# PNEI

## La proposta di un nuovo modello scientifico e culturale (seconda parte)

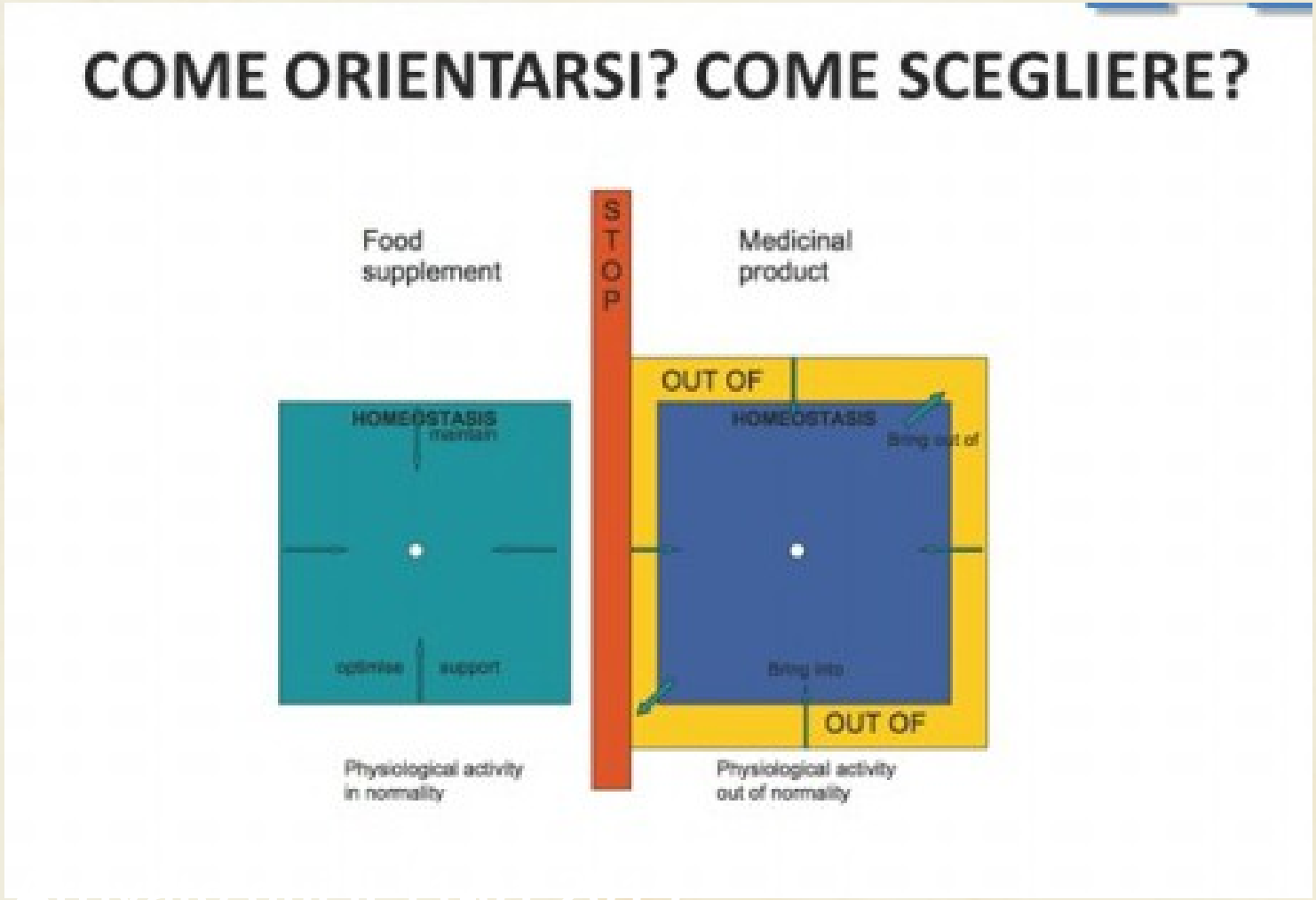
## Interpretare vecchie malattie secondo le nuove idee della PNEI e delle Neuroscienze

II Biennio – Seconda Lezione

AA 2014-15

Dott. Luciano Camerra

# Consiglio d'Europa 2008



# Una rivisitazione dei meccanismi d'azione

Vascular Health and Risk Management

Dovepress

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REVIEW

## Optimal therapeutic strategy for treating patients with hypertension and atherosclerosis: focus on olmesartan medoxomil

This article was published in the following Dove Press journal:
Vascular Health and Risk Management
23 June 2011
Number of times this article has been viewed

R Preston Mason

**Abstract:** Cardiovascular (CV) disease is a major factor in mortality rates around the world and

# Quanto finora noto

## ANTAGONISTI DEI RECETTORI $AT_1$

### Meccanismo d'azione

- antagonisti selettivi dei recettori $AT_1$; antagonismo di tipo competitivo
- prevengono tutti gli effetti dell'angiotensina II
- il profilo degli effetti è diverso da quello degli ACE inibitori:
  - gli effetti $AT_1$ sono ridotti di più;
  - i recettori $AT_2$ vengono comunque attivati
  - non ci sono aumenti significativi dell'Ang(1-7)
  - non ci sono effetti mediati da altri substrati dell'ACE (es. bradichinina)

