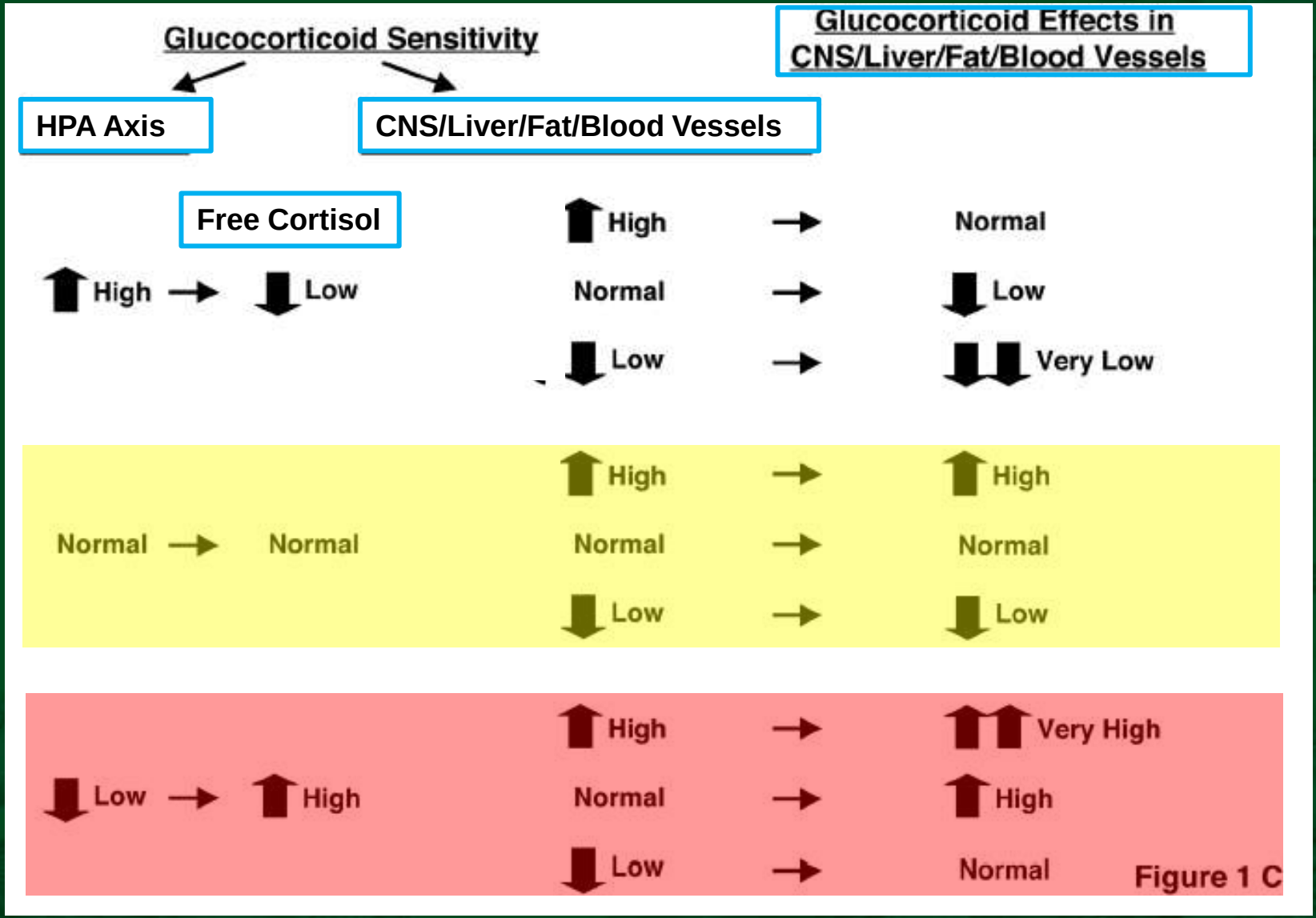
Function:

- Alteration of intracellular cortisol concentration
- Organ specific enhancement of cortisol effect

High expression: Liver, adipose tissue, lung, gonads, pituitary, bone, eye


Steroid
hormone
(cortisol)
S
Receptor-Hsp
complex
CYTOPLASM
GR
S
GR
Hsp
proteins
S
S
NUCLEUS
GR
GR
DNA
Transcription
activated
RNA
Glucocorticoid
response element

