

**AGEING SOCIETY
PREVENZIONE, RIABILITAZIONE,
BENESSERE ANZIANI-PROTAGONISTI E
METODOLOGIE DI CAPACITAZIONE**

Palazzo Strozzi, Firenze 28 aprile 2017

I ritmi circadiani nell'arco della vita

**Alberto Angeli
Professore Emerito di Medicina Interna
Università degli Studi di Torino**





SPETTRO DEI RITMI BIOLOGICI

Periodo

- $\tau < 20 \text{ h}$
- $20 \text{ h} \leq \tau \leq 28 \text{ h}$
- $\tau > 28 \text{ h}$
- $\tau = 7 \pm 3 \text{ d}$
- $\tau = 30 \pm 5 \text{ d}$
- $\tau = 1 \text{ y} \pm 2 \text{ m}$

Termine

- Ultradiano
- Circadiano
- Infradiano
- Circasettano
- Circatrigintano
- Circannuale

τ = periodo; h = ora; d = giorno; m = mese; y = anno

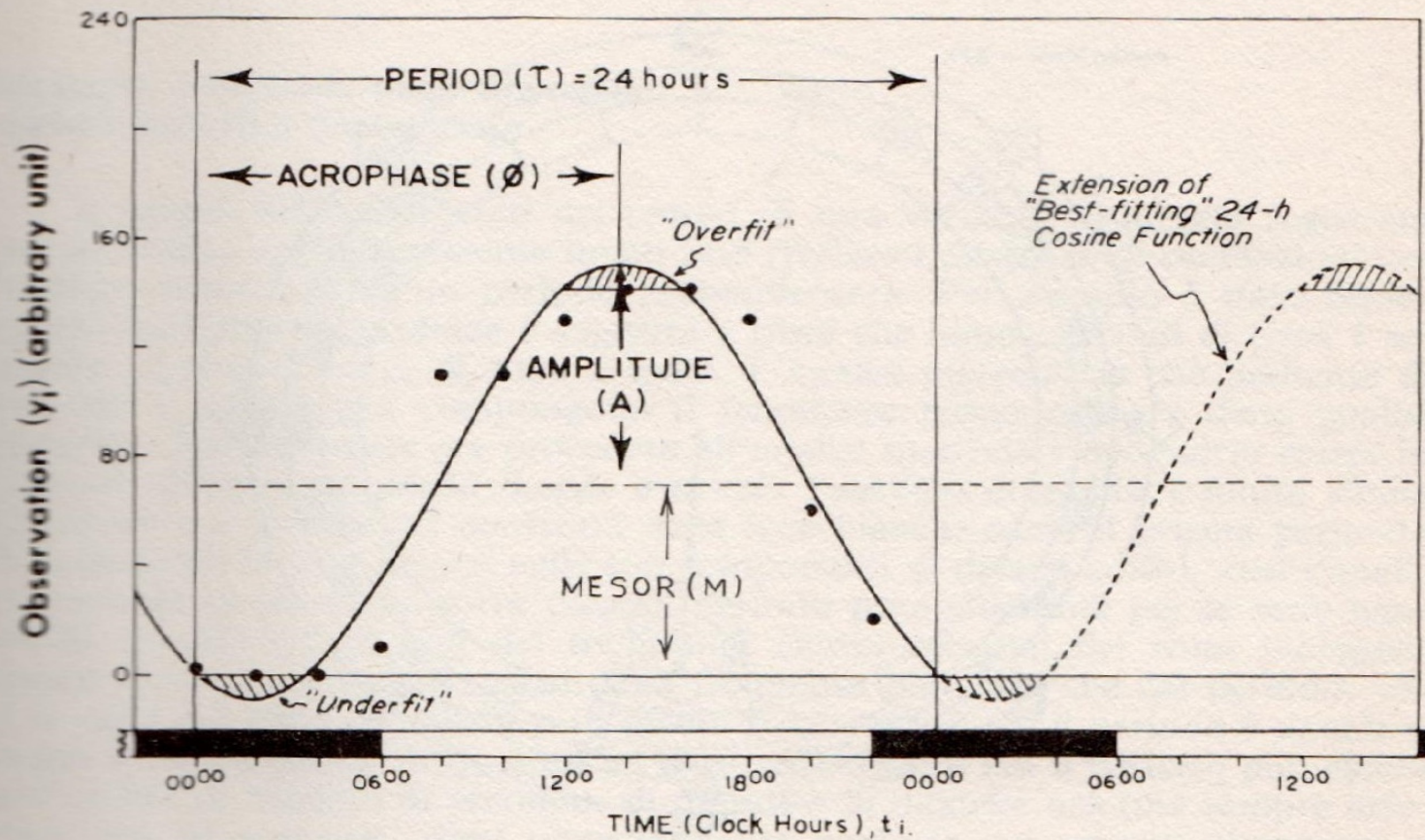
L'ORGANIZZAZIONE RITMICA E LE
INTERAZIONI FRA LE VARIE
COMPONENTI SPETTRALI
SOTTOLINEANO L'IMPORTANZA DI
CONSIDERARE E MISURARE I
FENOMENI BIOLOGICI (FISIOLOGICI;
PATOLOGICI) IN SENSO *TEMPORALE*
OLTRECHÈ *SPAZIALE*



*Omnia metire quaecumque licet
et immensa ad mensuram
tempestive redige*

Galileo

Estimation of Parameters M , A and ϕ by Least Squares Fit of Cosine Model with Fixed Period*

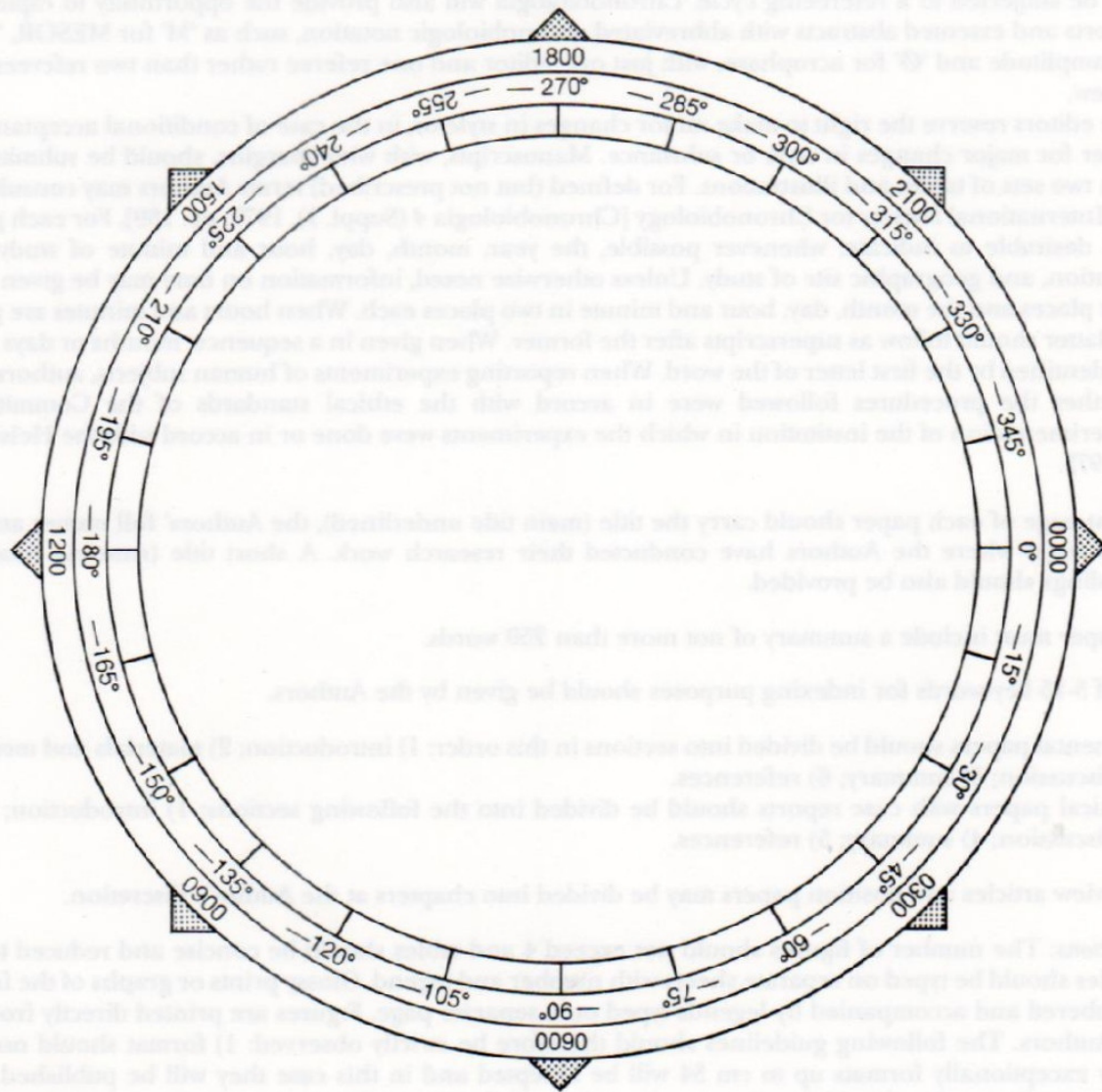


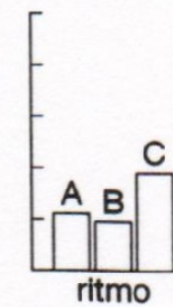
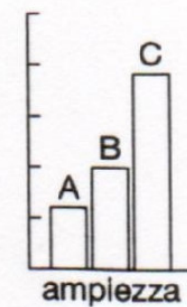
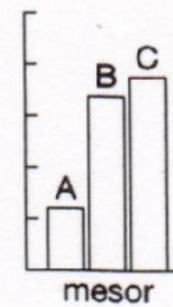
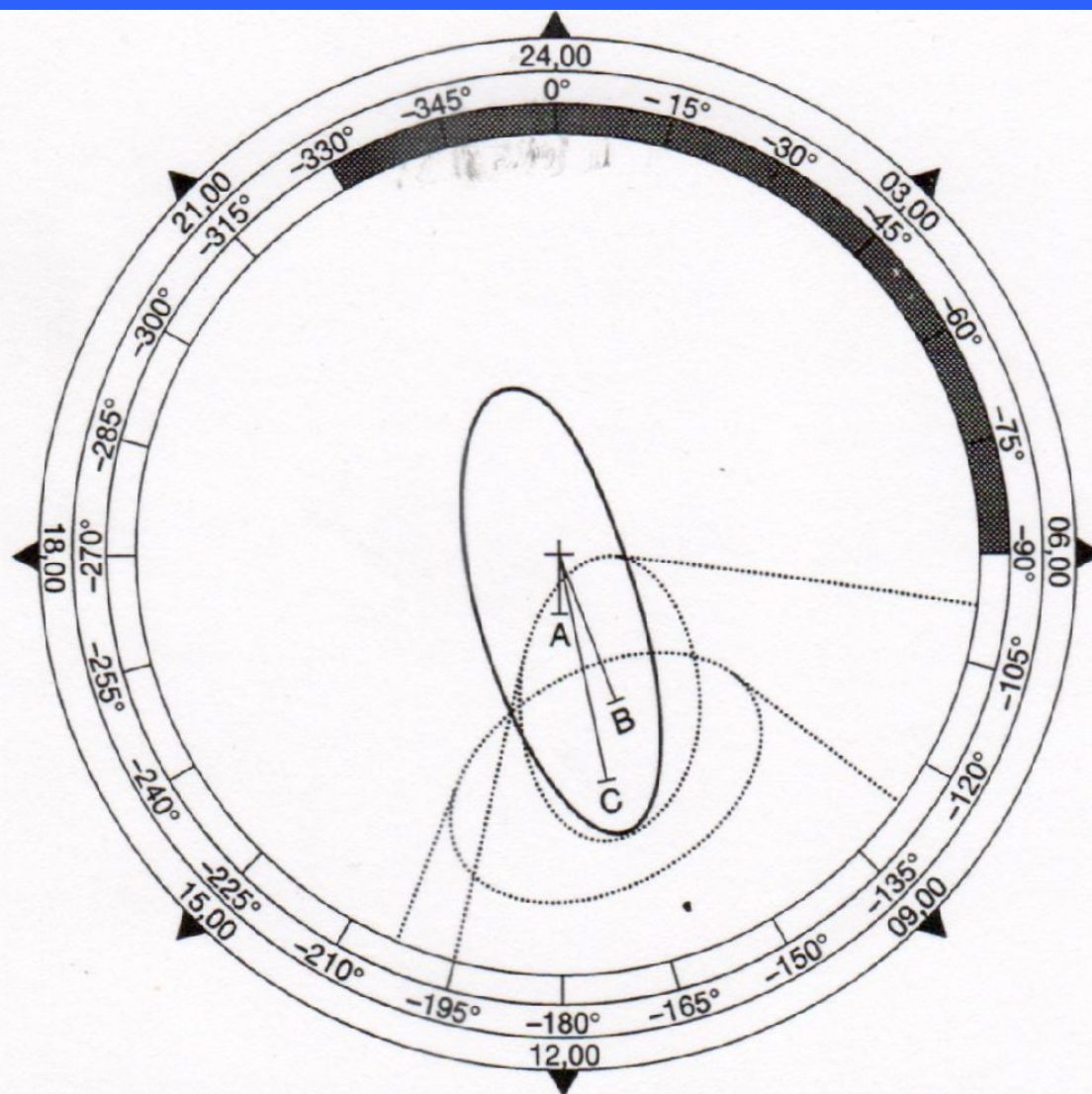
$$* y_i = M + A \cos(\phi + \omega t_i) + e_{ij} \quad \omega = 2\pi/T$$

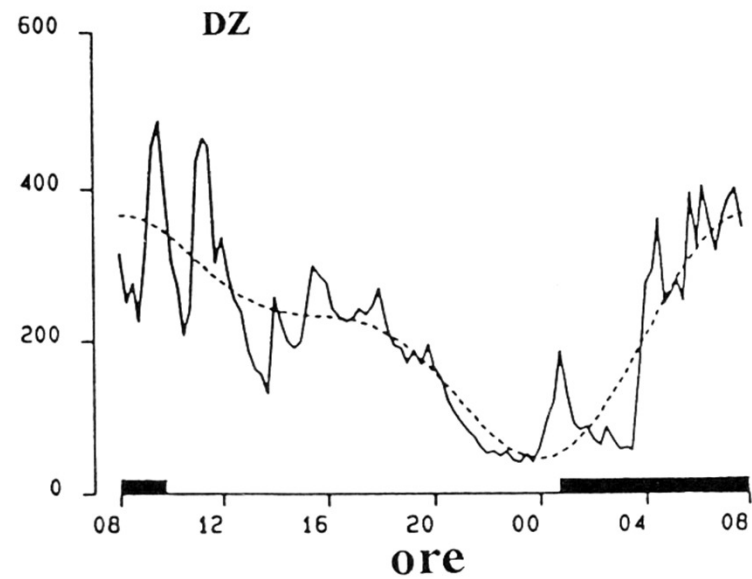
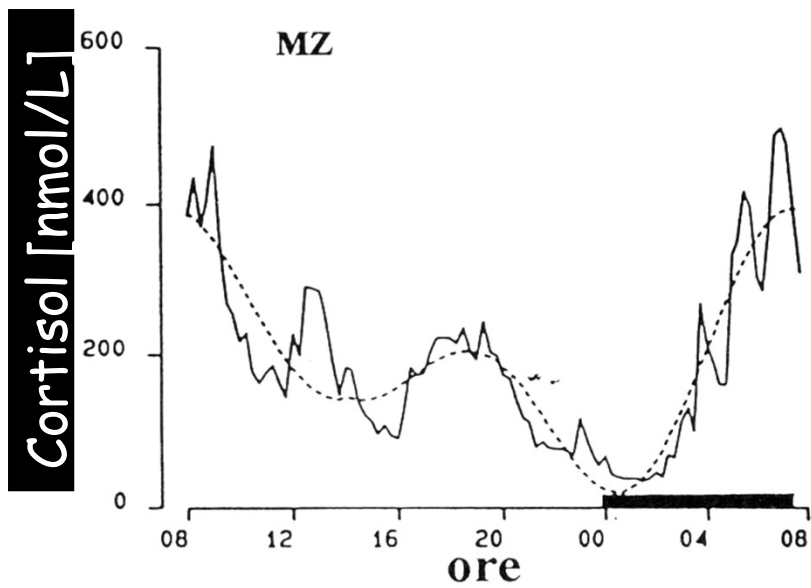
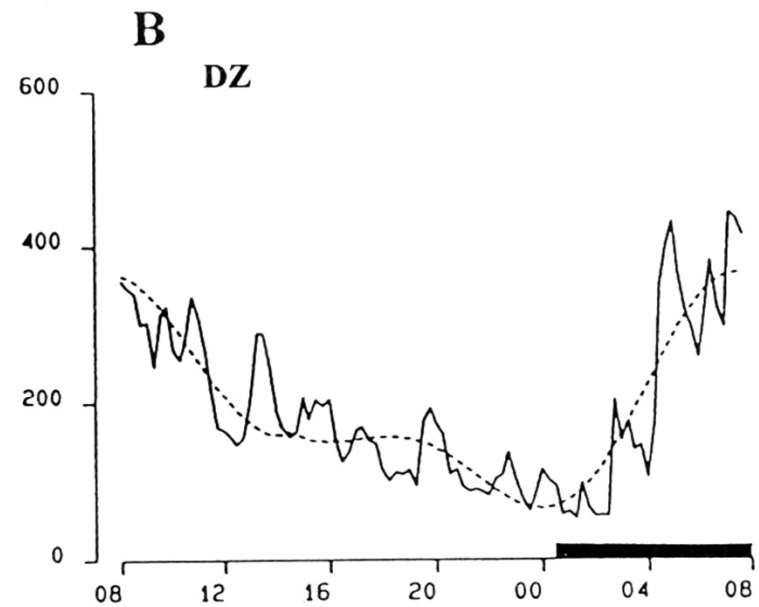
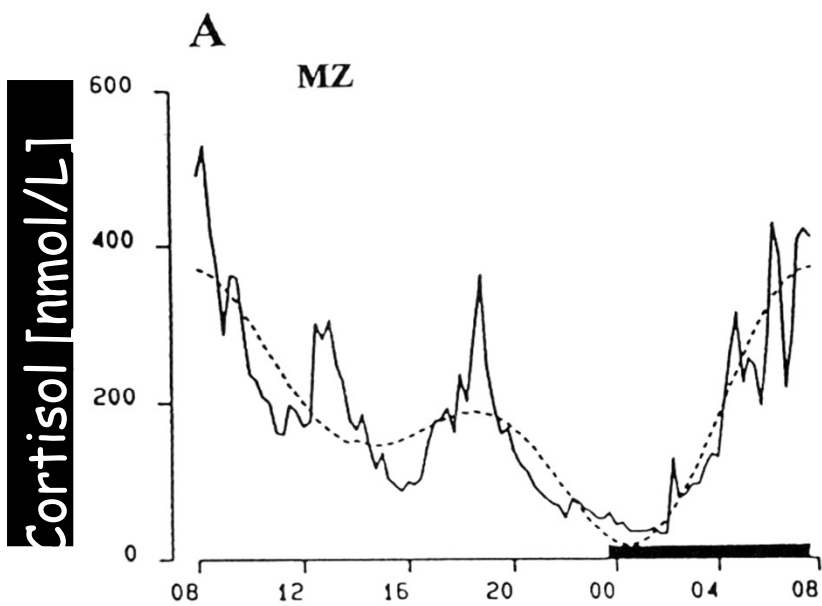
t_i = time

y_i = observation at t_i

e_{ij} = error at t_i , assumed to have the same independent normal distribution with mean zero and unknown variance σ^2 , regardless of time.







