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Ormoni dello Stress ed Immunità

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GENOVA

Risposta "fight or flight"



Ipo salivazione

Midriasi

Tensione muscolare, Tremore

Tachipnea (aumento del volume corrente)

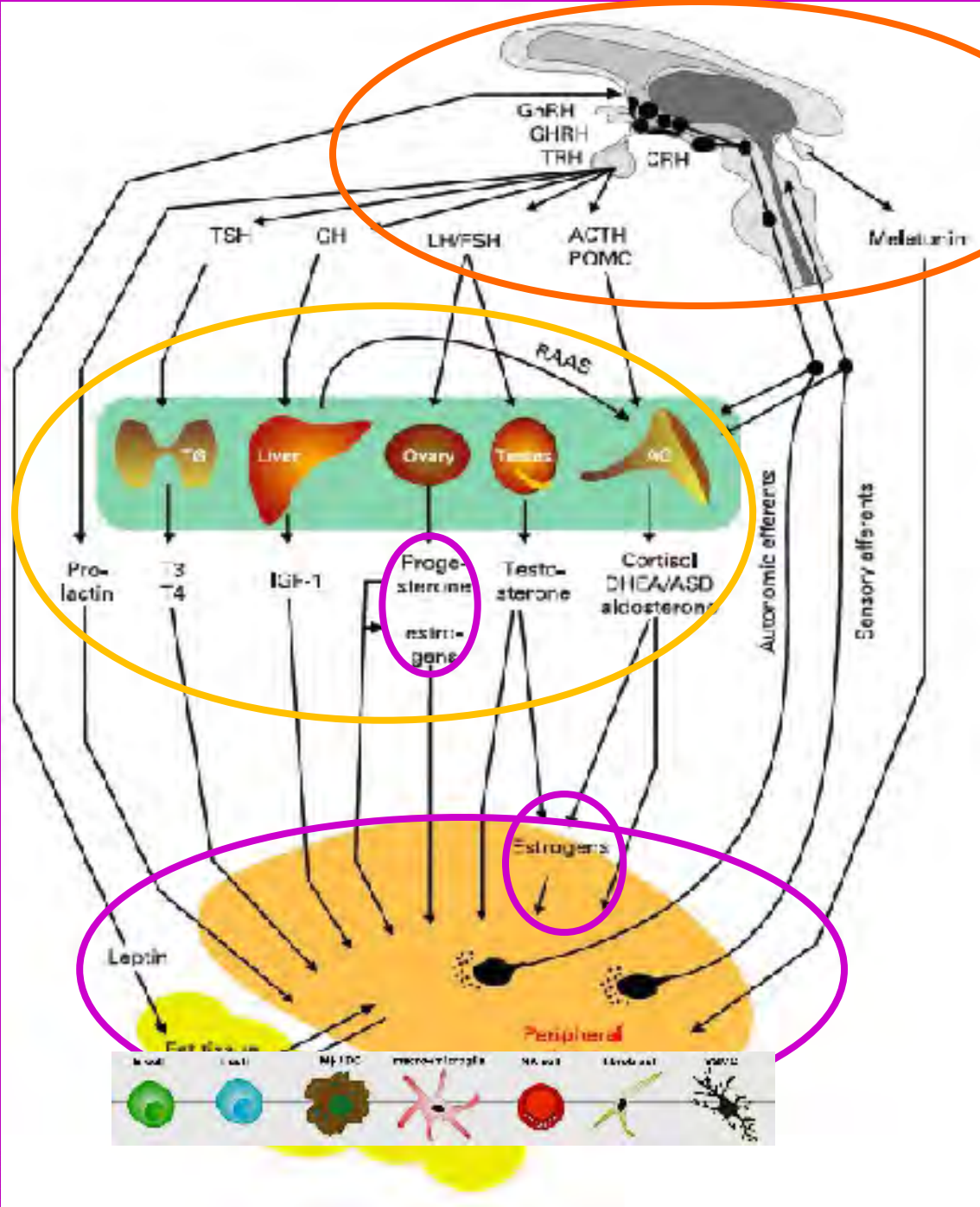
Tachicardia (aumento gittata)

Riduzione peristalsi

Iperglicemia (↑ glicogenolisi e gliconeogenesi)

Vasocostrizione (aumento PA)