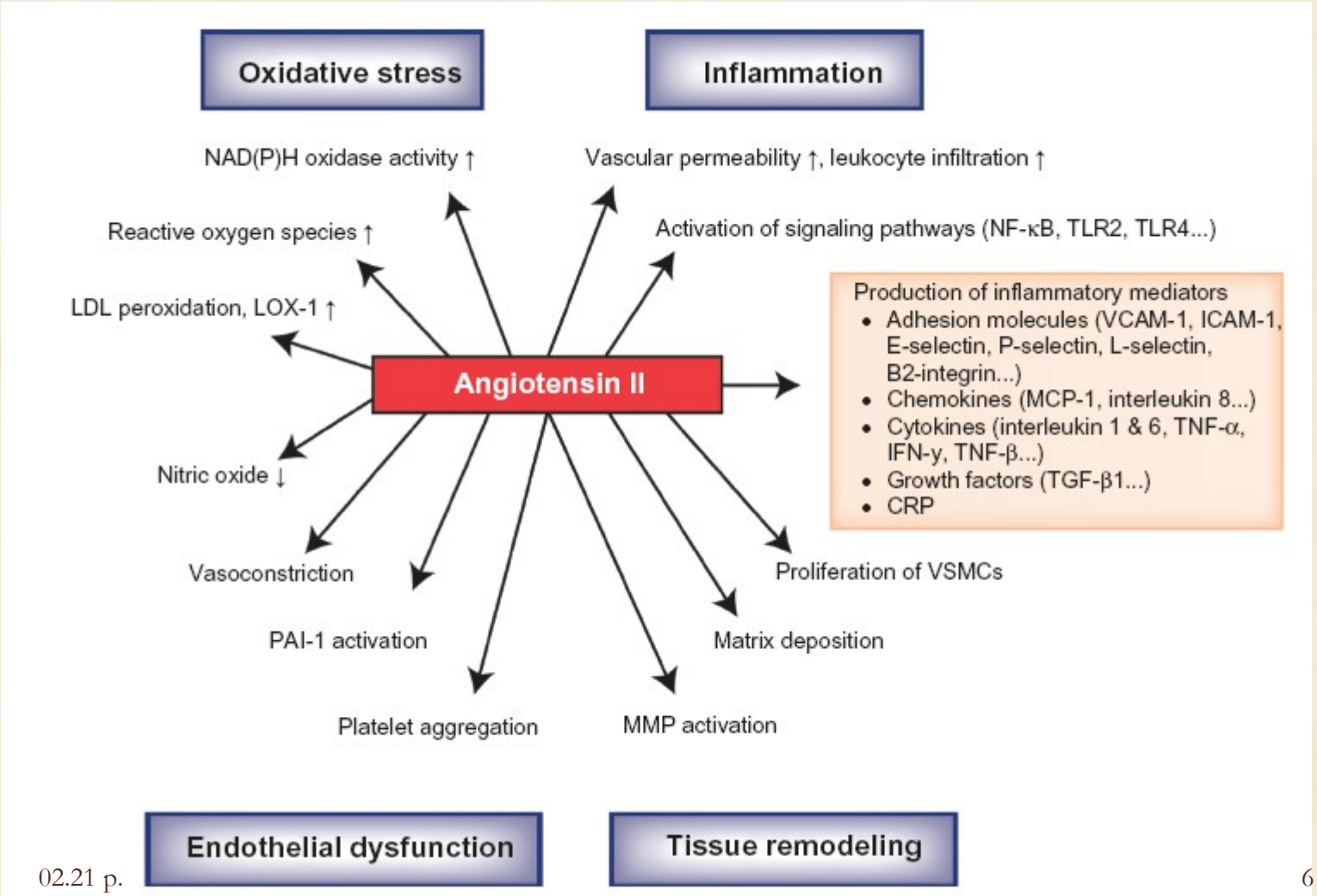
# Quanto finora noto

## ACE-INIBITORI

### Meccanismo d' azione

- inibizione dell'enzima di conversione dell'angiotensina I
- blocco della sintesi di angiotensina II
- accumulo di angiotensina I e suoi metaboliti alternativi [angiotensina (1-7)]
- accumulo di bradichinina

# Una rivisitazione dei meccanismi d'azione



# L'omeostasi

## OMEOSTASI

- In fisiologia:
  condizione di relativa **stabilità** della composizione,
  delle proprietà dell'ambiente interno e delle più importanti
  funzioni fisiologiche basali di un organismo vivente,
  condizione necessaria al mantenimento della vita.
- Parametri fisiologici: "costanti" e compresi all'interno di limiti considerati come "normali"

# L'allostasi

## ALLOSTASI

- *"Mantenere l'omeostasi (stabilità) attraverso il cambiamento"* (McEwen, Wingfield, 2003)
- Complesso dei processi messi in atto dai sistemi fisiologici di ciascun organismo (sistema nervoso autonomo, asse ipotalamo-ipofisi-surrene, apparato cardiovascolare, sistema immunitario, metabolismo) per far fronte alle "sfide" di ordine fisico, psicosociale ed ambientale.

# Grazie all'allostasi è possibile

- mantenere la postura eretta, evitare fenomeni tipo black-out, compiere attività fisica
- attivare e conservare, al bisogno, le energie di riserva, a livello fisico e nervoso
- far fronte agli attacchi di agenti patogeni e tenere sotto controllo lo sviluppo di potenziali tumori
- apprendere, memorizzare e regolare la secrezione neuroendocrina

# Lo stato allostatico

- Può essere mantenuto per brevi periodi con risultati adattativi (**carico allostatico**)
  → "logorio" dell'organismo ("prezzo" che l'organismo paga per essere costretto ad adattarsi alle situazioni avverse fisiche o psicosociali)
- Ottenuto un nuovo livello di adattamento, l'organismo dovrebbe **uscire** dallo stato allostatico
- In caso contrario (persistenza dello stato allostatico) intervengono conseguenze negative **(sovraccarico allostatico)**

*(McEwen BS, 2002)*

# L'AREA DI OMEOSTASI
## Spazio di salute allargato

# Il sovraccarico allostatico

- Conseguenza di un **carico allostatico protratto a lungo** fino a diventare indipendente dalle condizioni che lo hanno richiesto
- **Sbilanciamento** negativo o positivo del rapporto tra energia richiesta dalle condizioni ambientali e risorse energetiche disponibili.
- **Misurabile** a livello cerebrale, cardiovascolare, immunitario e metabolico

# E allora cosa accade quando il carico è eccessivo o anche tr

- mantenere la postura eretta, evitando fenomeni tipo black-out, e di compiere attività fisica.
  - Sovraccarico allostatico → ipertensione arteriosa e condizioni predisponenti a IMA e stroke.
- attivare e conservare, al bisogno, le energie di riserva, a livello sia fisico sia nervoso.
  - Sovraccarico allostatico → obesità, diabete, aterosclerosi.
- far fronte agli attacchi di agenti patogeni
  - Sovraccarico allostatico → infiammazione e malattie autoimmuni.