HPA Axis/Cortisol Sensitivity



Central Nervous System

Cortisol excess or hypersensitivity

- = Insomnia
- = Anxiety
- = Depression
- = Defective cognition

Cortisol deficiency or resistance

- = Fatigue
- = Somnolence
- = Malaise
- = Defective cognition

Blood Vessels

Cortisol excess or hypersensitivity

= Hypertension

Cortisol deficiency or resistance

= Hypotension

Adipose Tissue

Cortisol excess or hypersensitivity

= Accumulation of visceral fat

= Metabolic syndrome

Cortisol deficiency or resistance

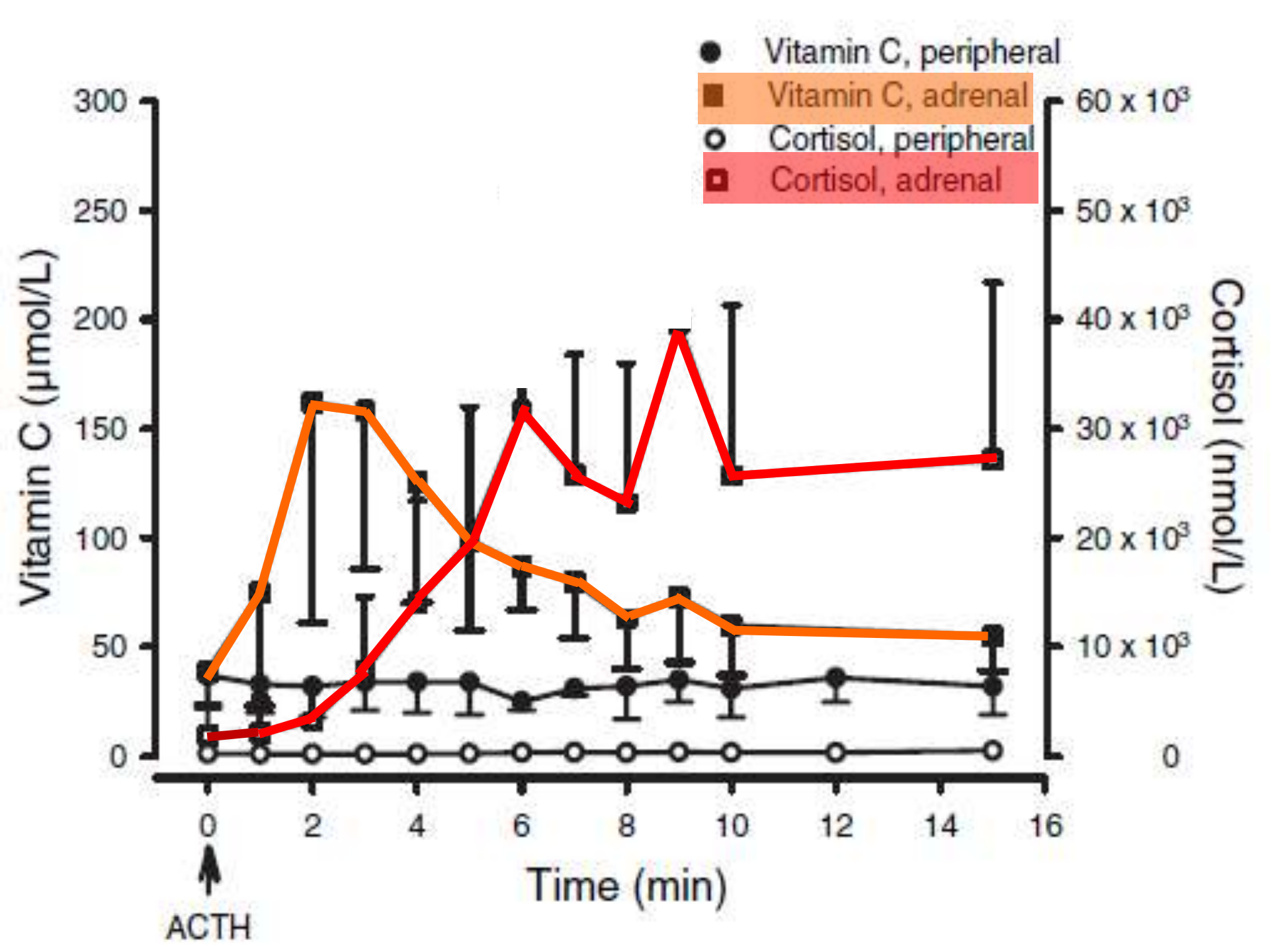
