Awakenings from Sleep: Medical Conditions and Other Origins and Potential Consequences on Circadian Systems

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Chronic Medical Conditions that Can Potentially Cause Sleep Awakening and Sleep Dissatisfaction

Inflammatory Conditions

- Allergic and Non-Allergic Rhinitis
- Nocturnal Asthma
- Rheumatoid Arthritis/Osteoarthritis

Mood/Psychiatry Disorders

- Anxiety Syndrome
- Manic Disorder
- Bipolar Disorder
- Clinical Depression/Major Depressive Disorder

Endocrine Conditions

- Thyroid (hyperthyroidism)
- Menopause
- Metabolic Syndrome/Obesity
- Nocturnal polyuria (ADH deficiency)

COPD (Bronchitis & Emphysema)

Organ Failure

- Heart , Liver, Kidney, Lung

Chronic Medical Conditions that Can Potentially Cause Sleep Awakening and Sleep Dissatisfaction

Neuromuscular Conditions

- Huntington's disease
- Parkinson's Disease
- Multiple Sclerosis
- Epilepsy
- Head Trauma
- Dementia
- Dyskinesias
- Dystonias

Gastrointestinal Conditions

- GERD
- Peptic Ulcer Disease

Pain Syndromes

- Chronic back
- Cancer
- Fibromyalgia

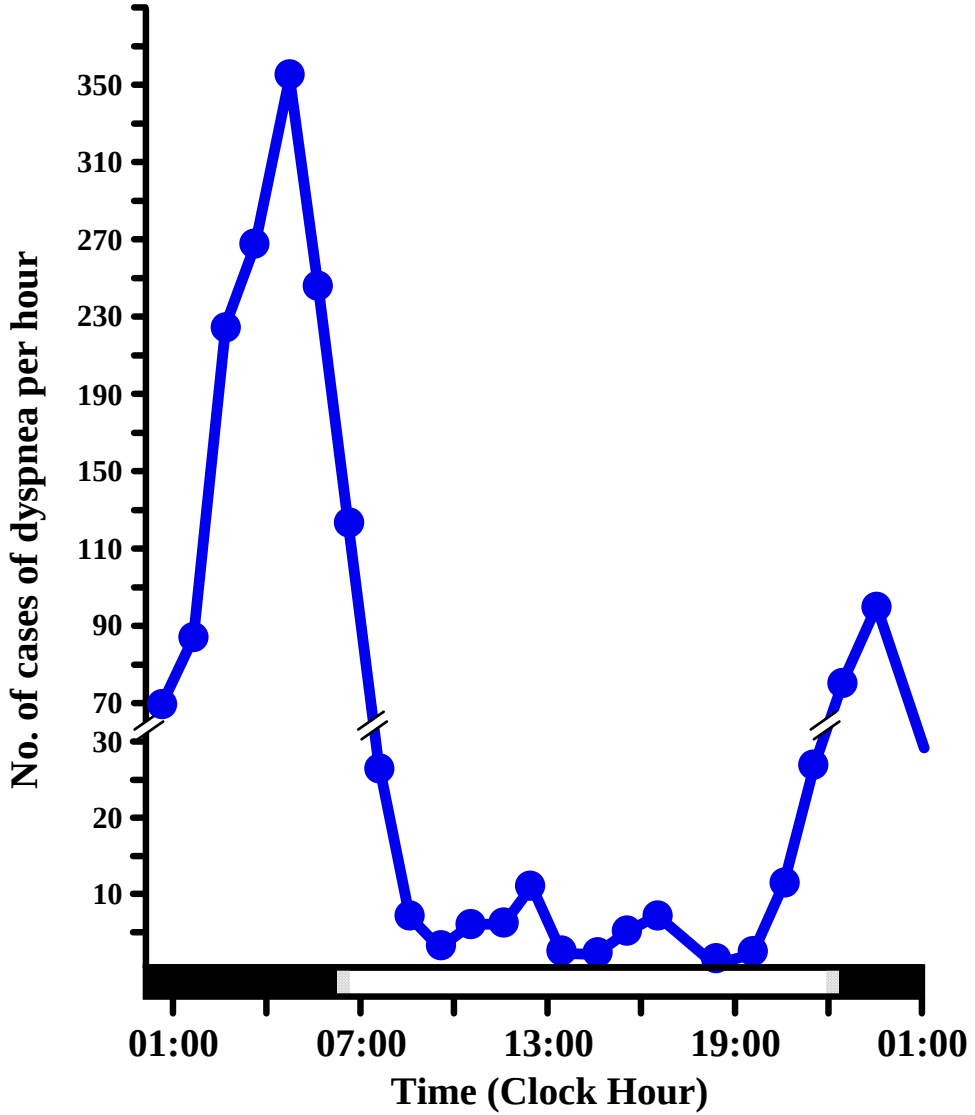
Circadian Variation in Disease and Symptom Intensity: Conditions that worsen between 00:00 & 06:00

- Nocturia
- Peptic Ulcer & GERD
- Gout & Gallbladder Attacks
- Congestive Heart Failure
- Acute Cardiogenic Pulmonary Edema
- Prinzmetal's Variant Angina
- Allergic Rhinitis & Asthma
- Acute Urticaria/Allergic Dermatitis
- Glaucoma (IOP)

Asthma and Sleep Awakenings

Day-Night Pattern of Asthma

1631 Episodes of Dyspnea/3129 Untreated Subjects



after Dethlefsen and Repges, 1985;
Med Klin, 80:44-47

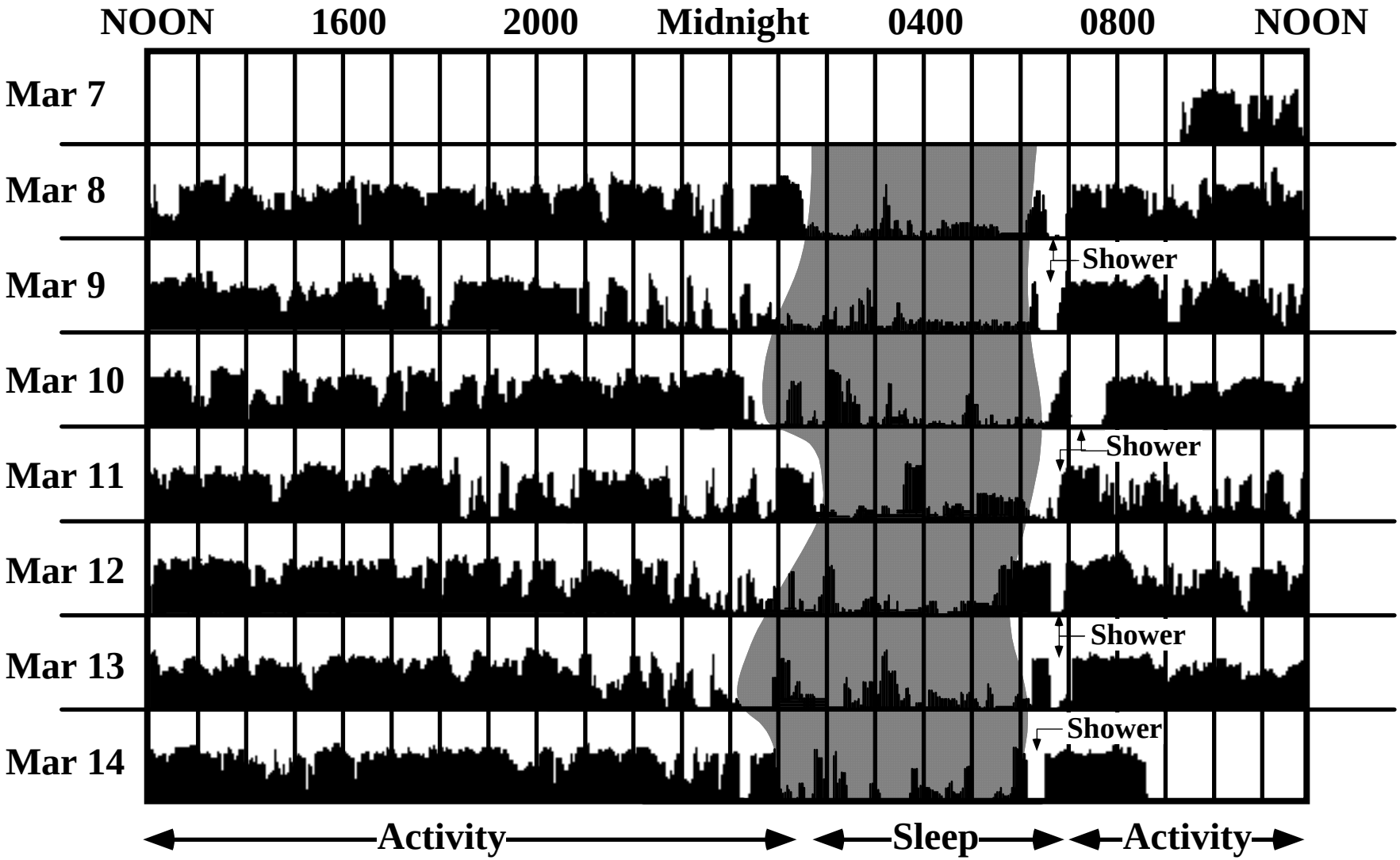
Frequency of Waking
(n = 7729)