STUDIO DELLA VARIABILITA' DELL'INTERVALLO R-R

- A- Esecuzione di ECG e/o monitoraggio Holter 24 ore
- B- Memorizzazione del singolo intervallo R-R in forma di tacogramma
- C- Valutazione dei dati con il metodo dell'analisi spettrale
- D- Identificazione di due componenti:
 - 1) Componente ad alta frequenza-HF (0.27 Hz)
 - ▶ marker di attività vagale
 - 2) Componente a bassa frequenza-LF (0.12 Hz)
 - ▶ marker di attività simpatica

Is Circadian Rhythm the Rhythm of Life?

Pre-ovulatory hormone surge and ovulation may be controlled by novel circadian hierarchy.

- by Salynn Boyles
Contributing Writer

Sexagenarian Awakens To His Biological Clock

WILLIAMSTOWN, Mass. — Lifetime movies and Philip Roth don't usually pop up in the same frame of reference. Yet it's hard to avoid thinking of both those sudsy topical television films and the author of "Portnoy's Complaint" as you watch "Legacy," Daniel Goldfarb's uneasy comedy of morals at the Williamstown Theater Festival here.

**BEN
BRANTLEY**
THEATER
REVIEW

You might even, if you were in a whimsical mood, perceive this play as a sort of custom-made fantasy purgatory whipped up for Mr. Roth, a just dessert of womanly woes served to a writer who has sometimes been accused of misogyny. Not that Mr. Goldfarb, a dramatist who spe-

(hooray!) Jessica Hecht — has felt more like one of those risqué Broadway comedies about infidelity that flourished in the 1960s and '70s, when the middle class was playing catch-up with the sexual revolution. It also recalls those equally smirky plays and movies about unexpected pregnancy with titles like "Never Too Late" and "Prudence and the Pill."

Of course, such froth generally didn't include copious references to the Holocaust and grave considerations of the ethics of surrogate motherhood. Mr. Goldfarb, as you may have gathered, likes to set his works at a dangerous intersection where influences and genres collide. That the presentation here is doggedly naturalistic, never acknowledging the



T. CHARLES ERICKSON

Jessica Hecht and Eric Bogosian in "Legacy," at the Williamstown Theater Festival.

CIRCADIAN RHYTHMS

Midnight snacks are bad for the heart

Circadian clocks help animals coordinate their active and rest periods with the daily cycles of light and darkness. As anyone who has suffered jet lag or worked night shifts knows, losing this coordination can have deleterious effects. Gill

CIRCADIAN RHYTHMS

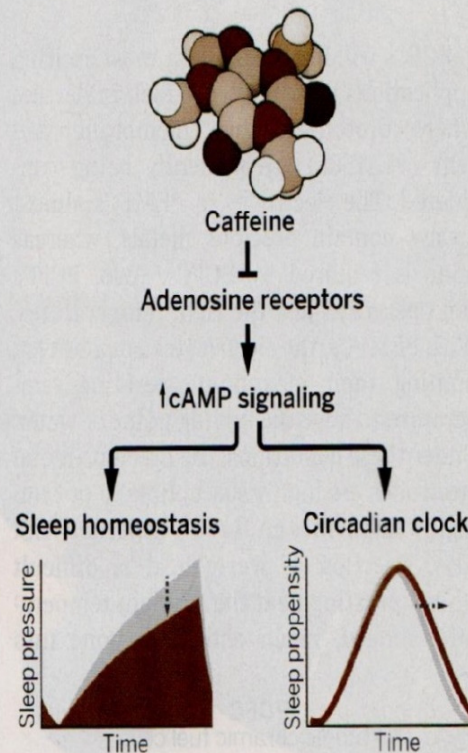
Caffeine, the circadian clock, and sleep

Why is caffeine intake at bedtime a sleep disrupter?

By Hans Peter Landolt

Caffeine wakes people up but also disrupts the quality of sleep. A new study by Burke *et al.* (1) reveals that consuming caffeine in the evening—the equivalent of a double espresso—delays the human endogenous circadian clock by antagonizing receptors for the endogenous sleep factor adenosine in the brain (see the figure). Mistimed caffeine consumption may contribute to the growing incidence of sleep problems in society.

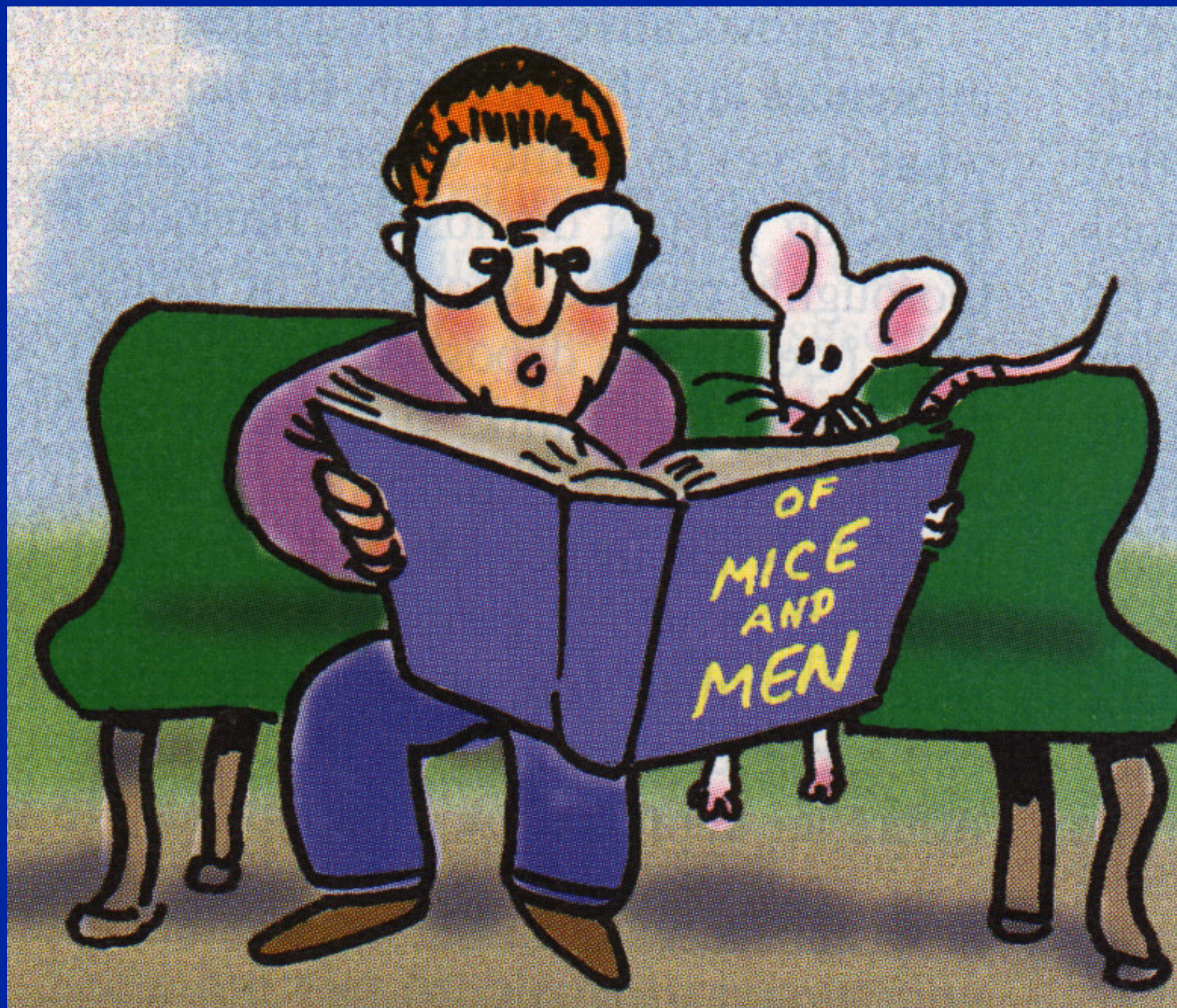
Many people worldwide consume caffeine daily. Normal dietary consumption is sufficient to antagonize up to 50% of the inhibitory A_1 and the facilitatory A_{2A} adenosine receptors in the brain (2, 3). This increases alertness and allays drowsiness and fatigue, but may also induce restlessness and prolong the time to fall asleep.

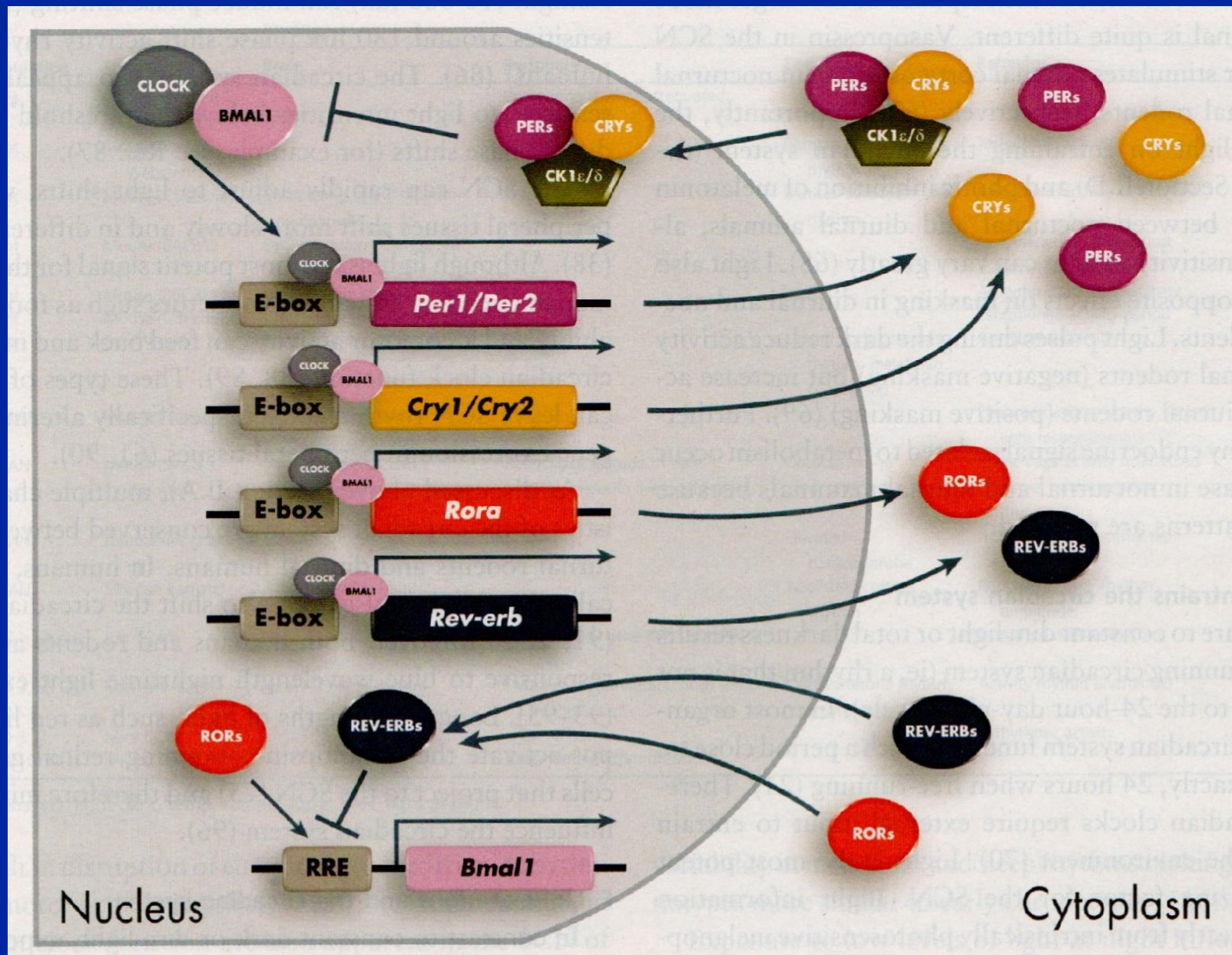


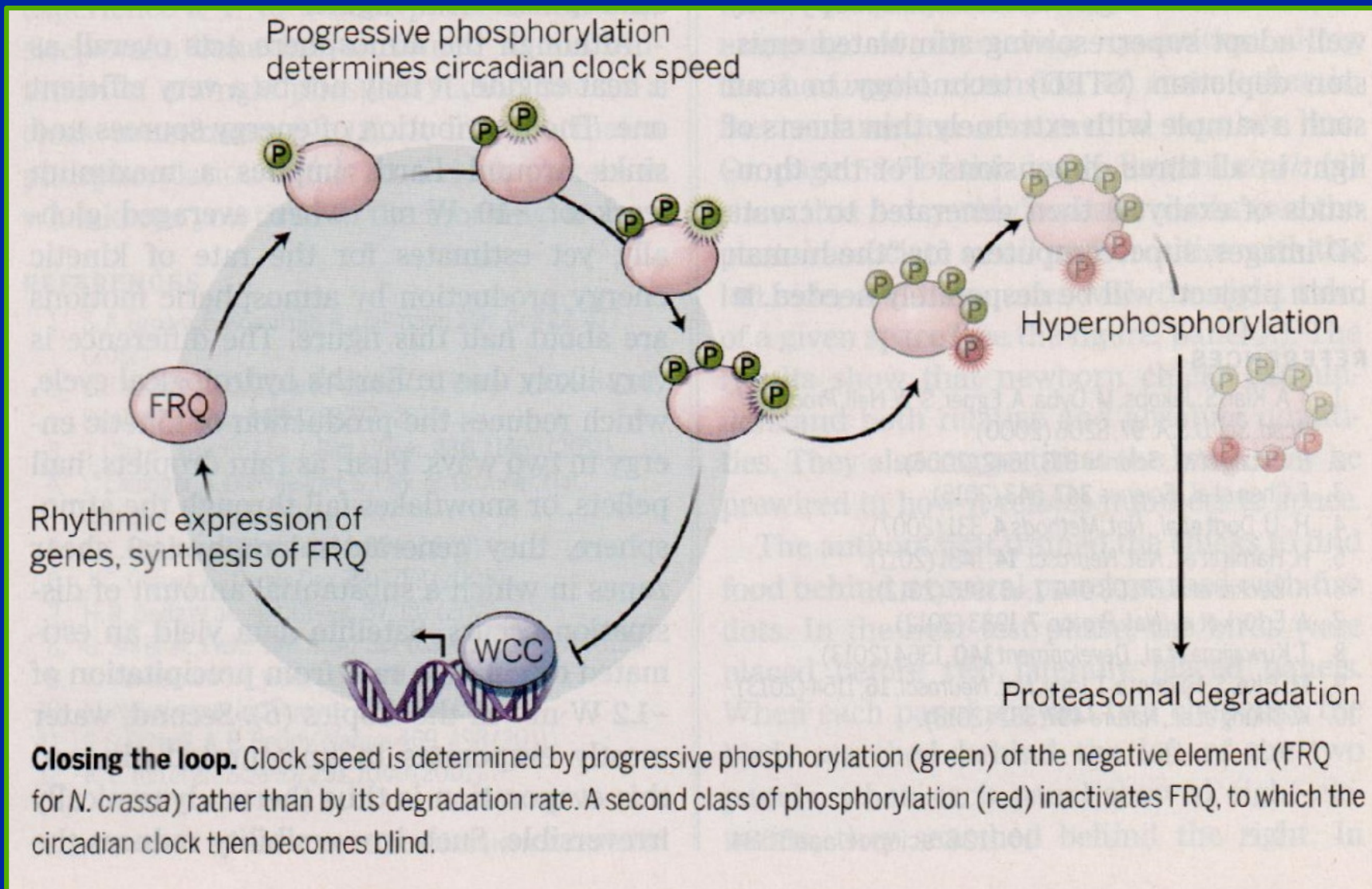
suggest an adenosine A_1 receptor-mediated, cAMP-dependent mechanism.

Caffeine-induced interference with the circadian clock may contribute to the high incidence of sleep problems in society and have a negative impact on brain functions that rely on undisturbed slow-wave sleep (11). Indeed, circadian rhythmicity modulates important functional characteristics of slow-wave sleep in humans (12). Yet, properly timed caffeine could alleviate jet lag and help patients with circadian sleep-wake disorders. Research on causal relationships among caffeine, circadian timekeeping, sleep, and health is warranted.

Apart from the circadian clock, cAMP signaling also plays an important role in sleep homeostasis and in the effects of caffeine on the consequences of sleep loss in animals (13, 14). In humans, the physiological study of wakefulness and sleep is laborious,



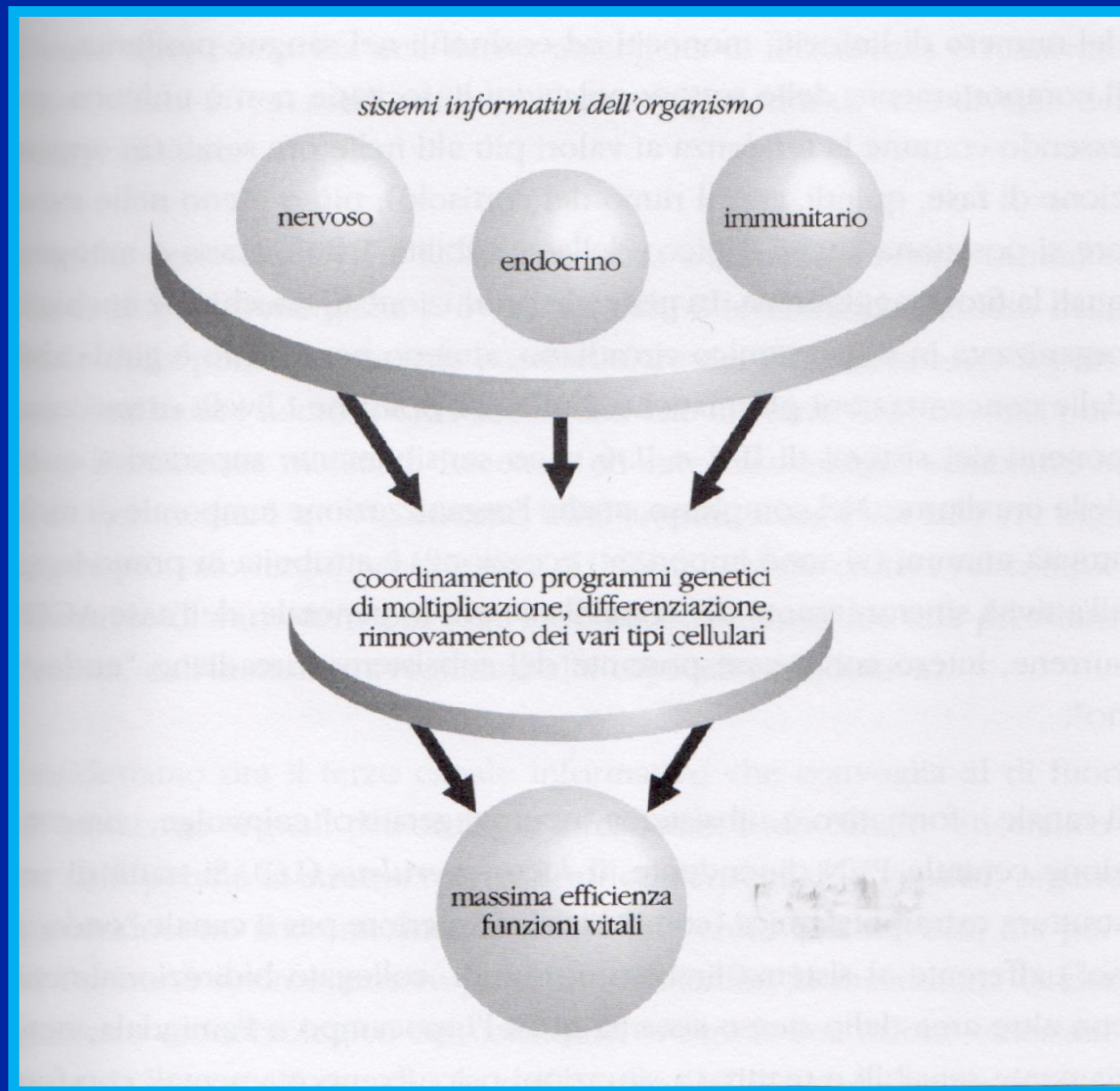




Science (2015) 347: 476-477

When the circadian clock becomes blind

Kramer A.