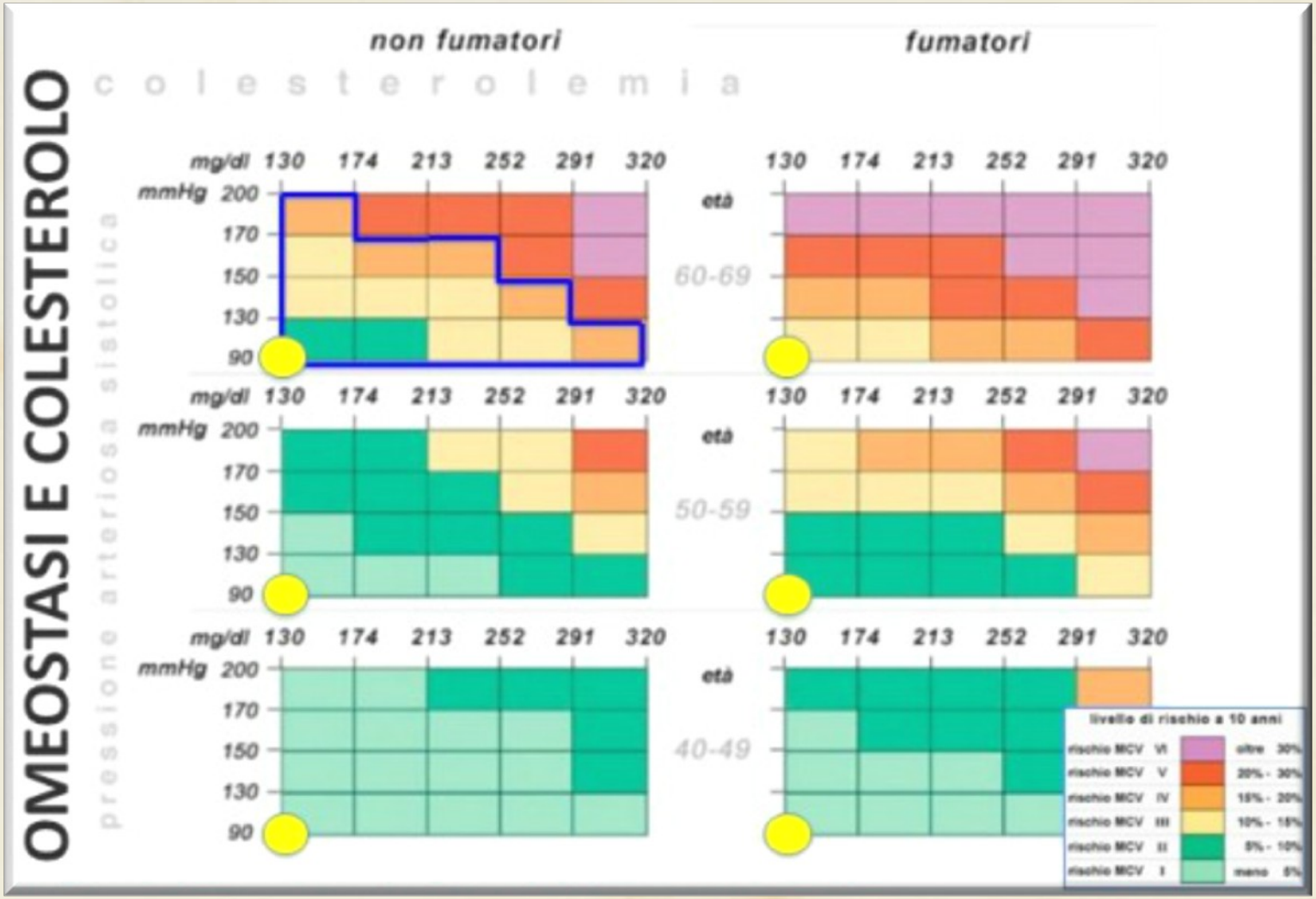
**OBIETTIVI:**

**1. RICONOSCERE LE CONDIZIONI DI CARICO ALLOSTATICO**

**E**

**2. PREVENIRE IL SOVRACCARICO ALLOSTATICO**

# Omeostasi e rischio CV



# VERSO NUOVI PARADIGMI DI RICERCA?

"L'oggetto delle nostre osservazioni non è la natura stessa, ma la natura esposta al nostro metodo di indagine"

*W. Heisenberg*

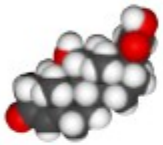
# Rivolto ai Medici

*"I medici non dovrebbero mai dimenticare*
*che le certezze della scienza medica*
*non sono nulla più che delle certezze.*
*Non sono la Verità.*
*Tutt'al più delle verità soltanto parziali e provvisorie.*
*Nel corso della sua carriera,*
*ogni medico ha dovuto rettificare varie volte*
*le certezze sulle quali fondava il suo operato.*
*Eppure, ogni volta, la medicina pare credere*
*che le sue verità del giorno siano assolute e definitive."*

Norbert Bensaïd

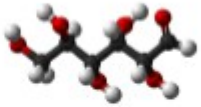
# ALLOSTATIC LOAD
# "Domino Effect"

Cortisol

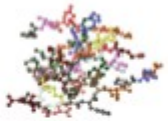


Catechol

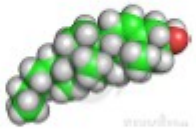
Glucose



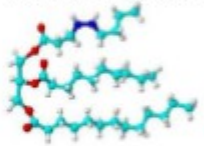
Insulin



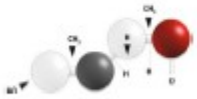
Cholesterol



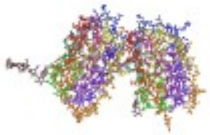
Triglycerides



Dheas



Cytochines



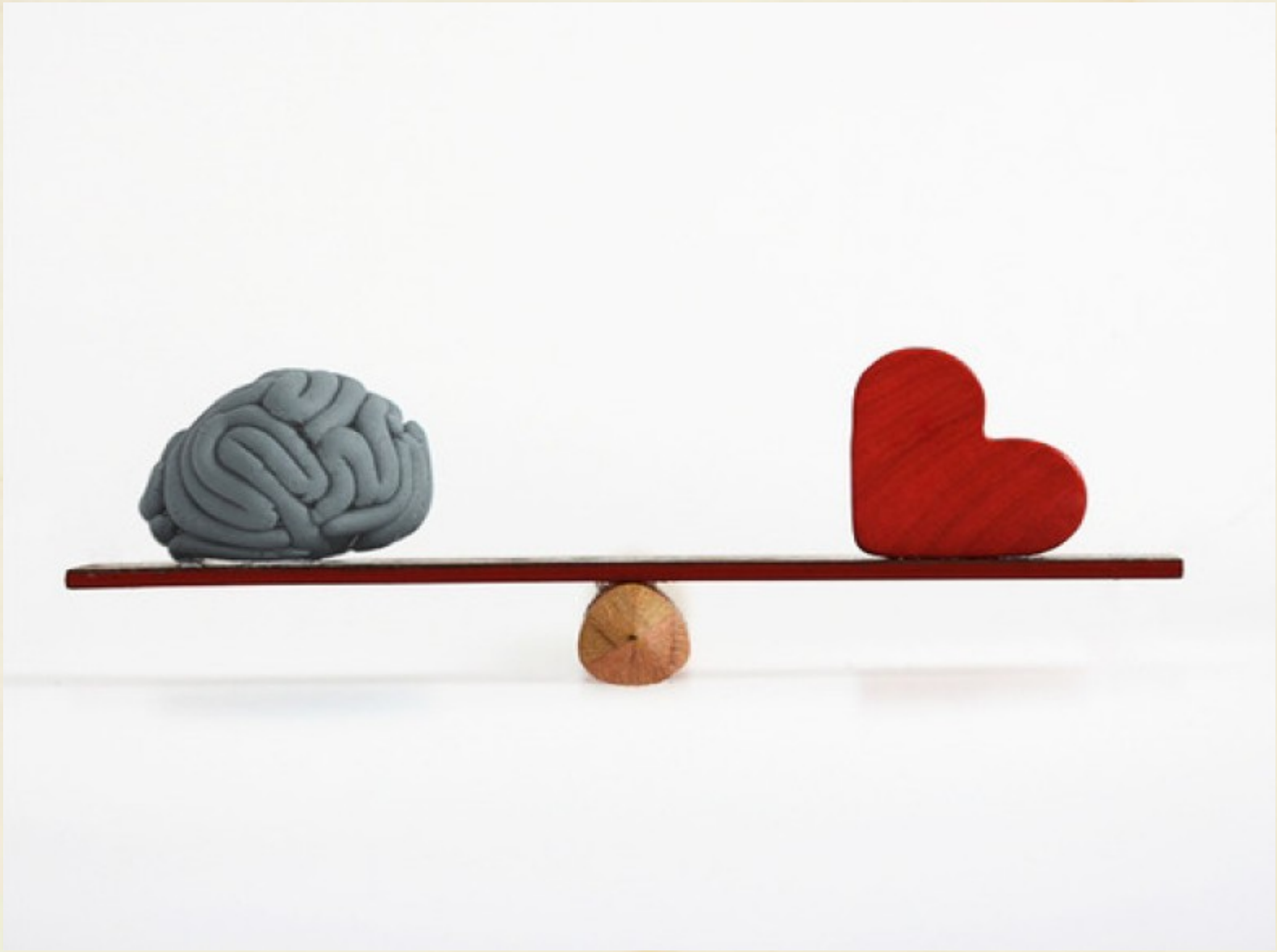
Fibrinogen

PCR

BP

W-H ratio

Adapted from Juster-Mc Ewen-Lupien, 2010



# I PIÙ FREQUENTI GUASTI DELL'OROLOGIO BIOLOGICO

Tecniche antistress e meditative
Tecniche per la mente

Terapie naturali

Alimentazione

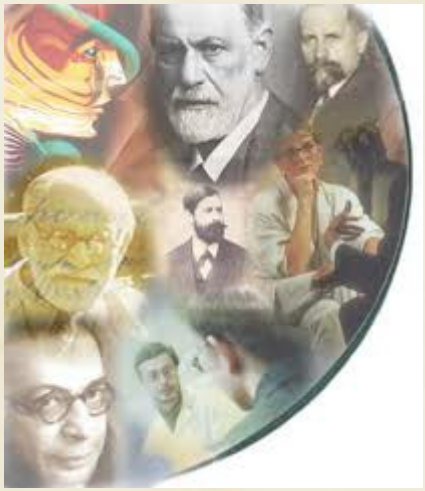
Ritmi
biologici

Attività fisica

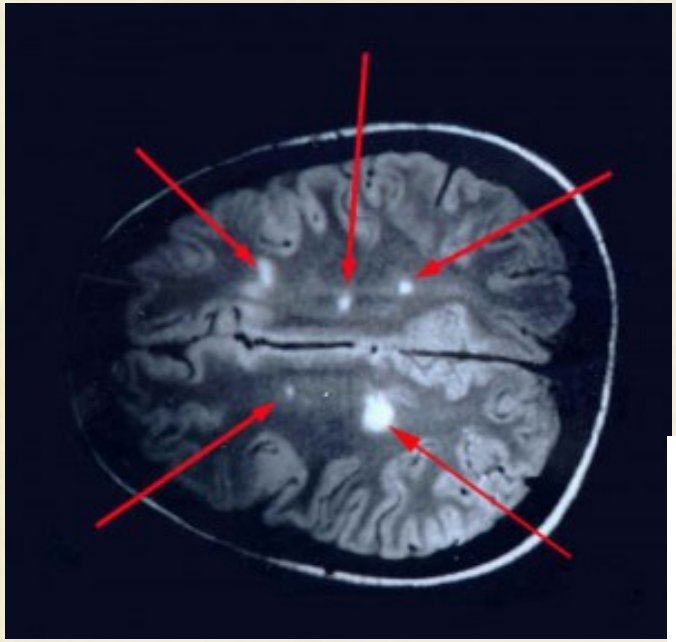
Farmaci regolatori

# L’epigenetica

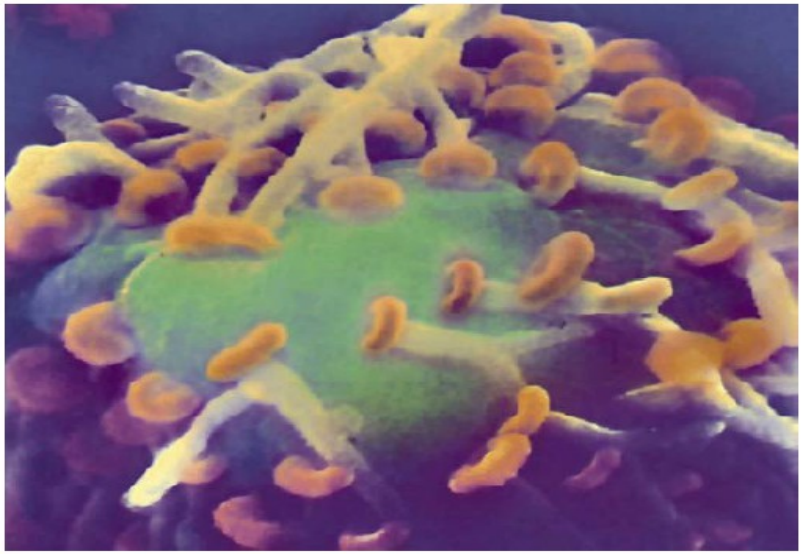
## Psicoterapie modulatrici del Network Umano