	%
Every Night	**39**
At Least 3 Nights/Week	**64**
At Least 1 Night/Week	**74**
At Least 1 Night/Month	**94**

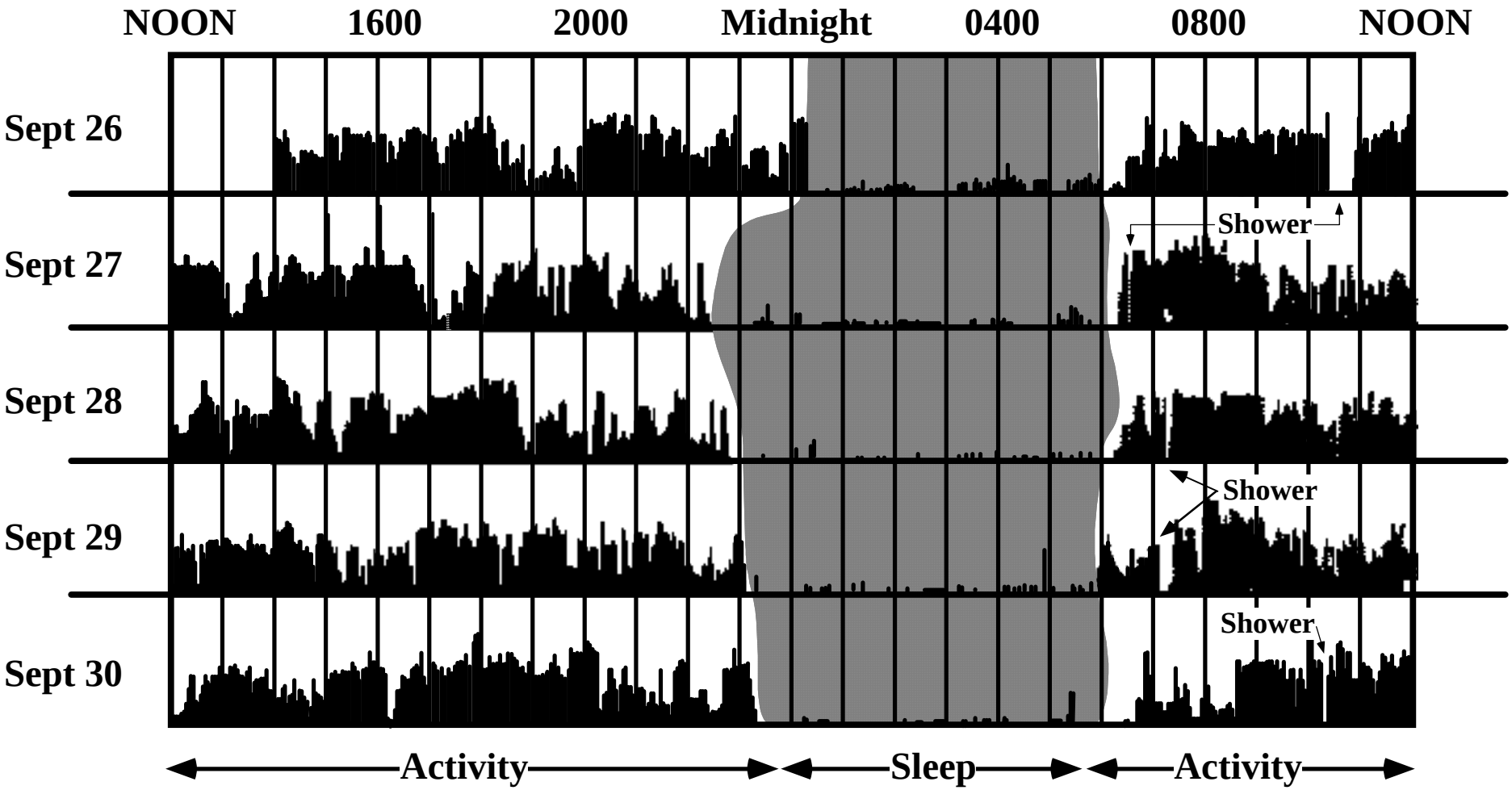
(Missing = 68)