A decline in homeostasis and a loss of integration among the body's interdependent systems seem to be the general mechanisms by which aging progresses over time

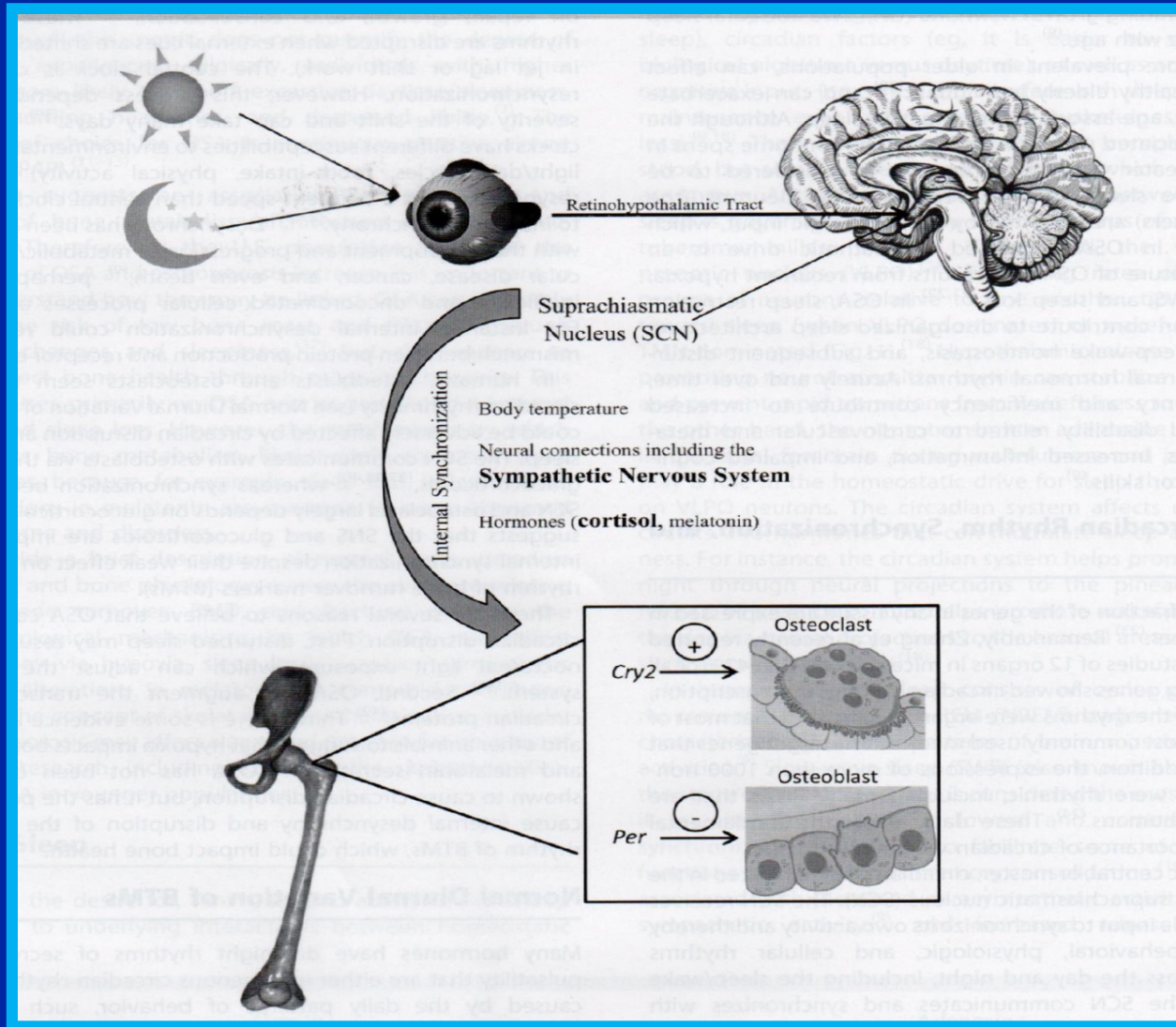
Tamas Fulop. Karger Gazette 2012



SINCRONIZZATORI ESTERNI : luce/buio; t° ; campi elettromagnetici; cibo; vita sociale.

SINCRONIZZATORI INTERNI : sonno/veglia; cortisolo; melatonina; citochine;
sistema neurovegetativo;

DESINCRONIZZAZIONE : Ritmi free-running



J Bone Miner Res (2015) 30: 199-221

Obstructive Sleep Apnea and Metabolic Bone Disease: Insight Into the Relationship Between Bone and Sleep

Swanson et al

Table 1. Units of Radiometry and Photometry:

(A) Radiometric measures

Measurement of electromagnetic energy within the optical spectrum, which includes ultraviolet radiation, visible light, and infrared radiation. An ideal radiometric detector has a „flat“ spectral response.



Irradiance:

Measure of radiant energy from all directions over a 180° field of view.

Radiance:

Measure of radiant energy viewed from a specific direction or region in space.

Common Units:

erg/s/cm^2

$\mu\text{W/cm}^2$

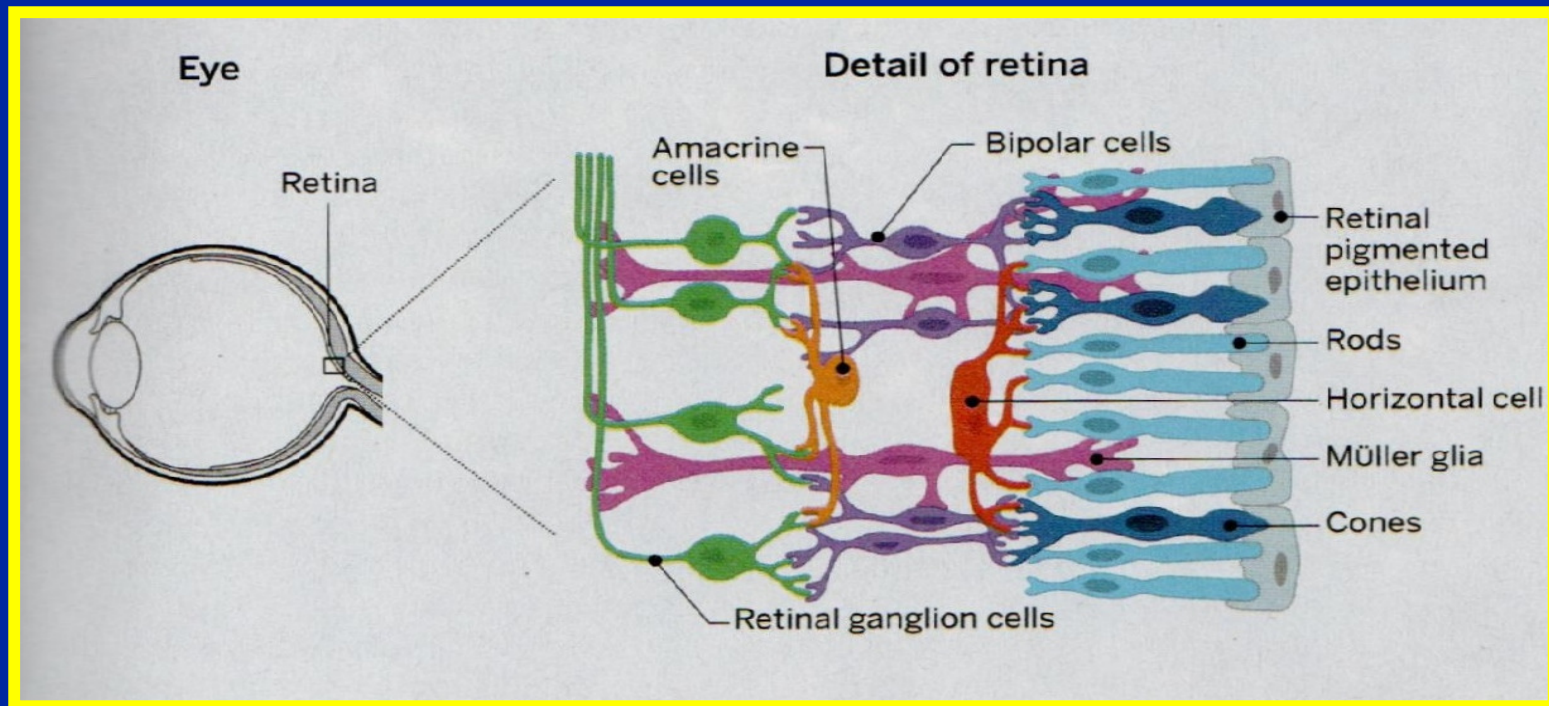
$\text{photons/cm}^2/\text{s}$

Common Units:

$\text{erg/s/cm}^2/\text{sr}$

$\mu\text{W/cm}^2/\text{sr}$

$\text{photons/cm}^2/\text{s/sr}$



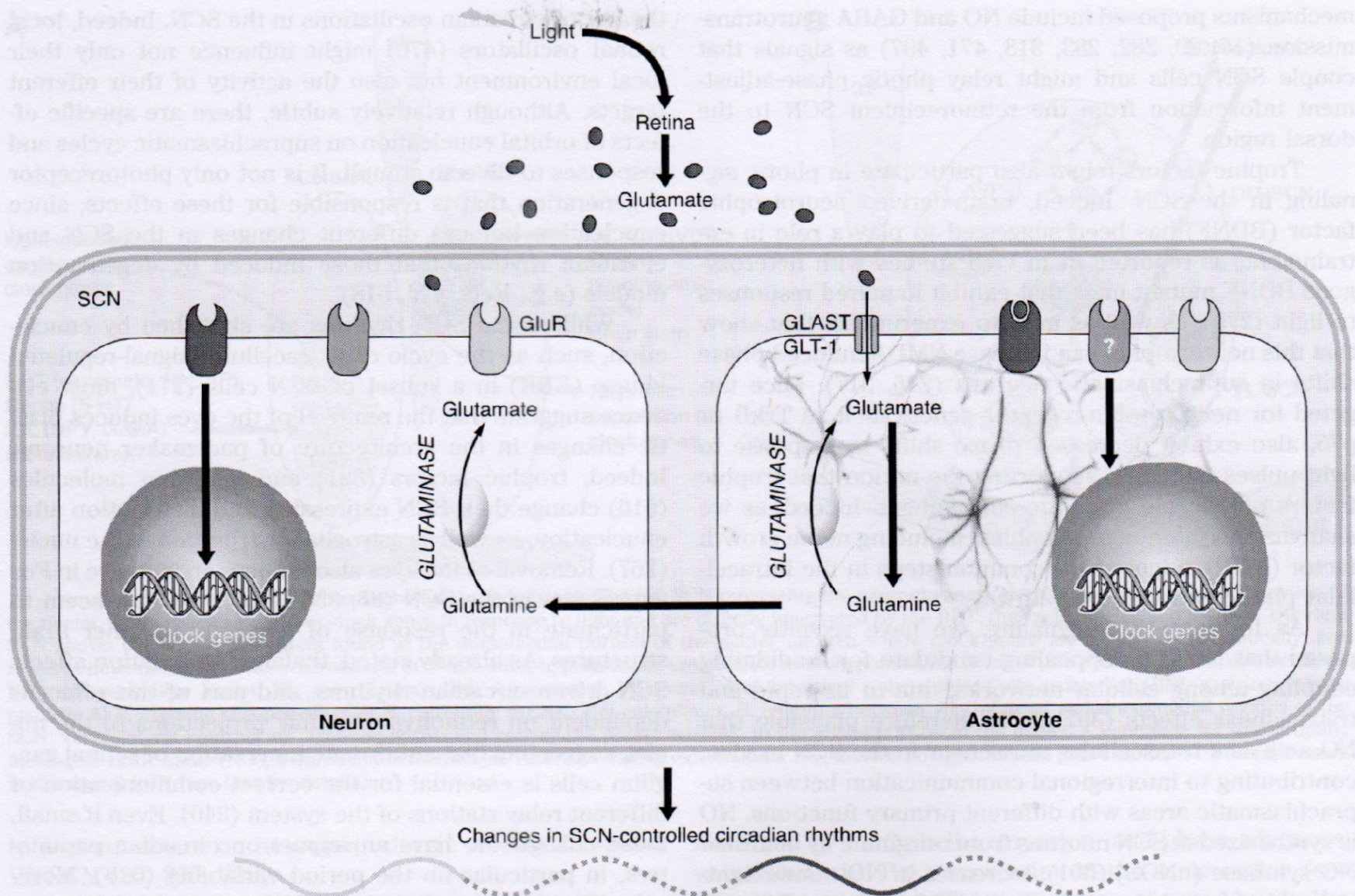
Tipi cellulari della retina

MELANOPSINA

- Identificata / sequenziata alla fine del secolo scorso (1997-1998).
- < 1% delle proteine retiniche.
- Espressa nei melanofori cutanei, alcune aree encefaliche, retina.
- Proteina transmembrana ~ 50kDa (porzione extracellulare, sette porzioni transmembrana, porzione intracellulare).
- Nella famiglia delle opsine, maggiore affinità strutturale con opsine di invertebrati che con altre opsine di vertebrati
- Nella retina, è espressa da una specifica popolazione di cellule gangliari, definite ipRGC (intrinsically photoreceptive retinal gangliar cells).
- Le cellule gangliari retiniche che esprimono melanopsina inviano segnali (proiezioni monosinaptiche) attraverso i tratti retino-ipotalamici ai nuclei soprachiasmatici (SCN)

NUCLEI SOPRACHIASMATICI (SNC)

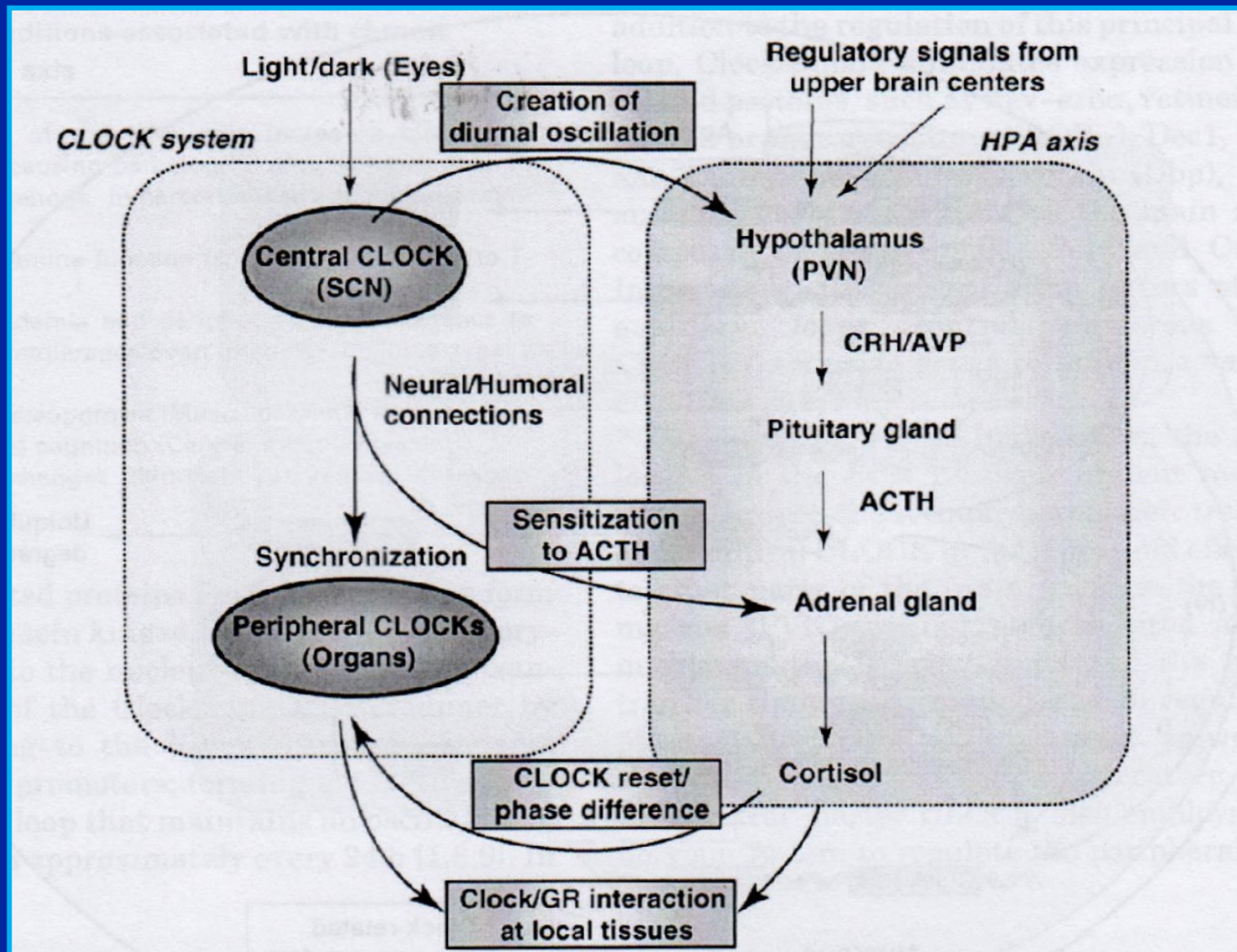
- Posizionati nell'ipotalamo ventrale sopra il chiasma ottico, costituiti da diverse popolazioni di piccoli neuroni e astrociti fittamente addensati (densely packed).
- Numero di neuroni stabile in tutte le specie di mammiferi (30.000-40.000).
- Espressione genica di neuropeptidi (neuroni peptidergici).
- Principali meccanismi afferenti (varie aree encefaliche; tratti retino-ipotalamici; pineale) : GABA, glutammato, melatonina, serotonina (5-HT).
- Principali meccanismi efferenti (varie aree encefaliche ; nuclei paraventricolari (PVN) ; pineale; periferia?) : vasopressina (AVP), *vasoactive, intestinal peptide* (VIP), met-enkefalina (mENK), galanina, sistema simpato- adrenergico.