# La psicoterapia

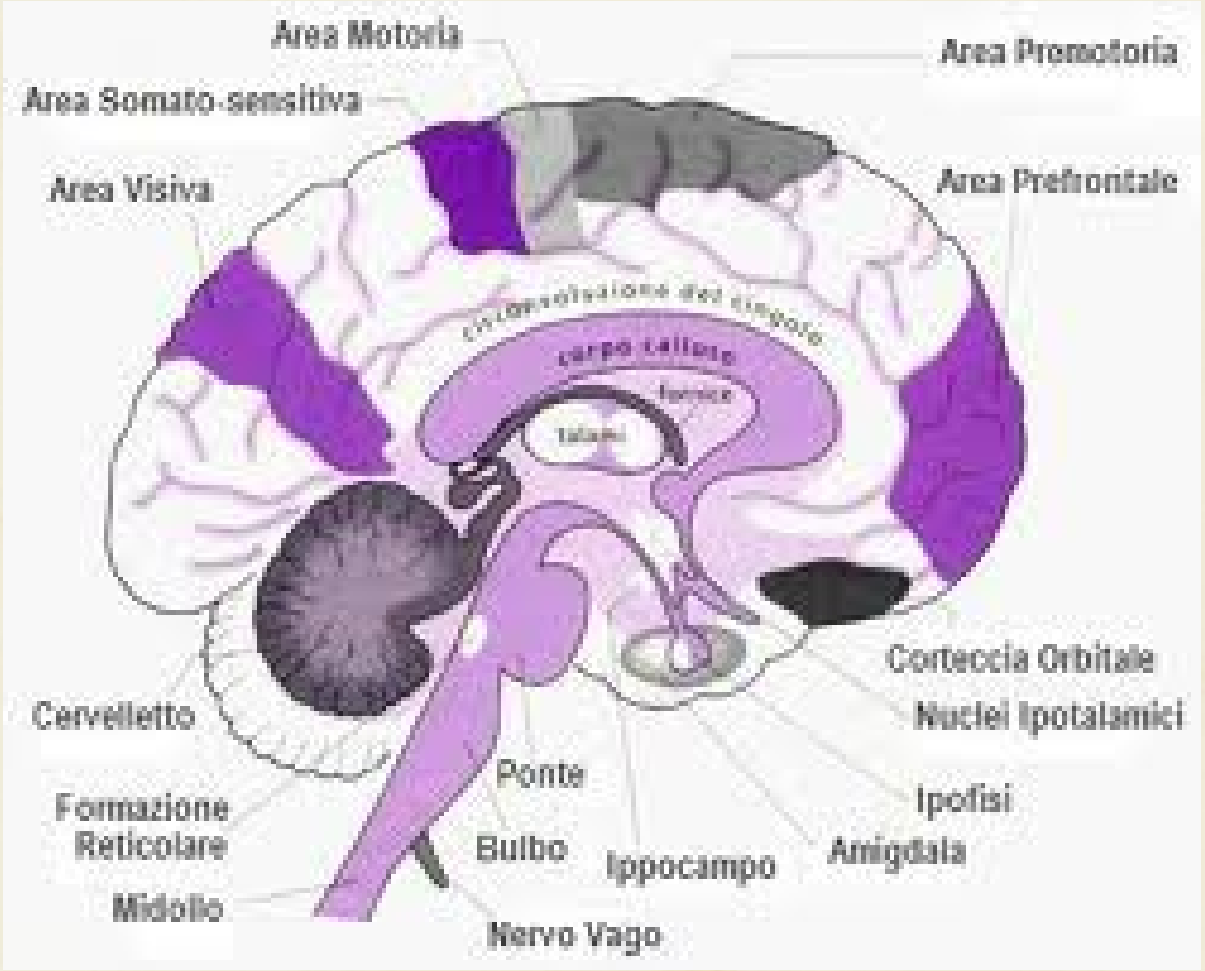


La terapia della psiche è in grado di far cambiare forma e anche attività al cervello



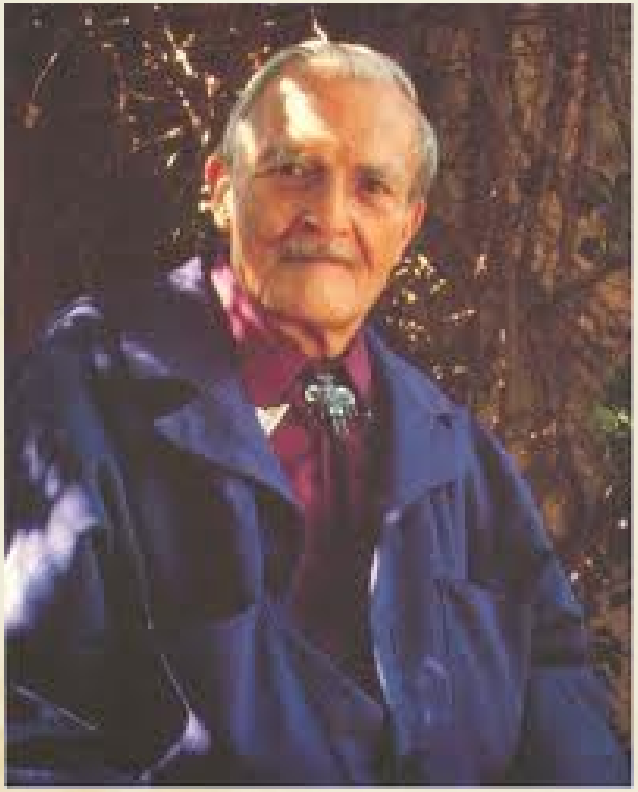
Microfotografia a scansione elettronica del corpo cellulare di un neurone (in verde) coperto da bottoni terminali (in arancione)