= Loss of weight

= Resistance to weight gain

Adrenal Glands & Vitamin C

- When Vit C intake is from food fasting plasma levels don't exceed 80µmol/L
- Levels in the adrenal gland can be as high as 10 mmol/L (125 times higher)
- How do adrenals concentrate Vit C to such high levels and why?
- In humans, adrenal Vit C secretion is an integral part of the stress response

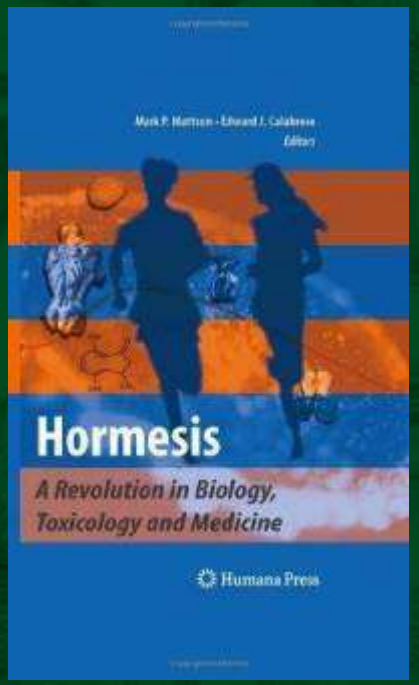
Padayatty SJ, et al 2007, Human adrenal glands secrete vitamin C in response to adrenocorticotrophic hormone. *Am J Clin Nutr* 86:145–9