Physiol Rev 2010; 90: 1063-1102

Physiology of Circadian Entrainment

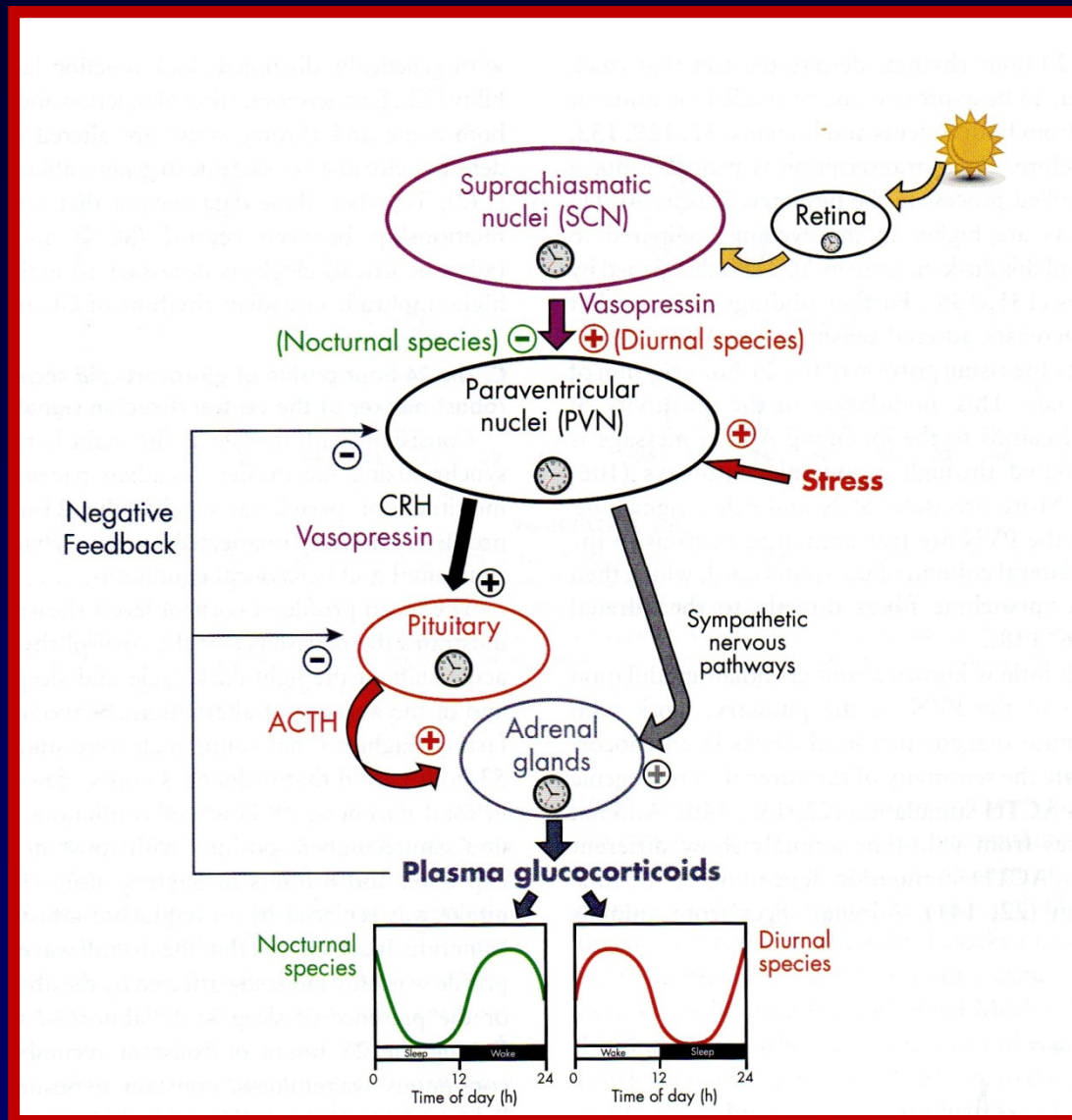
Golombek DA, Rosenstein RE



Trends Endocrinol Metab 2010, 21 : 277-286

Interactions of the circadian CLOCK system and HPA axis

Nader N et al



Endocrine Reviews, February 2017, 38(1):3-45

The Functional and Clinical Significance of the 24-Hour Rhythm of Circulating Glucocorticoids

Henrik Oster,* Etienne Challet,* Volker Ott, Emanuela Arvat, E. Ronald de Kloet, Derk-Jan Dijk, Stafford Lightman, Alexandros Vgontzas, and Eve Van Cauter

Physiol Genomics 44: 607–621, 2012.

First published April 17, 2012; doi:10.1152/physiolgenomics.00001.2012.

Entrainment of peripheral clock genes by cortisol

Panteleimon D. Mavroudis,¹ Jeremy D. Scheff,² Steve E. Calvano,³ Stephen F. Lowry,³
and Ioannis P. Androulakis^{1,2,3}

Glucocorticoid Signaling Synchronizes the Liver Circadian Transcriptome

Akhilesh B. Reddy,¹ Elizabeth S. Maywood,¹ Natasha A. Karp,² Verdun M. King,³ Yusuke Inoue,⁴ Frank J. Gonzalez,⁴
Kathryn S. Lilley,² Charalambos P. Kyriacou,⁵ and Michael H. Hastings¹

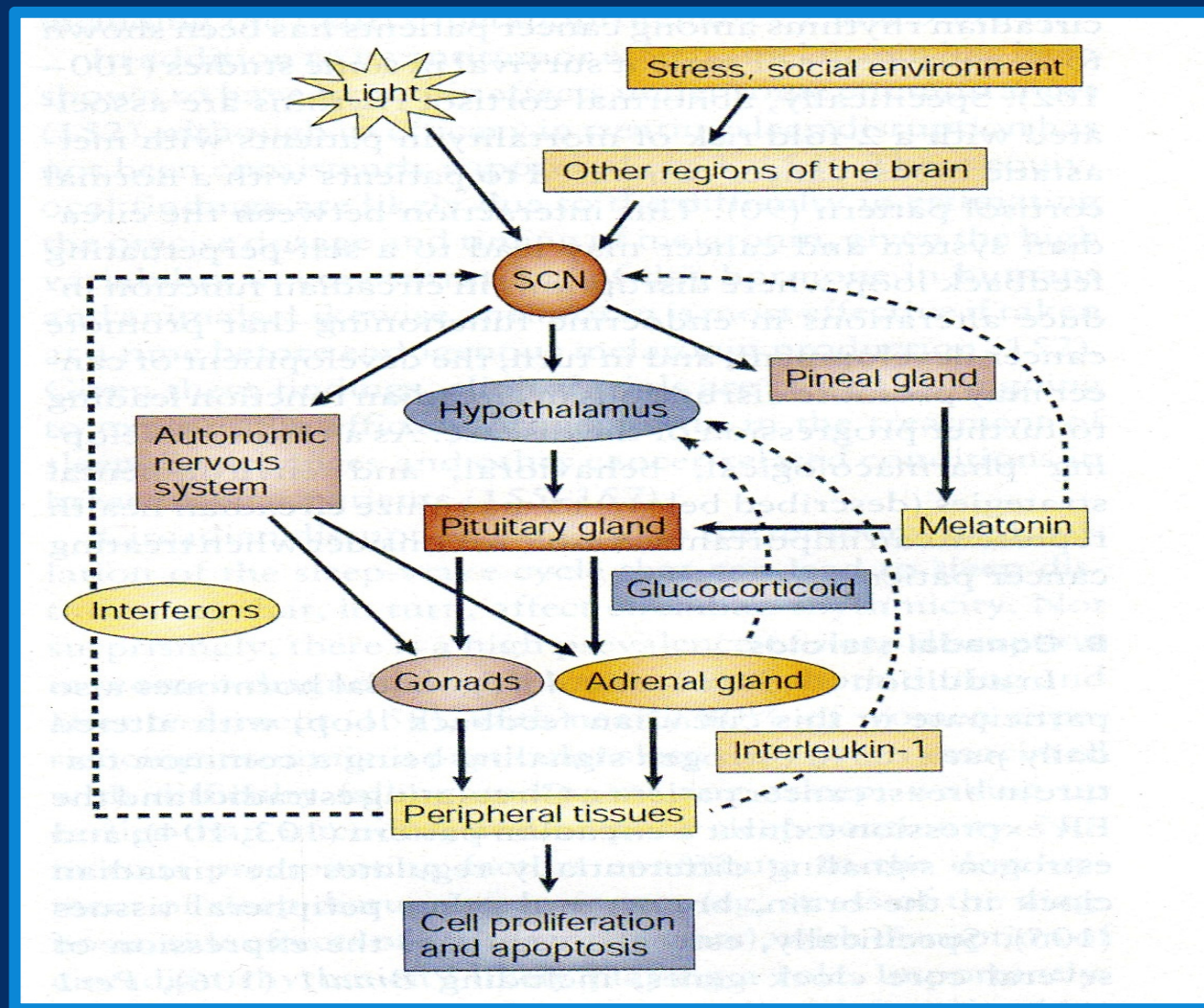
J Steroid Biochem. 1983 Jul;19(1B):545-54.

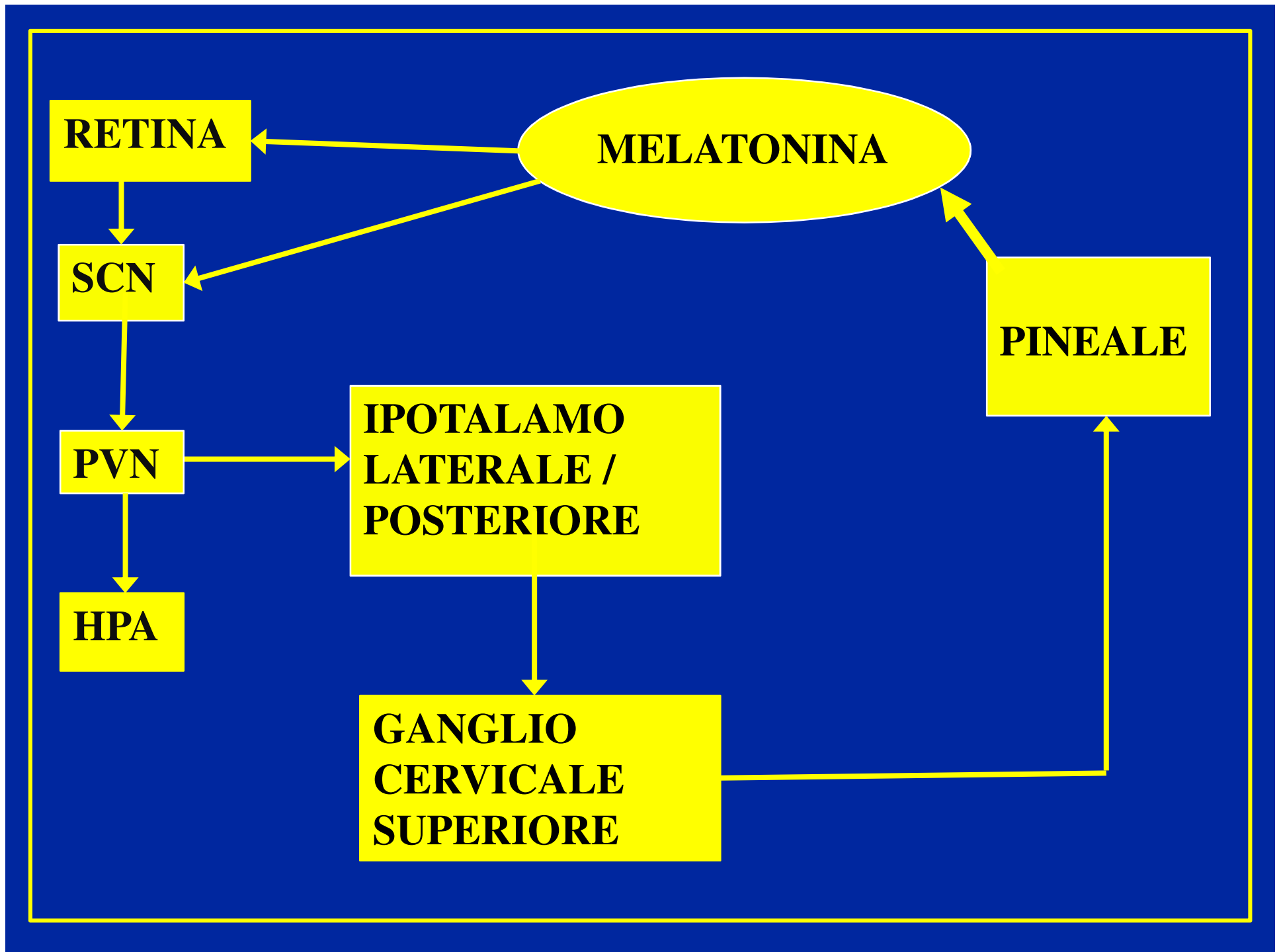
Glucocorticoid secretion: a circadian synchronizer of the human temporal structure.

Angeli A.

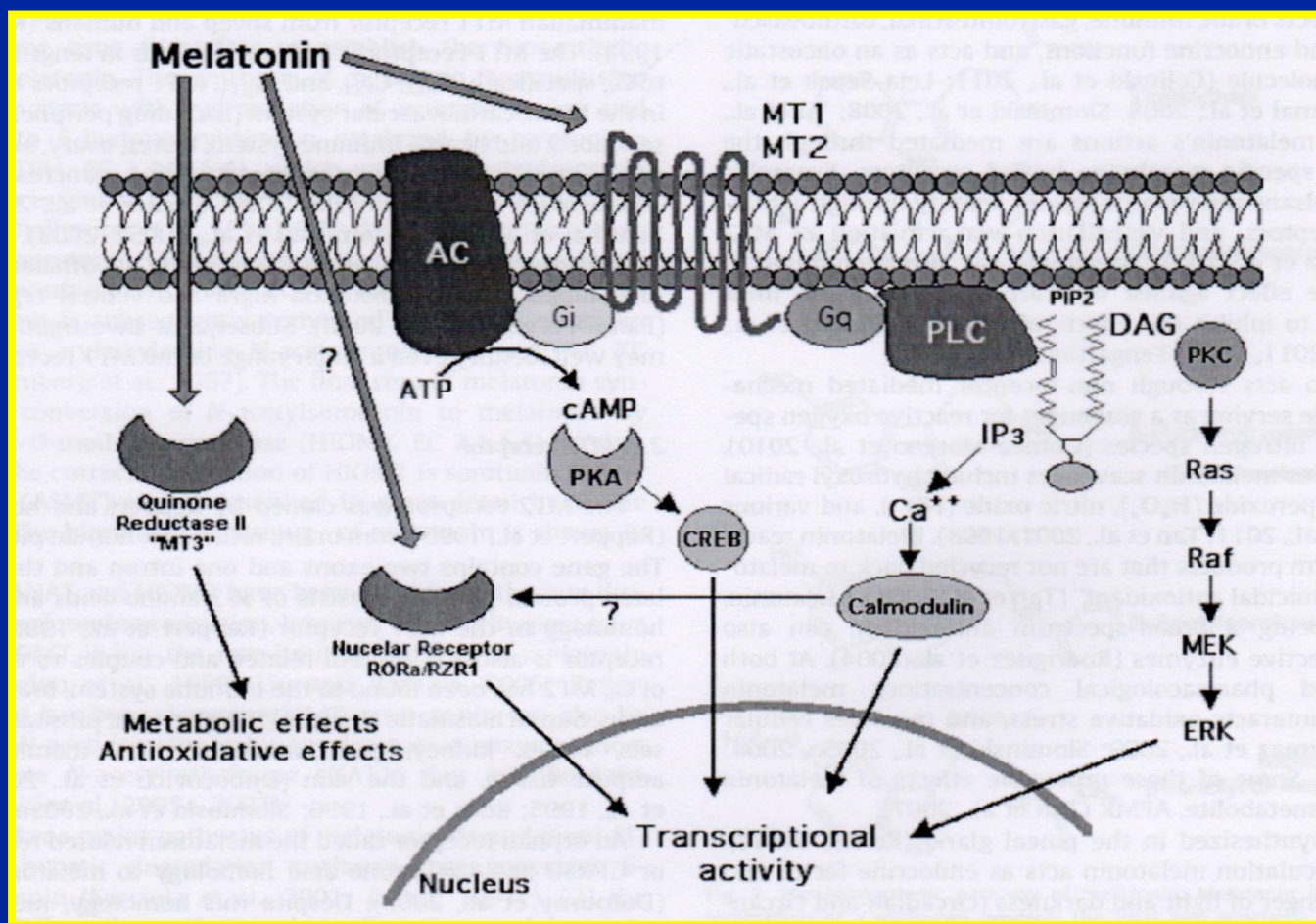
Abstract

The circadian rhythm of glucocorticoid secretion represents an important endogenous synchronizer, a signal to place other bioperiodicities along an appropriate time scale. The results obtained both in experimental animals and in man by properly-timed administration of corticoids as well as personal observations in patients with Addison's disease given replacement therapy suggest that glucocorticoid action may not need continuous supply of hormone molecules to target cells but appropriate waves complying with the peripheral susceptibility. Furthermore, circadian changes in the susceptibility to glucocorticoid action may be phase-shifted among different targets. Evidence is presented that in human beings ACTH secretion is exquisitely sensitive to the negative feed-back effect by cortisol in the nocturnal hours following midnight, i.e. in a circadian stage preceding the acrophase of plasma glucocorticoid levels. In the circadian domain multiple rhythmic events, including chrono-feed-back and chrono-feed-forward mechanisms as well as the organization of steroid binding to plasma corticosteroid-binding globulin, provide stability, plasticity and economy to the activity of the entire hypothalamo-pituitary-adrenal system by conveying genetic and environmental control into a well-defined temporal program.





Melatonina e suoi recettori

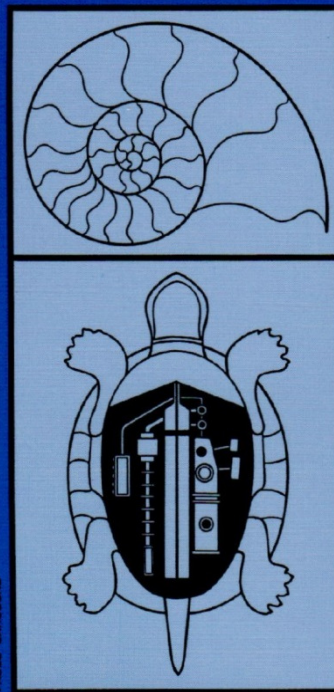


Mol Cell Endocrinol 2012 ; 351:152-166
Slominski RM et al

Third Stromboli Conference
on Aging and
Cancer

THE AGING CLOCK

The Pineal Gland and Other Pacemakers
in the Progression of Aging and Carcinogenesis