# La psicoterapia

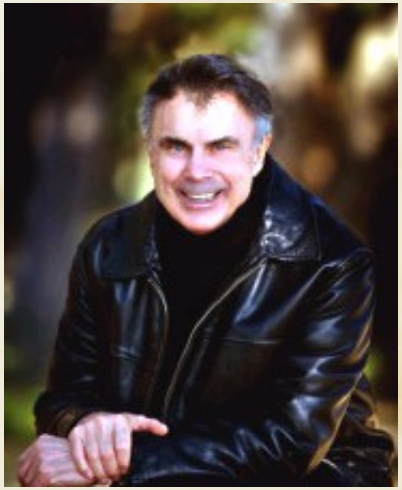


# La psicoterapia

Il Maestro



L'allievo

# Dalla teoria alla pratica

**Vaccines for preventing influenza in healthy adults (Review)**

Demicheli V, Di Pietrantonj C, Jefferson T, Rivetti A, Rivetti D

**L'influenza**

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 3

http://www.thecochranelibrary.com

# Emozioni negative

## Affective style and *in vivo* immune response: Neurobehavioral mechanisms

Melissa A. Rosenkranz*, Daren C. Jackson*, Kim M. Dalton*, Isa Dolski*, Carol D. Ryff†, Burt H. Singer†‡, Daniel Muller§, Ned H. Kalin¶, and Richard J. Davidson*‖

*Laboratory for Affective Neuroscience, Department of Psychology, University of Wisconsin, 1202 W. Johnson Street, Madison, WI 53706; †Institute on Aging and §Department of Medicine, University of Wisconsin, 1300 University Avenue, Madison, WI 53706; ‡Woodrow Wilson School of Public and International Affairs, Princeton University, 245 Wallace Hall, Princeton, NJ 08544; and ¶Department of Psychiatry, University of Wisconsin, 6001 Research Park Boulevard, Madison, WI 53711

Contributed by Burt H. Singer, July 25, 2003

# Il virus erpetico

PERSPECTIVES

SCIENCE AND SOCIETY

## Stress-induced immune dysfunction: implications for health

*Ronald Glaser and Janice K. Kiecolt-Glaser*

Abstract | Folk wisdom has long suggested that stressful events take a toll on health ... ability to cope[4]. Researchers often categorize stressors by their duration and course (discrete

Stressors can increase susceptibility to infectious agents, influence the severity of infectious disease, diminish the strength of immune responses to vaccines, reactivate latent herpesviruses and slow wound healing. Moreover, stressful events and the distress that they evoke can also substantially increase the production of pro-inflammatory cytokines that are associated with a spectrum of age-related diseases. Accordingly, stress-related immune dysregulation might be one core mechanism behind a diverse set of health risks[1,3].

# Anche le ferite

THE LANCET

## Slowing of wound healing by psychological stress

*Janice K Kiecolt-Glaser, Phillip T Marucha, William B Malarkey, Ana M Mercado, Ronald Glaser*

**Summary**

There is evidence that psychological stress adversely affects the immune system. We have investigated the effects of such

In our study of antibody and virus-specific T-cell responses to an influenza virus vaccine (to be published elsewhere) caregivers showed significant deficits relative to controls. Caregivers were less likely to show a satisfactory increase in

# Anche i Medici

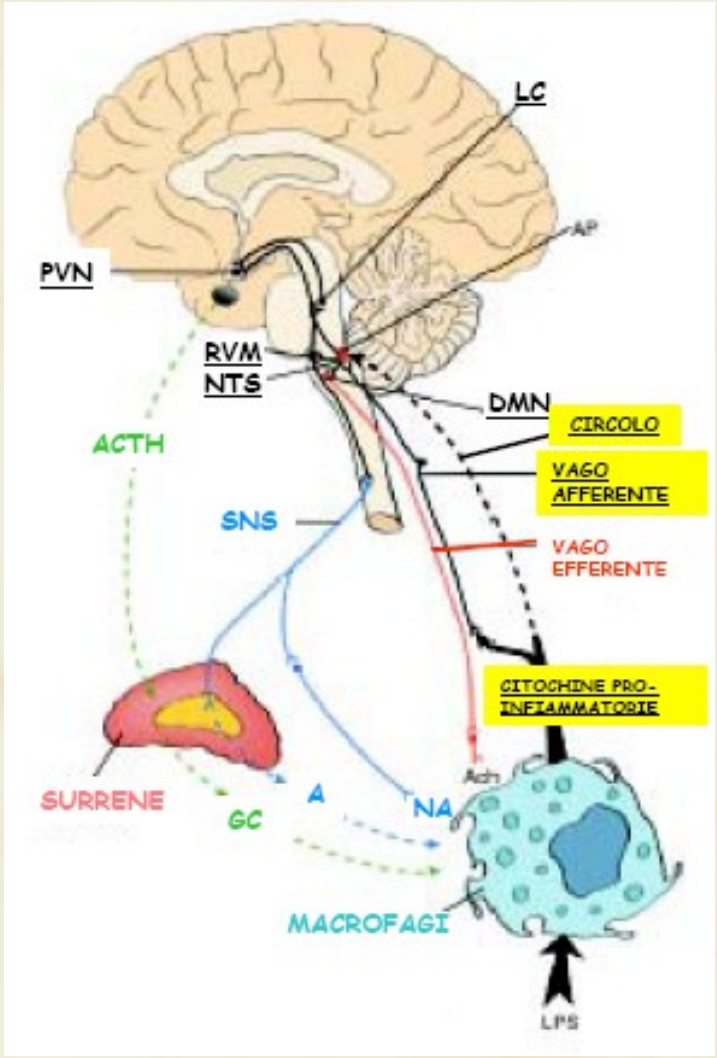
## Mucosal Wound Healing Is Impaired by Examination Stress

PHILLIP T. MARUCHA, DMD, PHD, JANICE K. KIECOLT-GLASER, PHD, AND MEHRDAD FAVAGEHI, DDS

*Objective:* Impairment of wound healing is a well-recognized sequelae of conditions that alter immune function, including diabetes, jaundice, and advanced age. There is also growing evidence that psychological stress has adverse consequences for immune function. This study addressed the effects of a commonplace stressor on wound healing. *Method:* Two punch biopsy wounds were placed on the hard palate of 11 dental students. The first wound was timed during summer vacation, whereas the second was placed on the contralateral side 3 days before the first major examination of the term; thus, each student served as her or his own control. Two independent methods assessed healing (daily photographs and a foaming response to hydrogen peroxide). *Results:* Students took an average of 3 days longer to completely heal the 3.5-mm wound during examinations, ie, 40% longer to heal a small, standardized wound. Production of interleukin 1$\beta$ (IL-1$\beta$) messenger RNA (mRNA) declined by 68% during examinations, providing evidence of one possible immunological mechanism. These differences were quite reliable: No student healed as rapidly or produced as much IL-1$\beta$ mRNA during examinations as during vacation. *Conclusions:* These data suggest that even something as transient, predictable, and relatively benign as examination stress can have significant consequences for wound healing. **Key words:** oral, wound repair, interleukin 1, psychological stress, surgery.

# L'infiammazione e la depressione hanno un'unica origine?


# L'infiammazione e la depressione hanno un'unica origine?



# Lo stress esacerba la malattia



# LA TRASCRIZIONE CELLULARE DI UN'EMOZIONE

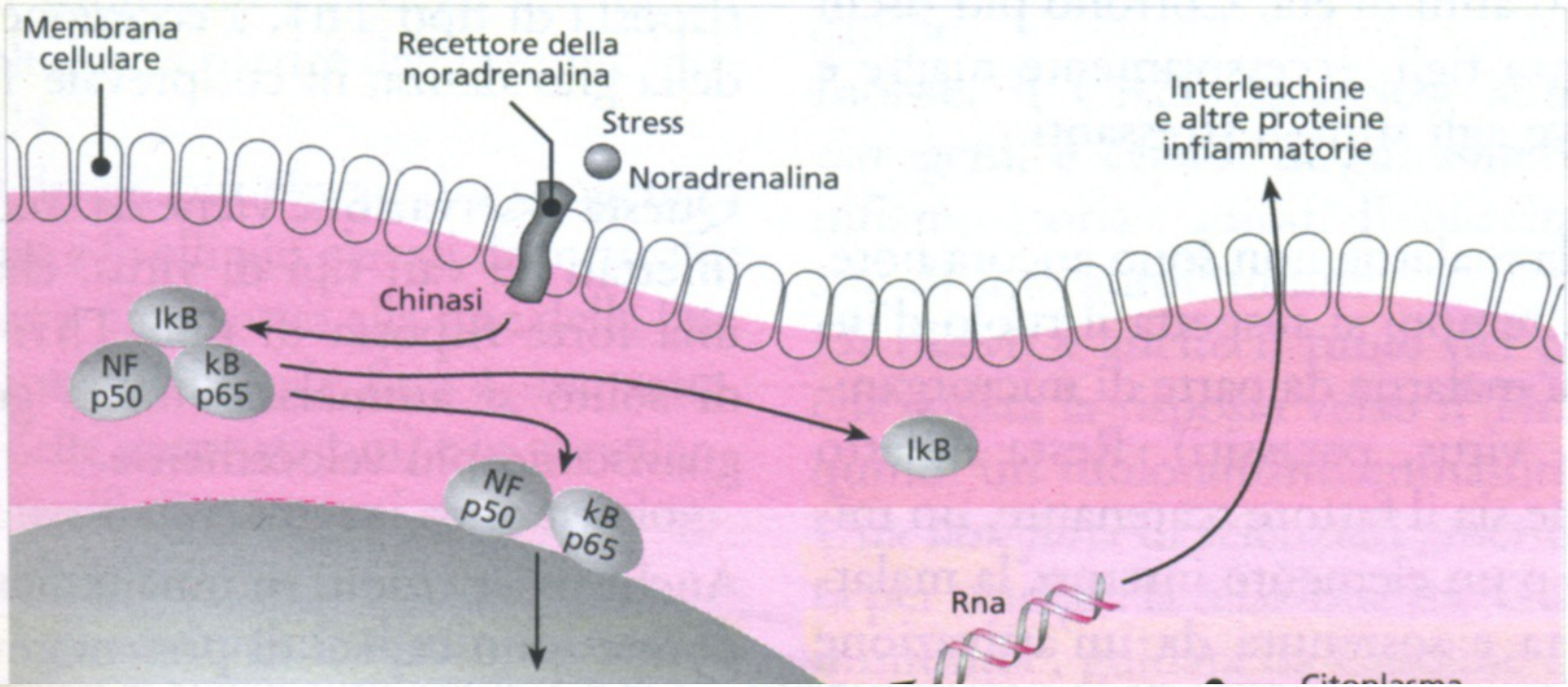



Fig. XII-4. *Lo stress, tramite la noradrenalina, attiva un enzima, una chinasi, che attacca un complesso inerte presente nel citoplasma della cellula immunitaria, lo libera dal fattore inibitorio (IkB) e mette in azione NFkB. Il fattore entra nel nucleo del monocita e attiva una sessantina di geni, i quali, a loro volta, comanderanno la produzione di proteine infiammatorie, soprattutto citochine (IL-1 e TNF-alfa) e molecole di adesione (VCAM e ICAM), essenziali per lo sviluppo della risposta infiammatoria.*

ORIGINAL ARTICLE

# A Dose-Ranging Study of the Effects of Ethyl-Eicosapentaenoate in Patients With Ongoing Depression Despite Apparently Adequate Treatment With Standard Drugs

*Malcolm Peet, MB, ChB, FRCPsych; David F. Horrobin, DPhil, BM, BCh*

**Background:** In depressed patients, low blood levels of eicosapentaenoic acid are seen. We tested the antidepressive effect of ethyl-eicosapentaenoate in these patients.

**Methods:** We included 70 patients with persistent depression despite ongoing treatment with an adequate dose of a standard antidepressant. Patients were randomized on a double-blind basis to placebo or ethyl-eicosapentaenoate at dosages of 1, 2, or 4 g/d for 12 weeks in addition to unchanged background medication. Patients underwent assessment using the 17-item Hamilton Depression Rating Scale, the Montgomery-Asberg Depression Rating Scale, and the Beck Depression Inventory.

**Results:** Forty-six (88%) of 52 patients receiving ethyl-eicosapentaenoate and 14 (78%) of 18 patients receiving placebo completed the 12-week study with no serious adverse events. The 1-g/d group showed a significantly better outcome than the placebo group on all 3 rating scales. In the intention-to-treat group, 5 (29%) of 17 patients receiving placebo and 9 (53%) of 17 patients receiving 1 g/d of ethyl-eicosapentaenoate achieved a 50% reduction on the Hamilton Depression Rating Scale score. In the per-protocol group, the corresponding figures were 3 (25%) of 12 patients for placebo and 9 (69%) of 13 patients for the 1-g/d group. The 2-g/d group showed little evidence of efficacy, whereas the 4-g/d group showed nonsignificant trends toward improvement. All of the individual items on all 3 rating scales improved with the 1-g/d dosage of ethyl-eicosapentaenoate vs placebo, with strong beneficial effects on items rating depression, anxiety, sleep, lassitude, libido, and suicidality.

**Conclusion:** Treatment with ethyl-eicosapentaenoate at a dosage of 1 g/d was effective in treating depression in patients who remained depressed despite adequate standard therapy.

*Arch Gen Psychiatry. 2002;59:913-919*

DEPRESSION REMAINS an illness in which existing treatments have limited efficacy. The most widely prescribed drug, fluoxetine hydrochloride, produces a 50% improvement in symptoms in only 38% of those who start treatment and in only 56% of those who complete a full course.[1] Other drugs are similar in their effects.[2] Tricyclic antidepressants and selective serotonin (SSRIs) and norepinephrine reuptake inhibitors are similar in their efficacy.[2,3] The SSRIs are marginally better tolerated, but the differences are small. On average, for every 100 patients who start treatment, 30 patients receiving a tricyclic compound during a 6-week trial will stop treatment compared with 27 receiving an SSRI.[3,4] Discontinuation rates in ordinary clinical practice are probably higher. Therefore, novel approaches to the management of depression are needed.

Lipids, most of which are phospholipids, constitute 60% of the solid mass of the brain and are absolutely required for normal brain structure and function.[5,6] Each phospholipid consists of a 3-carbon glycerol backbone with a fatty acid, usually a highly unsaturated fatty acid, attached to the middle (Sn2) carbon.[5,6] The Sn2 highly unsaturated fatty acids may be of 2 common types, n-6 (also known as ω-6) derived from linoleic acid or n-3 (also know as ω-3) derived from α-linolenic acid. In the brain, the main n-6 fatty acid is arachidonic acid, with much smaller amounts of dihomogammalinolenic and adrenic acids. The main n-3 fatty acid is docosahexaenoic acid (DHA), with much smaller amounts of its precursors, eicosapentaenoic acid (EPA) and docosapentaenoic acid. The metabolic pathways are shown in the **Figure**.

The fatty acids at the Sn2 position have important roles in neuronal signal transduction processes.[5,6] Activation of most

From the Swallowcourt Court Hospital, Sheffield, England (Dr Peet); and Laxdale Research, Ltd, Stirling, Scotland (Dr Horrobin).





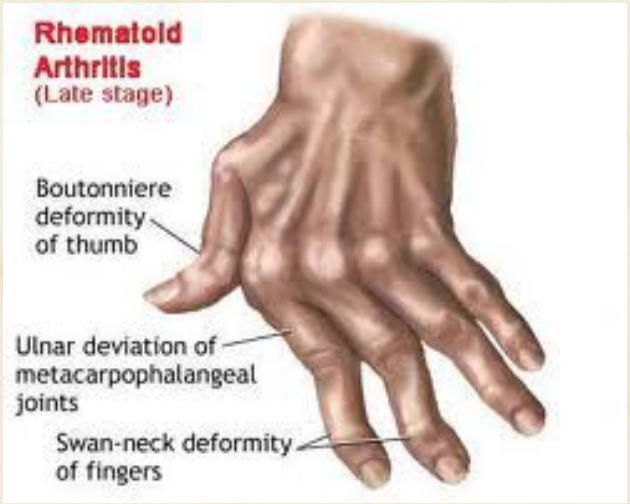
# L'olio di pesce per la depressione

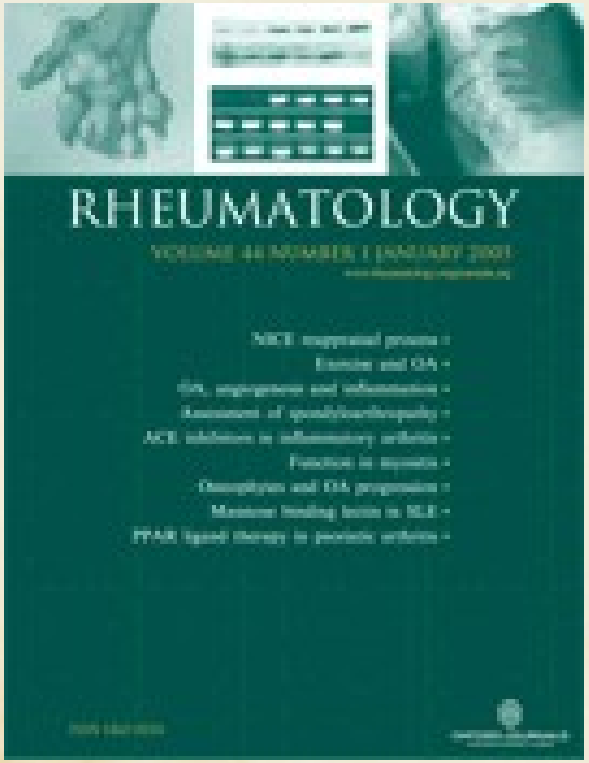
# Olio di pesce per la depressione

Studi preliminari (D.F.Horrobin e Malcom Peet -> "Archives of General Psychiatry") hanno dimostrato che l'olio di pesce (1g/die) migliora la depressione.

**Perché l'olio di pesce migliora i sintomi della depressione?**

# La psiche come risorsa nella terapia dell'artrite reumatoide




# La psiche come risorsa nella terapia dell'artrite reumatoide