Electric light disrupts circadian rhythmicity is that a problem?

Richard Stevens
UConn Health Center
Light at Night
U.S. - the Present
Light at Night
U.S. - the Past
http://www.earthview.mars/safe/
Circadian Rhythms
&
Circadian Disruption
Circadian Rhythmicity

- core body temperature
- sleep/wake cycle
- physical activity
- hunger and appetite
- metabolism
- hormone production (e.g., melatonin)
- expression of the circadian genes
Properties of a Circadian Rhythm

- An endogenous, self-sustained ~24-hour oscillation in biochemistry, physiology, or behavior under constant environmental conditions (i.e., constant dark)

- Entrainment by environmental cycles of light

Takahashi, Annu Rev Neurosci, 18:531, 1995
endogenous?

- advantage: can anticipate sunrise and sunset
- but how was the endogenous rhythm discovered?
- 1964 to 1989 the Andechs bunker in Germany funded in part by NASA
- German scientist Rütger Wever
Andechs Bunker (Germany)
results?

• endogenous rhythm anywhere from 19 hours to over 40, average about 25 hours

• however, fatal flaw: subjects controlled the lighting

• therefore most phase delayed themselves; i.e., turned lights out later and later each day for sleep
solution?

- the ‘bunker’ on the 9th floor of Brigham and Women’s hospital in Boston
- lighting carefully controlled by the researchers
Brigham and Women’s Hospital
BWH ‘bunker’

• an independent "floating" cement floor platform
• 5 suites that are self-contained, soundproof, and lightproof
• sophisticated computer system controls light, temperature, humidity, sound
• monitors physiologic functions like sleep, blood, urine
results

among young and old alike, cycle length of 24.1 hours with very little variation

Physiological Importance
Our Benefactor - Cyanobacteria -

contributions: oxygen in the atmosphere, and plant-life
Circadian Biology

• once thought to be an oddity; an interesting sub-topic in the larger arena of biology
• now increasingly seen as central to all biology for almost all organisms on the planet
• not surprising since we evolved over 3 billion years with the daily cycle of the Sun
Circadian Genes and Cancer

“When you're thinking about something that you don't understand, you have a terrible, uncomfortable feeling called confusion.”

- Richard Feynman, 1963
map of NYC subway system; tough for an out-of-towner
Links of circadian biology to physiology

(new knowledge in the last 10 years)
Circadian Control
(~10% of genome)

- metabolism (how we process the food we eat)
- DNA damage response (how we are protected from radiation and toxic chemicals)
- hormone production (how we grow and develop)
- cell cycle regulation (how our tissues are kept functional)
Circadian disruption
The Past
3 billion years ago to ~130 years ago

~12 hours sunlight
~12 hours dark
season and latitude permitting

The Present
~130 years ago to now

Electricity

shift work (evening, night, rotating)
late-night reading or TV
dimly-lit bedrooms during sleep
short sleep duration
bright bathroom light during night
night glow over cities (no Milky Way)
day work inside buildings (no Sun)

• dim days inside buildings
• lighted nights
leading to:
"circadian disruption"
“The term ‘circadian disruption’ includes disturbances such as phase shifts of the entire circadian system, the displacement of sleep relative to the circadian clock, and/or the acute suppression of nocturnal melatonin production whether or not a phase shift also occurs. All these disruptions can be elicited by ocular light exposure at night.”
Circadian Disruption

- cancer – breast and prostate, maybe others
- obesity – altered leptin and ghrelin
- diabetes – glucose metabolism
- mood disorders – depression, bipolar
Electric Light & Circadian Disruption
Spectral Irradiance of Natural and Artificial Light

nature’s choice?

UltraViolet

InfraRed

WAVELENGTH (nm)

Melatonin suppression

Visible

Watts / m² (daylight)

Watts / m² (electric light)
Light & Melatonin

- **intense light suppresses nocturnal melatonin in all sighted persons** (Lewy et al., *Science*, 210:1267, 1980)

- **spectrum** (Brainard et al., *J Neurosci*, 21:6405, 2001)
  - blue light most effective (~446-477 nm)
  - red light least effective (>600 nm)

- **some people more sensitive than others** (McIntyre et al., *Lancet*, 335:488, 1990)