PAOLO CAROSONE

Edited by Walter Pierpaoli,
William Regelson and Nicola Fabris

Annals of the New York Academy
of Sciences / Volume 719

Age dependence of plasma melatonin concentrations

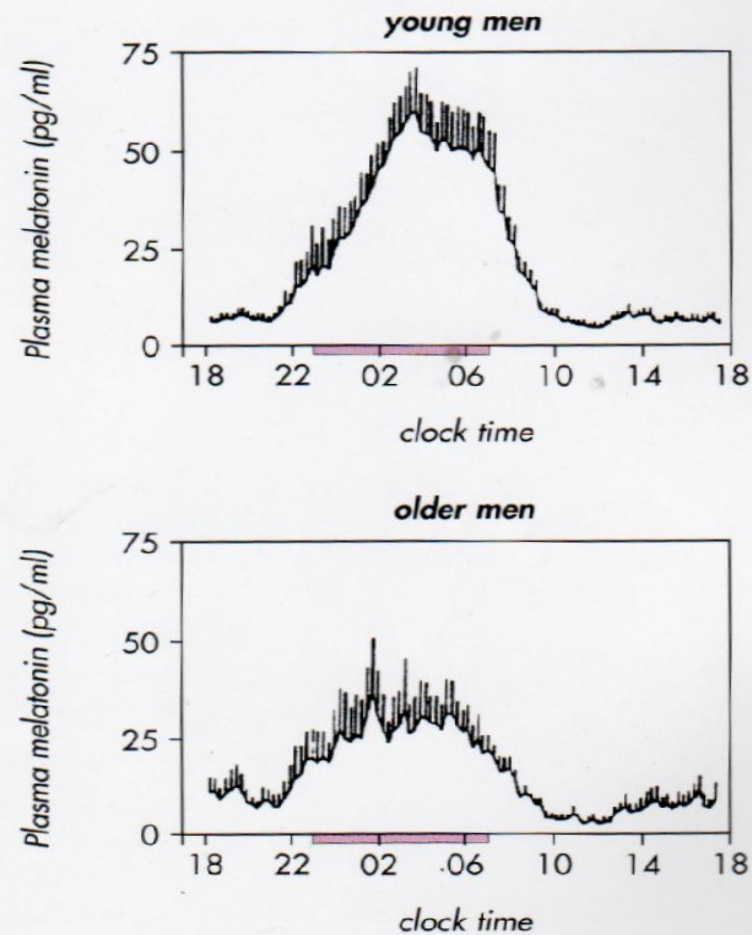


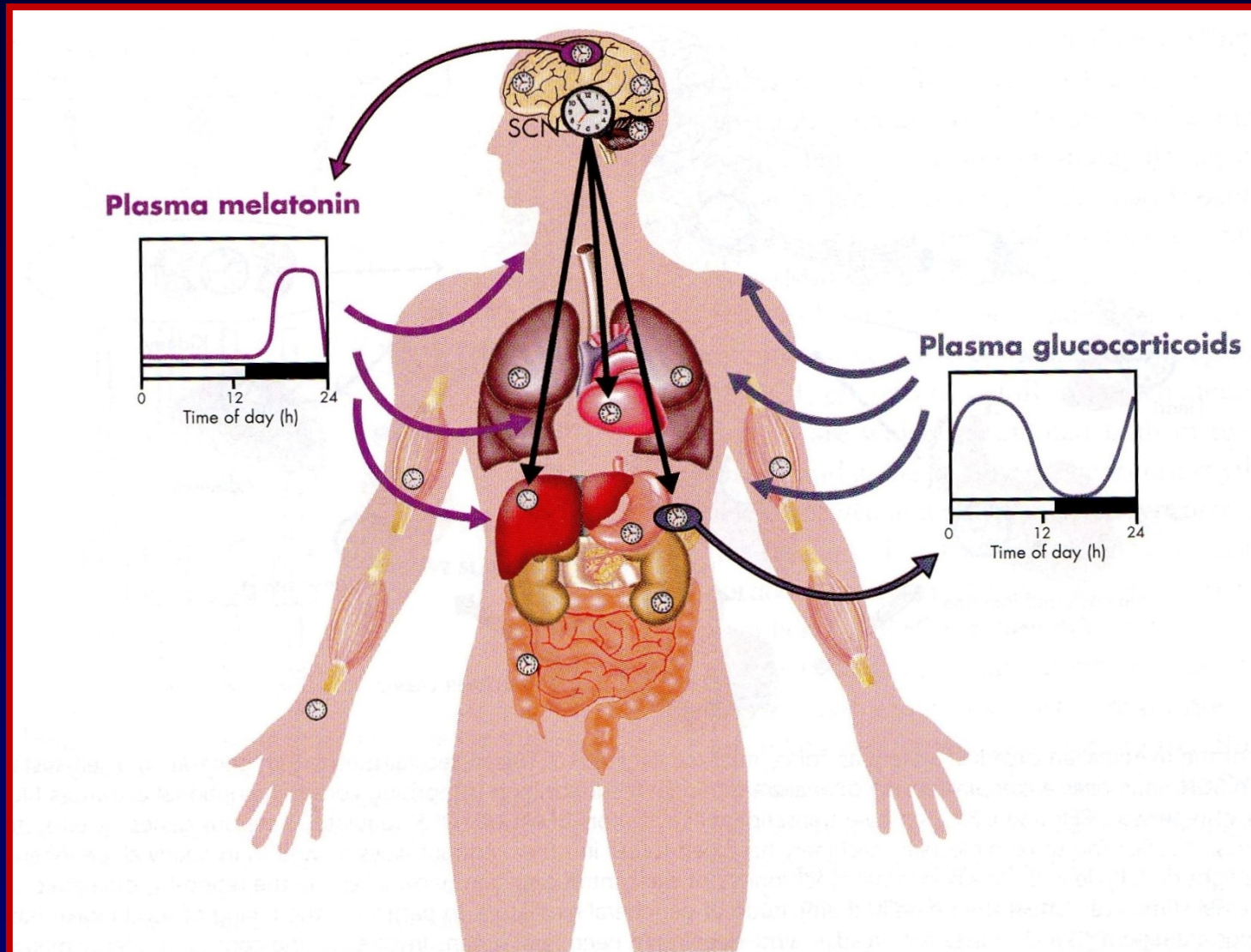
Fig.1: Daily plasma melatonin levels in young (20-27 year-olds) and old men (67-84 year-olds). night levels

***Melatonin -
a fountain of youth?***





The Kirtland's warbler
travels thousands
of kilometers in about
2 weeks.



SISTEMA CIRCADIANO :

DALLA FISIOLOGIA ALLA PATOLOGIA





**Abnormal
sleep**

Prolonged exposure to a toxic environment

Socioeconomic stress

Psychological and emotional stress

Changes in motivation and reward seeking

Fatigue, lack of vigor, reduced everyday activity

No regular exercise

Unhealthy food choices, alcohol, stimulant use

Changes in hunger and appetite

Autonomic dysfunction

Changes in fuel and metabolic hormone sensing (resistance to insulin)

Pro-inflammatory state, increased oxidative stress, hypothalamic dysfunction

Circadian desynchronization, nighttime eating

**Metabolic
syndrome
Diabetes**

DISORDERS ASSOCIATED WITH CIRCADIAN DESYNCHRONIZATION ALTERED SLEEP PATTERNS

Jet - Lag Syndrome

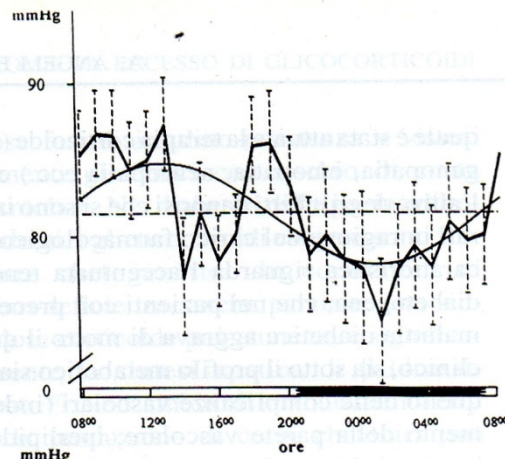
Shift - work Syndrome

Obstructive Sleep Apnea Syndrome (OSAS)

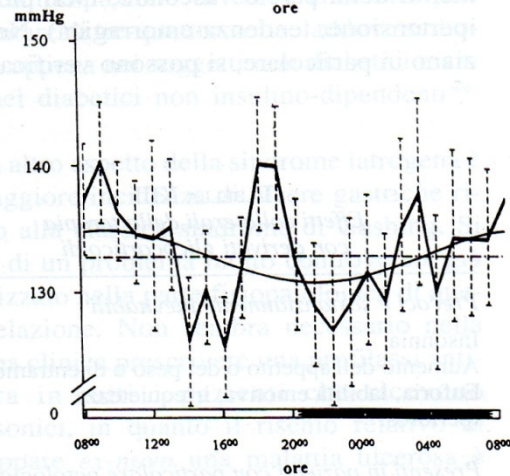
Cushing 's Syndrome

Autonomic dysfunction

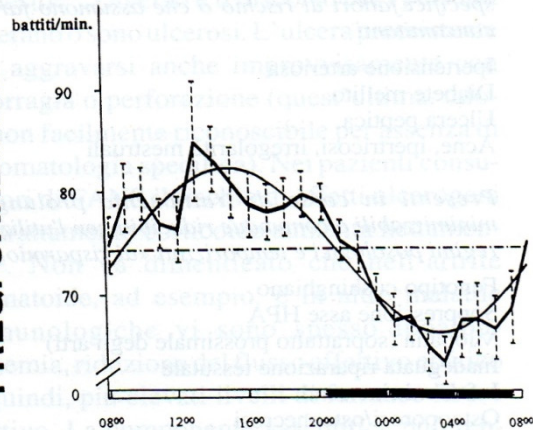
PRESS. DIASTOLICA



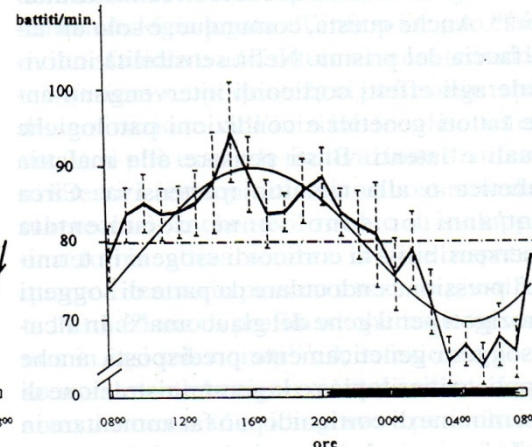
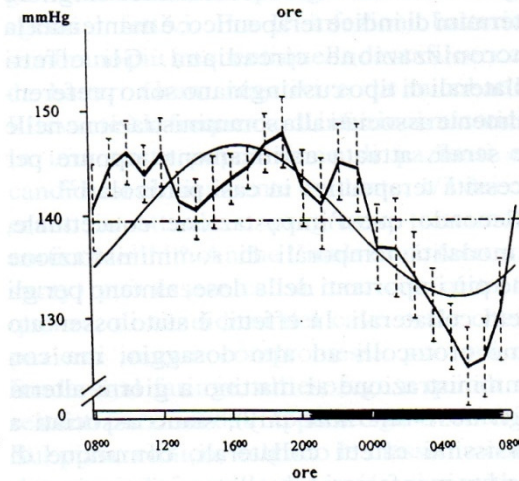
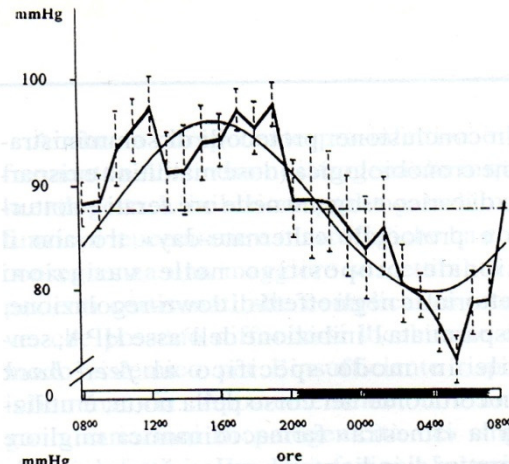
PRESS. SISTOLICA



FREQ. CARDIACA



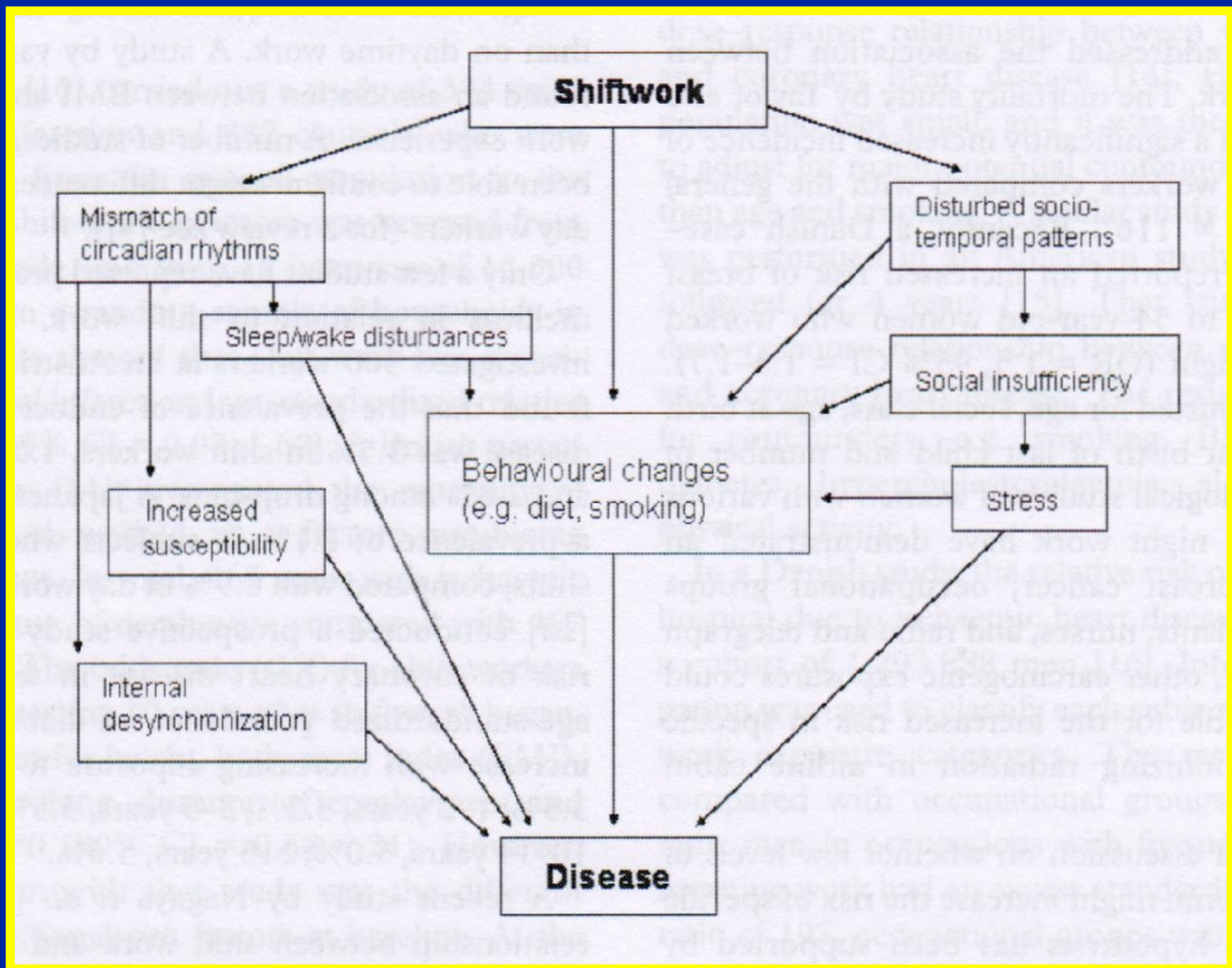
B



Sindromi da eccesso di glicocorticoidi

A. Angeli, R.G. Masera, F. Orlandi,
M. Terzolo

EDIZIONI LUIGI POZZI 1994



Circadian Rhythms and Metabolic Syndrome

From Experimental Genetics to Human Disease

Eleonore Maury, Kathryn Moynihan Ramsey, Joseph Bass

1860

Diabetes Volume 63, June 2014

Rachel Leproult,^{1,2} Ulf Holmbäck,^{1,3} and Eve Van Cauter¹



CrossMark

Circadian Misalignment Augments Markers of Insulin Resistance and Inflammation, Independently of Sleep Loss

Diabetes 2014;63:1860–1869 | DOI: 10.2337/db13-1546

There is substantial evidence that the disruption of the circadian system with exposure to light at night affects human health and increases the risk of developing significant disease conditions.

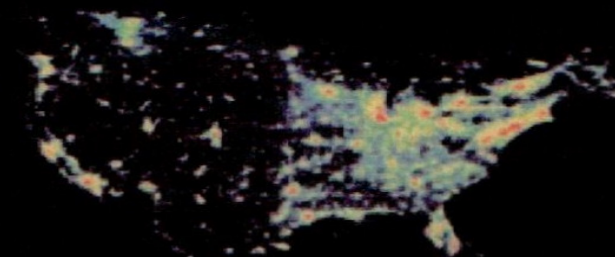
- Sleep disturbances
- Mood disorders
- Cognitive impairments
- Breast cancer
- Metabolic syndrome /Type 2 diabetes
- Hypertension/Atherosclerosis/Cardiovascular damage

Endocrine Rev (2014) 35: 648-670

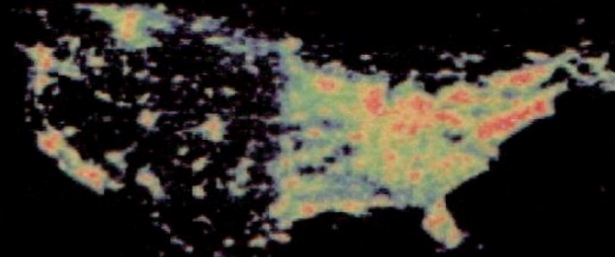
The effects of light at night on Circadian Clocks and Metabolism

Fonken LC, Nelson RJ

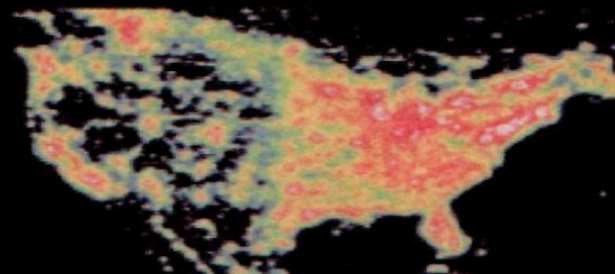
US light pollution



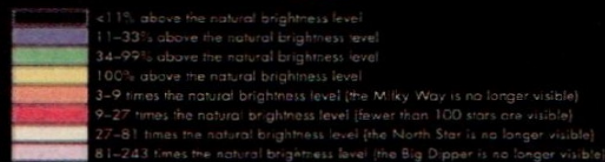
Mid 1970s



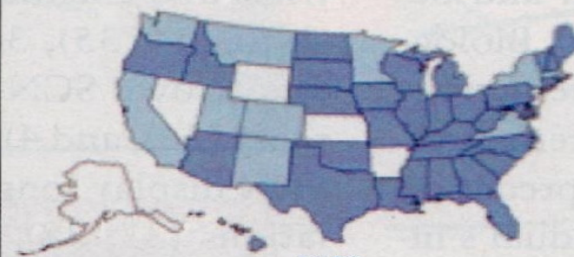
1977



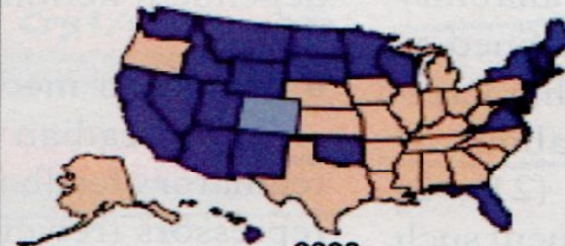
2025



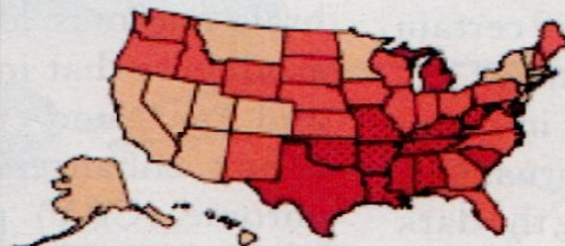
US obesity trends



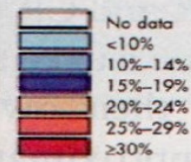
1990



2000



2010



Obesity is defined as BMI ≥ 30 , or ~30 lbs. overweight for 5'4" person



RESEARCH ARTICLE

ENVIRONMENTAL PROTECTION

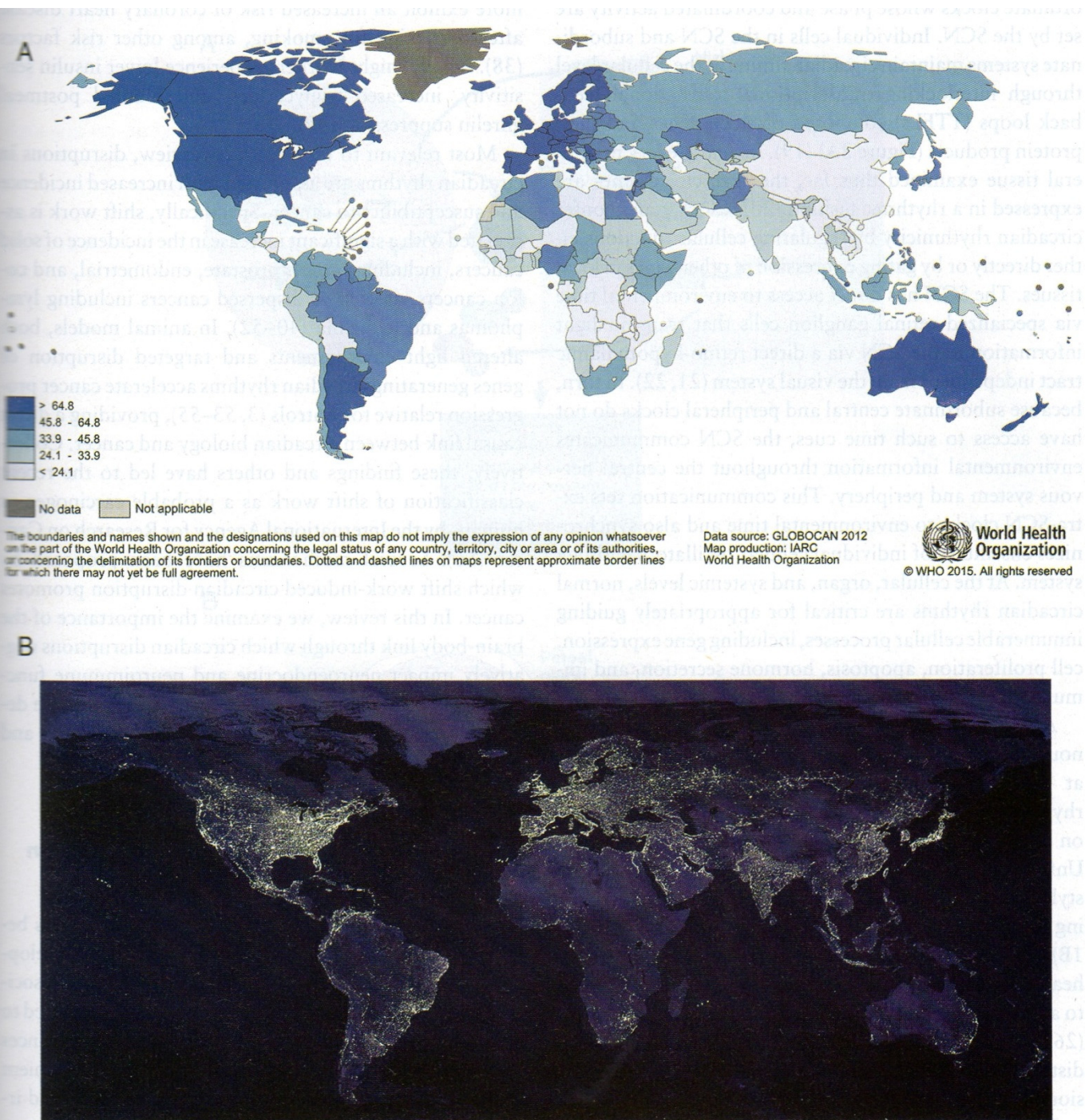
The new world atlas of artificial night sky brightness