Turner-Warwick, 1988;
Am J Med Sci, 85(Suppl 1B):6-8

Twenty-Four-Hour Activity Pattern: Severe Asthma Patient

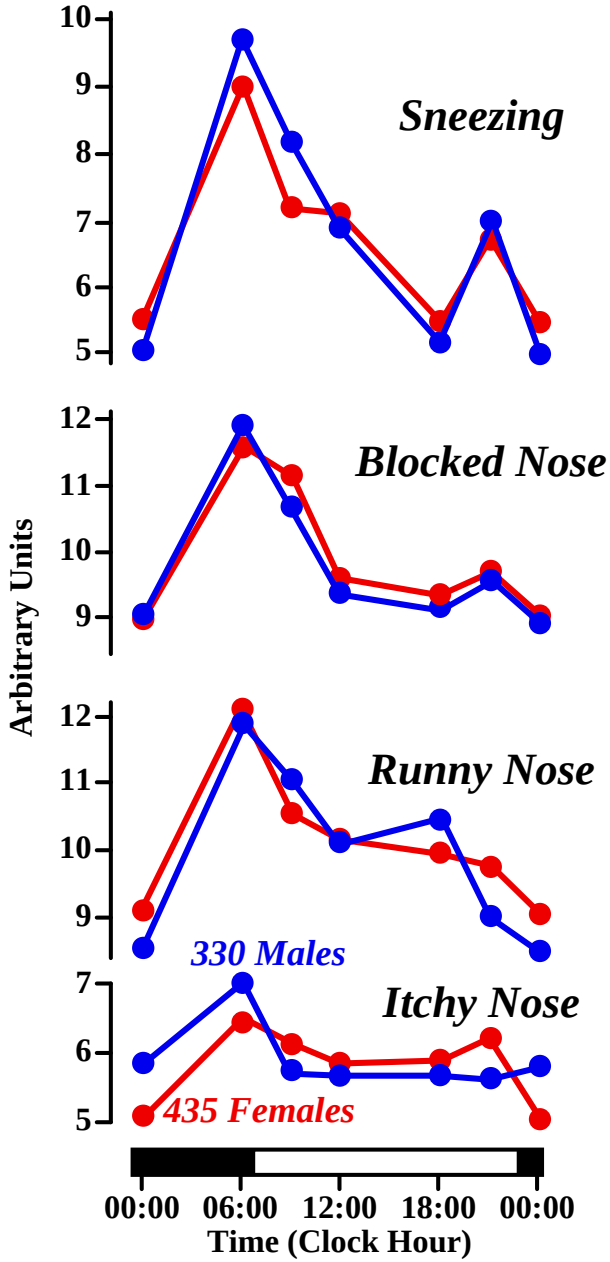


Twenty-Four-Hour Activity Pattern: Normal



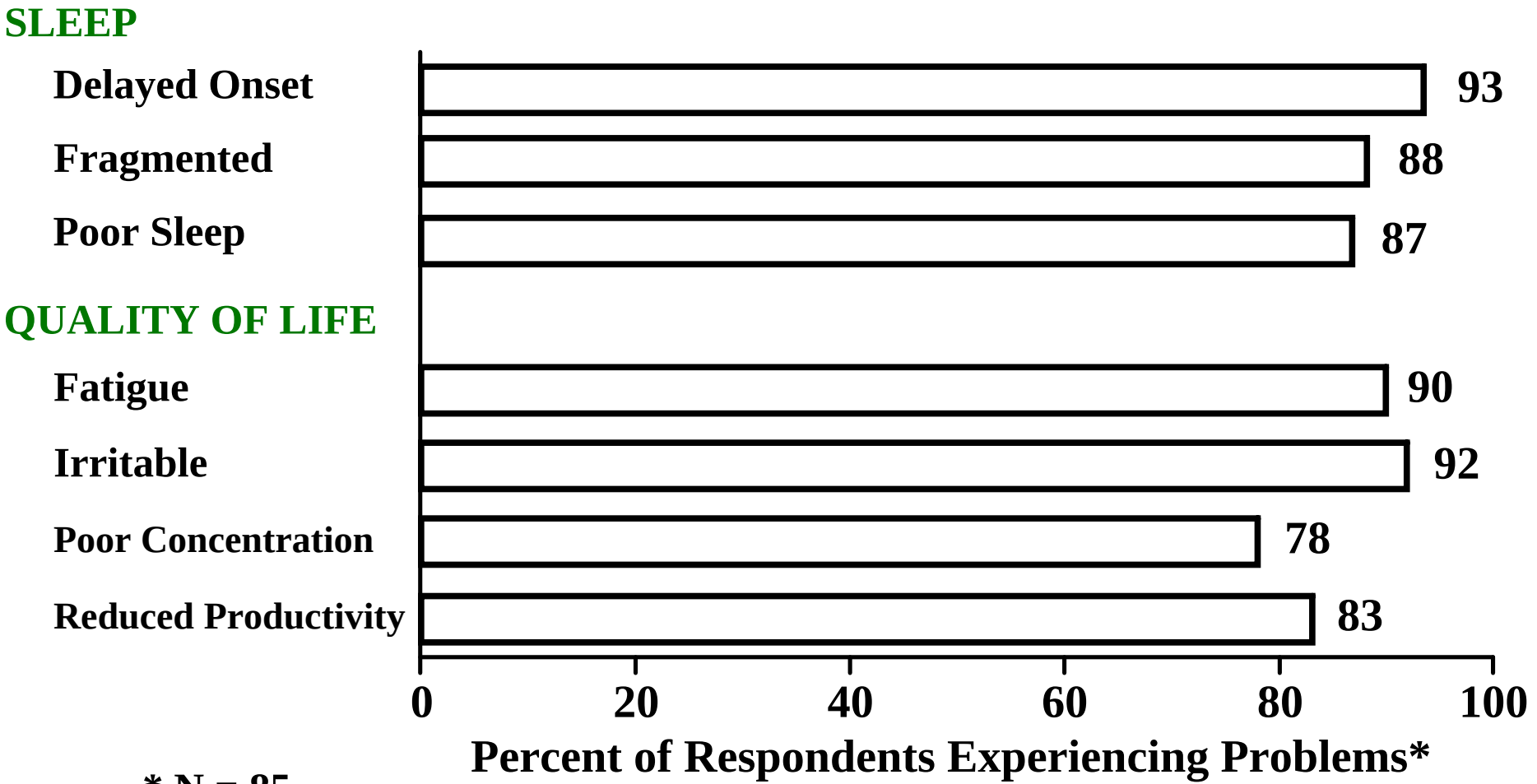
Allergic Rhinitis and Sleep Awakenings/Dissatisfaction

Diurnal Pattern in Intensity of Allergic Rhinitis



Reinberg *et al*, 1985
Chronobiologia, 12:87

Allergic Rhinitis Affects Sleep & Quality of Life



* N = 85

after Juniper, 1991; Clin Exp Allergy, 21:77-83

Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids

Timothy J Craig, DO, Stephanie Teets, Erik B Lehman, MS, Vernon M Chinchilli, PhD, and Clifford Zwillich, MD. ***Hershey, PA, and Denver, CO***

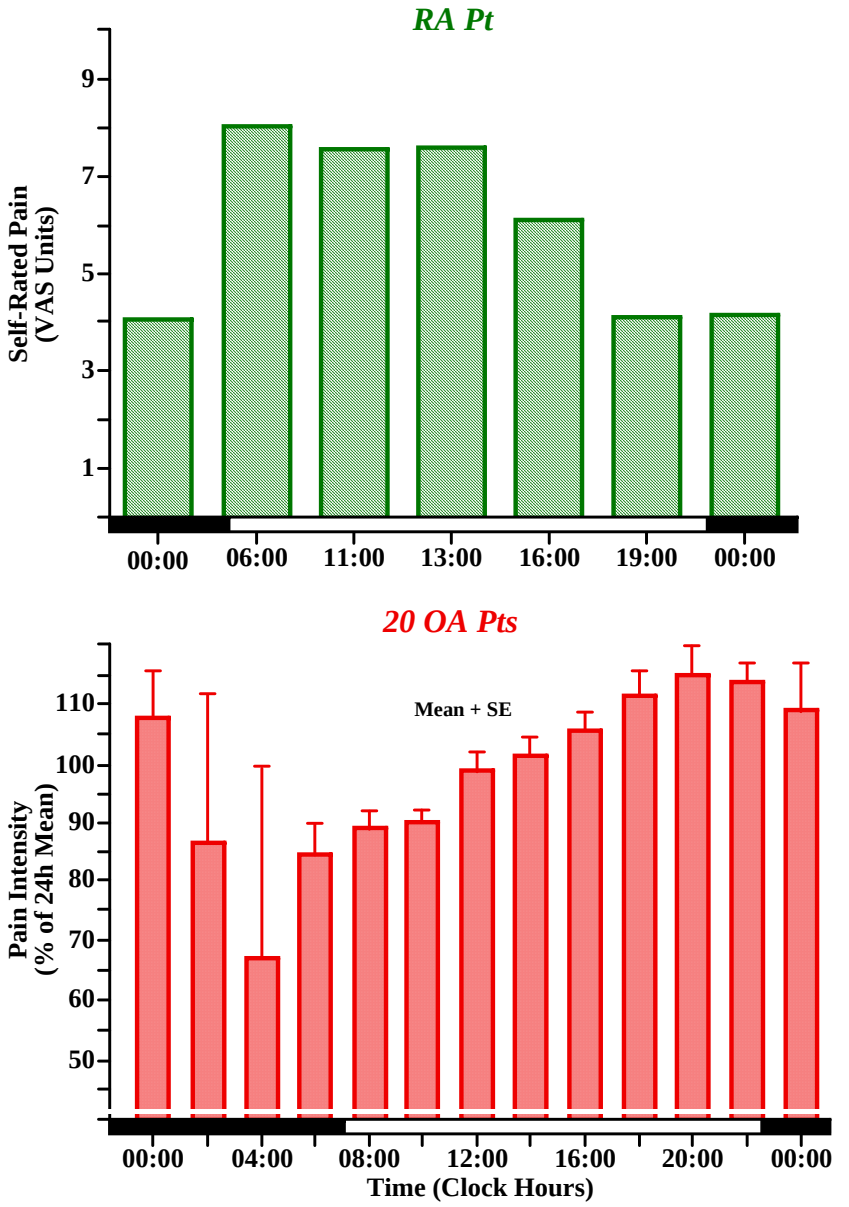
Background: *Allergic rhinitis (AR) is a frequent disease affecting up to 20% of the population. AR causes a hypersensitivity reaction, which results in inflamed nasal mucosa and nasal congestion. Negative pressure generated during inspiration in the nasal airway secondary to nasal congestion may lead to nasal collapse, airway obstruction, and an increased number of sleep microarousals. Sleep disturbances and microarousals can detrimentally affect daytime energy levels, mood, and daytime function. It is unknown whether treatment directed to reduced congestion may reduce these microarousals, sleep problems, and, consequently, associated daytime fatigue.*
Objective: *We sought to determine whether reducing nasal…*

Abbreviation used
AR: Allergic rhinitis

rhinomanometry, acoustic rhinometry, and nasal peak inspiratory flow have defined this subjective sensation of congestion as significant nasal passage obstruction. Nasal obstruction in healthy young adults can lead to marked interruption of the sleep cycle, with an increase in microarousals and daytime somnolence.[1,2]