- **dose-response; the higher the intensity, the greater percent reduction in nocturnal melatonin** (McIntyre et al., *J Pineal Res*, 6:149, 1989)
• daytime light exposure can affect nocturnal sensitivity to light (Hébert et al., *J Pineal Res*, 33:198, 2002)

• daytime light can affect nocturnal melatonin production (Hashimoto et al., *Neurosci Lett*, 221:89, 1997; Wehr et al., *Am J Physiol*, 269:R173, 1995)

• women may be more sensitive to suppressive effect of light than men (Monteleone et al., *J Neural Transm*, 102:75, 1995)
Breast Cancer
The breast cancer burden

- Breast cancer is pandemic; high in the industrialized world, and rising fast in the developing world.
- No scientific consensus on one major cause.
- Unlike other common cancers for which the major causes are known such as lung (smoking), liver (HBV), cervix (HPV), stomach (H. pylori).
Breast Cancer and ‘Light-at-Night’

- **Theory:** electric light-at-night alters hormones, increasing risk, and thereby explains some of the high risk in industrialized societies
- **Predictions** (i.e., 'hypotheses'):
  - shift workers at higher risk
  - blind women at lower risk
  - lighted bedrooms at night increase risk
  - short sleep increases risk

Stevens RG. Electric light causes cancer? Surely you're joking, Mr. Stevens. Mutat Res. 2009;682:1-6.
IARC: shift work a probable human carcinogen, 2A

51 word sentence required many hours to write

“On the basis of ... bla, bla ... the Working Group concluded that ‘shift-work that involves circadian disruption is probably carcinogenic to humans’ (group 2A).”

"Due to the nearly ubiquitous exposure to light at inappropriate times relative to endogenous circadian rhythms, a need exists for further multidisciplinary research on occupational and environmental exposure to light-at-night, the risk of cancer, and effects on various chronic diseases."

“Resolved, that our American Medical Association: Supports the need for ... developing lighting technologies at home and at work that minimize circadian disruption, while maintaining visual efficiency."

Sleep disruption vs. circadian disruption

- many studies of shortened sleep or disrupted sleep and physiological changes in humans
- however, do these separate circadian disruption?
- does the lighting affect the circadian system via melatonin?
why it matters

• dark is required for nighttime melatonin rise, but sleep is not
• is it OK to awaken in the middle of the night if one stays calm and in the dark?
• or is sleep itself required for transition to nighttime physiology; for example, the rise in leptin; this among many other changes from daytime
SLEEP DURATION RECOMMENDATIONS

- **Newborn**: 0-3 months
  - Recommended: 14-17 hours
  - May Be Appropriate: 12-15 hours
  - Not Recommended: 11-13 hours

- **Infant**: 4-11 months
  - Recommended: 14-17 hours
  - May Be Appropriate: 12-15 hours
  - Not Recommended: 11-13 hours

- **Toddler**: 1-2 years
  - Recommended: 12-15 hours
  - May Be Appropriate: 11-14 hours
  - Not Recommended: 10-11 hours

- **Preschool**: 3-5 years
  - Recommended: 10-13 hours
  - May Be Appropriate: 9-11 hours
  - Not Recommended: 8-9 hours

- **School-Age**: 5-13 years
  - Recommended: 9-11 hours
  - May Be Appropriate: 8-10 hours
  - Not Recommended: 7-8 hours

- **Teen**: 14-17 years
  - Recommended: 10-11 hours
  - May Be Appropriate: 7-9 hours
  - Not Recommended: 6 hours

- **Young Adult**: 18-25 years
  - Recommended: 7-9 hours
  - May Be Appropriate: 7-9 hours
  - Not Recommended: 6 hours

- **Adult**: 26-64 years
  - Recommended: 7-9 hours
  - May Be Appropriate: 7-9 hours
  - Not Recommended: 6 hours

- **Older Adult**: 65+
  - Recommended: 5-6 hours
  - May Be Appropriate: 7-8 hours
  - Not Recommended: 9 hours

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Normal Sleep?
Gallup Survey, 2013

- average in America about 6.8 hours
- 40% getting less than recommended amounts

- what’s normal from our distant past, before electricity?
Sleep periods, the times from onset to offset, averaged 6.9–8.5 hr, with sleep durations of 5.7–7.1 hr, amounts near the low end of those industrial societies [4–7]. There was a difference of nearly 1 hr between summer and winter sleep. Daily variation in sleep duration was strongly linked to time of onset, rather than offset. None of these groups began sleep near sunset, onset occurring, on average, 3.3 hr after sunset. Awakening was usually before sunrise.
Implications?