Fabio Falchi,^{1*} Pierantonio Cinzano,¹ Dan Duriscoe,² Christopher C. M. Kyba,^{3,4} Christopher D. Elvidge,⁵ Kimberly Baugh,⁶ Boris A. Portnov,⁷ Nataliya A. Rybnikova,⁷ Riccardo Furgoni^{1,8}

2016 © The Authors, some rights reserved;
exclusive licensee American Association for
the Advancement of Science. Distributed
under a Creative Commons Attribution
NonCommercial License 4.0 (CC BY-NC).
10.1126/sciadv.1600377



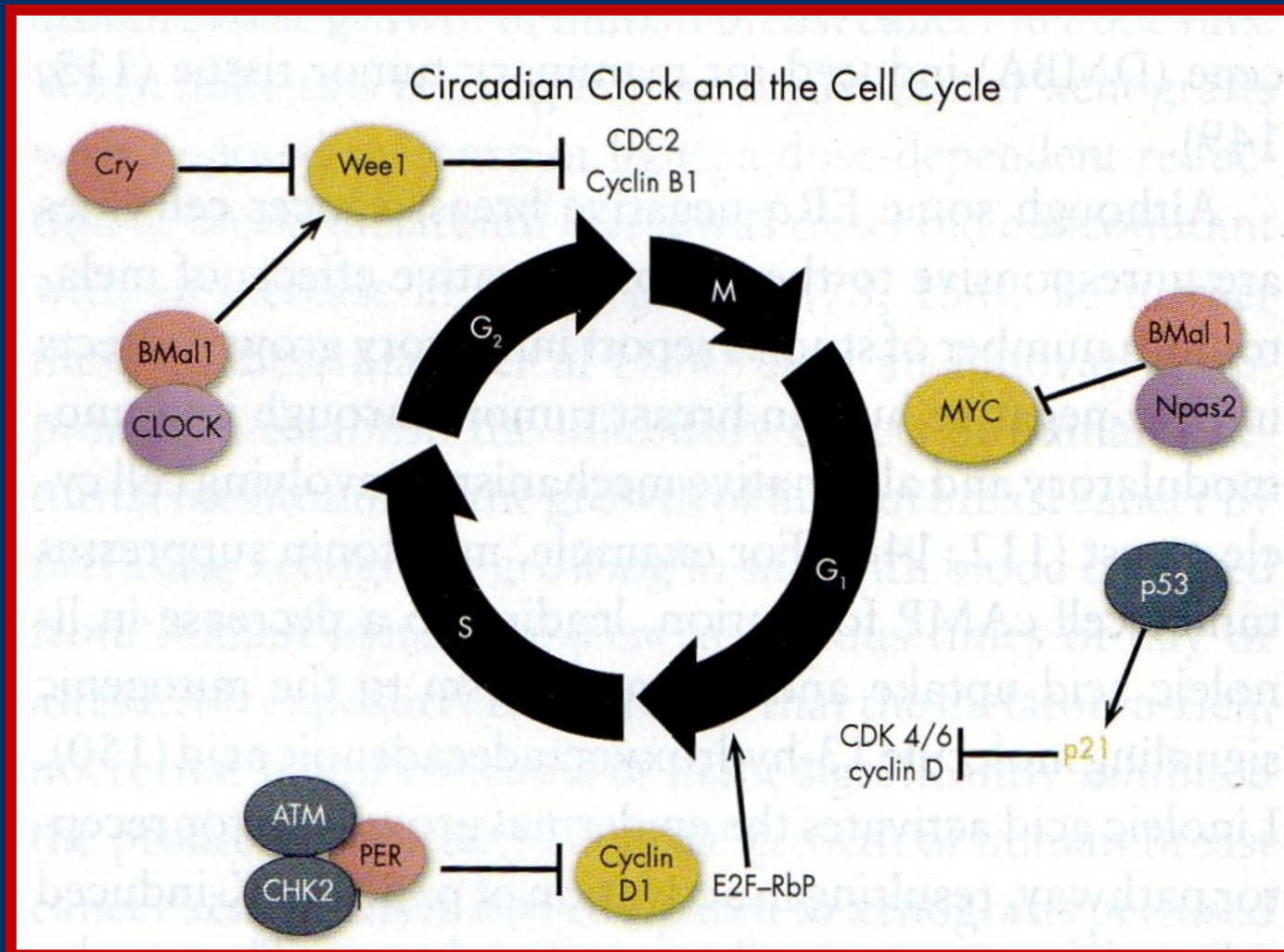
Fig. 2. World map of artificial sky brightness. The map shows, in twofold increasing steps, the artificial sky brightness as a ratio to the natural sky brightness (assumed to be $174 \mu\text{cd}/\text{m}^2$). Table 1 indicates the meaning of each color level.



REVIEW

The Pathophysiologic Role of Disrupted Circadian and Neuroendocrine Rhythms in Breast Carcinogenesis

Lonnele J. Ball, Oxana Palesh, and Lance J. Kriegsfeld



Cancer Lett. 2014; 342:9-18.

Circadian molecular clocks and cancer

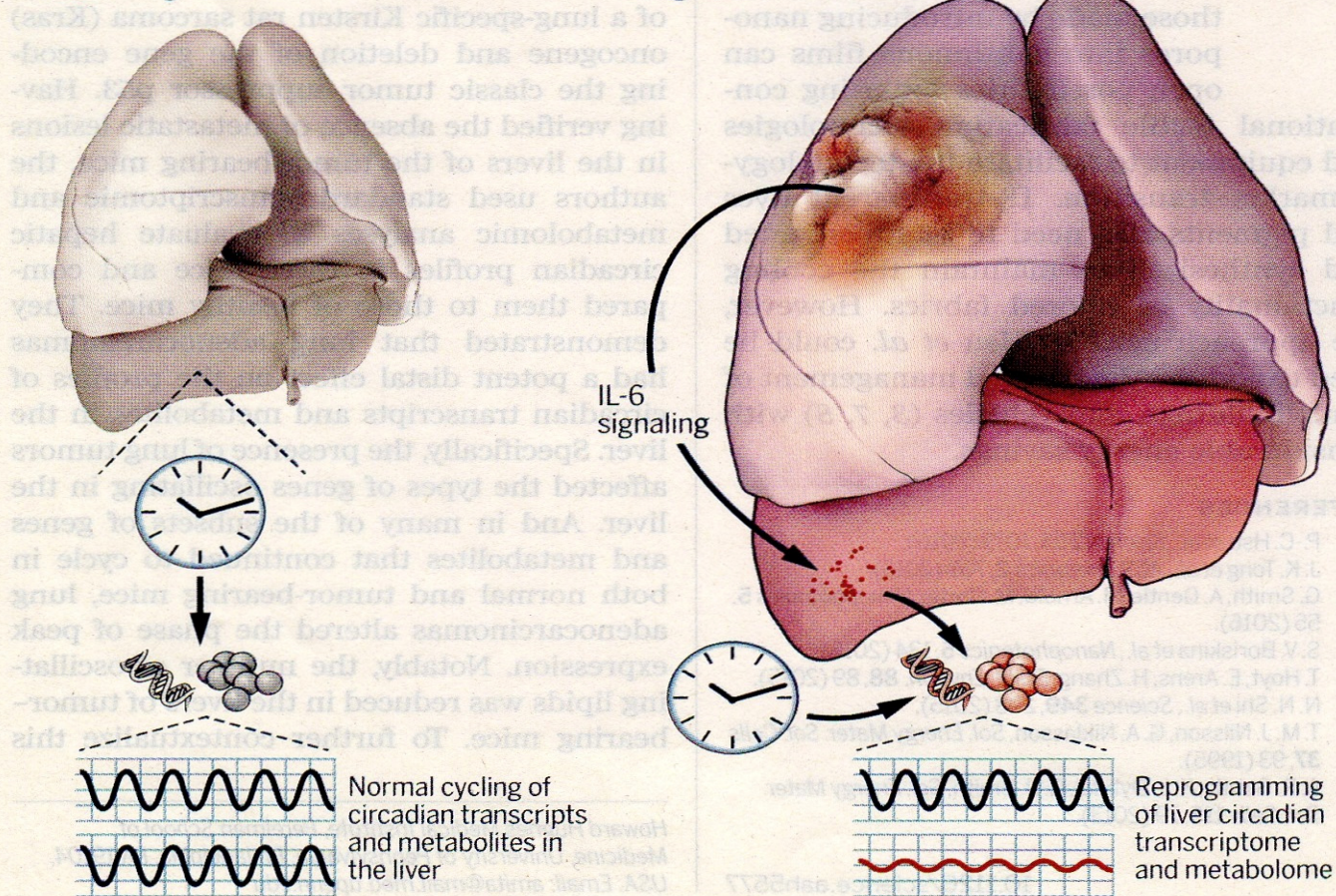
Kelleher FC, Rao A, Maguire A

Remote control

Lung adenocarcinoma (right) releases systemic inflammatory cytokines, such as IL-6, that can act distally to reprogram the circadian transcriptome and metabolome in the liver. It remains to be determined how IL-6 can globally rewire hepatic circadian outputs without affecting the ticking of the core circadian clock.

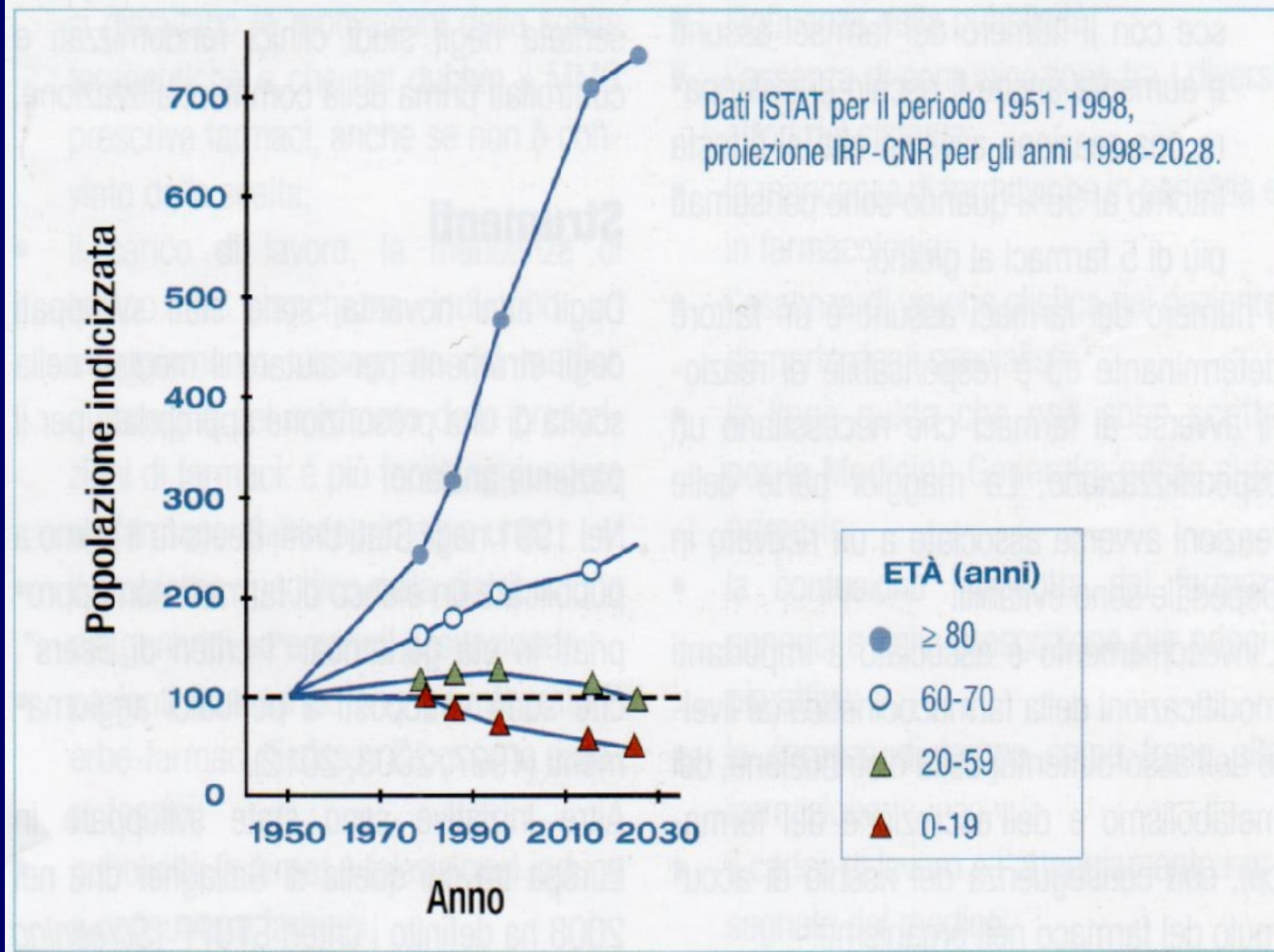
Normal lungs and liver

Lung adenocarcinoma

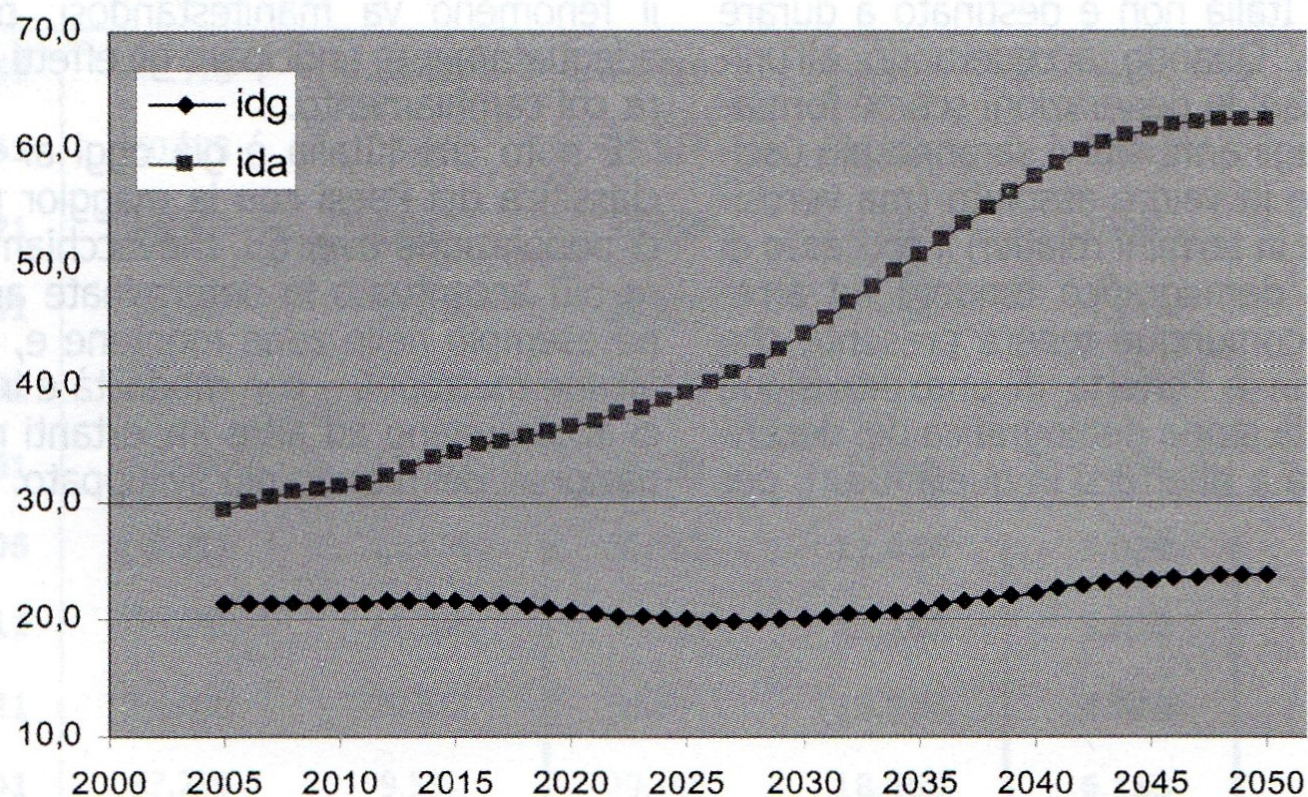




Tasso di crescita nella popolazione italiana 1950-2030.