Rheumatoid Arthritis, Osteoarthritis and Sleep Awakenings/Dissatisfaction

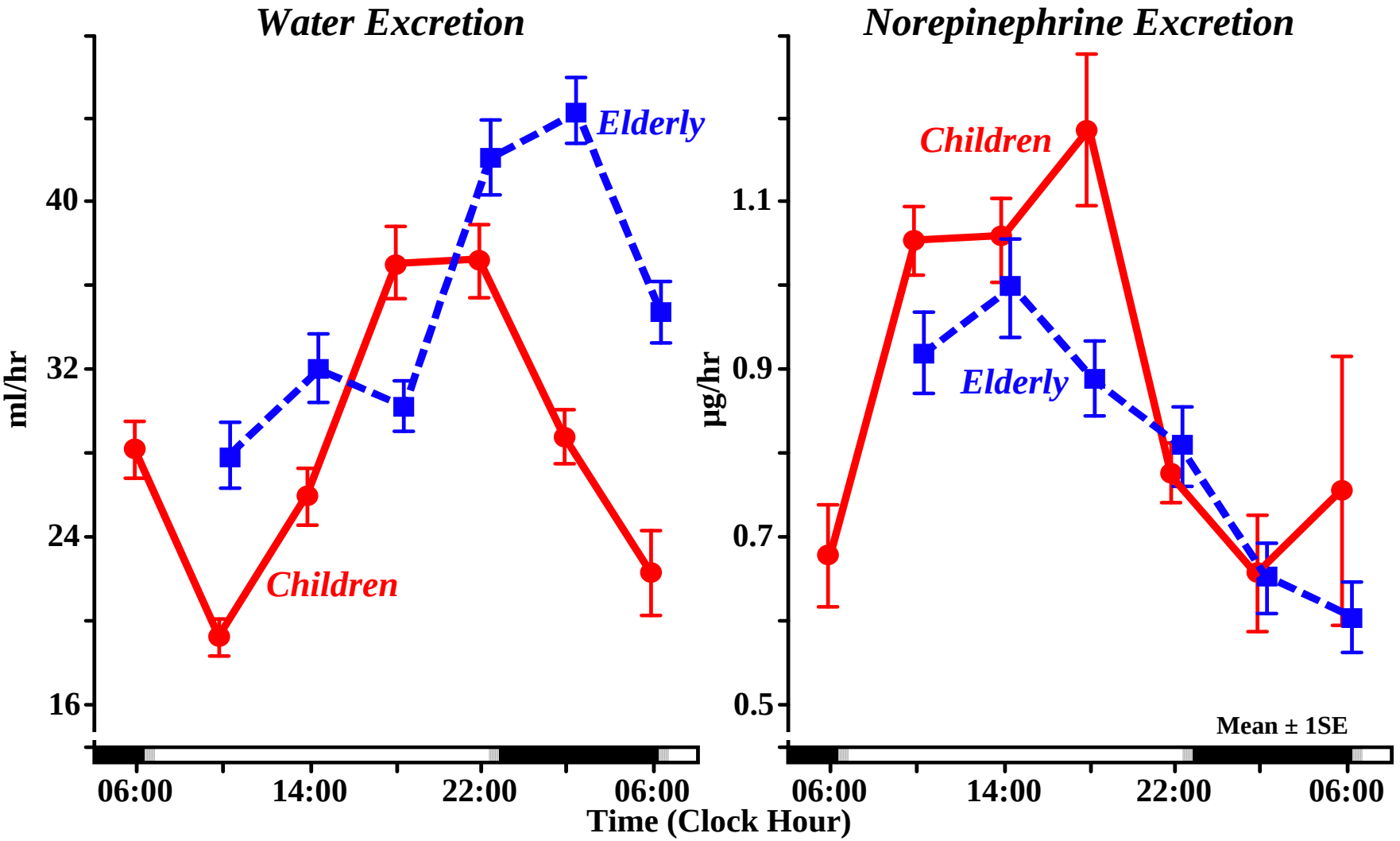
Circadian Pattern in Pain in RA & OA Patients



RA Pt after Kowanko *et al*, 1982
Ann Rheum Dis, 41:453-455
OA Pts after Bellamy *et al*, 1990
J Rheumatol, 17:364-372

Nocturia and Sleep Awakenings/Dissatisfaction

Circadian Rhythm in Timing of Water and Norepinephrine Excretion in Children* and Elderly** Subjects



*194 Children (11 ± 1.5 yrs of age), 87 boys and 106 girls

**260 24-hr Profiles (77 ± 8 yrs of age), 60 elderly men (113 profiles) and 83 elderly women (147 profiles)

Circadian Time Structure: Role of Environmental Light Time Cues

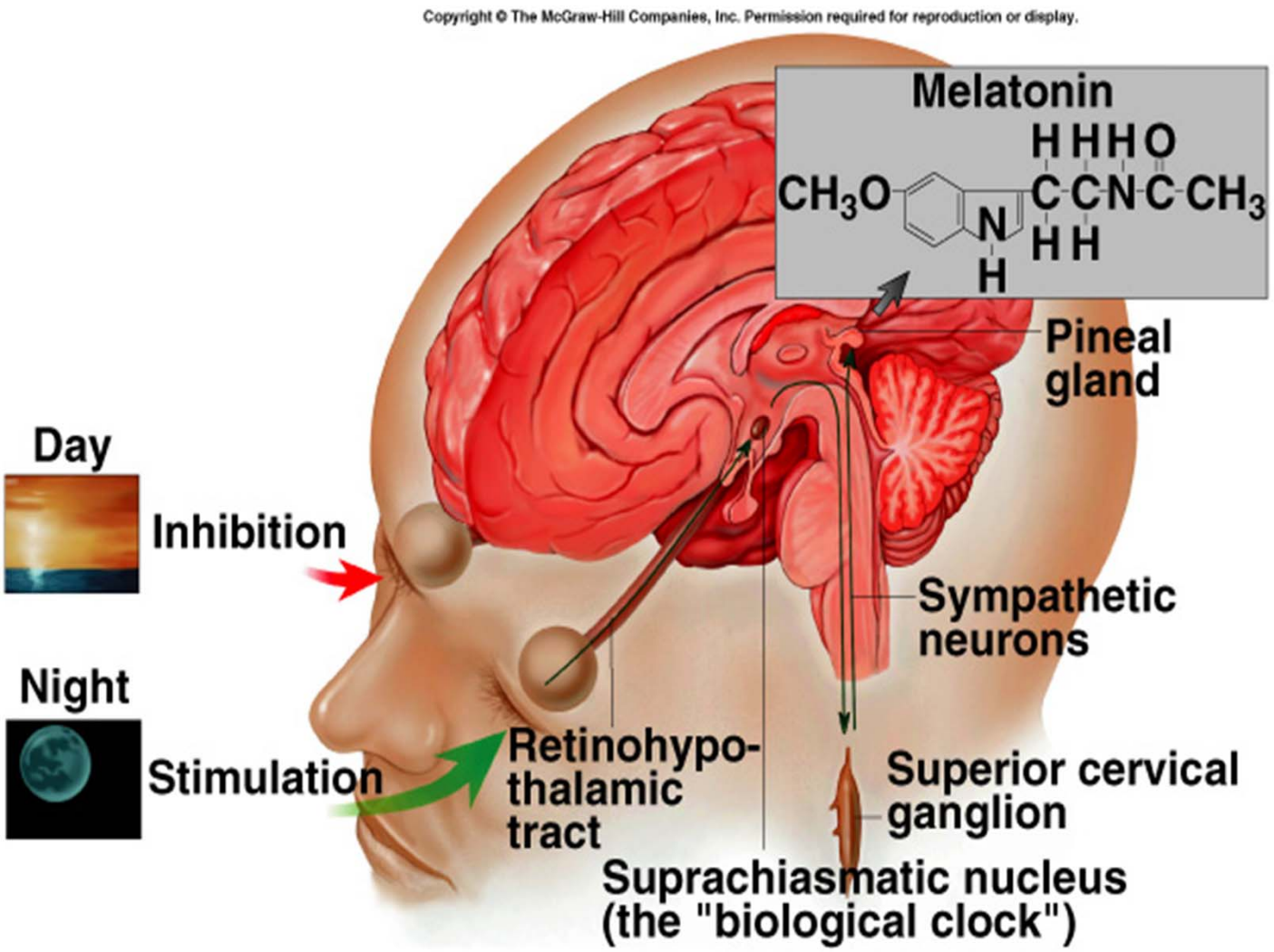
First Book of Moses: *Genesis*

In the beginning God created the heavens and the earth. The earth was without form and void, and darkness was upon the upon the face of the deep……
And God said, "let there be light"; and there was light. And God saw the light was good; and God separated the light from the darkness. God called light Day, and the darkness he called Night. And there was evening and there was morning, one day……