• maybe 5½ to 7 hours of sleep is natural and not the problem the CDC and many other health organizations say it is
• however, crucial difference: total darkness was 11 to 12 hours, whereas it is confined to the sleep period in America: about 7 hours
• transition to nighttime physiology is delayed in America, but not in pre-electric societies
• 7 hours of sleep embedded within 11 hours of dark may be much more restorative than in only 7 hours of dark
• we need circadian dark in the evening
Solutions:
better lighting

Candle Light-Style Organic Light-Emitting Diodes

Jwo-Huei Jou,* Chun-Yu Hsieh, Jing-Ru Tseng, Shiang-Hau Peng, Yung-Cheng Jou, James H. Hong, Shih-Ming Shen, Ming-Chun Tang, Pin-Chu Chen, and Chun-Hao Lin
Lab studies of room light and electronic gadgets (computers, e-readers, smart phones)
ordinary evening room light? (2010)

J Clin Endocrin Metab. First published ahead of print December 30, 2010 as doi:10.1210/jc.2010-2098

ORIGINAL ARTICLE

Endocrine Research

Exposure to Room Light before Bedtime Suppresses Melatonin Onset and Shortens Melatonin Duration in Humans

Joshua J. Gooley, Kyle Chamberlain, Kurt A. Smith, Sat Bir S. Khalsa, Shantha M. W. Rajaratnam, Eliza Van Reen, Jamie M. Zeitzer, Charles A. Czeisler, and Steven W. Lockley

Division of Sleep Medicine (J.G., K.A.S., S.B.S.K., S.M.W.R., E.V.R., J.M.Z., C.A.C., S.W.L.), Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts 02115; and Faculty of Health and Medical Sciences (K.C.), University of Surrey, Guildford, Surrey GU2 7XH, United Kingdom
Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance

Christian Cajochen, Sylvia Frey, Doreen Anders, Jakub Späti, Matthias Bues, Achim Pross, Ralph Mager, Anna Wirz-Justice, and Oliver Stefani

Centres for Chronobiology and Applied Technologies in Neuroscience, Psychiatric Hospitals of the University of Basel, Basel, Switzerland; and Competence Team Visual Technologies, Fraunhofer IAO/University Stuttgart IAT, Stuttgart, Germany

Submitted 7 February 2011; accepted in final form 14 March 2011
Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness

Anne-Marie Chang\textsuperscript{a,b,1,2}, Daniel Aeschbach\textsuperscript{a,b,c}, Jeanne F. Duffy\textsuperscript{a,b}, and Charles A. Czeisler\textsuperscript{a,b}

\textsuperscript{a}Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA 02115; \textsuperscript{b}Division of Sleep Medicine, Harvard Medical School, Boston, MA 02115; and \textsuperscript{c}Institute of Aerospace Medicine, German Aerospace Center, 51147 Cologne, Germany

Edited by Joseph S. Takahashi, Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX, and approved November 26, 2014 (received for review September 24, 2014)

Stick To That Book. Your Tablet-Reading May Hurt More Than You Think

Sleep troubles? Maybe electronic devices are interfering with bedtime.

Reading On A Screen Before Bed Might Be Killing You
genetic differences in light sensitivity?

**Human Melatonin and Alerting Response to Blue-Enriched Light Depend on a Polymorphism in the Clock Gene PER3**

Sarah L. Chellappa, Antoine U. Viola, Christina Schmidt, Valérie Bachmann, Virginie Gabel, Micheline Maire, Carolin F. Reichert, Amandine Valomon, Thomas Götz, Hans-Peter Landolt, and Christian Cajochen

Centre for Chronobiology (S.L.C., A.U.V., C.S., V.G., M.M., C.F.R., A.V., T.G., C.C.), Psychiatric Hospital of the University of Basel, CH-4012 Basel, Switzerland; The CAPES Foundation/Ministry of Education of Brazil (S.L.C.), CEP 22641-310 Brasilia-DF, Brazil; and Institute of Pharmacology and Toxicology (V.B., H.-P.L.), University of Zurich, CH-8032 Zurich, