

Dose-Response 2010

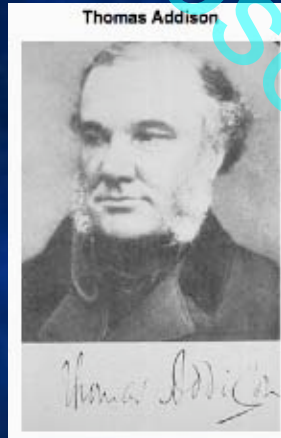
Cortisol Exerts Bi-Phasic Regulation of Inflammation in Humans

Mark P. Yeager, MD

Patricia A. Pidi, PhD

Paul M. Guyre, PhD

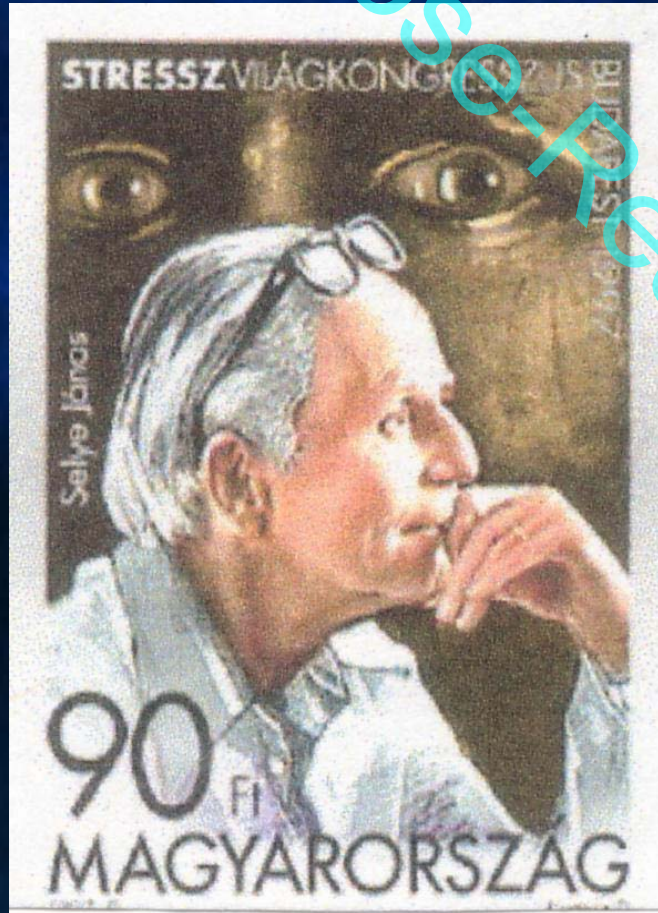
Glucocorticoid History and Physiology



- Thomas Addison
- On the Constitutional and Local Effects of Disease of the Suprarenal Capsules
1855 monograph
 - No extra-adrenal organ morbidity/pathology
 - “melasma suprerenale”
 - Progressive languor
- Addison died of ‘melancholia’ in 1860

Hans Selye, MD

1907-1982



- Austrian-born, 3rd generation physician
- Early interest in the 'shock response' as reproducible
- Leading researcher in 'shock' 1930's-1940's
- Systematically investigated the the role of adrenal cortical hormones on shock response *in vivo*.

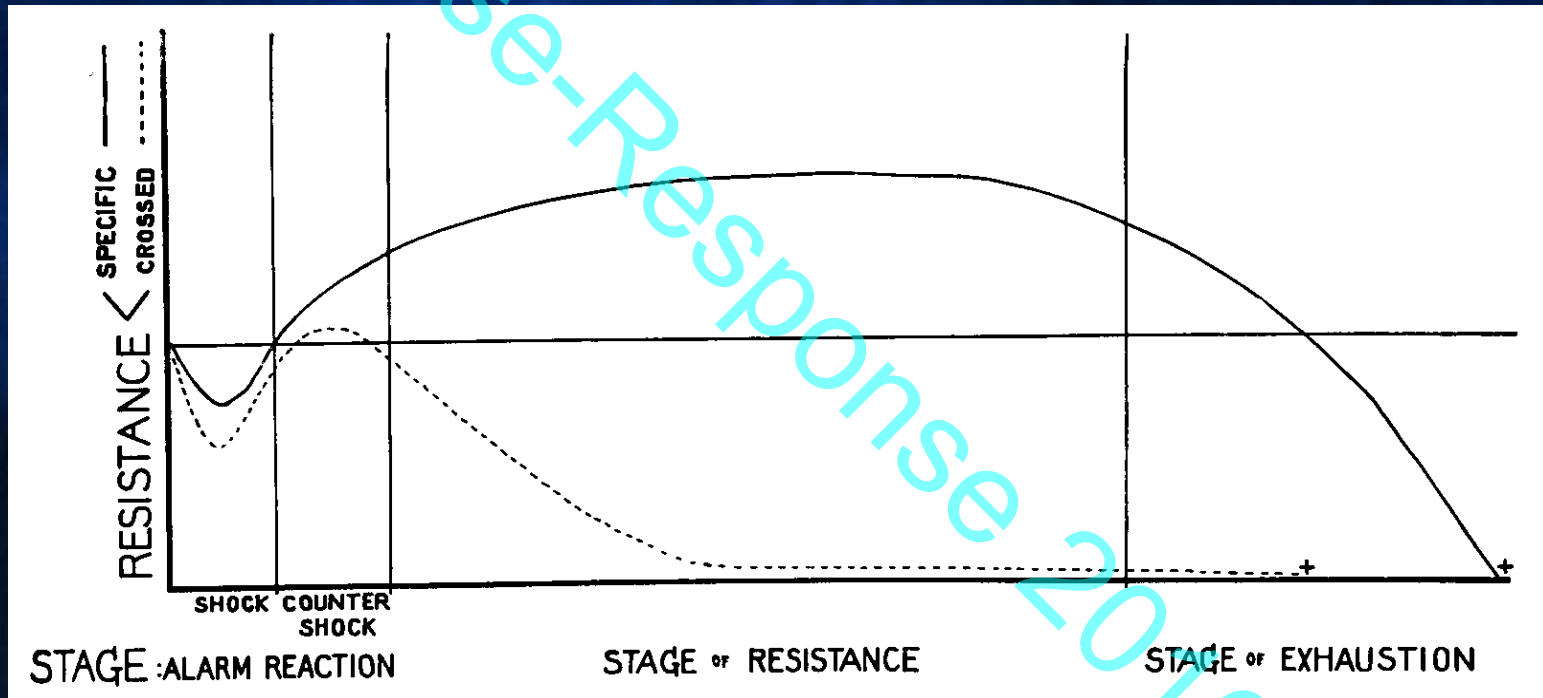
Injury (Shock) Response

Stress, 1950

- Shock phase (General Alarm Reaction)
 - Initial loss of adrenal cortical lipids
- Countershock phase (General Adaptation Syndrome)
 - Subsequent hypertrophy of adrenal cortex
 - Without adrenal cortex, countershock phase does not develop and animal dies
- General Adaptation Syndrome (GAS):
 - Any systemic stress elicits a similar syndrome
 - The syndrome helps adaptation (survival)
 - Adaptation causes disease

Selye: Systemic Injury Response

From *Stress* ©1950



‘Relative Adrenocortical Insufficiency’

Selye H. *Can Med Assoc J*, July 1940

“Our work...is definitely indicative of the existence of a relative adrenal cortical insufficiency in cases of shock...and clinical administration of cortin would seem promising in wound shock.”

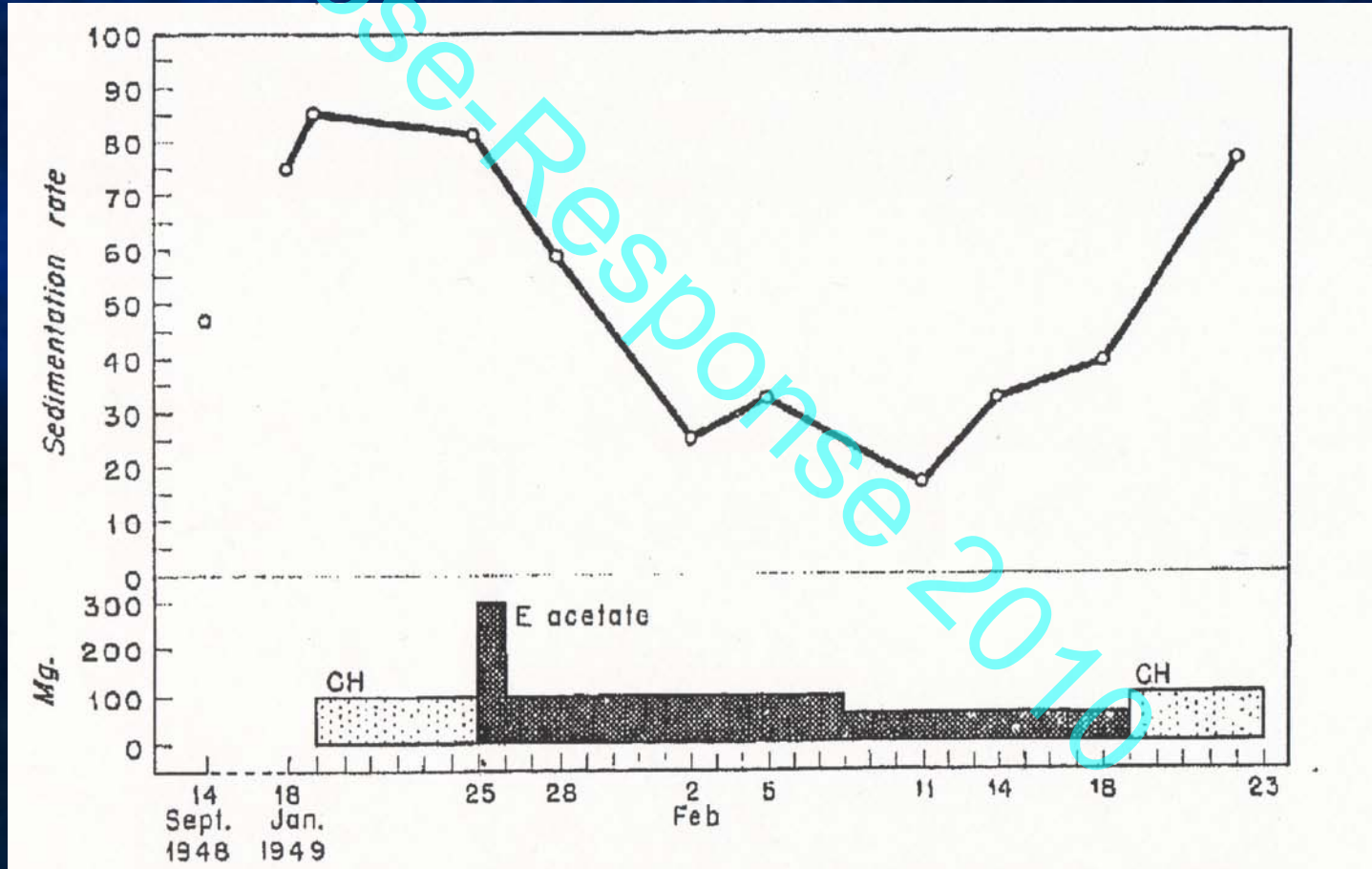
“These experiments confirmed our belief that it is primarily an increased adrenal cortical secretion which is responsible for the development of resistance in the countershock phase.”

Selye-Legacy

- Coined the term 'stress' as it is used in contemporary, non-engineering settings
- Identified the 'stress response' as a common response to any systemic stimulus
- Determined that the 'stress response' of an organism can, and does, lead to disease
- Profoundly wrong

“The Effect of a Hormone of the Adrenal Cortex and of (ACTH) on Rheumatoid Arthritis”

Hench et al, *Proc Mayo Clinic*, 1949



Philip Hench, MD

1950 (1 Year Later)

- Stockholm, 1950: “Dr Hench. The Caroline Institute has decided to award this year’s Nobel Prize in Medicine to you...for your discoveries regarding the hormones of the adrenal cortex...and their biologic effects.”
- Hans Selye was nominated for a Nobel Prize 3 times but never won the award.



Glucocorticoid Research 1950-2000

- Virtually ALL of the clinical GC research has focused on anti-inflammatory or suppressive properties of GCs
- Very little research has been done on supportive or stimulatory properties of GCs- Selye's 'resistance'

Glucocorticoid Physiologists at Dartmouth



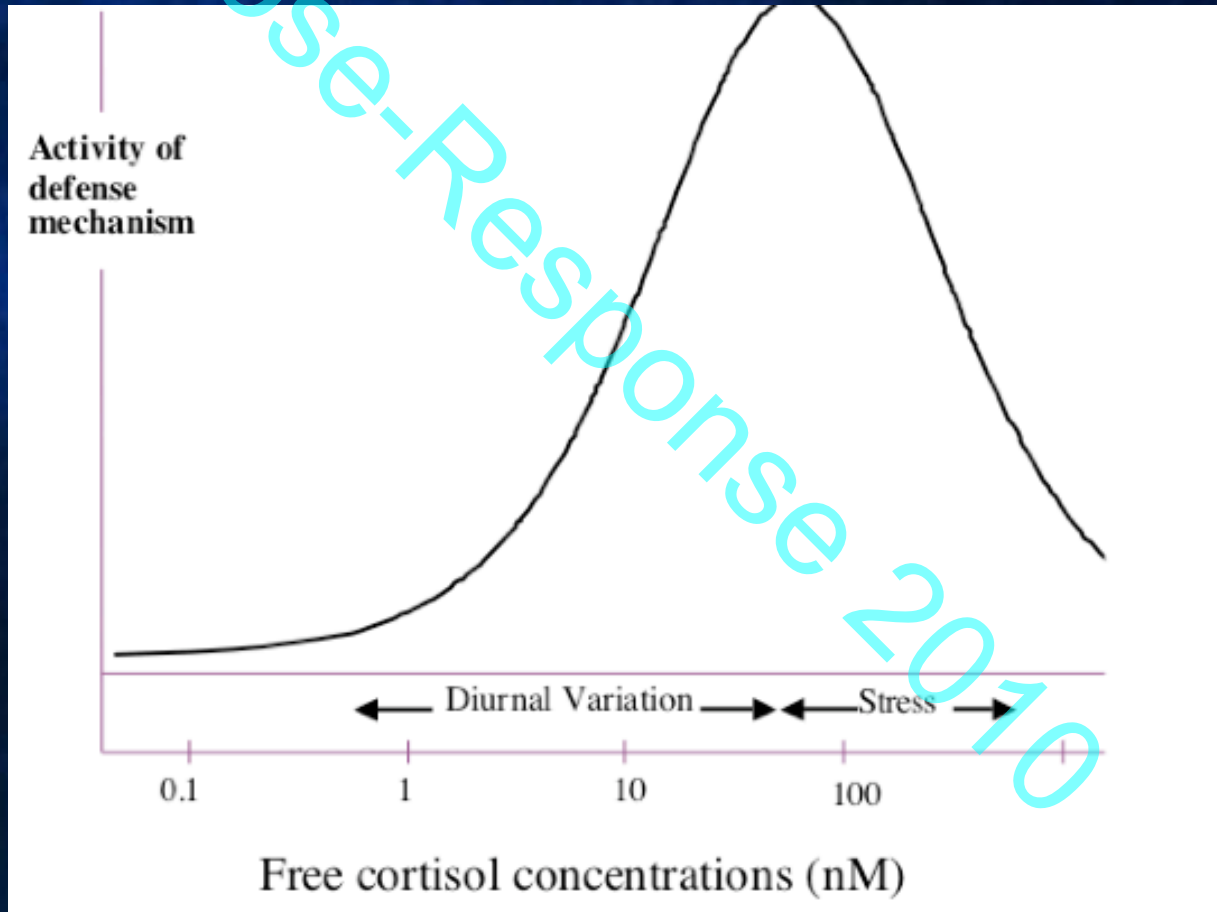
- Alan U. Munck, PhD
 - Third Century Professor, DMS