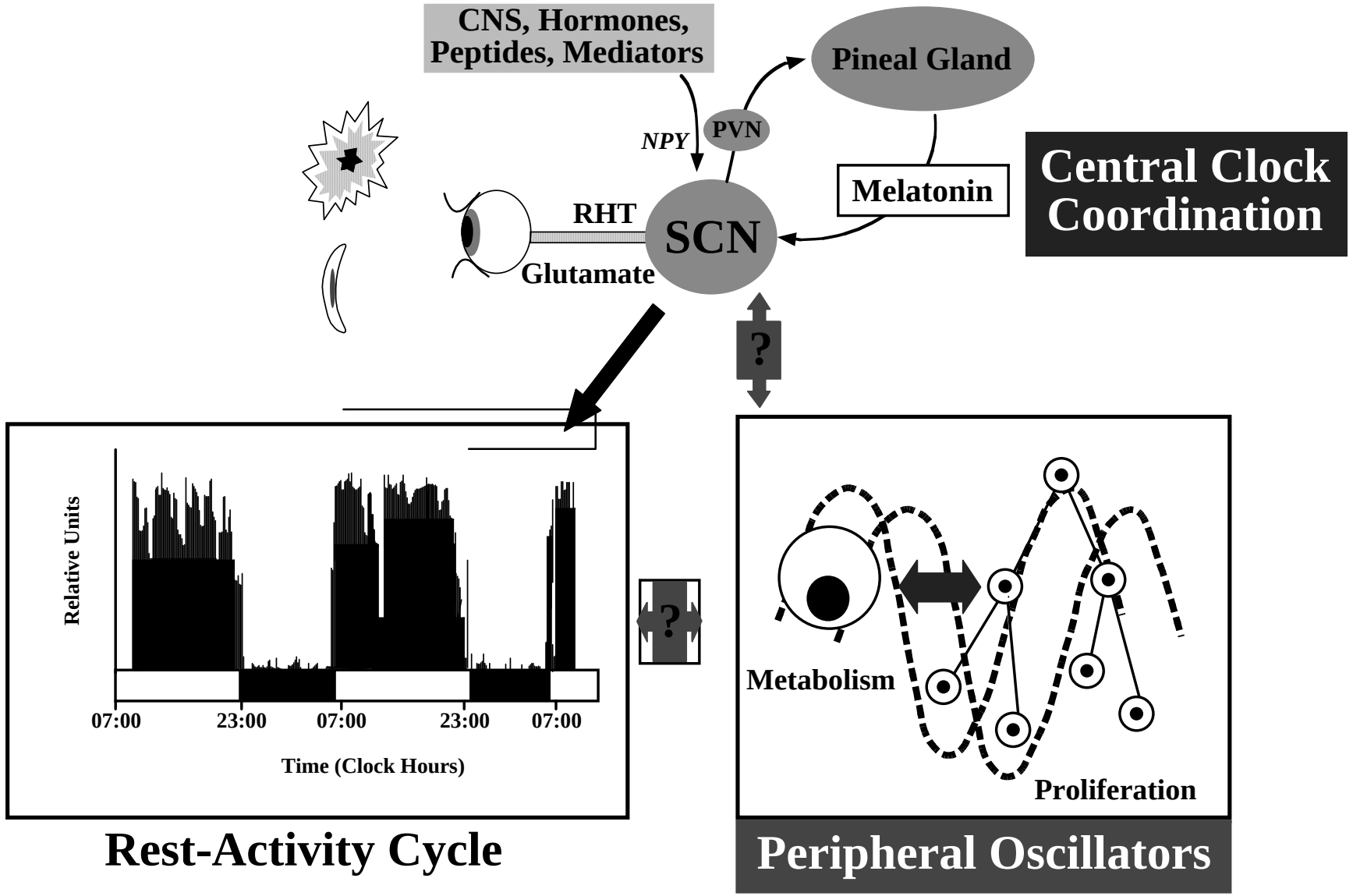
And God said, "Let there be lights in the firmament of the heavens to separate the day from the night; and let them be for signs and for seasons and for days and years, and let them be lights in the firmament of the heavens to give light upon the earth." And it so was.
And God made the two great lights, the greater light to rule the day, and the lesser light to rule the night; he made the stars also. And God set them in the firmament of the heavens to give light upon the earth, to rule over the day and over the night, and to separate the light from darkness. And God saw it was good. And there was evening and there was morning, a fourth day.

The Earth with the Full Moon

The biological clock system

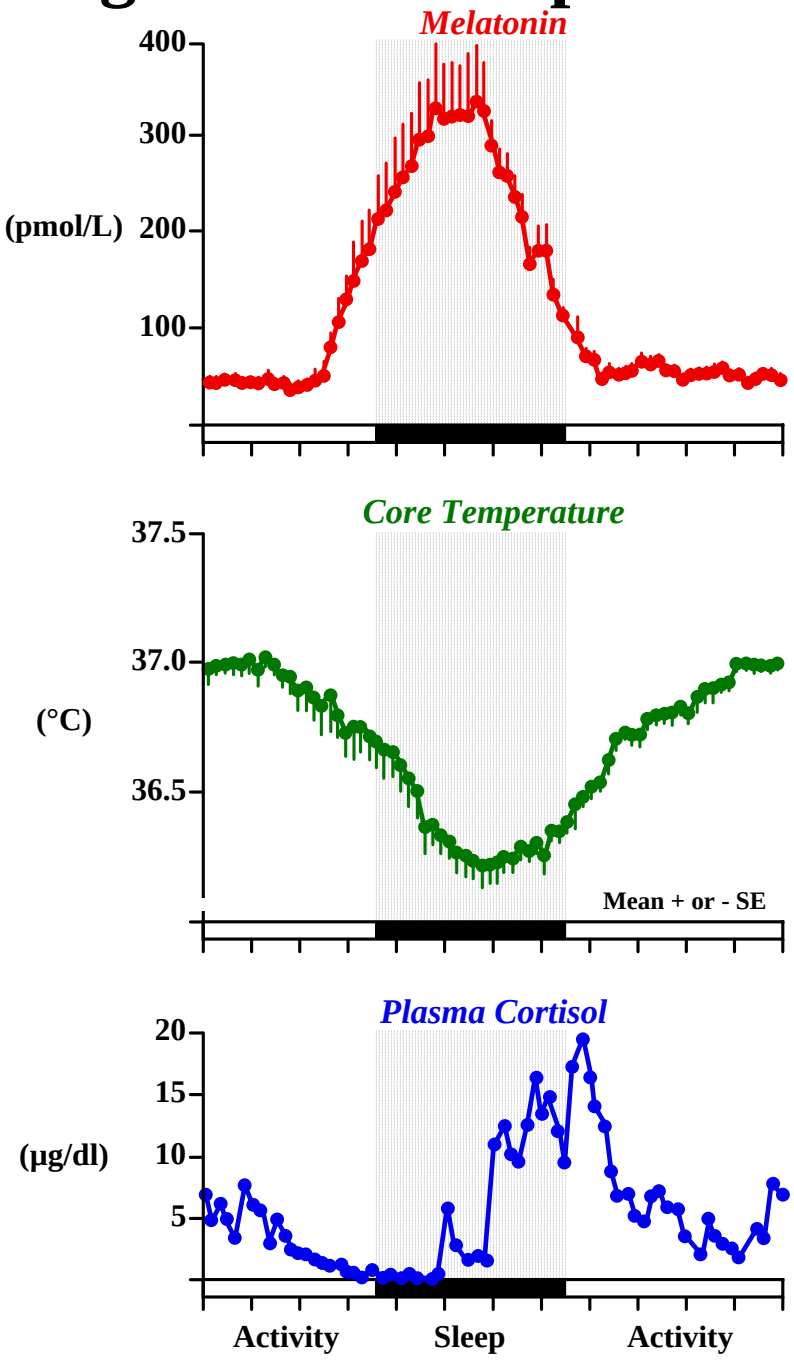


Schematic View of Human Circadian Clock System



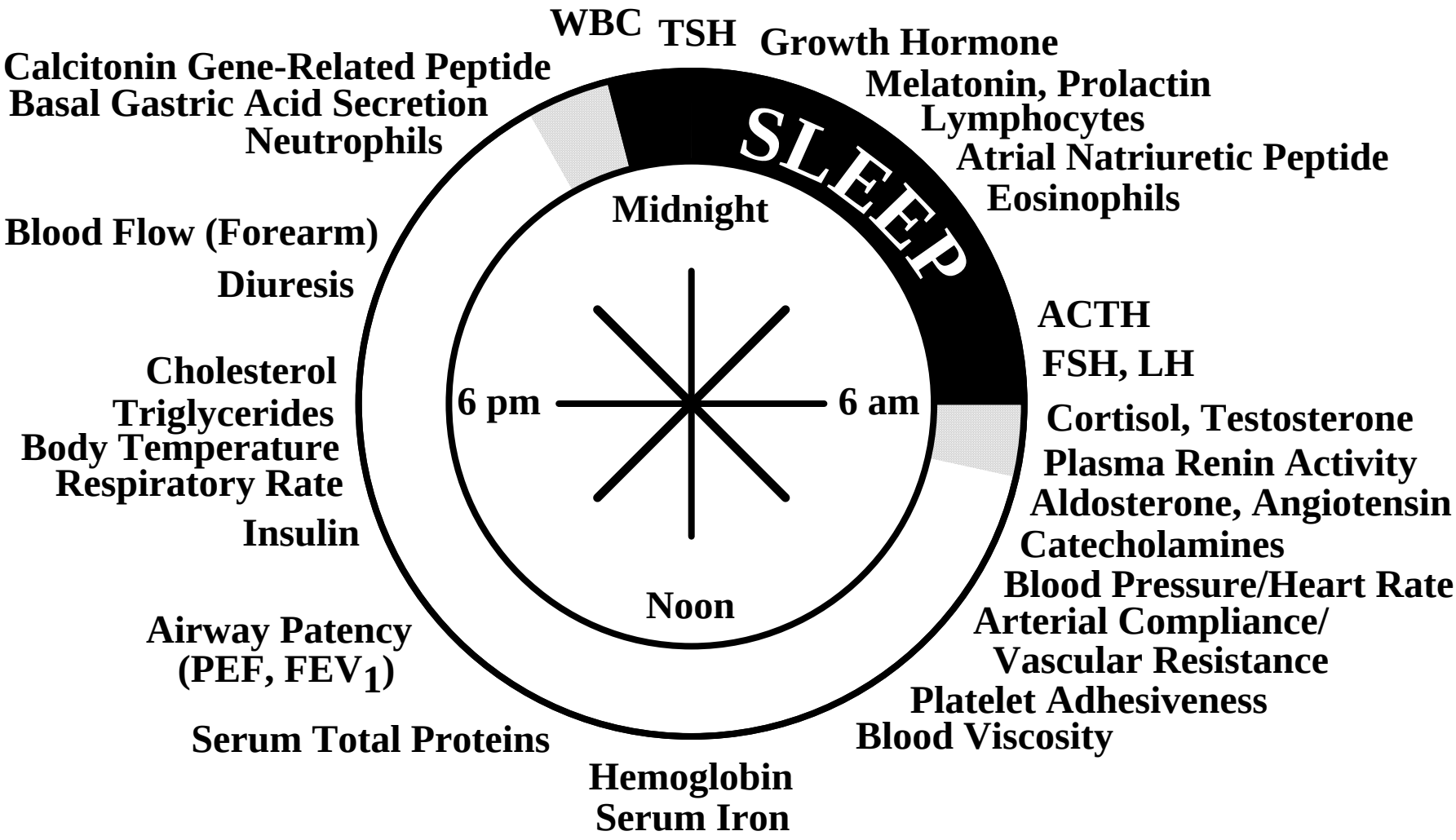
after Levi *et al*, 2002

Circadian Stage Relationship of Human Rhythms



Human Circadian Time Structure

Peak Time of Functions



Circadian Rhythm Synchronization Issues

The staging & period of circadian rhythms accomplished by the timed exposure to ambient cyclic time signals – the 24 h cycle of ambient light & darkness being most important

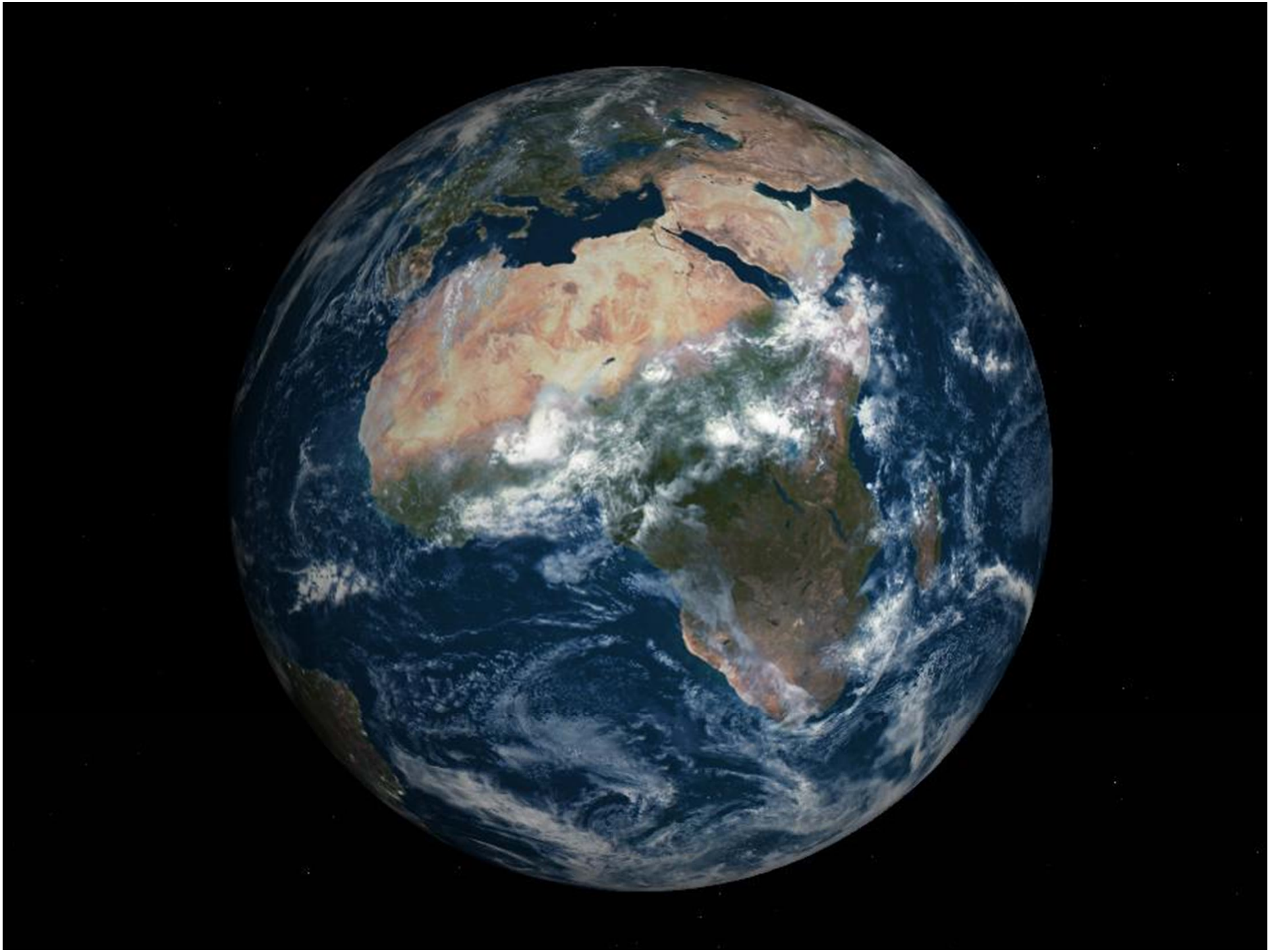
Internal Synchronization:

Staging of endogenous circadian rhythms precisely organized, to one another, to optimize internal biological efficiency relative to the sleep in darkness/activity in daylight 24 h cycle

External Synchronization:

Staging of circadian rhythms during the 24 h optimal to meet the predictable-in-time demands of the cyclic natural & man-made external environment

Sleep Awakenings and Light at Night (LAN)

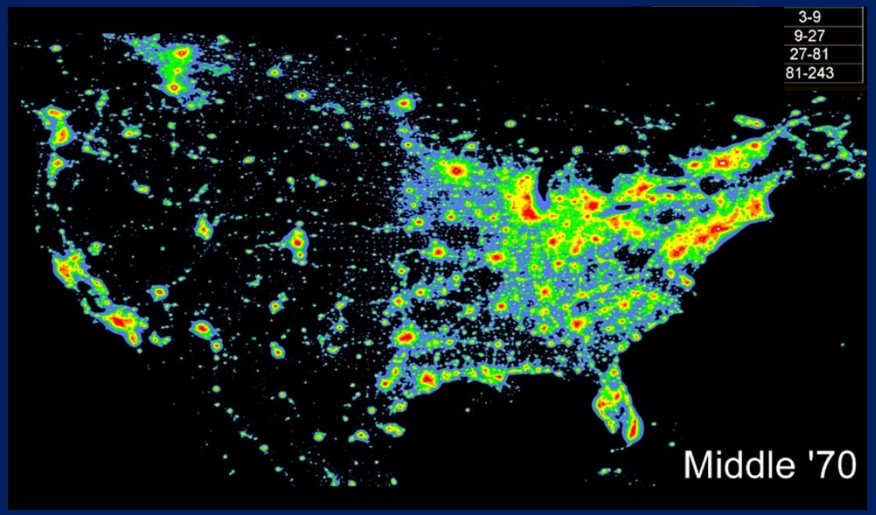


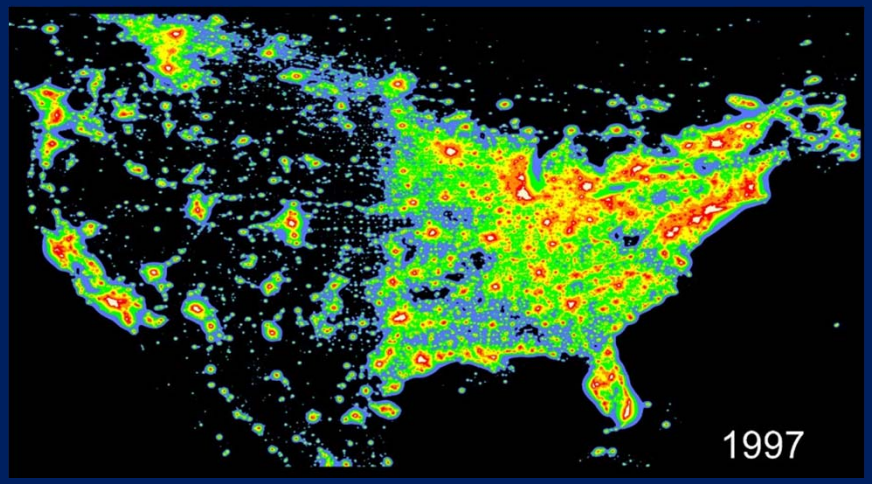
Thomas Alva Edison (1878)

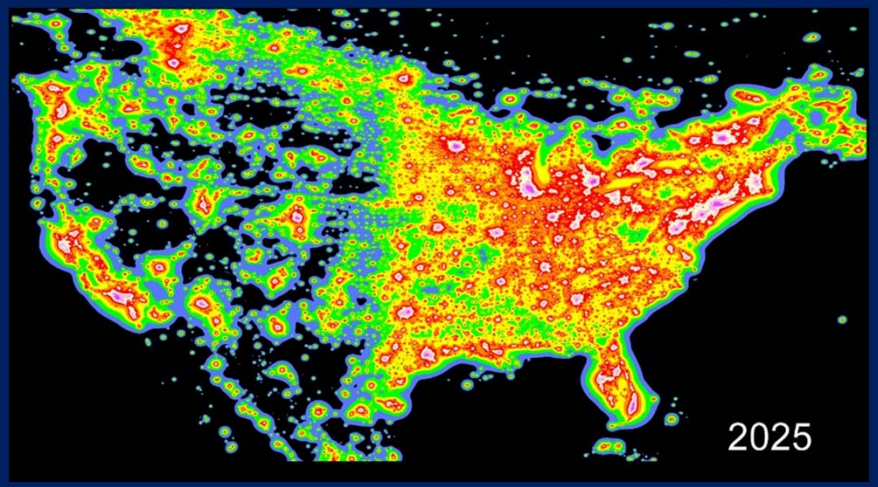
Edison Light Bulb

(January 27, 1880: Patent number 223,898)

LAN in the USA: Increase Over Time

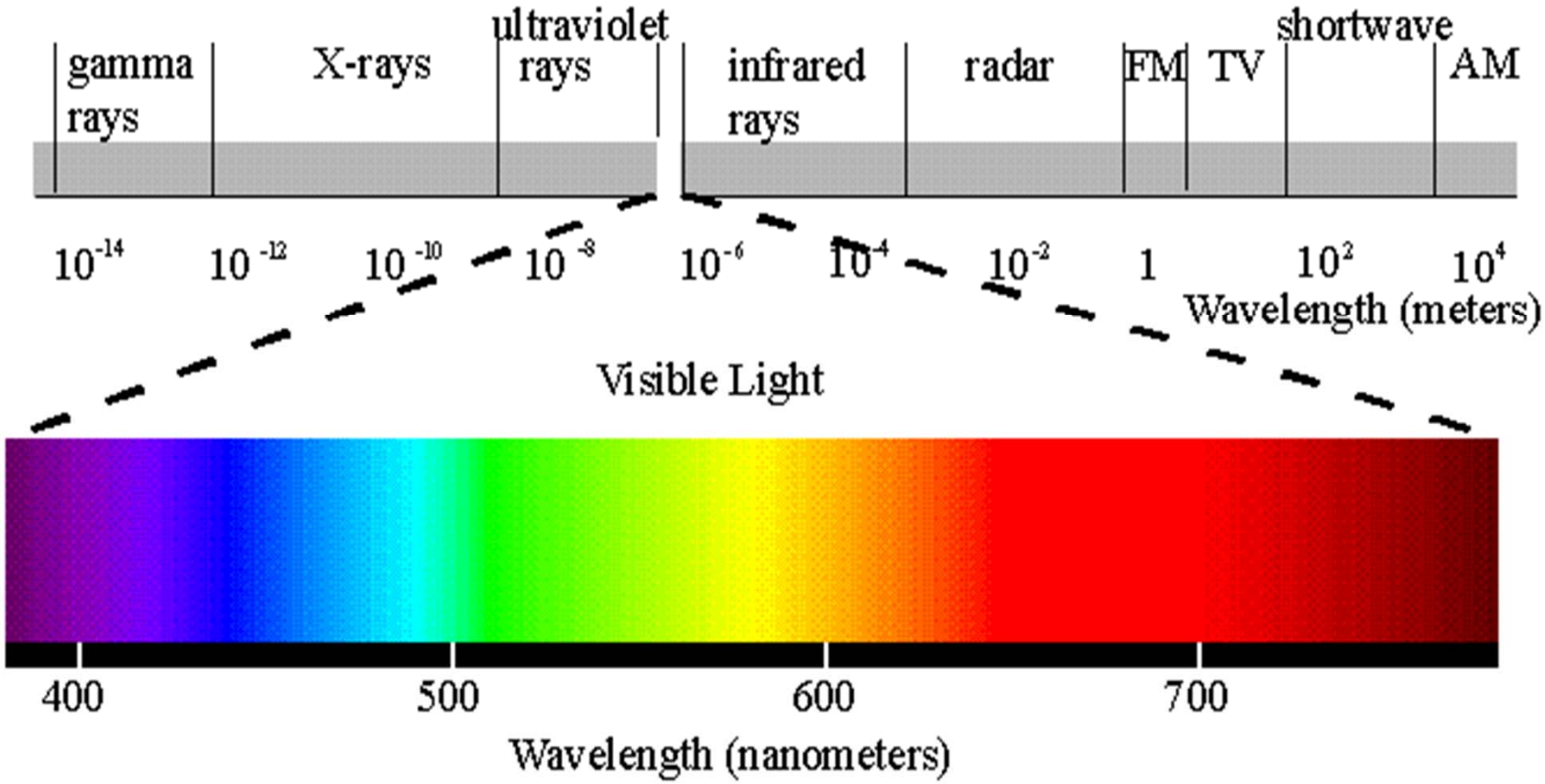






Cinzano, Falchi, and Elvidge, 2001)

Los Angeles in 1908 & 1988, as seen from Mt. Wilson Observatory



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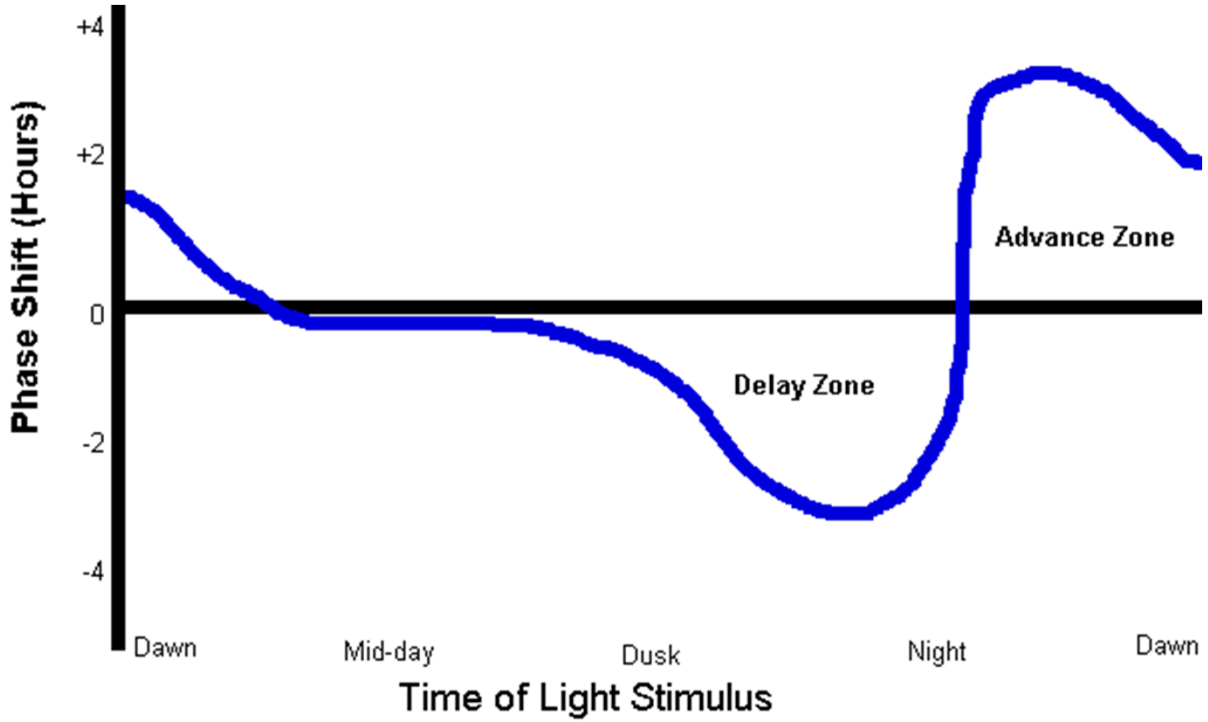
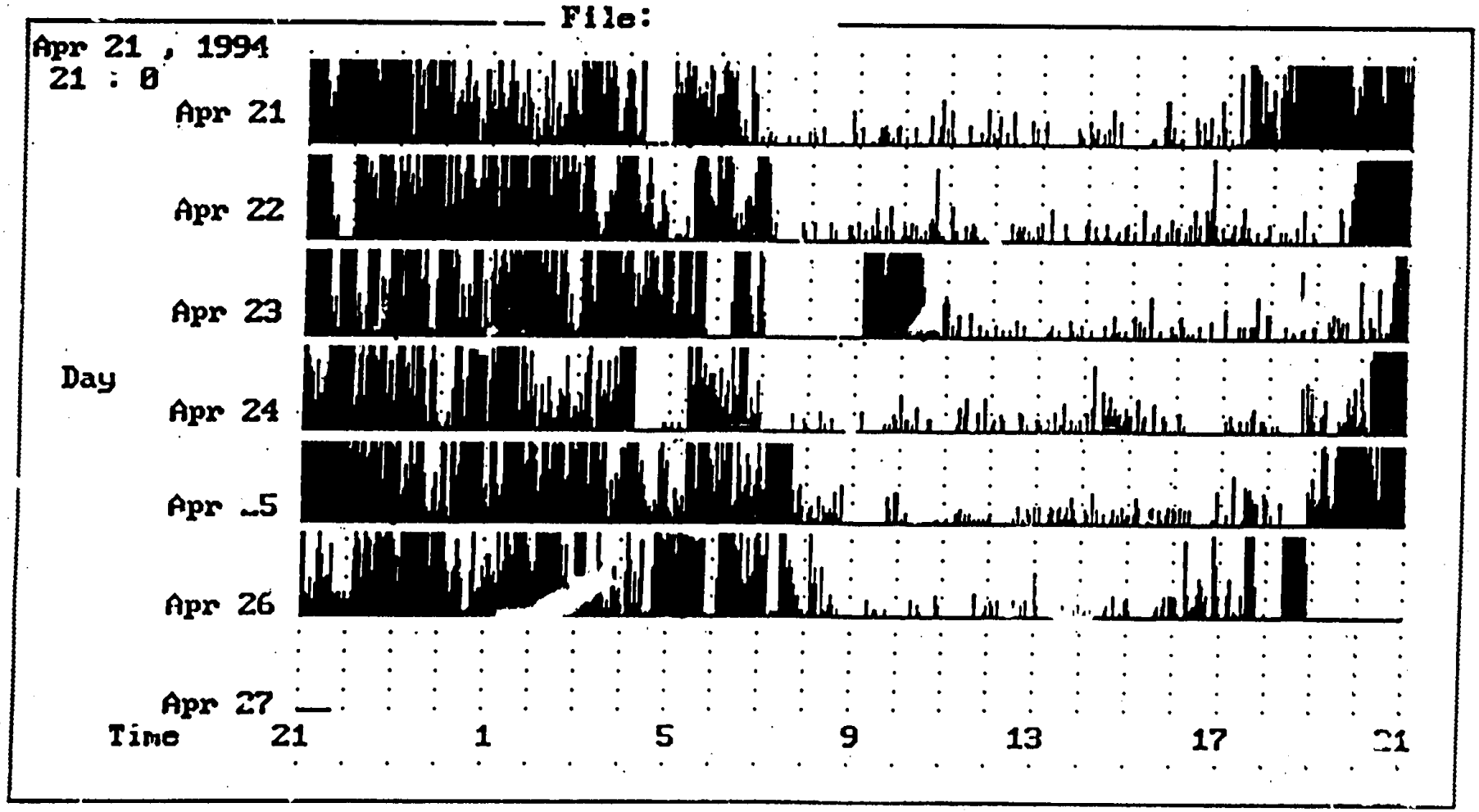
Visual Stimulus

Human Phase-Response Curve for Light

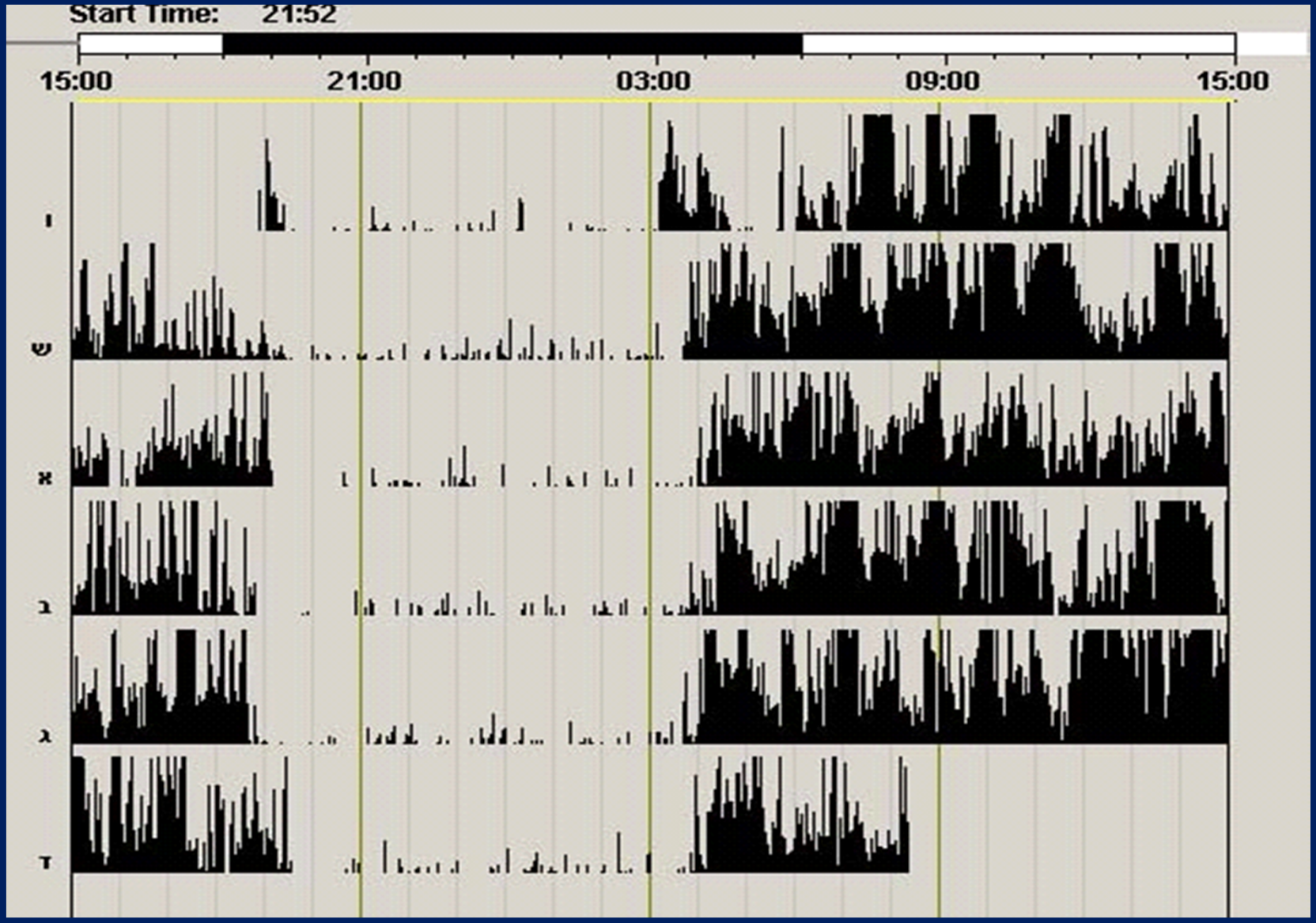


Delayed Sleep Phase Disorder (DSPD)



Dagan Y, Abadi J. Chronobiol .Int .2001;18(6):1019-27.

Advanced Sleep Phase Disorder



Potential Health Effects of Sleep Awakenings & Associated LAN

- **Altered quality of life**
- **Phase & period altered circadian sleep-wake rhythm**
- **Desynchronized circadian system**
- **Mood disorder (Depression)**
- **Nocturnal Hypertension**
- **Cancer: Breast, endometrial, colorectal in women & prostate in men**

Acute Effect of $Beta_1$-Adrenergic Blockade on Melatonin Suppression

- Atenolol (dose-dependent 12.5-50 mg)
- Propranolol (dose-dependent 10-40 mg)
- Metoprolol (dose-dependent 50-200 mg)

Arendt et al, J. Clin. Endocrinol. Metab. 1985; 60:1166-73
Nathan et al, J. Pineal Res. 1997; 23:131-5
Stoschitzky et al, Eur. J. Clin. Pharmacol. 1999; 55:111-5
Mayeda et al, Psychiatry Res. 1998; 81:9-17

Triamcinolone Administration and Adrenal Suppression:

Comparison of Single Daily vs. Divided Dose Schedules

Study Duration	Triamcinolone Dose (Schedule)	Plasma Cortisol (µg/dl)*	
		Baseline	Final
8 days	8 mg daily at 08:00	**20.2 ± 1.0**	**19.1 ± 1.6**
8 days	8 mg daily - 2 mg/divided	**21.5 ± 1.4**	**9.0 ± 2.1** [§]

*Mean ± SE of 6 Males; [§]$p<0.05$

Grant *et al*, 1965;
NEJM, 273:1115-1118

Summary

- **Many chronic medical conditions can cause sleep awakenings and sleep dissatisfaction**
- **Sleep awakenings often are accompanied by light at night (LAN) exposure(s)**
- **LAN can further impact sleep satisfaction by sleep disruptions of delayed sleep onset (insomnia) or advanced sleep termination (insomnia)**
- **LAN + phase alterations can potentially lead to negative effects on health status**