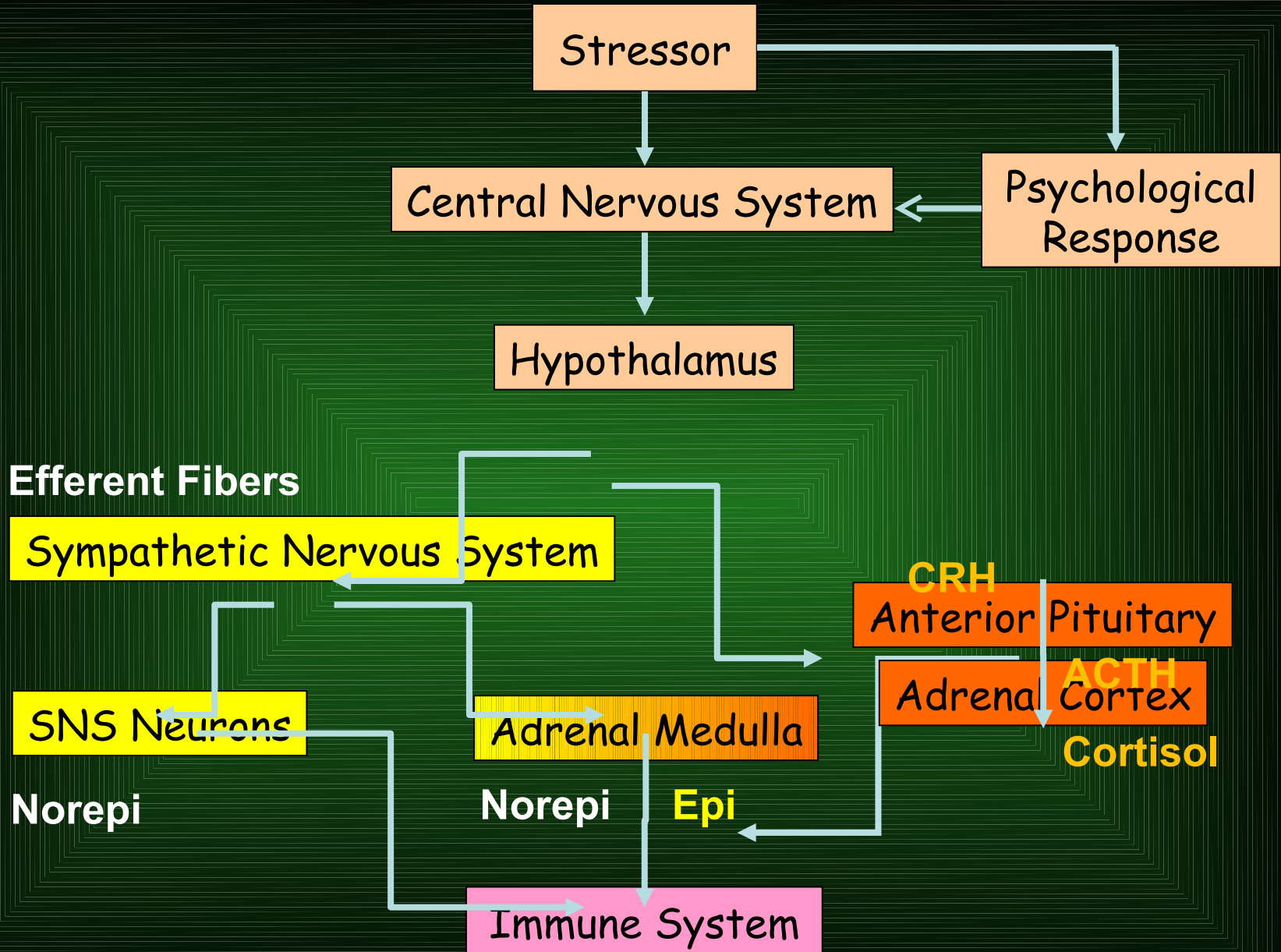
The Neuroendocrine Immune System

SNC
+

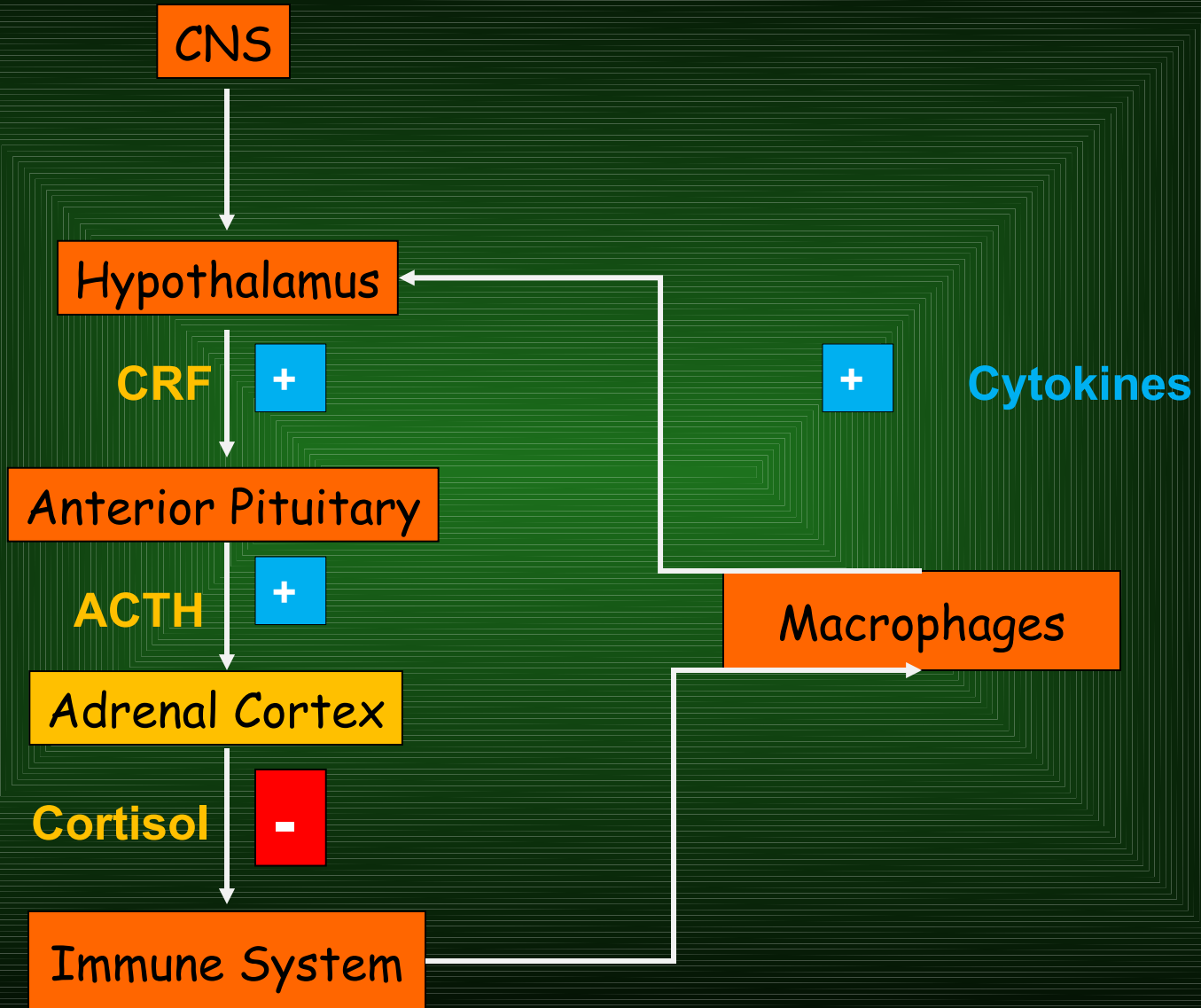
SNP
+

Endocrine System
=
“Integrated Immune System”

The stress network



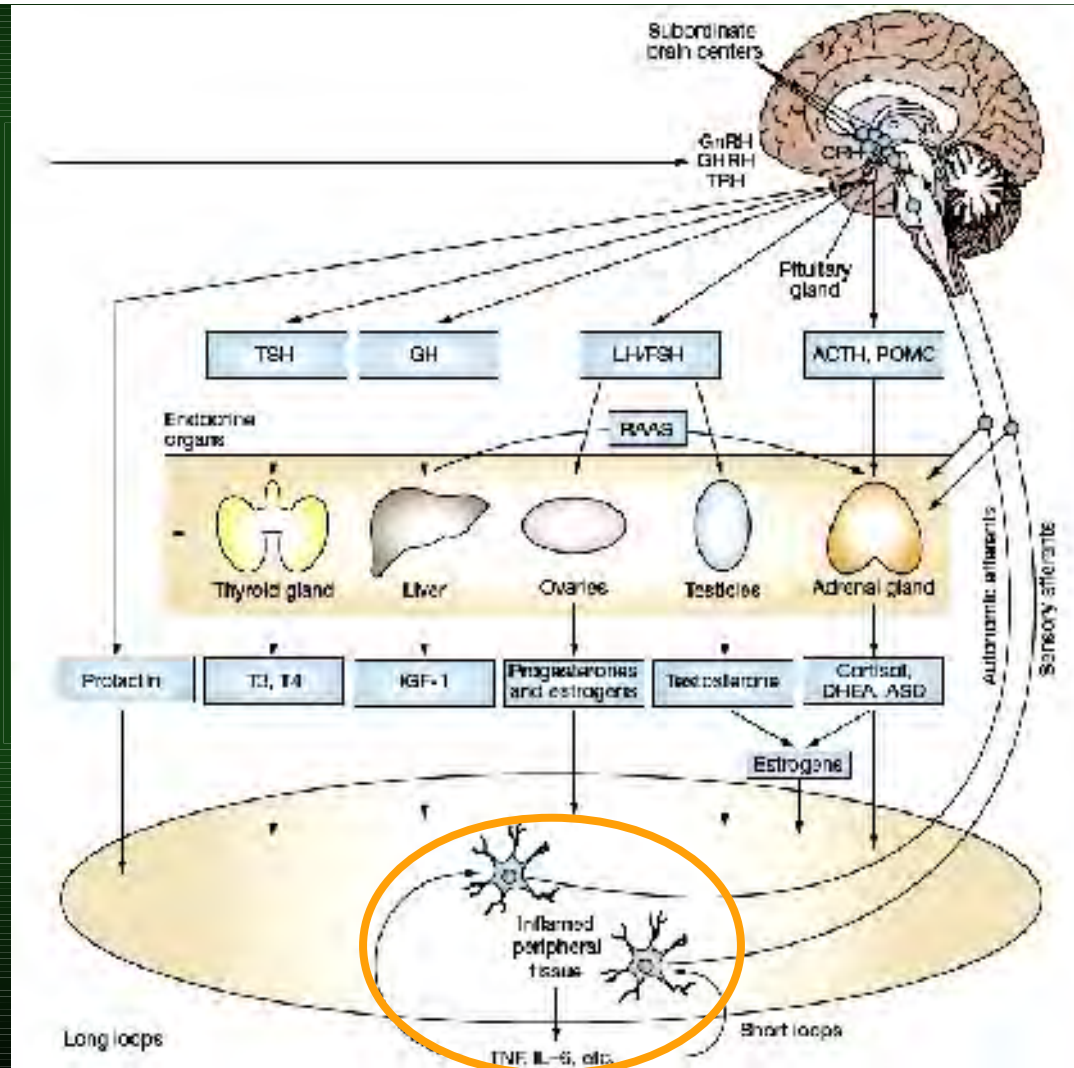
The stress immune response pathway



Nature Clin Pract Rheum 2007

Neuroendocrine-immune interactions in synovitis

Maurizio Cutolo*, Rainer H Straub and Johannes WJ Bijlsma



Lo Stress Condiziona il Sistema Immunitario

HPA axis and cortisol (anti-inflammatory role)

Stress causes dysregulated cortisol response

- Short term stressor – raises it
- Chronic stress – inadequate cortisol secretion

Long term and long past stresses might result in too low of cortisol – no inflammation suppression

- Flattens out the diurnal cycle of cortisol production

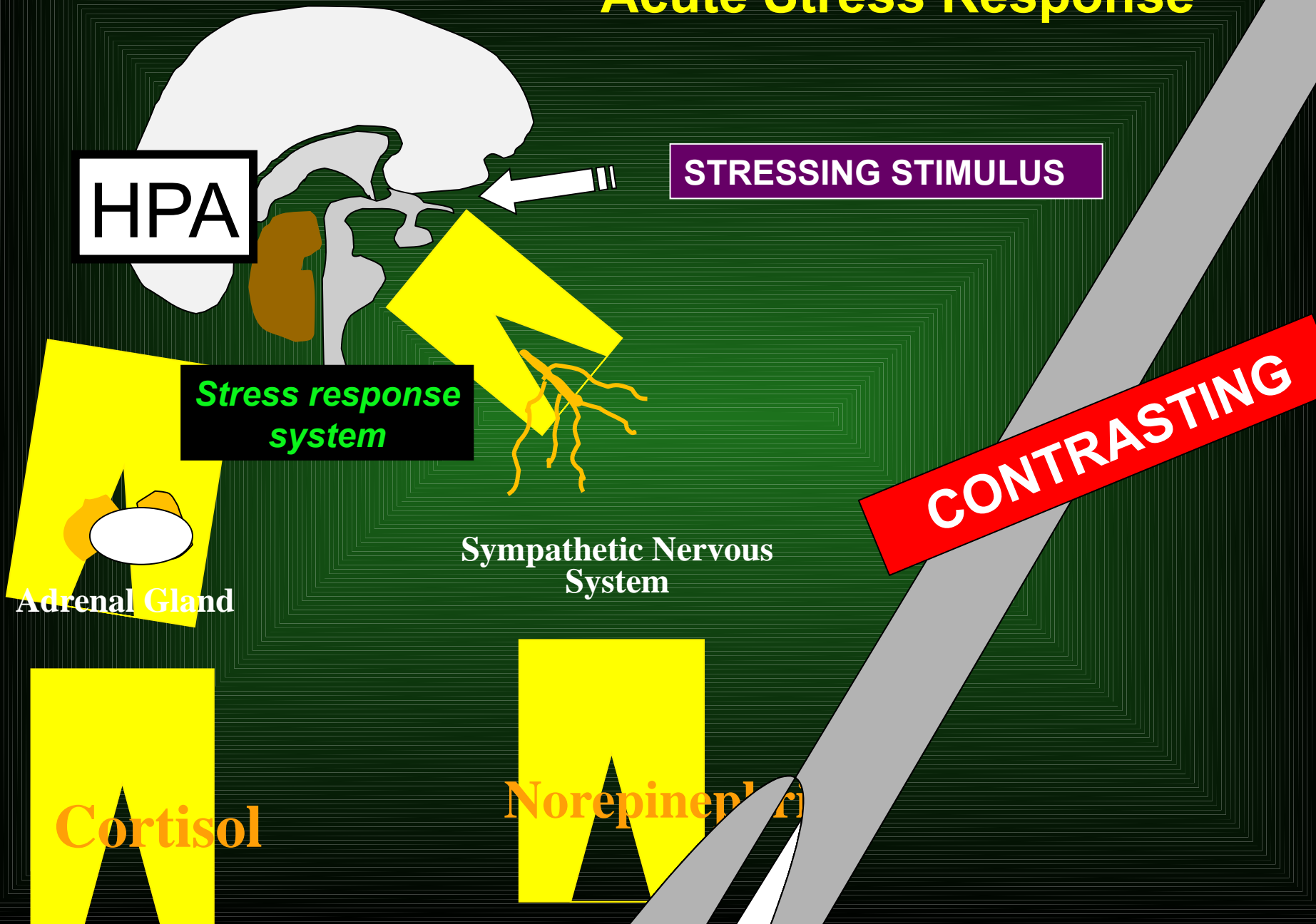
RA (and depressed!) patients have blunted cortisol secretion: not enough!

Cutolo M, Straub RH, Bijlsma JWJ Nature 2007

Kemeny M, Schledowski M Brain Behaviour Immunity 2007

Davis MC et al. M Brain Behaviour Immunity 2007

Acute Stress Response



HPA

STRESSING STIMULUS

Stress response system

Adrenal Gland

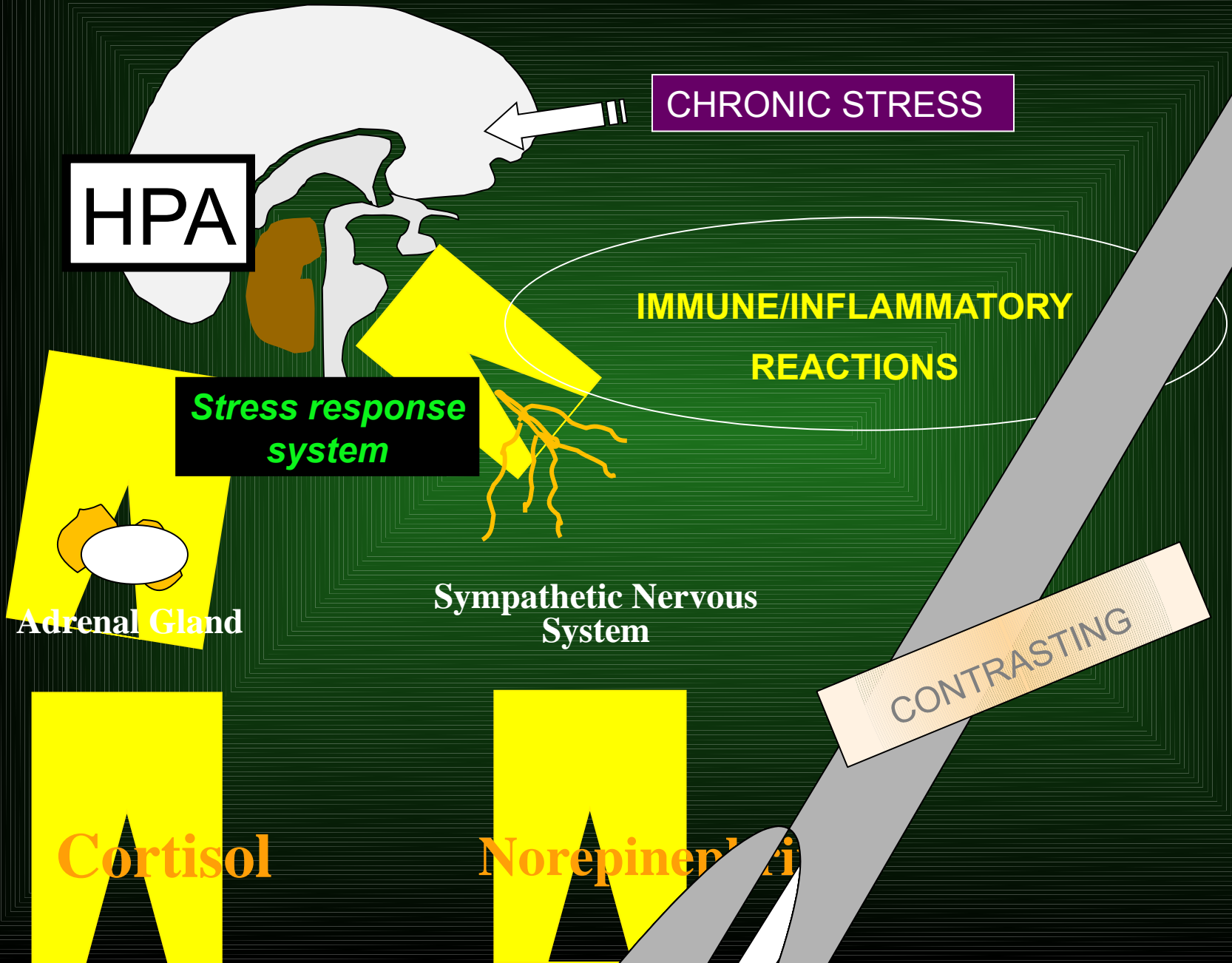
Sympathetic Nervous System

CONTRASTING

Cortisol

Norepinephrine

Chronic Stress Response



CHRONIC STRESS

HPA

Stress response system

Adrenal Gland

Sympathetic Nervous System

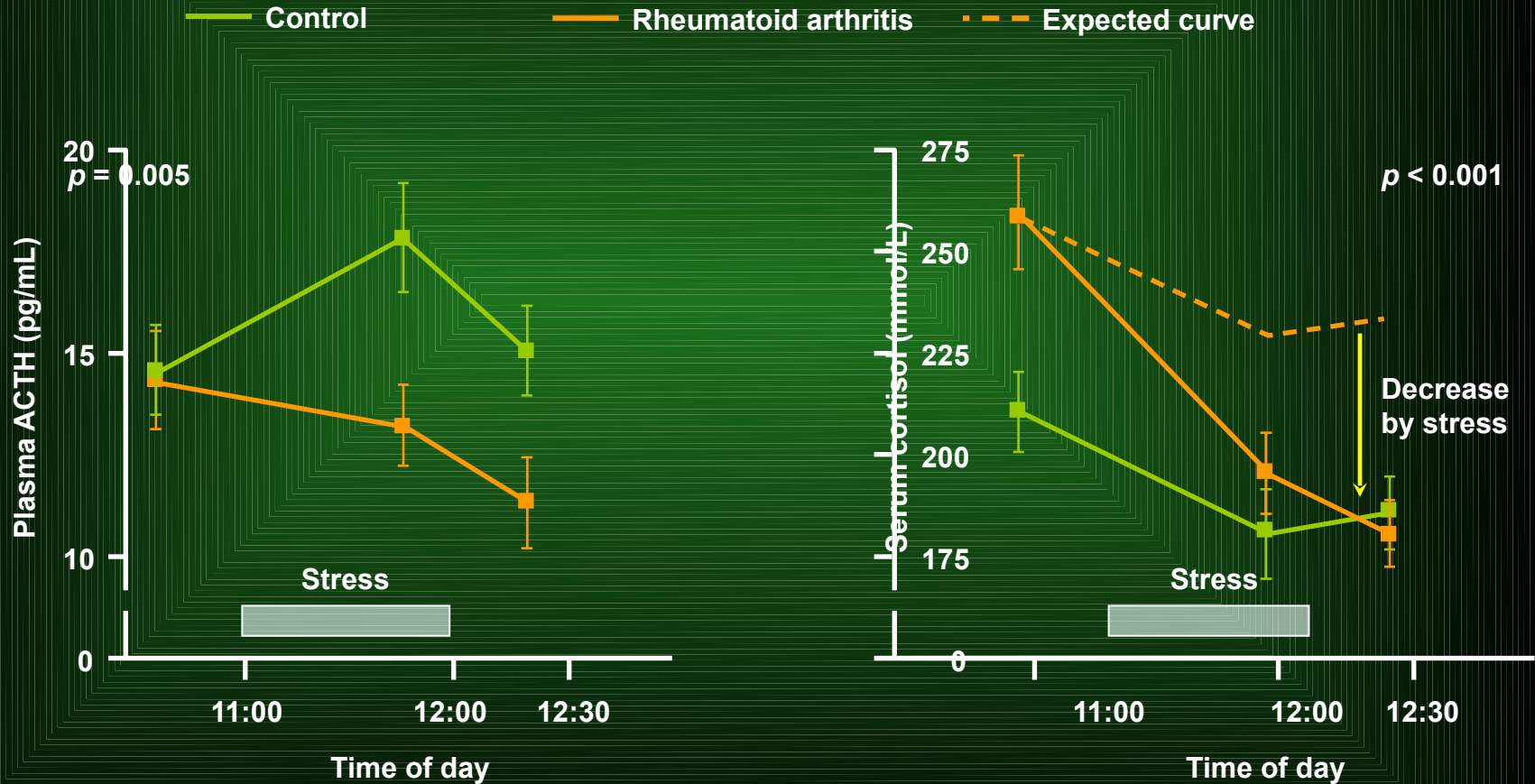
IMMUNE/INFLAMMATORY REACTIONS

CONTRASTING

Cortisol

Norepinephrine

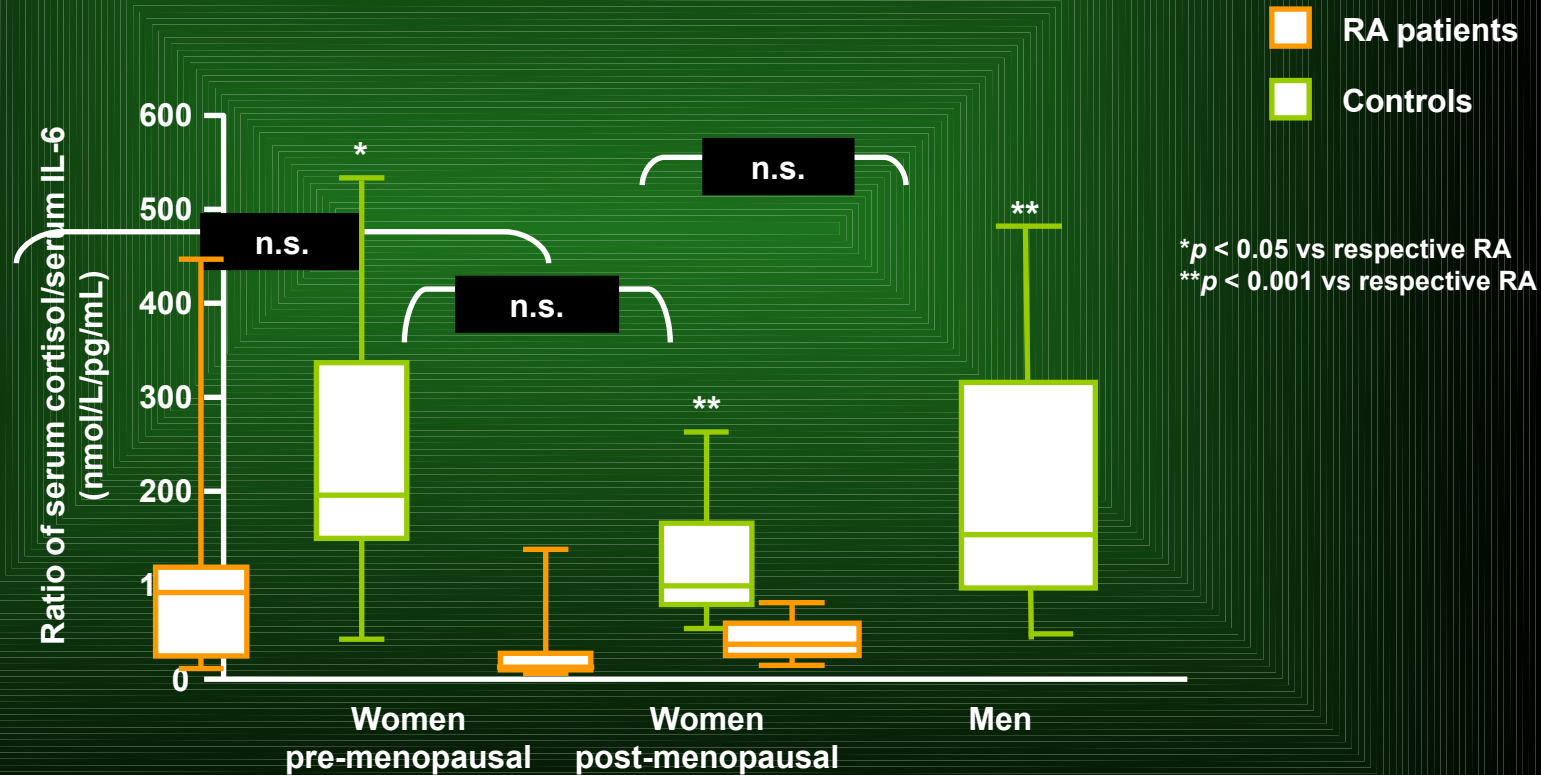
The Neuroendocrine-Immune System Effects of Incoming Stress in RA

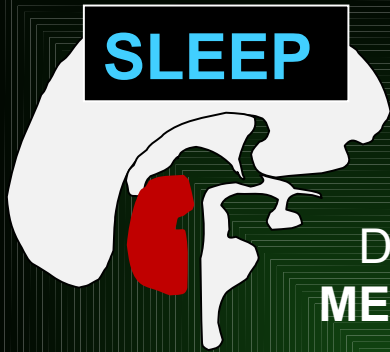


Stress: combination of bicycle ergometer + cold water + computer stress test

La secrezione notturna di cortisolo nei pazienti con AR è insufficiente per contrastare lo stato infiammatorio

- Conseguenza: infiammazione marcata con picco notturno





SLEEP

Circadian Rhythms

Loss of **SLEEP**

STRESS

ACUTE

CHRONIC

Darkness DayLight
MELATONIN CORTISOL

INCREASE

DECREASE

INCREASE

DECREASE

CORTISOL
Normal

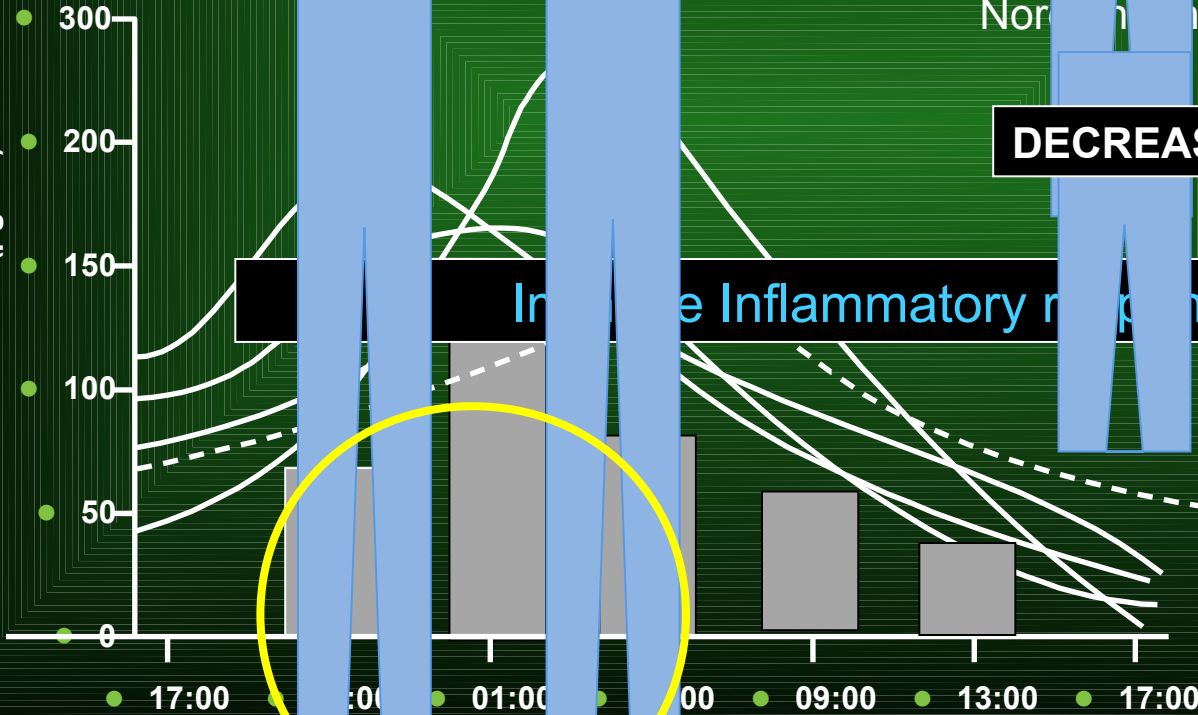
CORTISOL
Normal

DECREASE

INCREASE

Increase Inflammatory response

Serum levels (pg/mL)



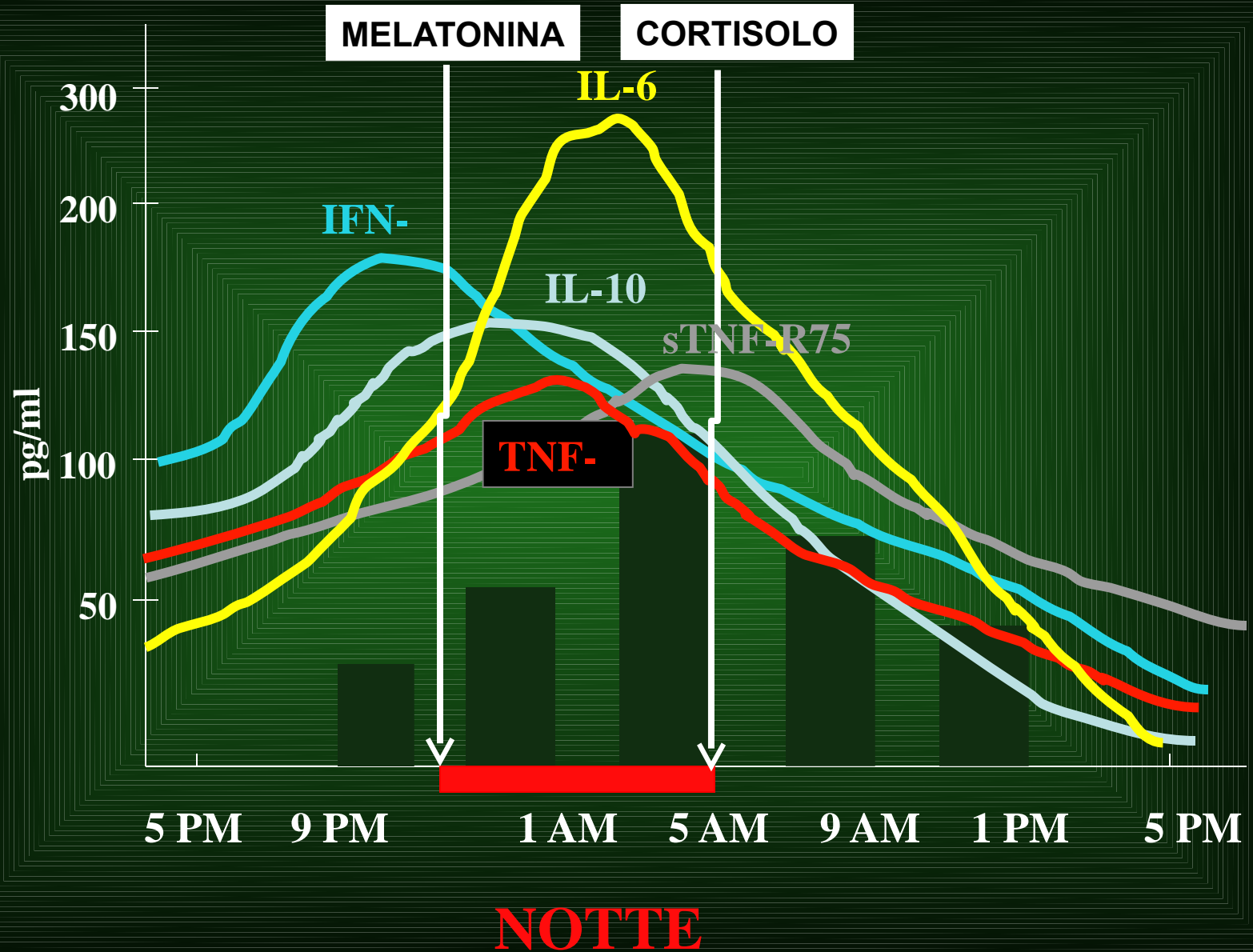
Time of day

NIGHT

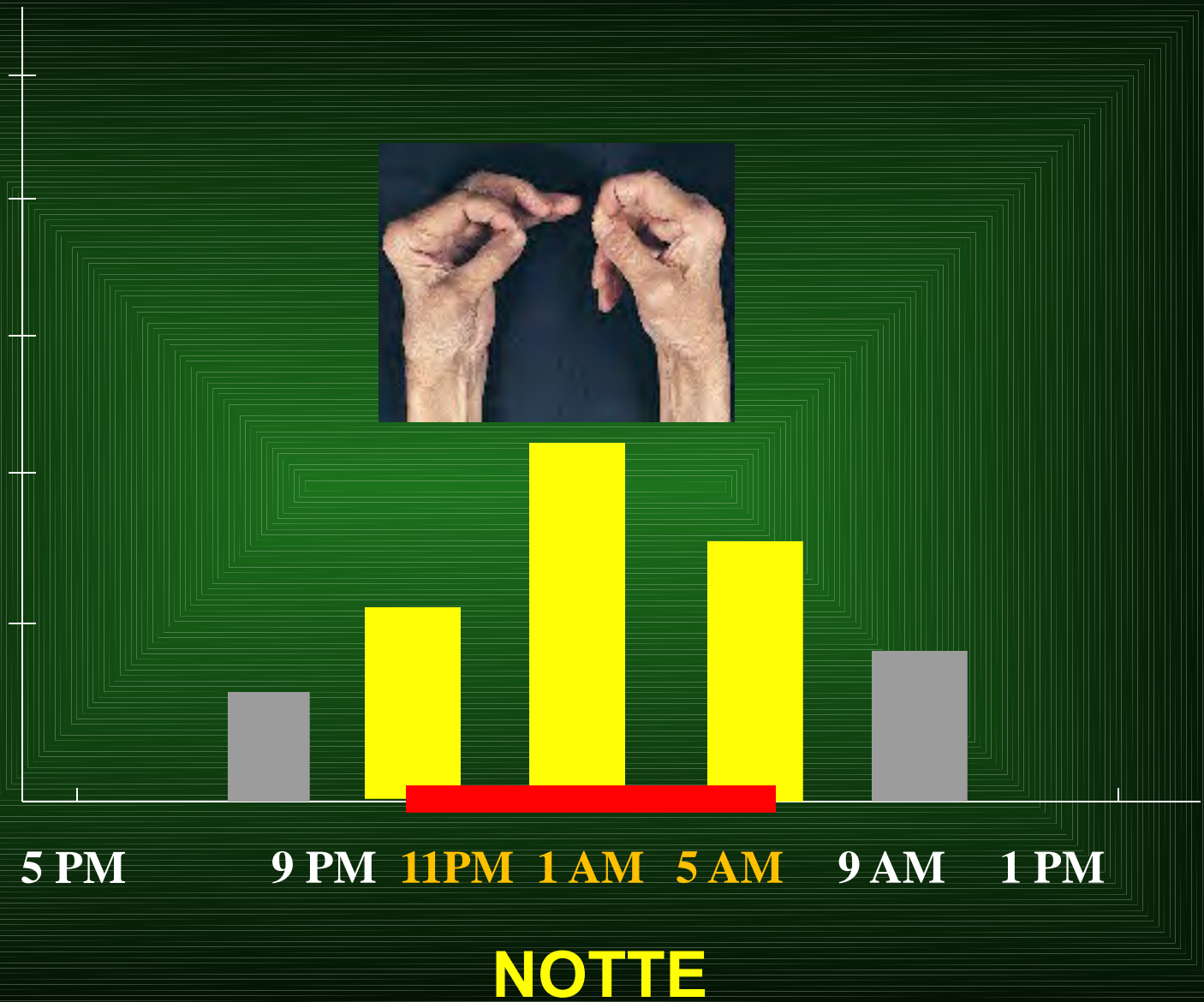
DAY

- Neutrophils
- Inflammatory cytokines
- Immune Response

Andamento circadiano della secrezione citochinica



Andamento circadiano dei sintomi dell'AR

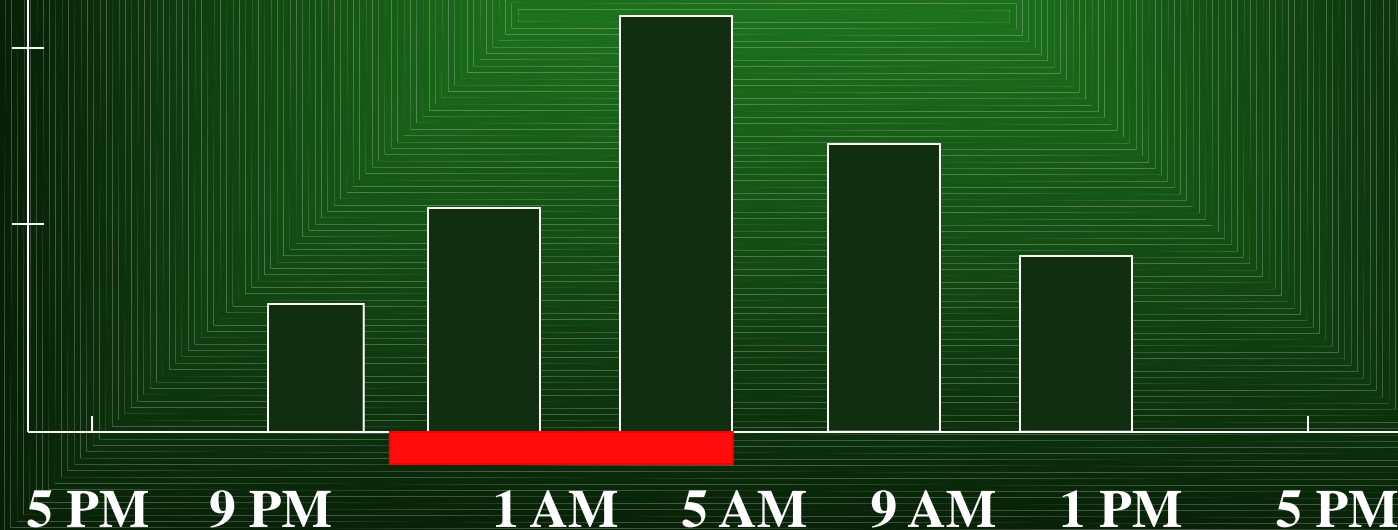


Andamento circadiano dei livelli di Fattore Reumatoide nell'AR

Nell'AR le Ig seguono un ritmo circadiano, come è stato dimostrato per:

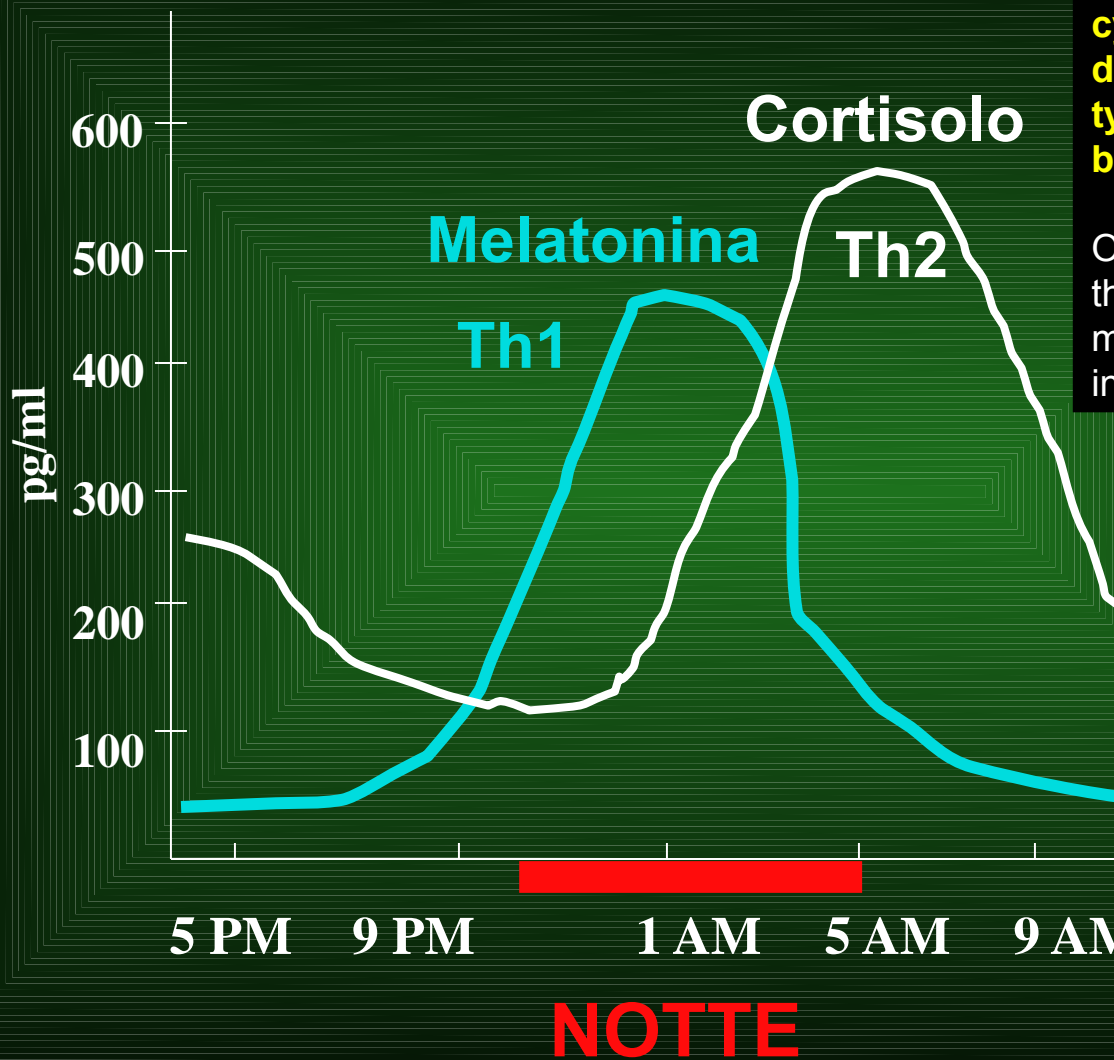
- ◆ Fattore Reumatoide IgA (picco sierico alle 8 del mattino)
- ◆ Fattore Reumatoide IgM (picco sierico alle 2 del mattino)

Inoltre gli Immunocomplessi circolanti nell'AR seguono un ritmo circadiano, con un picco tra le 6 e le 9 del mattino



NOTTE

Ritmi circadiani nell'ARTRITE REUMATOIDE



J Immunol 1997 Jun 1;158(11):5163-8
Diurnal rhythmicity of human cytokine production: a dynamic disequilibrium in T helper cell type 1/T helper cell type 2 balance? Petrovsky N, Harrison LC.

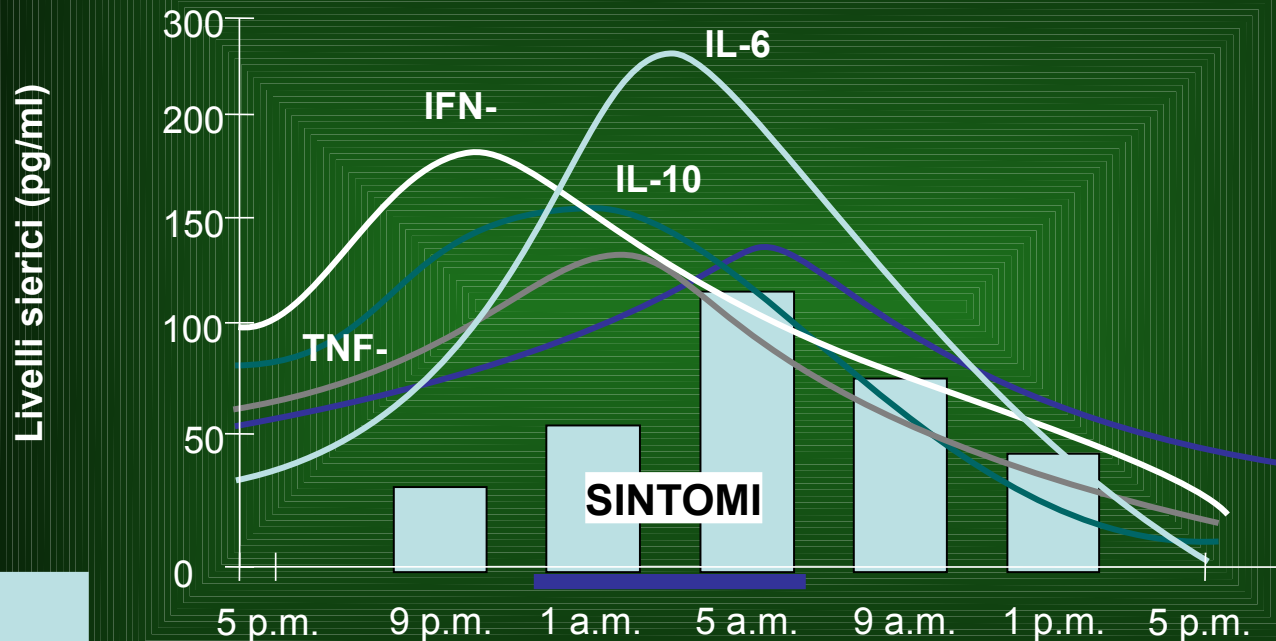
Our findings support the concept that plasma cortisol and possibly melatonin regulate diurnal variation in the IFN-gamma/IL-10 ratio.

Int Rev Immunol 1998;16(5-6):635-49
The chronobiology of human cytokine production. Petrovsky N, Harrison LC.

Peak production of the pro-inflammatory cytokines IFN-gamma, TNF-alpha, IL-1 and IL-12 occurs during the night and early morning at a time when plasma cortisol is lowest.

Cronobiologia dell'ARTRITE REUMATOIDE

La concentrazione elevata di citochine pro-infiammatorie durante la notte comporta un peggioramento della sintomatologia mattutina tipica



“... the timing of low-dose glucocorticoid administration should be adapted to the biological rhythms of the inflammatory process in RA.”

Soggetti sani

Melatonina

Cortisolo

NOTTE

5 PM

9 PM

1 AM

5 AM

9 AM

1 PM

5 PM

Pazienti con AR

Melatonina

Cortisolo

NOTTE

5 PM

9 PM

1 AM

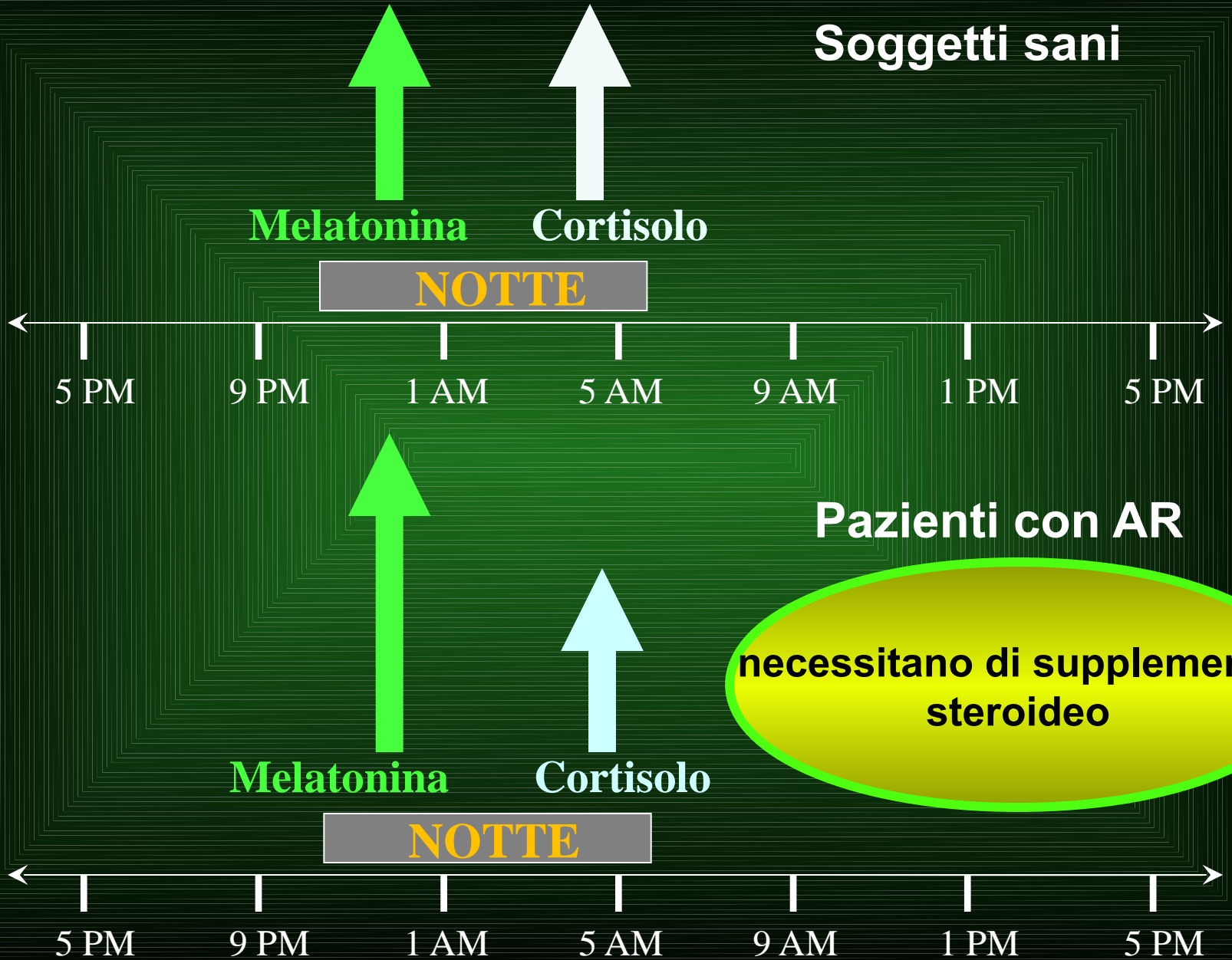
5 AM

9 AM

1 PM

5 PM

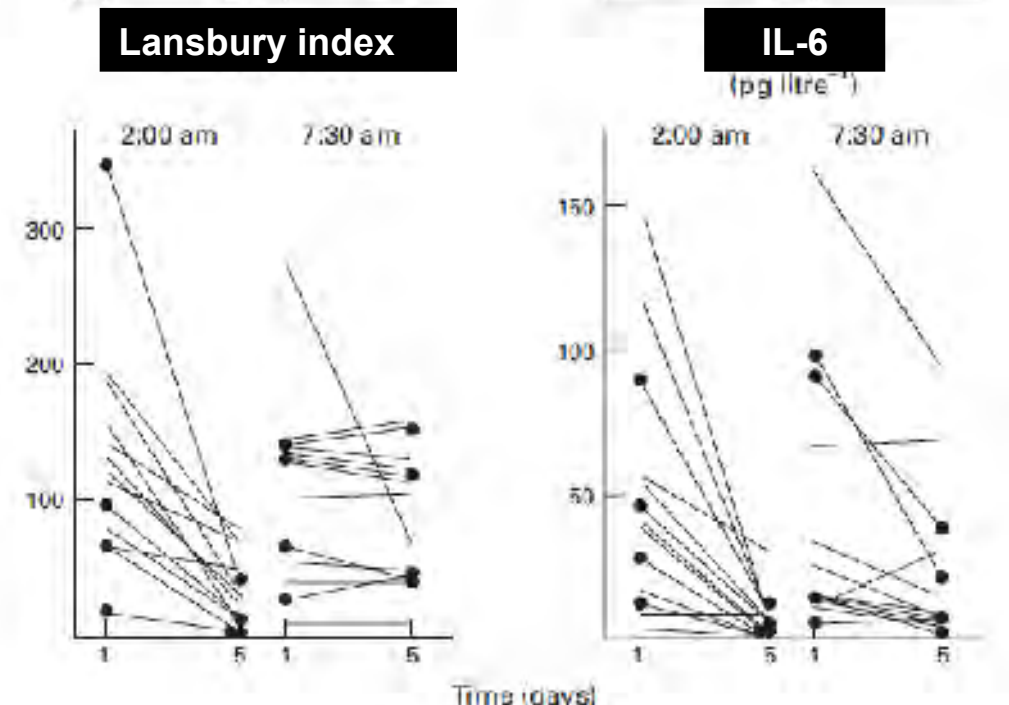
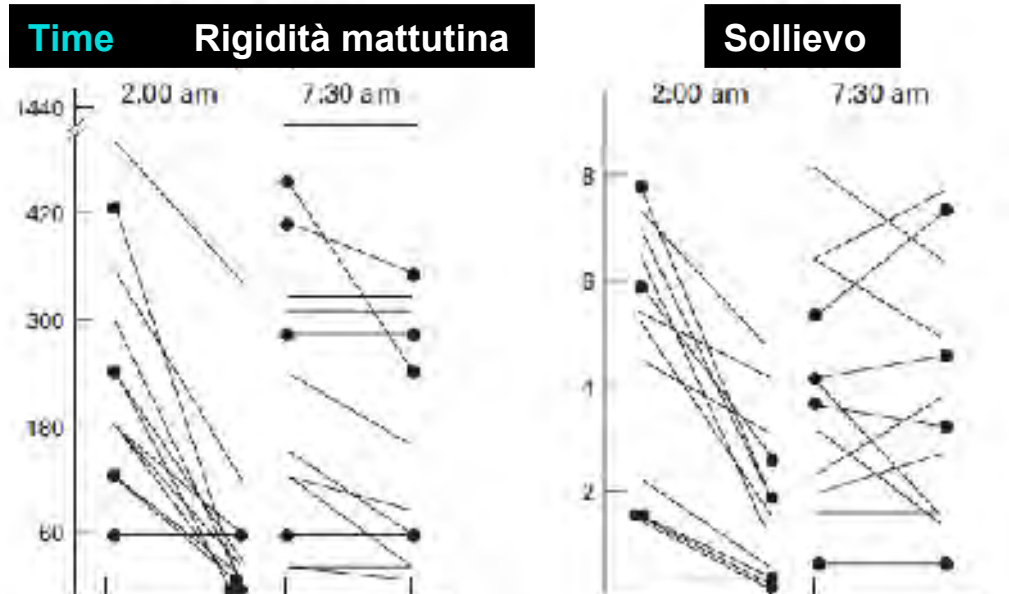
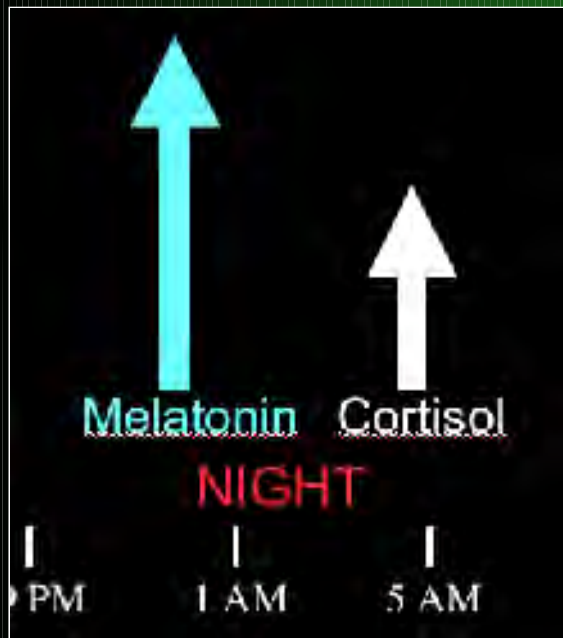
**necessitano di supplemento
steroido**



The timing of glucocorticoid administration in rheumatoid arthritis

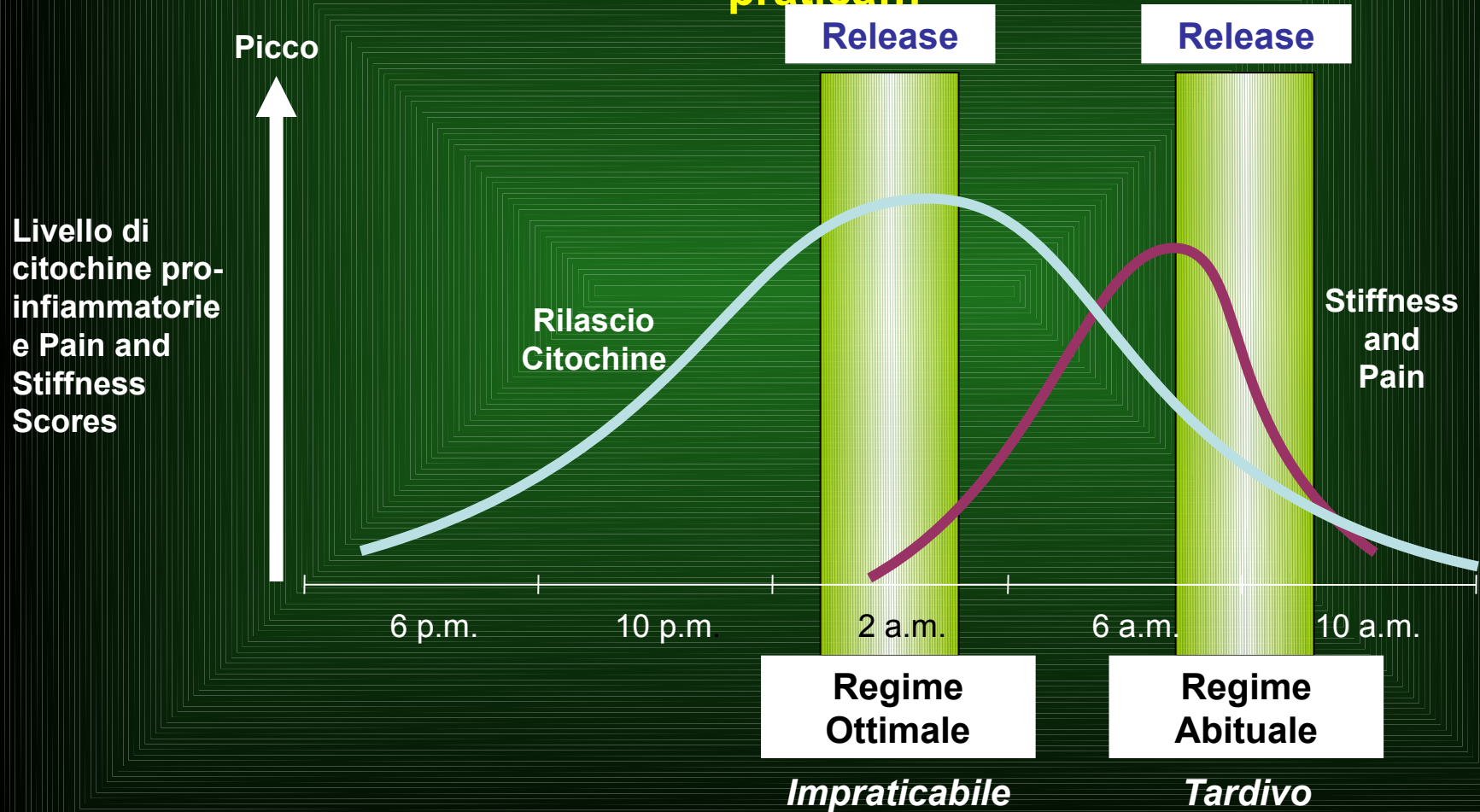
Arvidson NA et al.

Ann Rheum Dis 1997;56:27-31 (January)

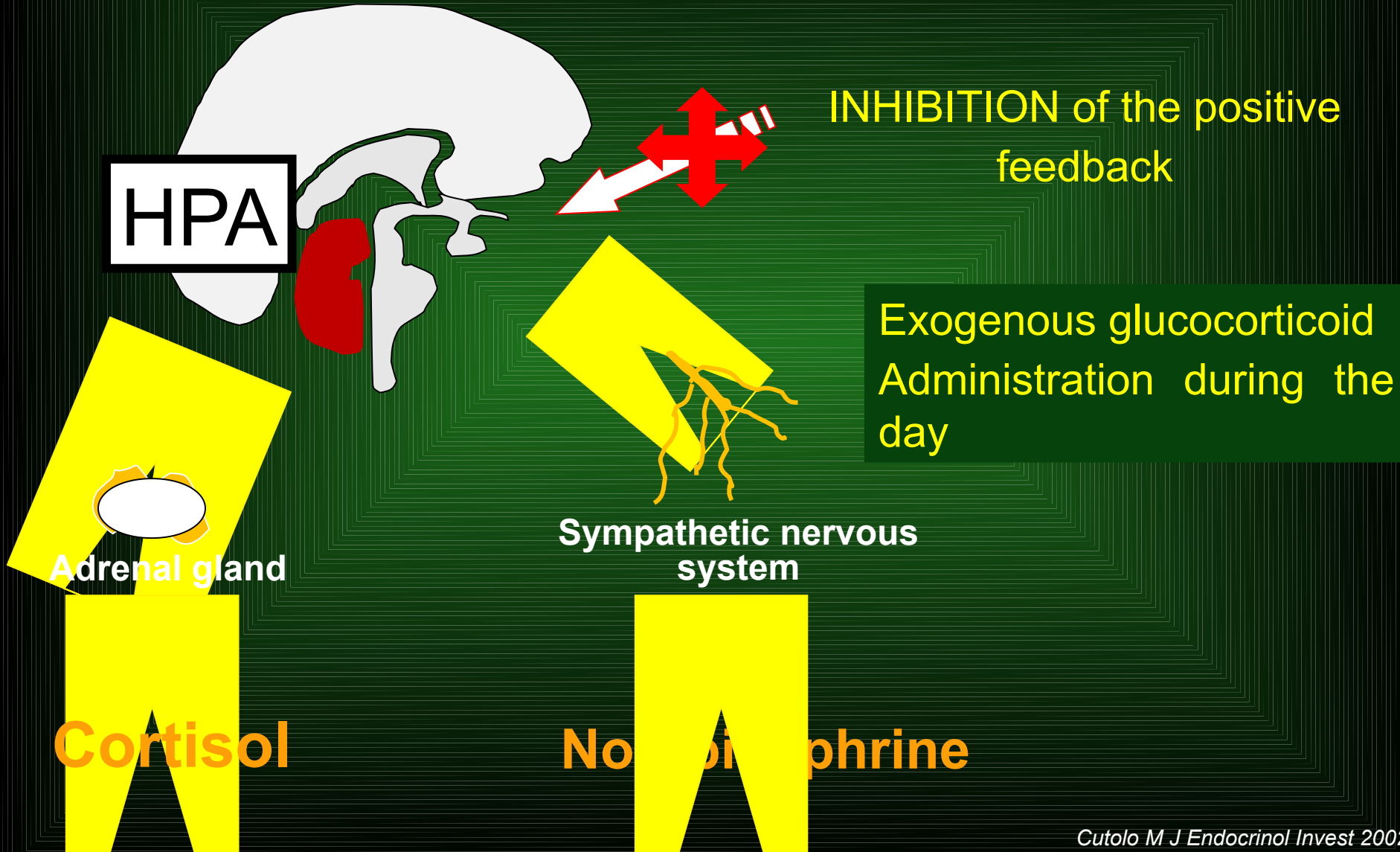


La tipica somministrazione mattutina dello steroide è tardiva

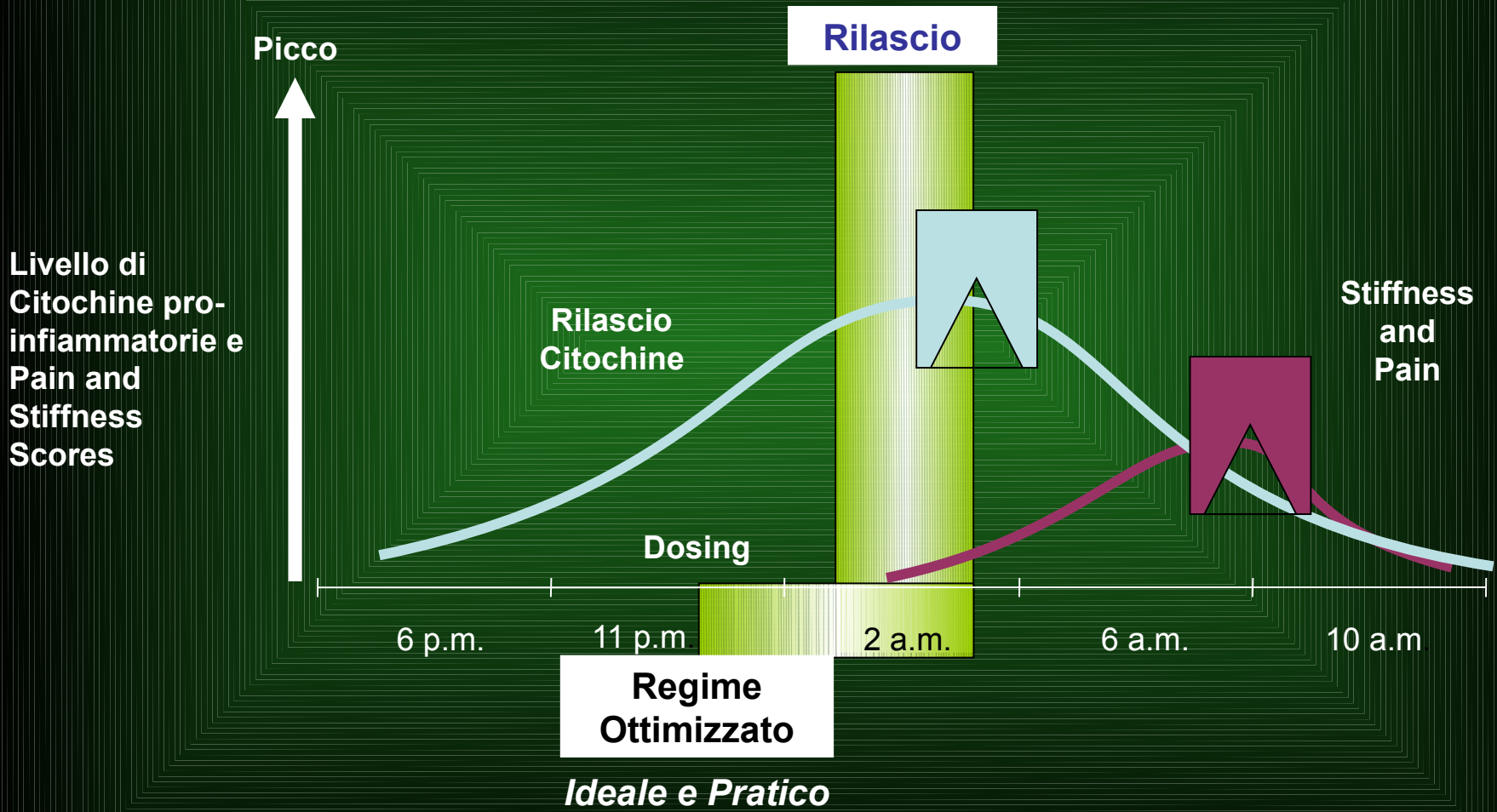
rispetto al fisiologico picco notturno endogeno di citochine, mentre una somministrazione alle 2 sarebbe ideale ma poco pratica...



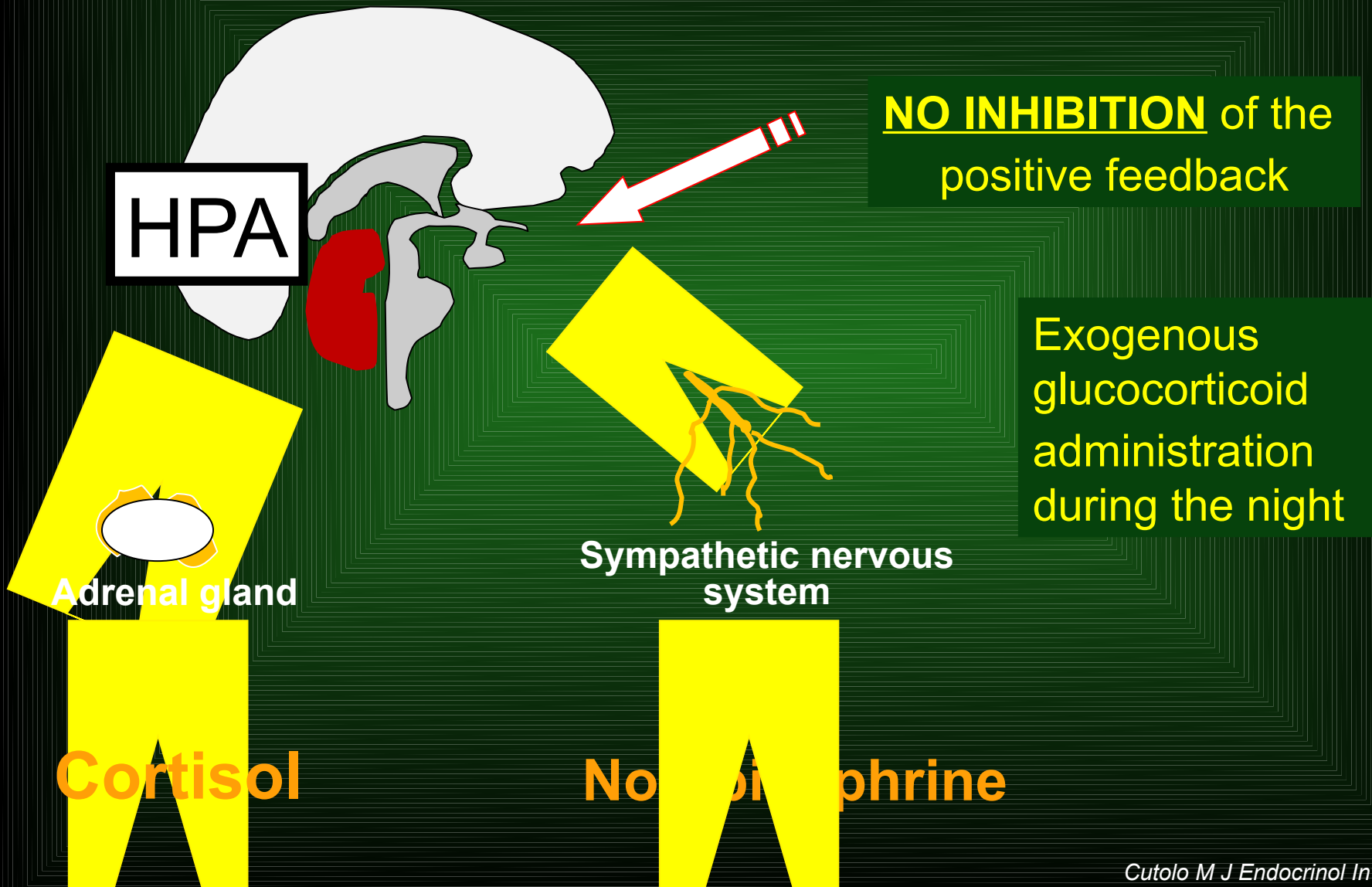
Effetti della somministrazione cronica di steroide diurna sull'asse HPA



Ma ora abbiamo formule a rilascio programmato...



Effetti della somministrazione cronica di steroide notturna sull'asse HPA



Hypothalamus-Pituitary-Adrenal Axis Function in Patients with Rheumatoid Arthritis Treated with Nighttime-Release Prednisone.

Alten R, Döring G, Cutolo M, Gromnica-Ihle E, Witte S, Straub R, Buttgereit F.

- **RESULTS:** The increase (mean, SD) of cortisol plasma concentrations after injection of corticorelin was 5.5 (4.37) microg/dl on IR prednisone at baseline (n = 21) and 5.3 (4.07) microg/dl on MR prednisone at 12 months (n = 22). Numbers of normal/suppressed/no response reactions did not differ among treatments. Switching from IR to MR prednisone did not influence responses, nor did longterm treatment of up to 12 months with MR prednisone. **No worsening of adrenal impairment was observed on treatment with nighttime-release prednisone in patients with low responsiveness to CRH testing before the treatment with MR prednisone.**
- **CONCLUSION:** **Treatment with nighttime-release prednisone did not change adrenocortical function over 12 months. We presume that chronotherapy with this nighttime-release prednisone may improve the efficacy of longterm low-dose glucocorticoid treatment in patients with RA.**

TAKE-HOME MESSAGES

Gli eventi stressogeni (psichici e fisici come traumi, infezioni, etc.) rivestono un importante ruolo di concausa nel trigger dell'autoimmunità

I pazienti con malattia infiammatoria cronica (AR) hanno un'insufficienza corticosurrenalica relativa

I pazienti con malattia infiammatoria cronica (AR) necessitano di una supplementazione steroidea come terapia eziologica

Il timing di somministrazione di questa terapia è fondamentale

La somministrazione notturna di prednisone, basata sul ritmo circadiano fisiologico di escrezione di tale ormone, determina un miglioramento clinico dei sintomi dell'AR superiore a quanto riscontrato in caso di somministrazione mattutina "classica"



GRAZIE PER L'ATTENZIONE!