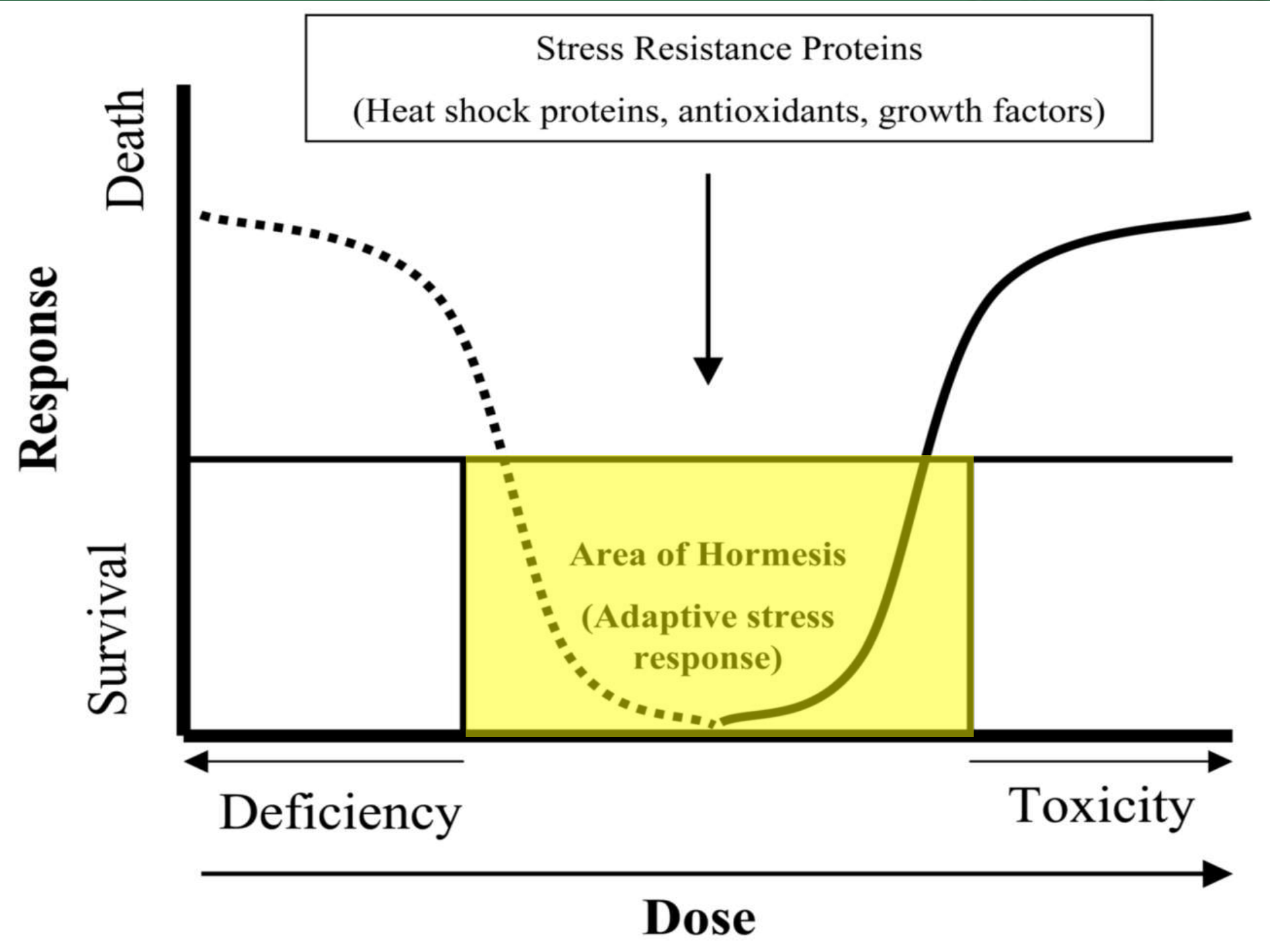

Vitamin C, peripheral
Vitamin C, adrenal
Cortisol, peripheral
Cortisol, adrenal
Vitamin C (µmol/L)
Cortisol (nmol/L)
300
250
200
150
100
50
0
60 x 10³
50 x 10³
40 x 10³
30 x 10³
20 x 10³
10 x 10³
0
0
2
4
6
8
10
12
14
16
Time (min)
ACTH

Hormesis

What Doesn't Kill You Makes You Stronger!

- Stimulatory or beneficial effects at low doses and inhibitory or toxic effects at high doses
- Hormesis is now the standard terminology used to describe the beneficial adaptive response of cells and organisms to moderate stress




Stress Resistance Proteins
(Heat shock proteins, antioxidants, growth factors)
Death
Response
Survival
Area of Hormesis
(Adaptive stress response)
Deficiency
Toxicity
Dose

How is Moderate Stress Beneficial?

- Mild stress induces the activation of signalling pathways, leading to intrinsic changes conferring resistance to a more severe stress
- The stress-inducing agent elicits molecular responses that not only protect the cell against higher doses of the same agent, but also against other agents or even less specific stressors including oxidative, metabolic and thermal stress
- They can even repair existing damage

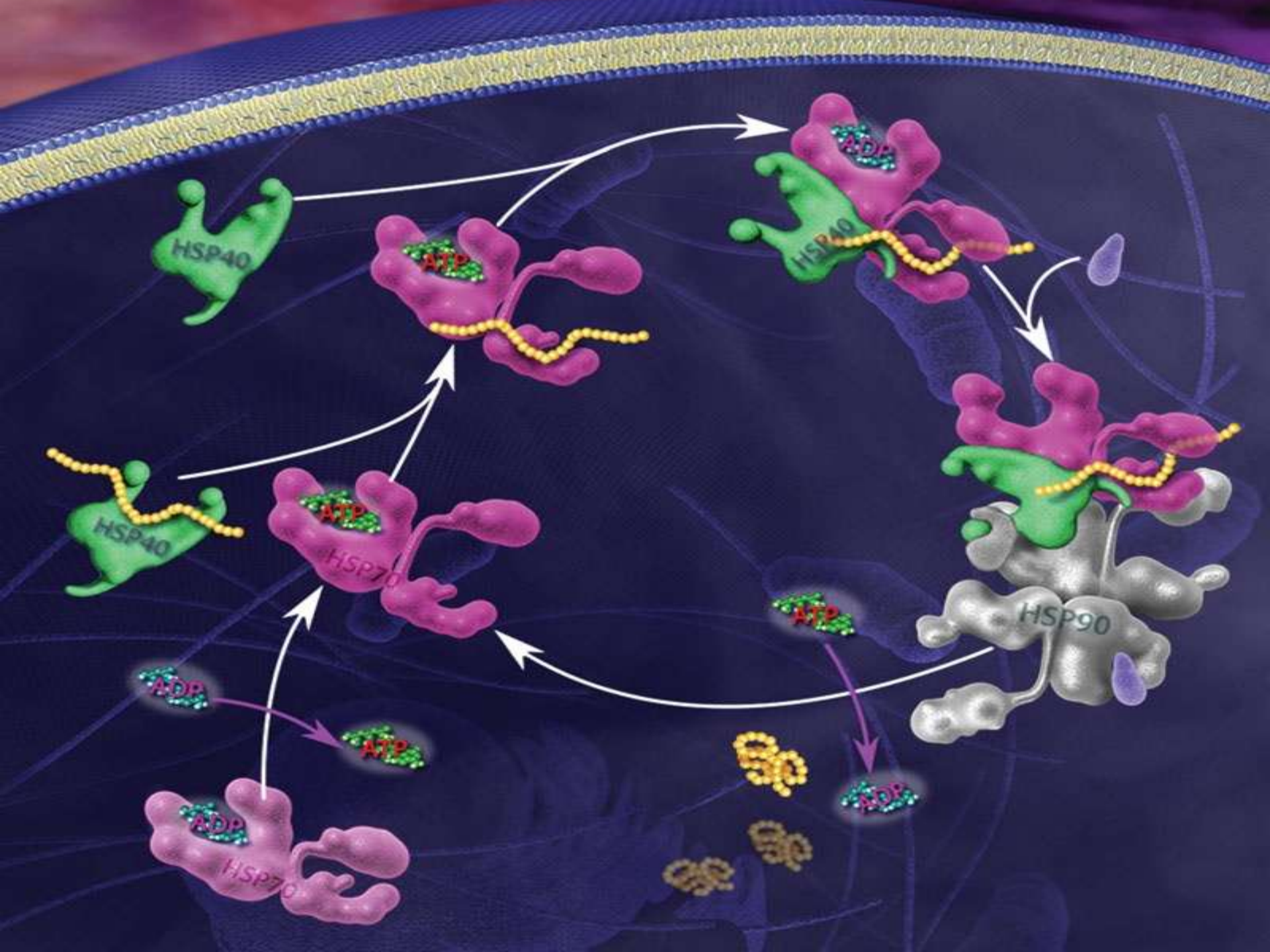
Hormesis

- Major components of the hormetic response include various stress resistance proteins such as heat shock proteins (HSP), sirtuin1, growth factors and cell kinases
- Classical examples of hormetic stress are exercise and calorie restriction
- Many phytochemicals consumed in our diet are hormetic:
  - Ferulic acid from tomatoes, sweet corn, rice
  - EGCG from Green tea
  - Curcumin from Turmeric
  - Sulforafane and isothiocyanate from cruciferous vegetables

Hormesis and HSP

- HSP are produced when cells are exposed to stress
- Their job is to protect (chaperone) other proteins from damage by binding to them and shielding them from attack
- HSP play an important role in the conservation & maintenance:
  - Protein homeostasis
  - The cellular stress response
  - Aging

Mattson M, Calabrese E. Best in small doses. The *New Scientist* 2008; **199**(2668): 36-39


HSP40
ATP
ADP
HSP40
HSP40
ATP
HSP70
ATP
HSP90
ADP
ATP
ADP
HSP70
ADP

Adaptogens and Hormesis

- Adaptogens are herbs that help the body better adapt to stressors by fine-tuning the stress response
- The stress–protective effect of adaptogens is the result of the adaptation of the organism to the mild stressful effects of the adaptogen
- Adaptogens are Hormetic

Adaptogens and Hormesis

The regular consumption of adaptogens gives rise to an adaptogenic or stress–protective effect in a manner analogous to repeated physical exercise, leading to prolonged state of non-specific resistance to stress and increased endurance and stamina under extreme conditions