Indice di dipendenza dei giovani (idg = giovani per ogni 100 attivi) e degli anziani (ida = anziani per ogni 100 attivi) in Italia, 2005-2050



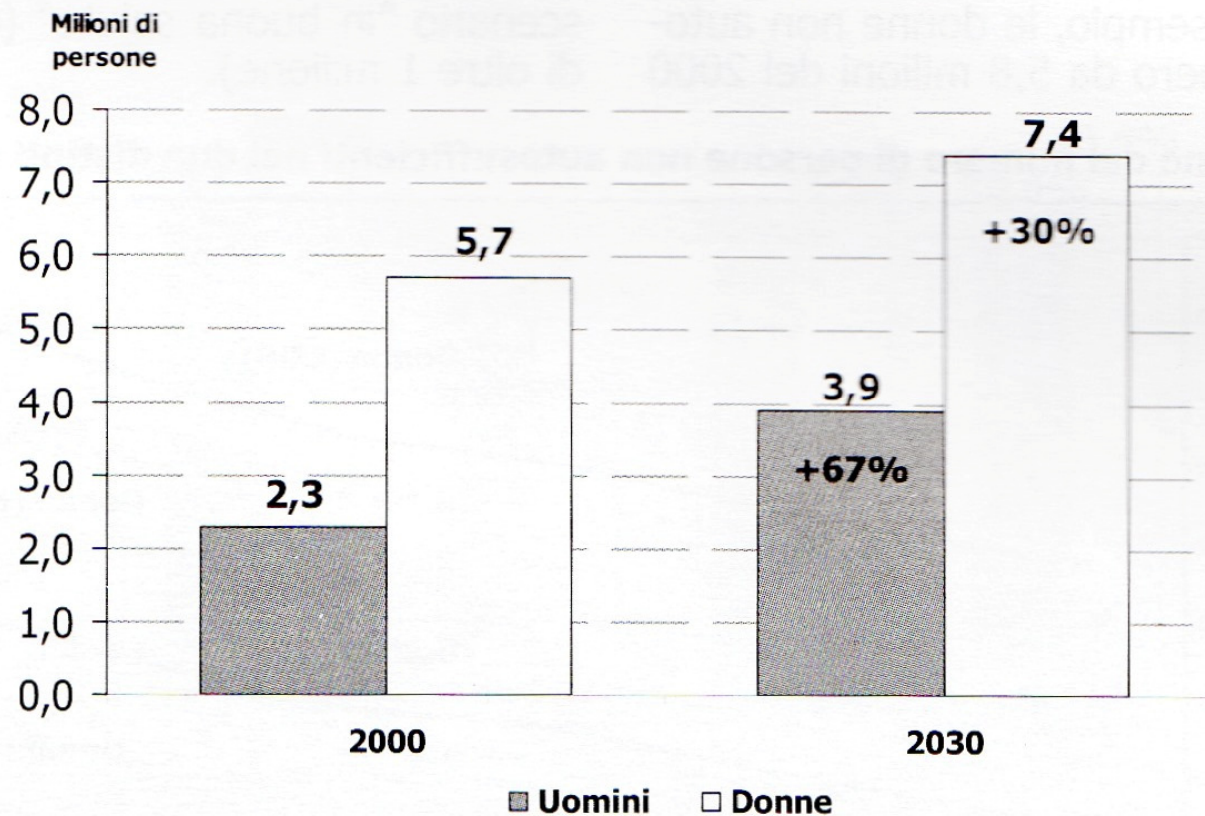
Fonte: elaborazioni su dati Istat, previsioni della popolazione 2006

SOCIALITA' e RICERCHE

TERZA ECONOMIA SEMPRE PIU' VALORE ALLA TERZA ETA'

Quad 2, 22 gennaio 2008

Evoluzione del numero di persone non autosufficienti nello scenario "in buona salute", 2000 - 2030



Fonte: Programma Future Elderly Living Conditions in Europe

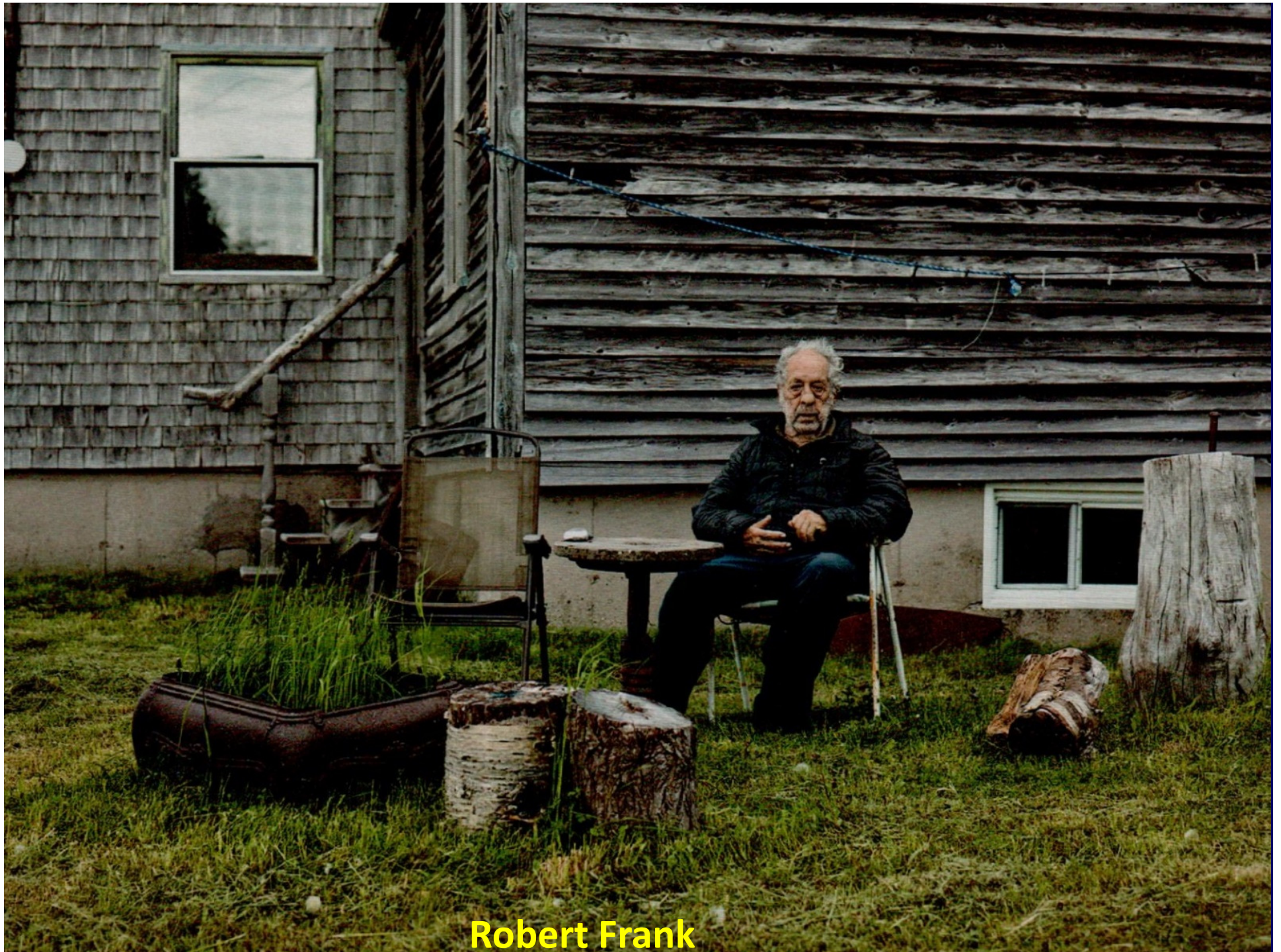
SOCIALITA' e RICERCHE

TERZA ECONOMIA SEMPRE PIU' VALORE ALLA TERZA ETA'

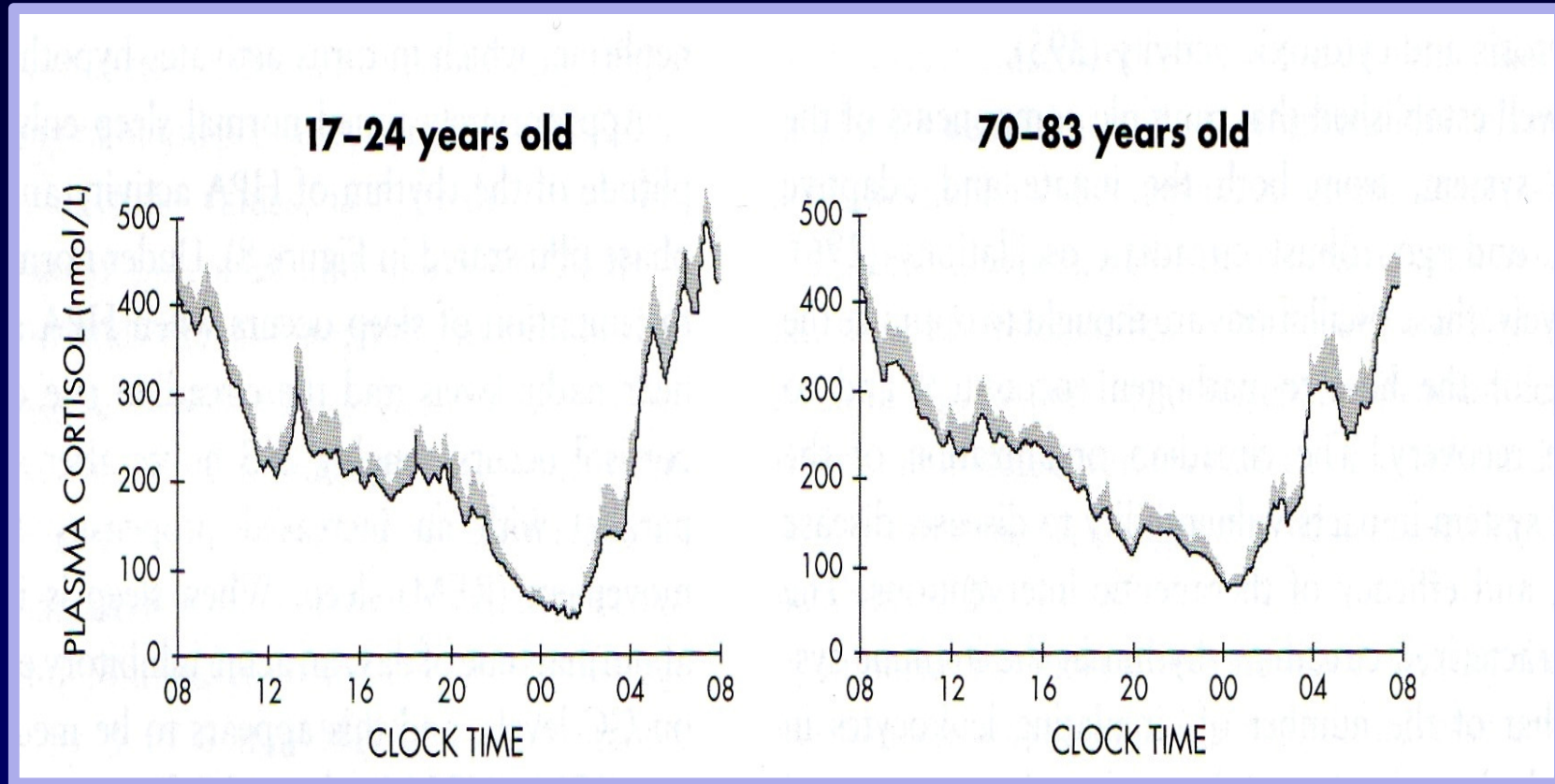
Quad 2, 22 gennaio 2008

Hypercortisolism and the aging brain

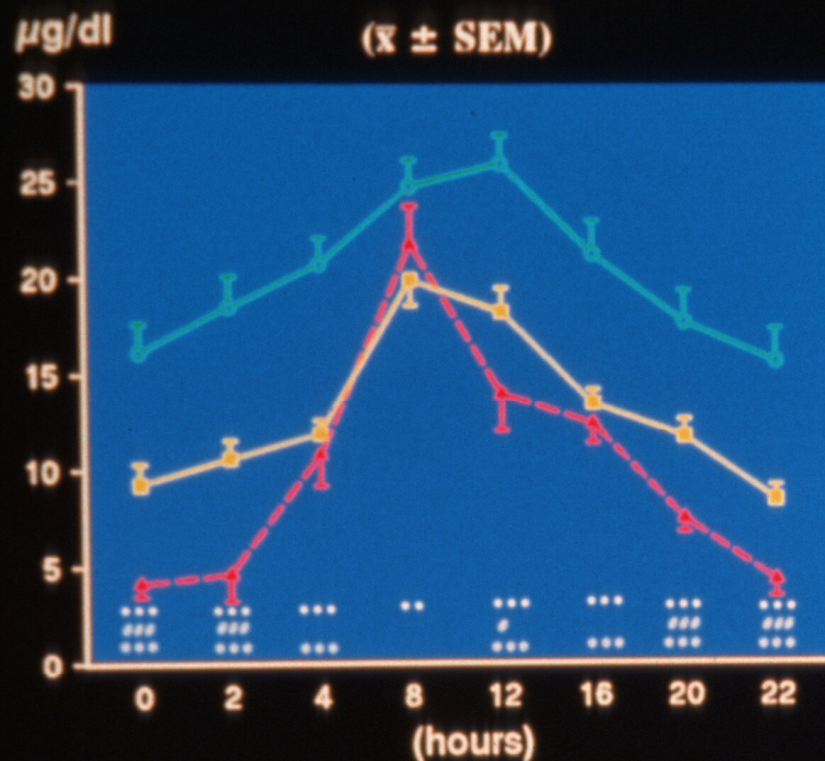
- An increasing body of evidence points to excess cortisol secretion and/or action in aged individuals, notably in demented patients
- Multiple mechanisms account for a vicious circle between brain and adrenals leading to progressive up-regulation of glucocorticoid action and progressive neurotoxic effects at various limbic sites
- The pathogenetic role of subclinical hypercortisolism in age-related neurodegenerative diseases still raises many more questions than answers. Clinical research is expected to focus on comorbidities and dynamics of functional deterioration



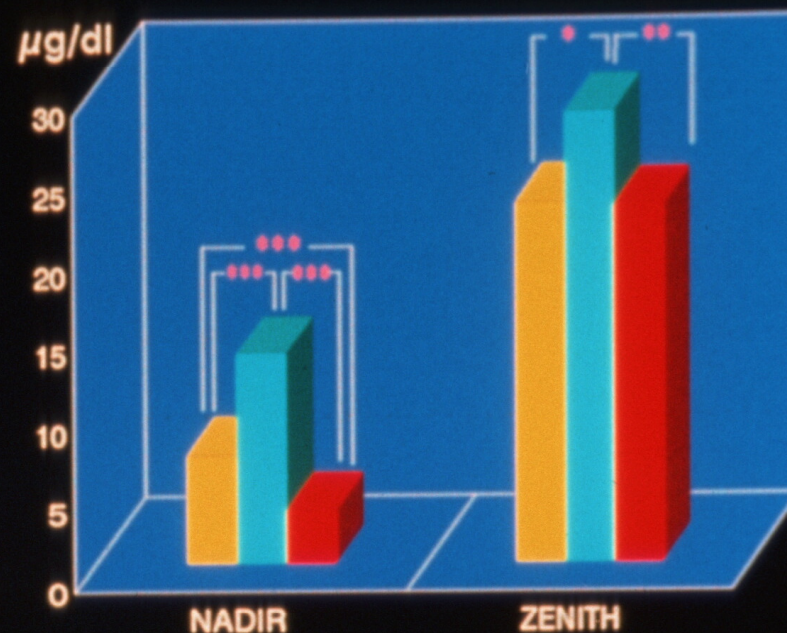
Robert Frank



PLASMA CORTISOL CIRCADIAN RHYTHM



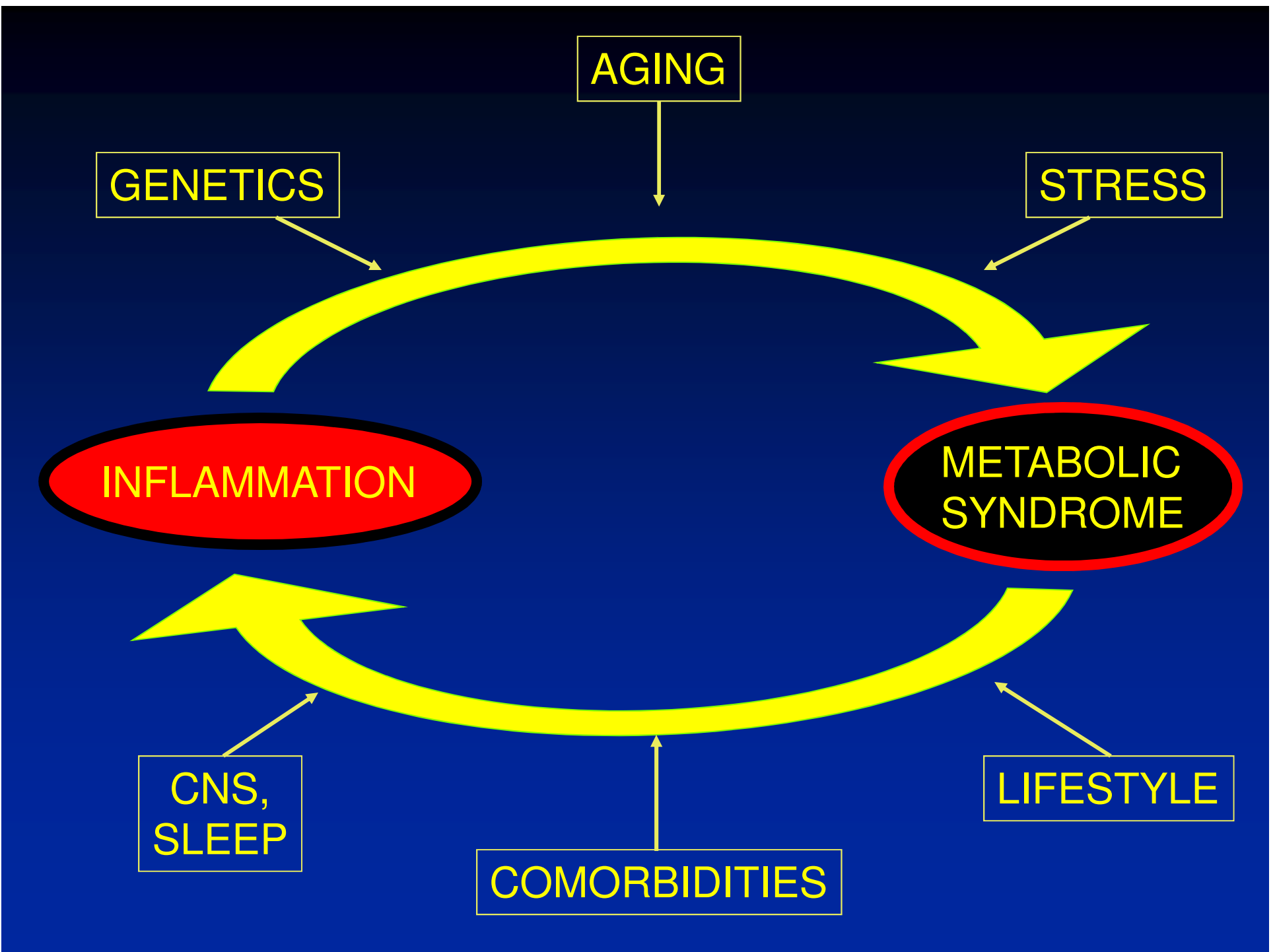
■ OLD SUBJECTS
 ■ OLD DEMENTED
 ■ YOUNG CONTROLS



Old subjects vs young controls # $p < .05$; ## $p < .01$; ### $p < .001$
 Old demented vs young controls * $p < .05$; ** $p < .01$; *** $p < .001$
 Old demented vs old subjects • $p < .05$; •• $p < .01$; ••• $p < .001$

Conditions associated with subclinical hypercortisolism

- Central adiposity
- Alcohol consumption
- Smoking
- Physical/Emotional Stress
- Altered Sleep patterns
- Strenuous exercise/Overtraining
- Adrenal incidentaloma
- Anorexia nervosa
- Endogenous depression
- Dementia
- Stress-related disorders
- Chronic inflammatory state
- Aging



ENDOCRINE SOCIETY 2014 LAUREATE AWARDS

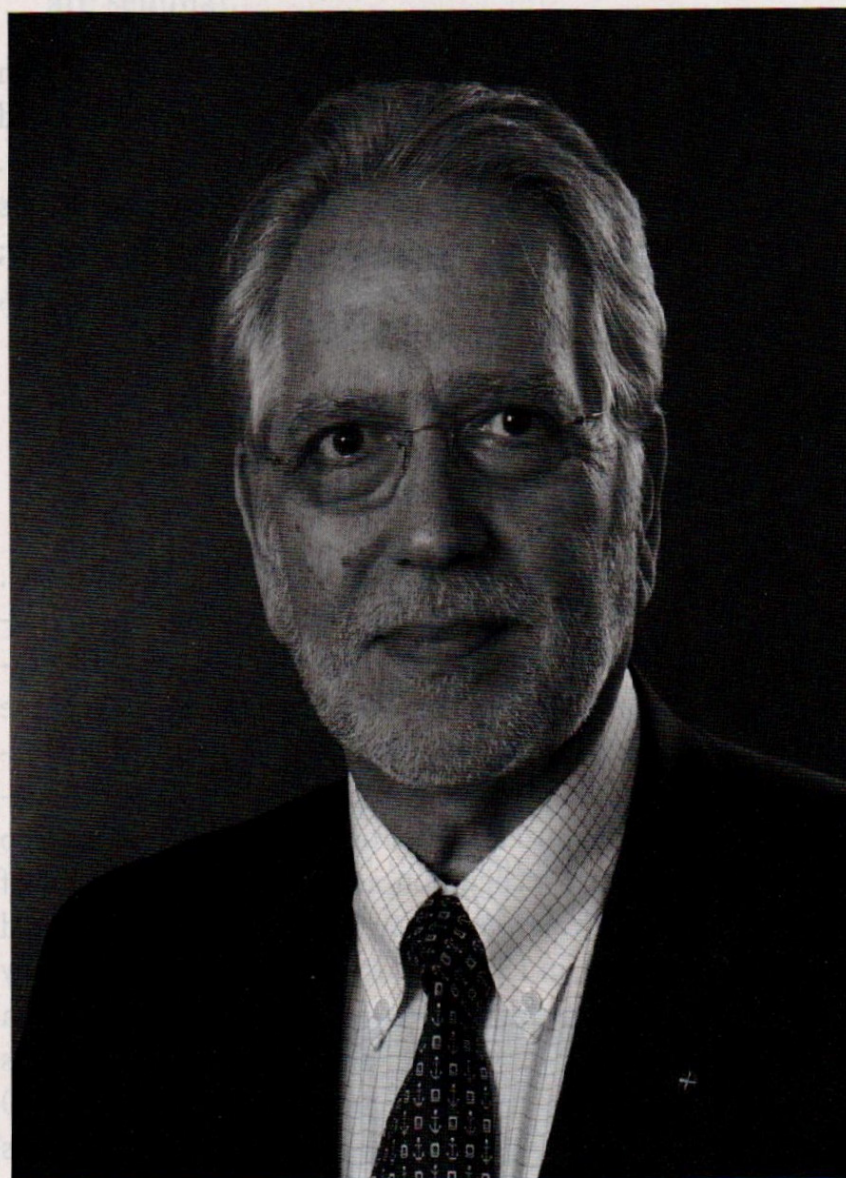
The Endocrine Society's distinguished Laureate Awards are presented in recognition of extraordinary achievements in the field of endocrinology. Award recipients are the top clinical and basic scientists, innovators, leaders, educators, and practitioners whose dedication and accomplishments are unmatched. Award recipients were honored at the Annual Awards Dinner on June 20, 2014, International Society of Endocrinology and the Endocrine Society, Chicago, Illinois.