- Paul M. Guyre, PhD
 - Professor of Physiology, DMS

Unifying Hypothesis of GC Actions

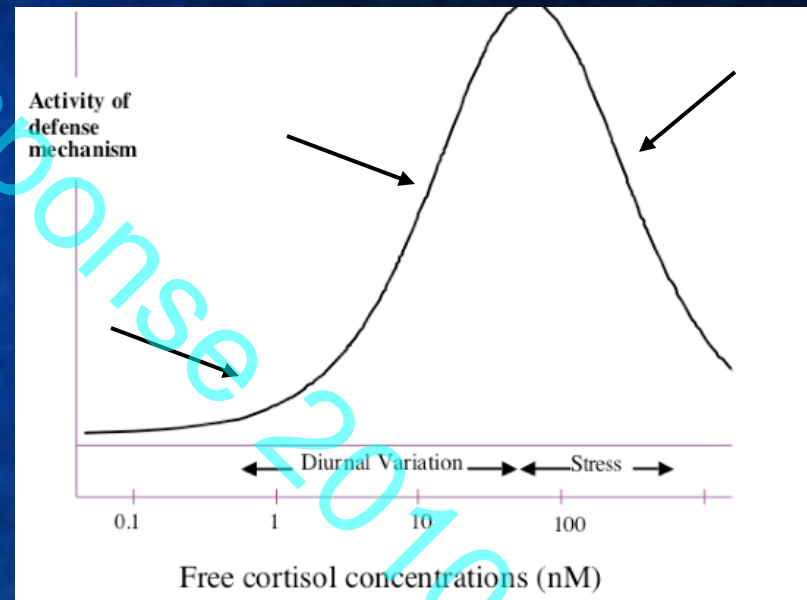
Munck, Guyre, Holbrook, 1984



Unifying Hypothesis of GC Actions

- “Activity of Defense Mechanism”:
 - Permissive (anti-Addisonian)
 - Suppressive
 - Stimulatory

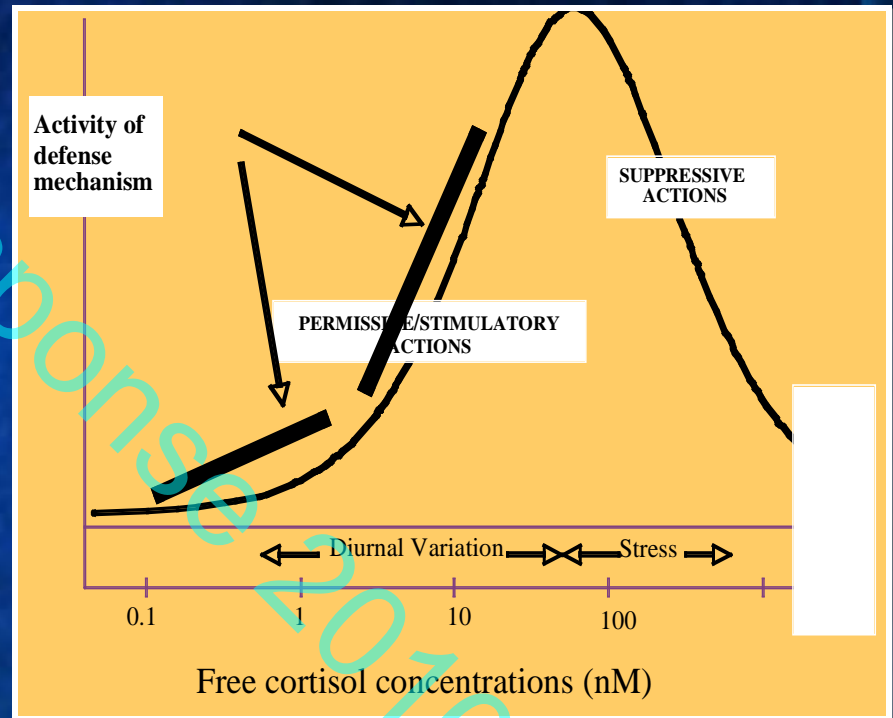
- Preparative (time)



In Vivo Exposure to High or Low Cortisol Has Bi-Phasic Effects on Inflammatory Response Pathways of Human Monocytes

Anesth Analg, 2008

- What would happen if we depleted GC effects *in vivo*?
- Would we uncover evidence of suppressive or stimulatory effects of diurnal cortisol?
- Mechanism: block both cortisol receptor & synthesis



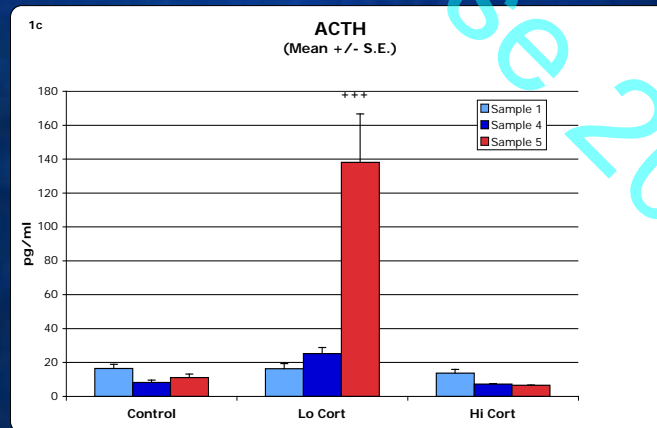
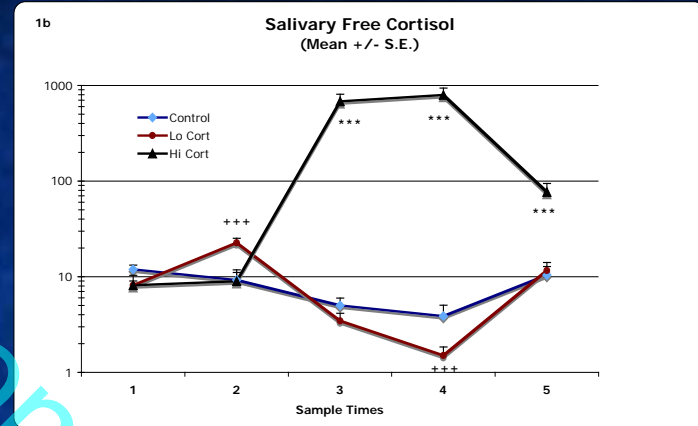
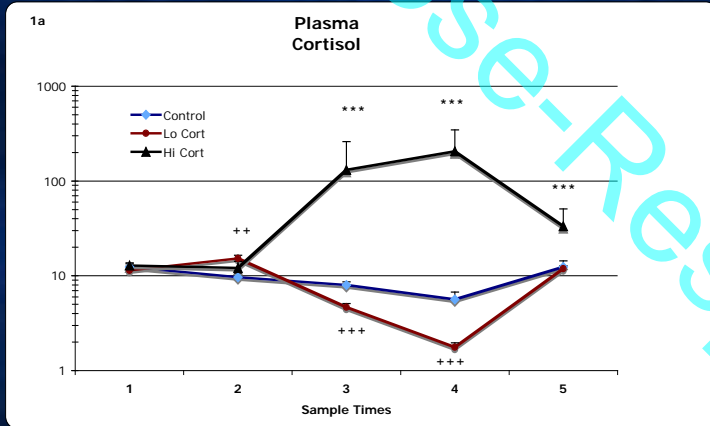
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Anesth Analg, 2008

	Time-->	Day 1	Day 2	Day 3	Day 4				
	Blood sampling	7AM X	4AM	7AM	Noon X	4PM X	7PM	Day 3 7AM X	Day 4 7AM X
	TREATMENTS								
Treatment A-Control	Placebo		Placebo			Placebo			
	Saline			Saline infusion					
Treatment B-Hi cortisol	Placebo		Placebo			Placebo			
	Hydrocortisone			8 ug/kg / min iv		HC p.o.			
Treatment C-Lo Cortisol	RU486		RU486			RU486			
	Etomidate			0.15 ug/kg/ hr					

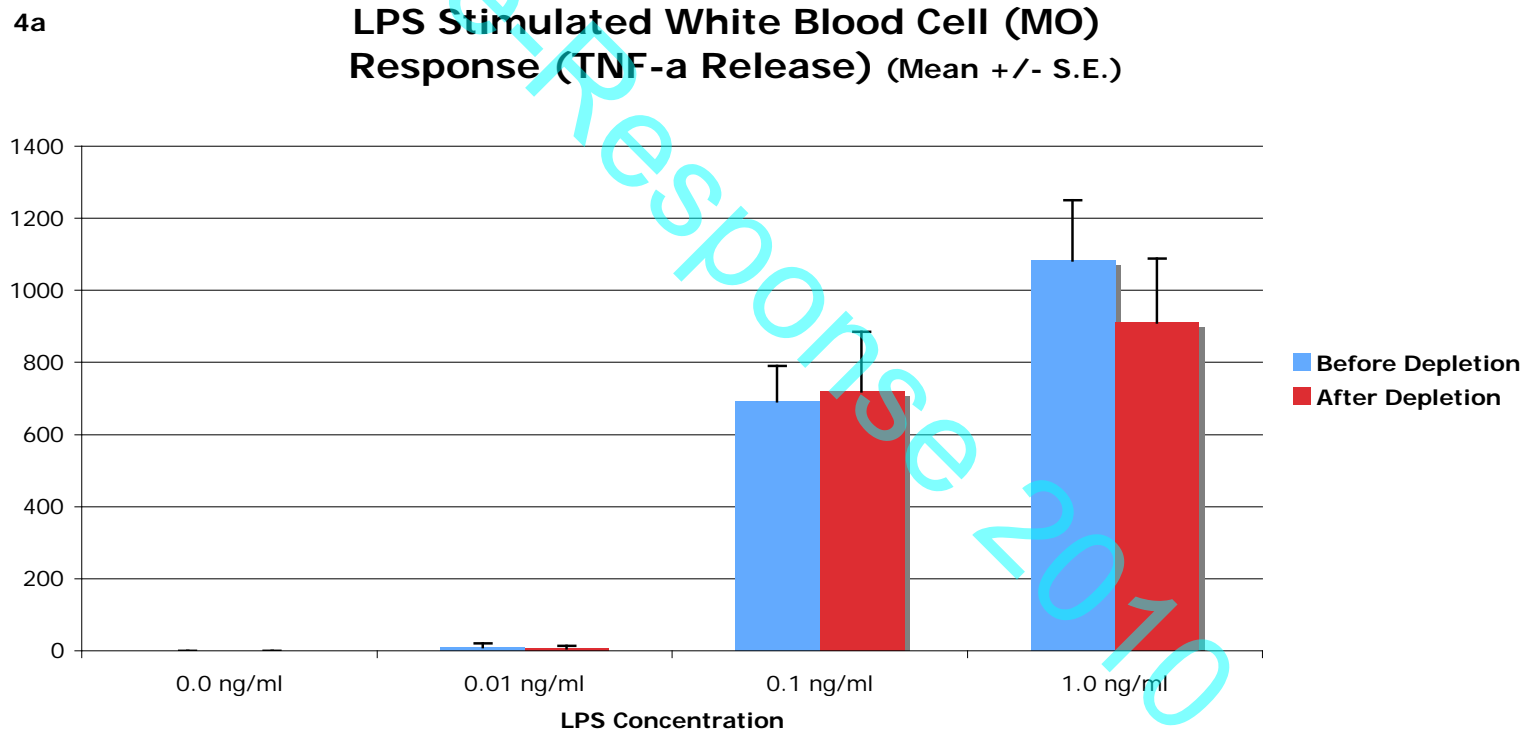
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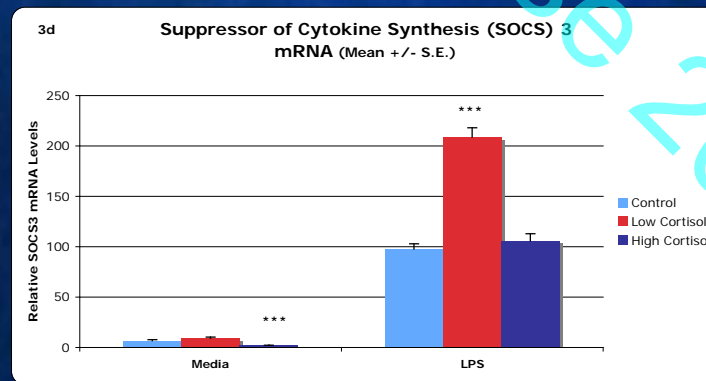
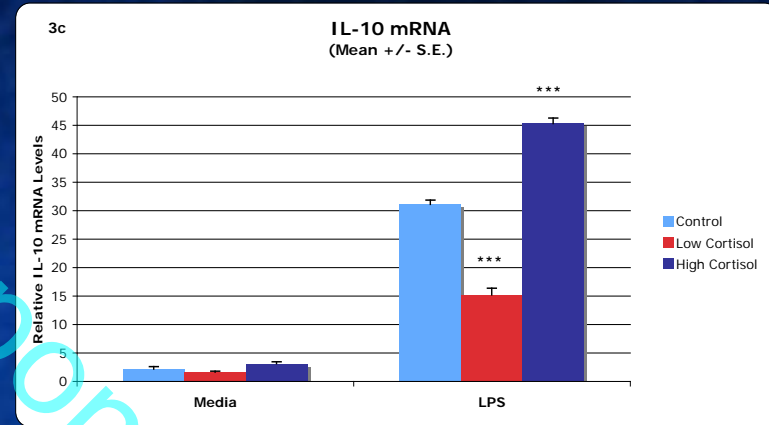
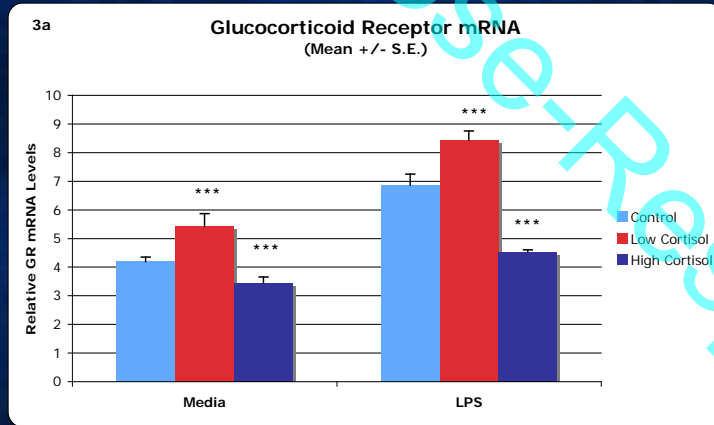
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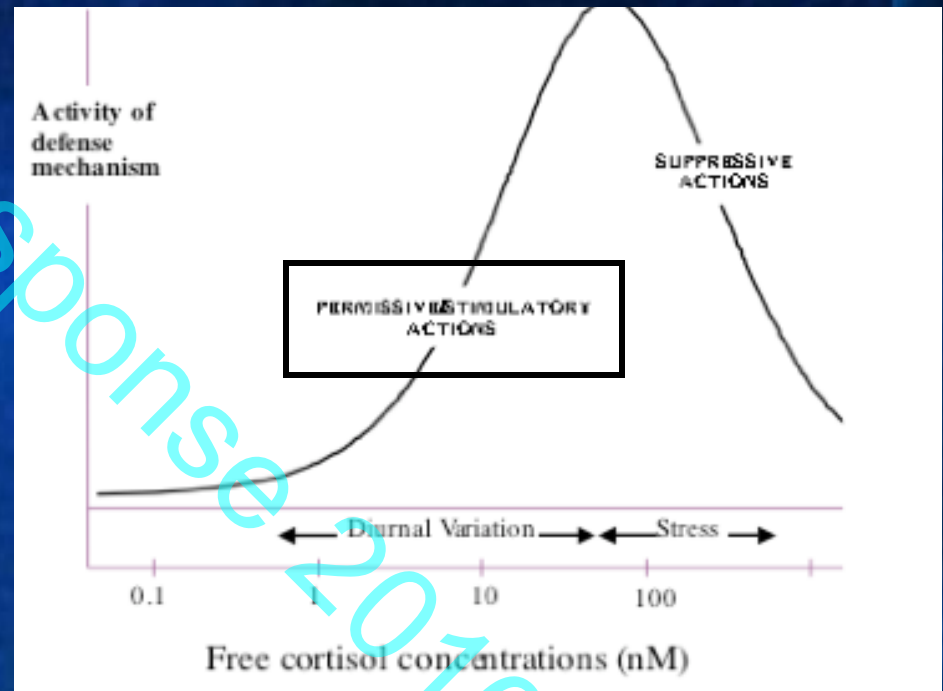
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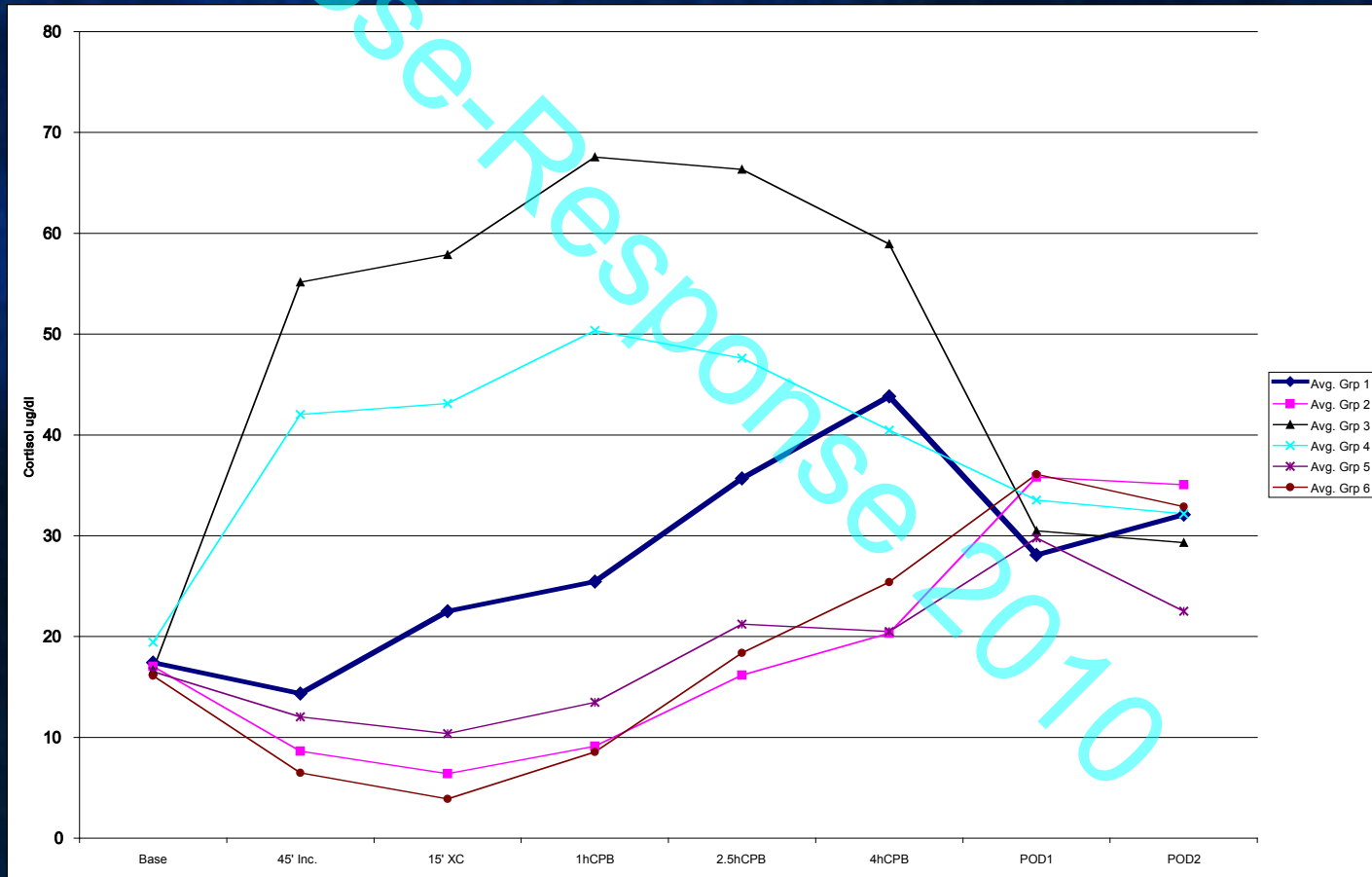
Cortisol Anti-inflammatory Effects are Maximal at Postoperative Plasma Concentrations

Yeager MP et al. *Crit Care Med* 2005.

- 1st Case CABG, Valve
- Etomidate to limit endogenous synthesis
- Added back varying doses of cortisol (SoluCortef)
- Cytokine response (IL-6, IL-10)
- Looking for evidence of GC-mediated stimulation of inflammatory response

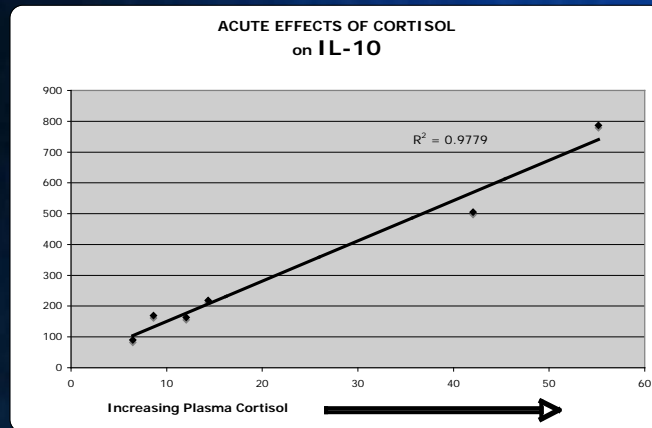
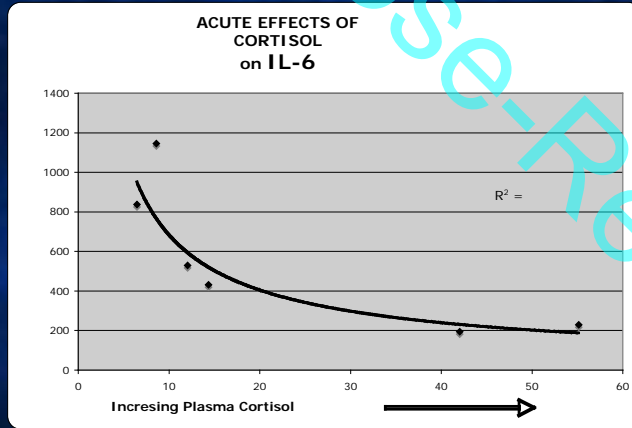
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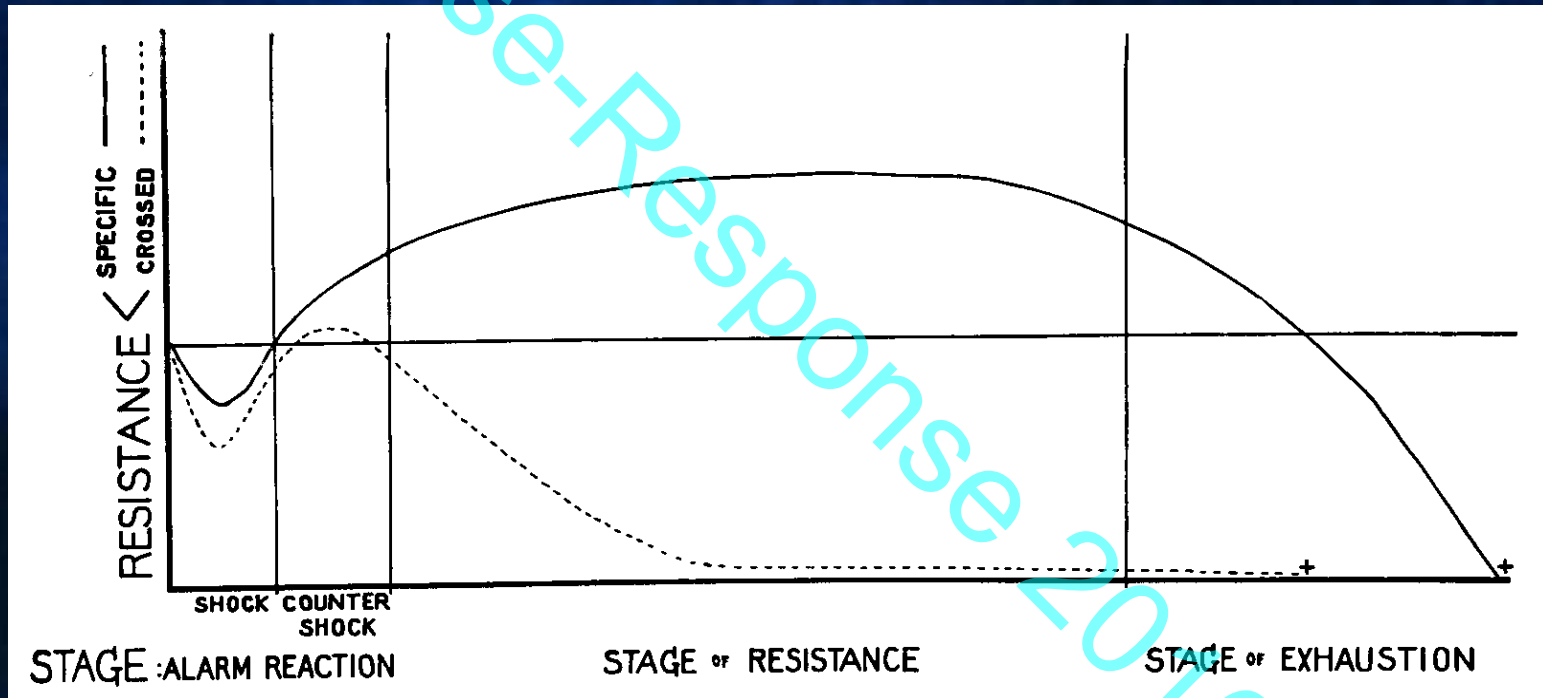
Yeager MP et al. Crit Care Med 2005.



- Where is the Bell?
- GCs, when present or administered coincident with an inflammatory stimulus, are anti-inflammatory in a dose-dependent manner.

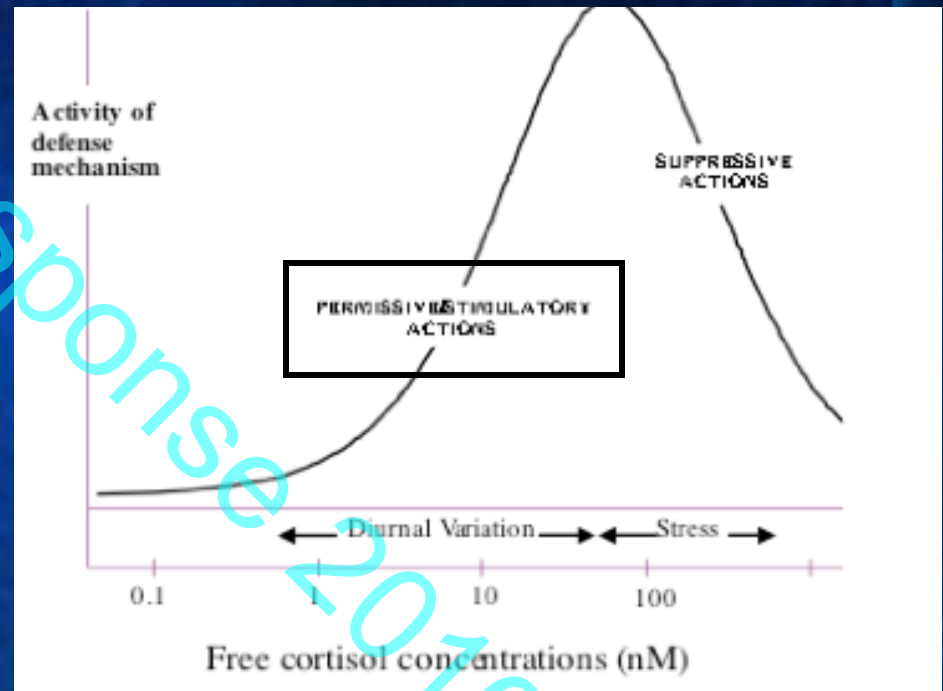
Selye: Systemic Injury Response

From *Stress* ©1950



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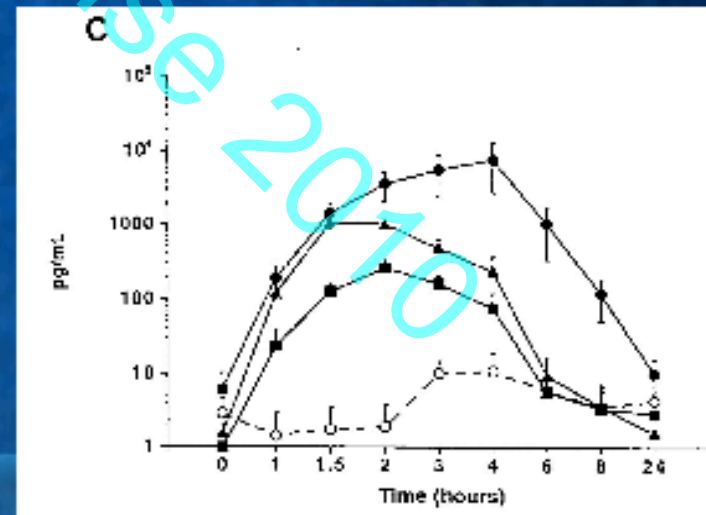
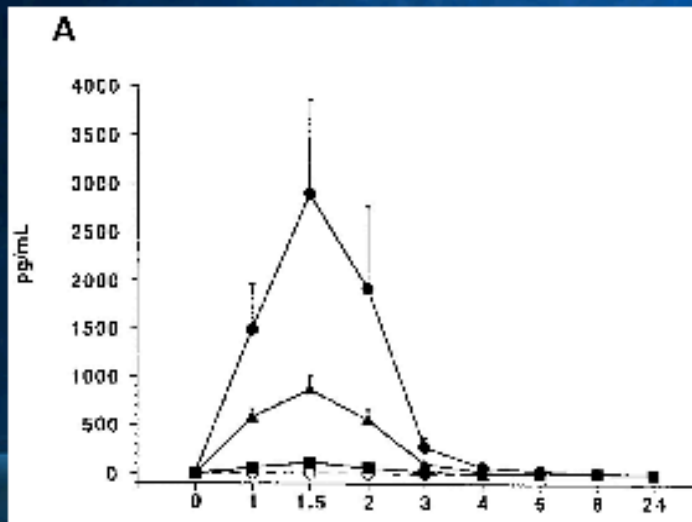
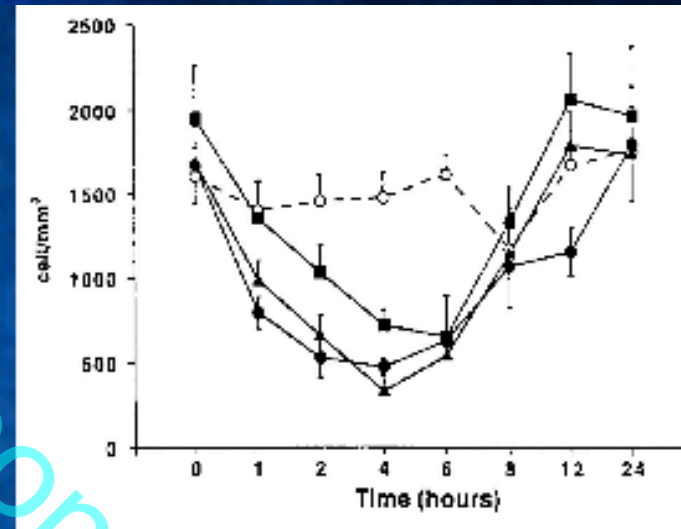
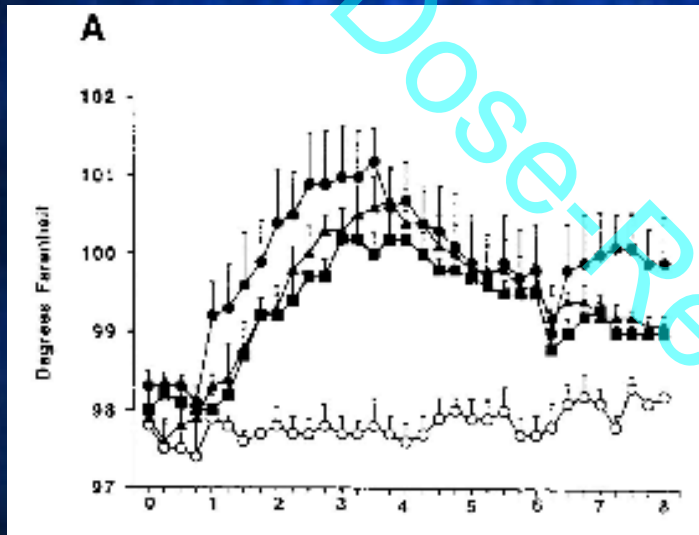


Experimental Stress in Humans

Experimental Endotoxemia

- Bacterial endotoxin as a model of systemic inflammation in human volunteers:
 - E.Coli (Lot EC-6; O:113) 'US Standard Reference Grade Endotoxin'
 - Pharmacy Development Service, Clinical Center, NIH--arrives as lyophilized powder
 - 2 ng/kg I/V--what happens?
 - Nothing for ~ 1 hour
 - Headache, chills, myalgia, tachycardia, fever, lethargy
 - Resolution in 4-6 hours

Endotoxin Model of SIRS



Pre-treatment With Stress Cortisol Enhances the Human Systemic Inflammatory Response to Bacterial Endotoxin

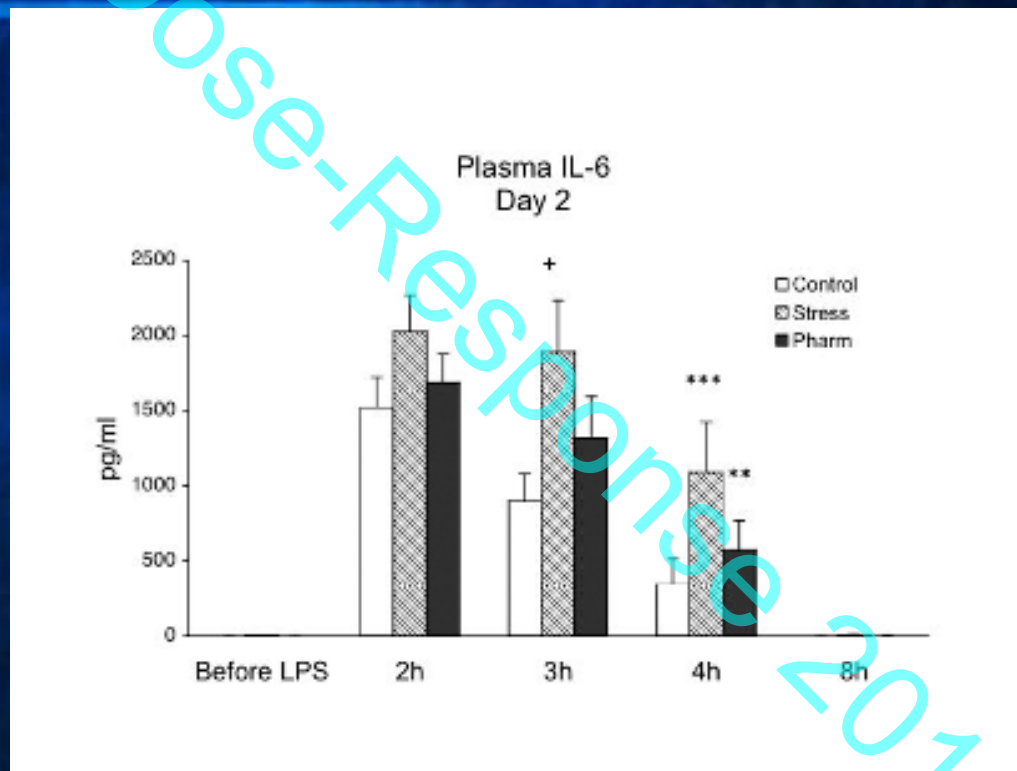
Yeager et al, *Crit Care Med*, In Press

	MONDAY			TUES				WED	FRI
n=12/grp	8-9AM	9AM----->	3PM	7-8AM	8AM	9AM 11AM Noon 2PM	6-7PM		
GROUP 1	Pregnancy test ^a , I/V placement	Saline I/V		Vascular catheter placement ^b	LPS 2ng/kg I/V		Discharge ^c		
GROUP 2	Pregnancy test ^a , I/V placement	Hydrocortisone 1.5 ug/kg/min I/V		Vascular catheter placement ^b	LPS 2ng/kg I/V		Discharge ^c		
GROUP 3	Pregnancy test ^a , I/V placement	Hydrocortisone 3 ug/kg/min I/V		Vascular catheter placement ^b	LPS 2ng/kg I/V		Discharge ^c		
Blood sample^d	X				X	X		X	X

I/V = intravenous LPS = lipopolysaccharide (E.Coli endotoxin)

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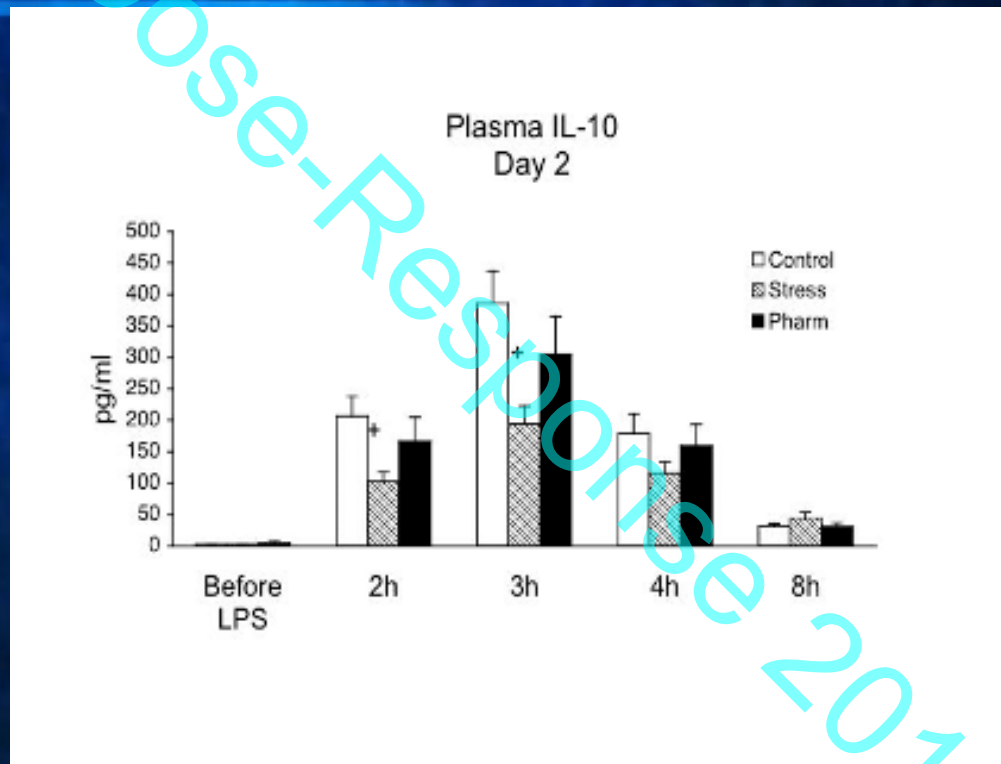
Crit Care Med, 2009



- Plasma IL-6 response to LPS
- P=0.004 Stress vs. Control

Pre-treatment With Stress Cortisol Enhances the Human Systemic Inflammatory Response to Bacterial Endotoxin

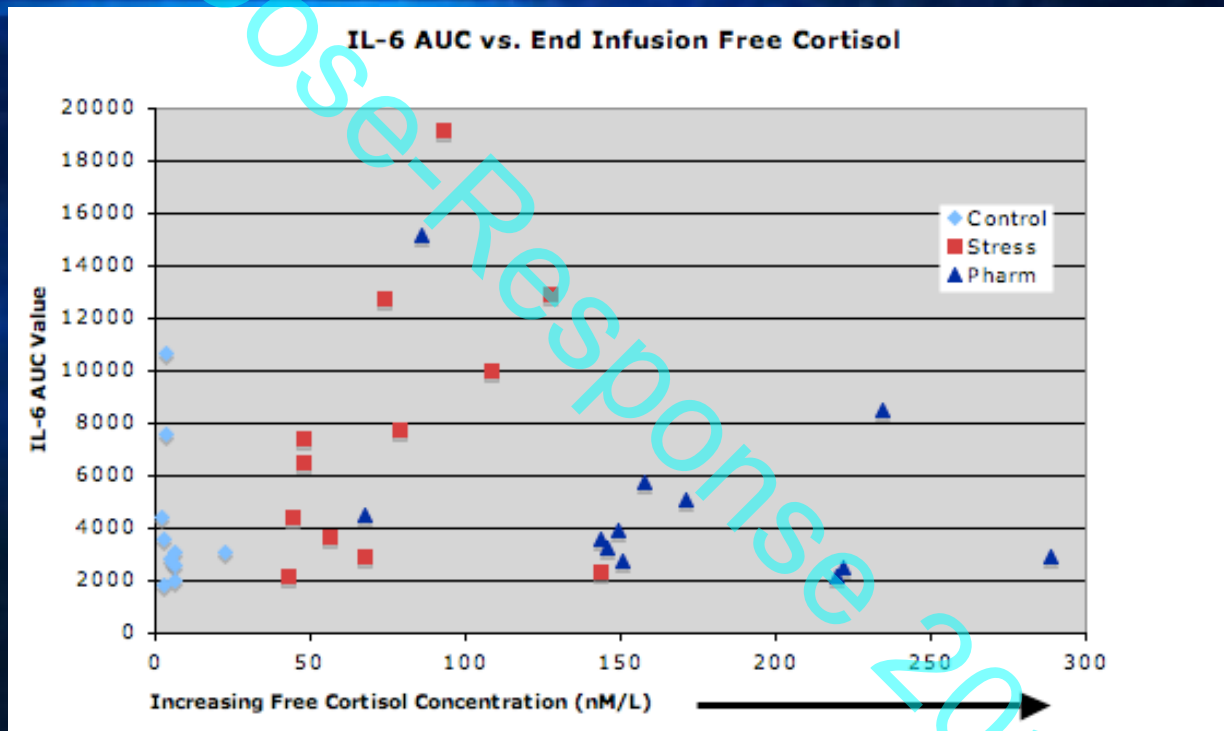
Crit Care Med, In Press



- Plasma IL-10 response to LPS
- $P=0.03$ Stress vs. Control

The Bell Curve

What would be the relationship between the free cortisol concentration achieved on Day 1 to IL-6 Response on Day 2



- Abscissa: Free cortisol at end of Day 1 infusion
- Ordinate: Total IL-6 release (AUC) on Day 2

SUMMARY

- Cortisol regulation of human inflammation:
 - Is not fully represented by a linear anti-inflammatory dose-response
 - Is both dose (concentration) and time-dependent
 - Exhibits delayed (preparative) effects that are bi-phasic: either suppressive or stimulatory depending on cortisol concentration

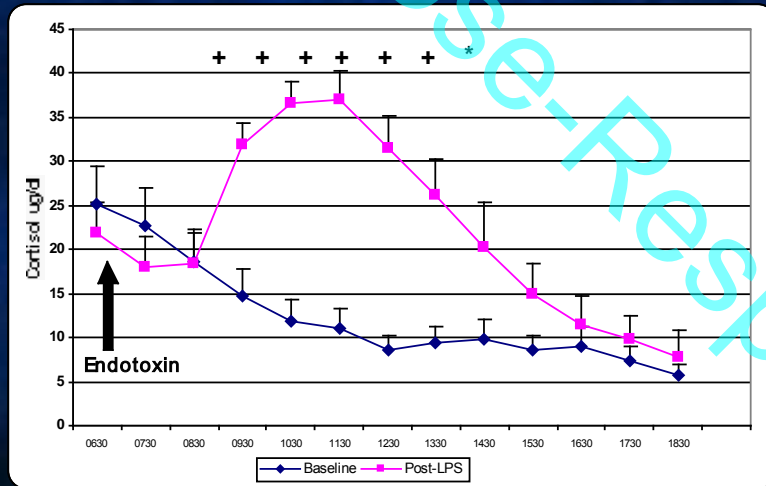
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Clinical Remnants of Selye's Work: Acute Addisonian Crisis

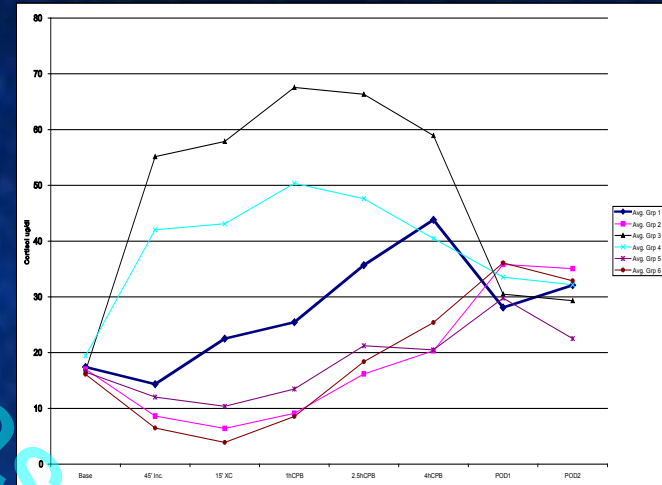
- 34 y.o. male with rheumatoid arthritis
- Oral cortisone for 8 months
- Hip surgery
- Hypotensive immediately after surgery and died
- Autopsy: adrenal cortical atrophy

Fraser et al. *JAMA*, 1952

What is a 'Physiologic' Cortisol Response to Acute Systemic Stress?



Rassias et al, CCM 2005

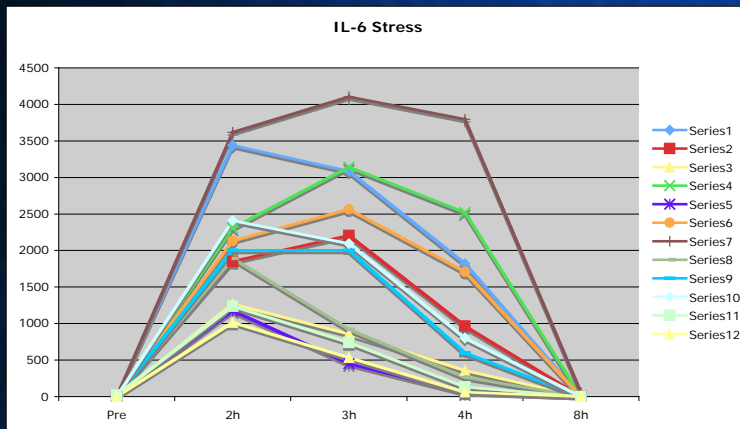


Yeager et al, JCTA, 2005

Following major systemic stress, the plasma cortisol increases to approximately 35-45 ug/dl

Pre-treatment With Stress Cortisol Enhances the Human Systemic Inflammatory Response to Bacterial Endotoxin

Crit Care Med, In Press



- What next?
- Marked individual variability in GC-induced responses
 - Large databases
 - Cellular/molecular mechanisms