For information on Laureate Award category descriptions, current and past award recipients, visit the Laureate Awards webpage at www.endocrine.org/laureate.

Congratulations to the 2014 Laureate Award recipients!

Citation for the 2014 Fred Conrad Koch Award of the Endocrine Society to Dr George P. Chrousos

George P. Chrousos has made outstanding and broad contributions to Biomedical Research. Currently, he is Professor and Chairperson of the First Department of Pedi-



PRECISION MEDICINE



INDIVIDUALIZED MEDICINE

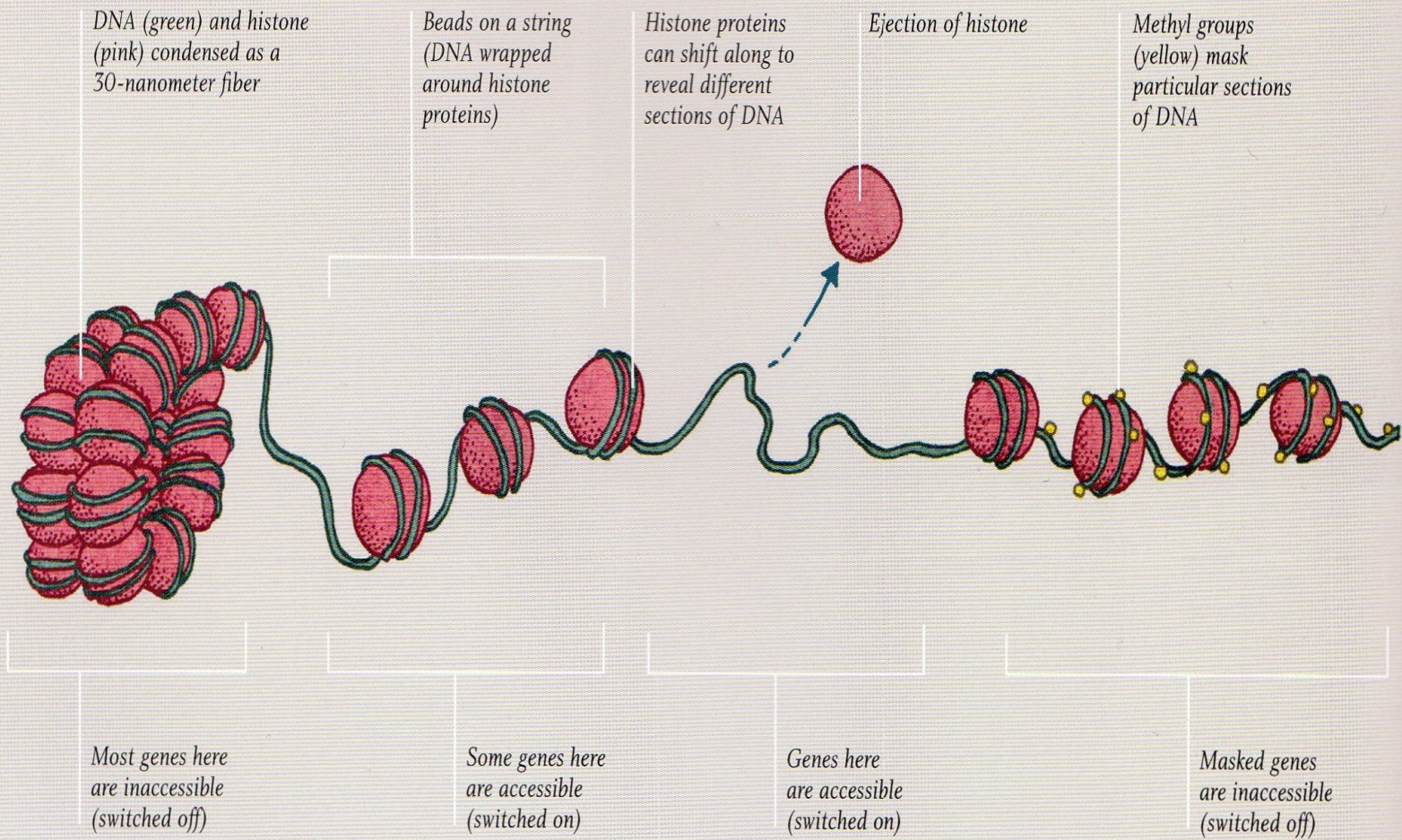


**- PATIENT ON BOARD -
- NO MORE AFLOAT -**

MEDICINA DI PRECISIONE

Messa a punto e attuazione di protocolli di prevenzione, diagnosi e terapia basati su evidenze acquisite con l'analisi del genoma e/o dell'espressione genica individuali.

CHROMATIN REMODELING





VIEWPOINT

SCIENTIFIC DISCOVERY AND THE FUTURE OF MEDICINE

Epigenetics at the Crossroads of Genes and the Environment

JAMA, September 15, 2015, 314: 1129-1130

Feinberg AP, Fallin MD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

Amit V. Khera, M.D., Connor A. Emdin, D.Phil., Isabel Drake, Ph.D.,
Pradeep Natarajan, M.D., Alexander G. Bick, M.D., Ph.D., Nancy R. Cook, Ph.D.,
Daniel I. Chasman, Ph.D., Usman Baber, M.D., Roxana Mehran, M.D.,
Daniel J. Rader, M.D., Valentin Fuster, M.D., Ph.D., Eric Boerwinkle, Ph.D.,
Olle Melander, M.D., Ph.D., Marju Orho-Melander, Ph.D., Paul M Ridker, M.D.,
and Sekar Kathiresan, M.D.

CHRONOTYPE

Individuals and populations can be stratified by circadian preference

- MORNING TYPE (Larks)
- EVENING TYPE (Owls)

Assessment using internationally validated questionnaires :

- Morningness-Eveningness Questionnaire (MEQ)
- Munich Chronotype Questionnaire (MCQ)



at least one other circadian phase marker
(e.g. the preferred midpoint of sleep)

Chronobiology International, 29(7): 920–927, (2012)

Copyright © Informa Healthcare USA, Inc.

ISSN 0742-0528 print/1525-6073 online

DOI: 10.3109/07420528.2012.699128

informa
healthcare

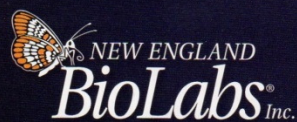
Tendency Toward Eveningness Is Associated With Unhealthy Dietary Habits

Noora Kanerva,¹ Erkki Kronholm,¹ Timo Partonen,² Marja-Leena Ovaskainen,³ Niina E. Kaartinen,¹ Hanna Konttinen,⁴ Ulla Broms,^{2,5} and Satu Männistö¹

CIRCADIAN RHYTHMS

Midnight snacks are bad for the heart

Circadian clocks help animals coordinate their active and rest periods with the daily cycles of light and darkness. As anyone who has suffered jet lag or worked night shifts knows, losing this coordination can have deleterious effects. Gill

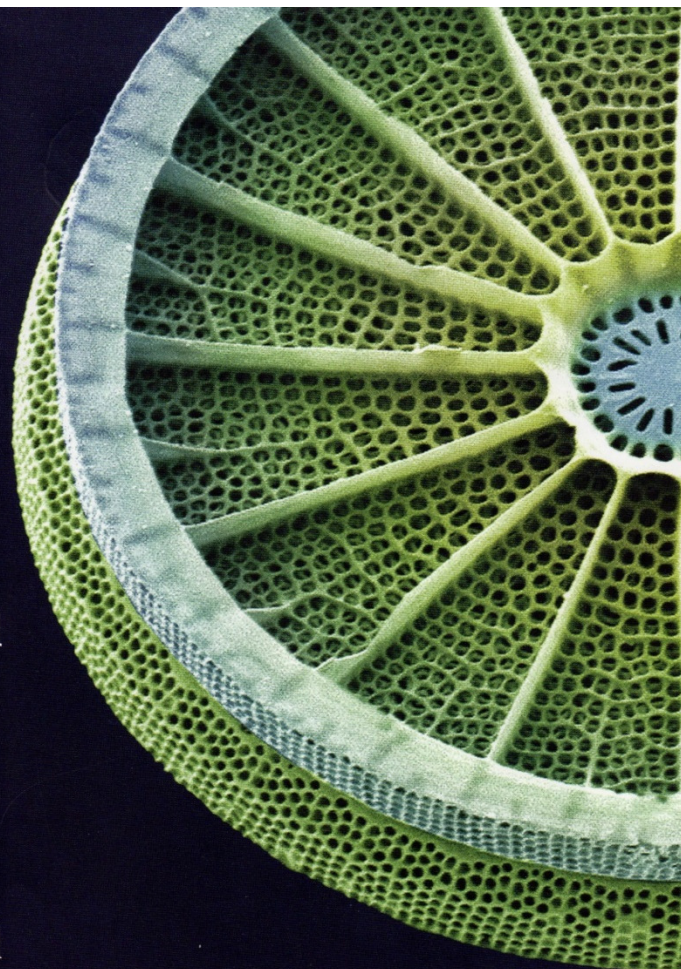


Target with precision.

Introducing the NEBNext Direct™ Cancer HotSpot Panel

Using a unique approach, the NEBNext Direct Cancer HotSpot Panel enriches for 190 common cancer targets from 50 genes prior to next generation sequencing. Combining a novel method for hybridization-based target enrichment with library preparation, the NEBNext Direct technology reduces processing time and minimizes sample loss. Ideal for automation, NEBNext Direct enables highly-specific deep sequencing of genomic regions of interest for the discovery and identification of low frequency variants from challenging sample types.

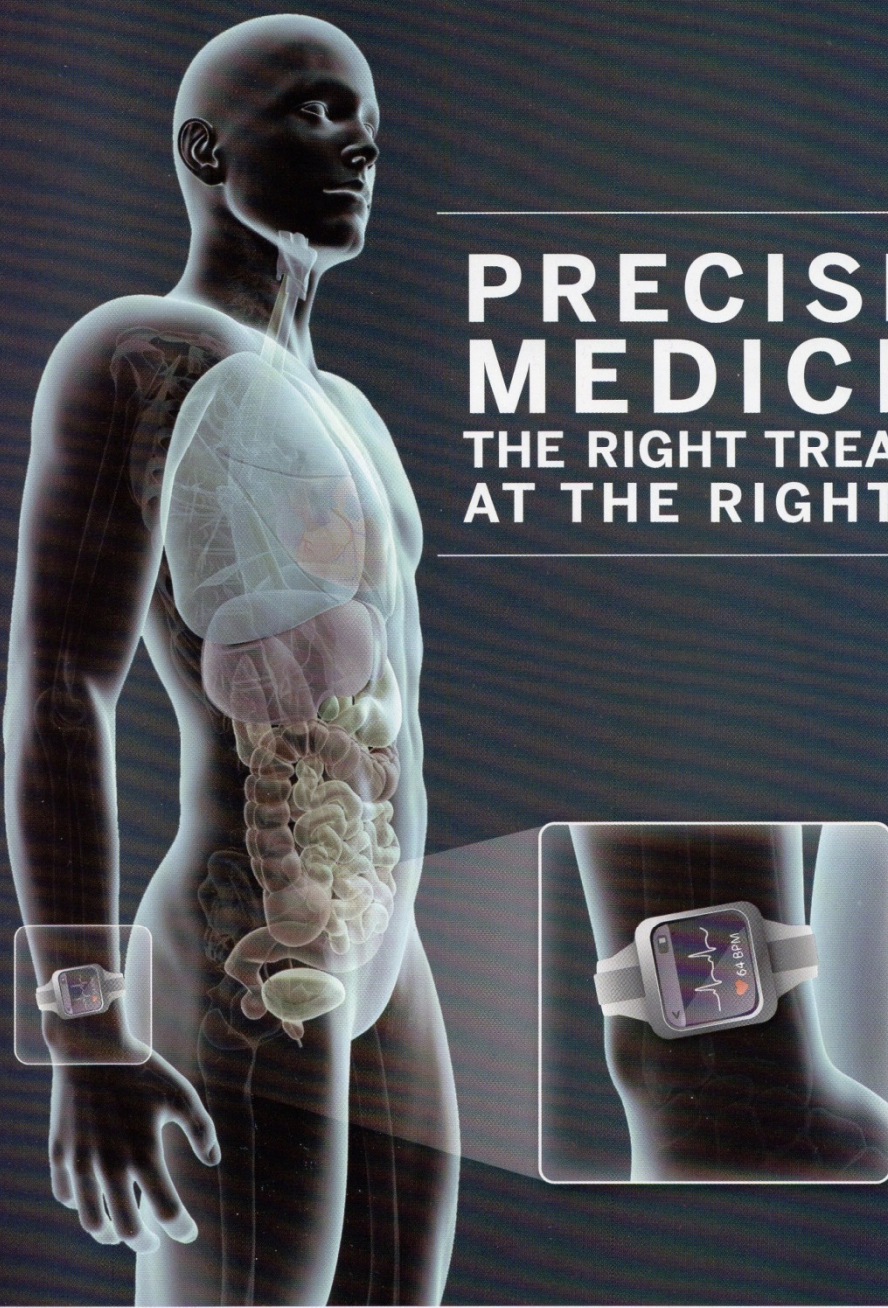
Visit NEBNextDirect.com to learn more
and to inquire about sampling this product.



TARGETS INCLUDE REGIONS FROM THE FOLLOWING CANCER-RELATED GENES, INCLUDING >18,000 COSMIC FEATURES:

ABL1	EGFR	GNAQ	KRAS	PTPN11
AKT1	ERBB2	GNAS	MET	RB1
ALK	ERBB4	HNF1A	MLH1	RET
APC	EZH2	HRAS	MPL	SMAD4
ATM	FBXW7	IDH1	NOTCH1	SMARCB1
BRAF	FGFR1	IDH2	NPM1	SMO
CDH1	FGFR2	JAK2	NRAS	SRC
CDKN2A	FGFR3	JAK3	PDGFRA	STK11
CSF1R	FLT3	KDR	PIK3CA	TP53
CTNNB1	GNA11	KIT	PTEN	VHL

For research use only; not intended for diagnostic use.



PRECISION MEDICINE

THE RIGHT TREATMENT
AT THE RIGHT TIME

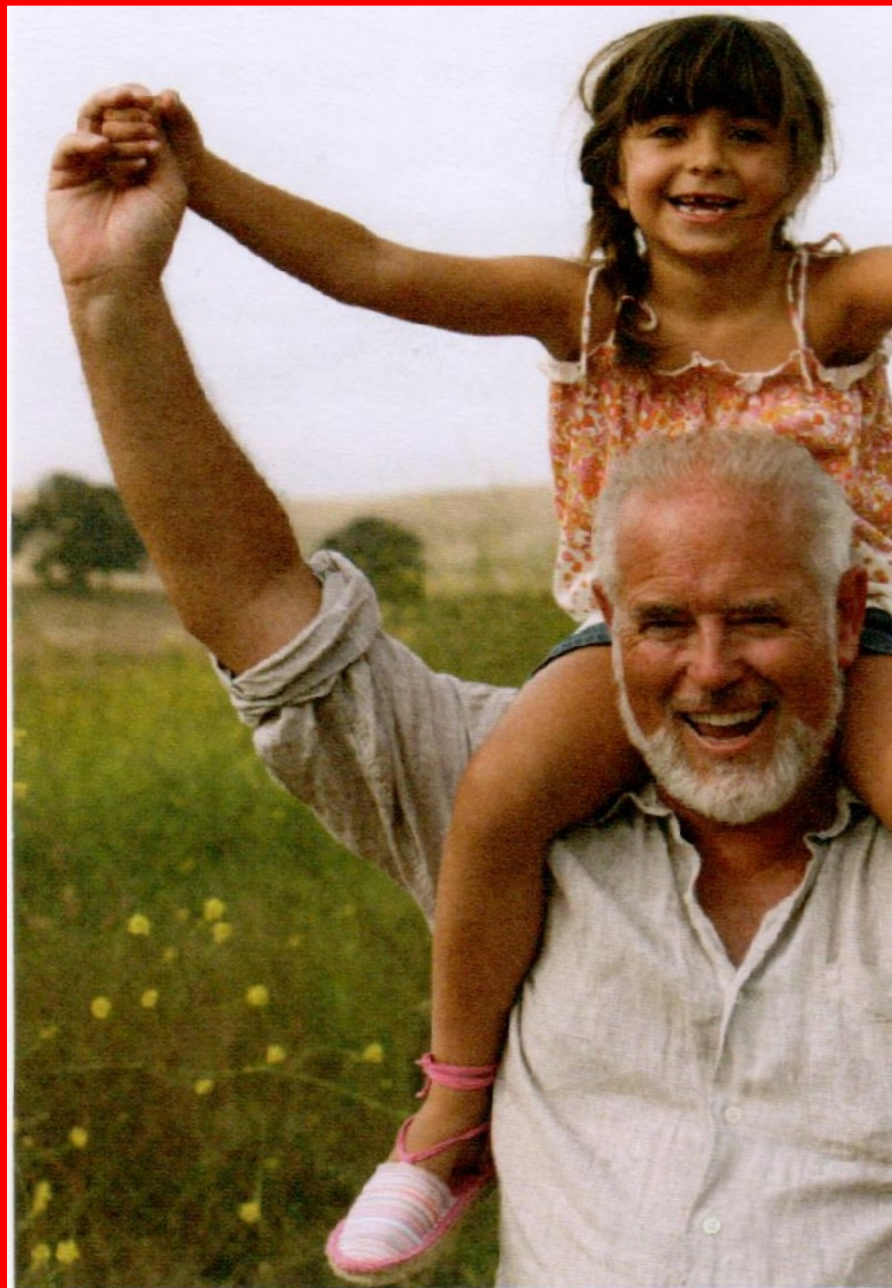
Crono chemioterapia

*Luigi Dogliotti
Marco Tampellini
Alberto Angeli*

*da Ippocrate
al chip*

PUBBLIEM





«Nell' "Impero delle luci" ho rappresentato due idee diverse, vale a dire un cielo notturno e un cielo come lo vediamo di giorno. Il paesaggio fa pensare alla notte e il cielo al giorno. Trovo che questa contemporaneità di giorno e notte abbia la forza di sorprendere e di incantare. Chiamo questa forza poesia».

Magritte

Ringraziamento
Maria Luisa Sartori

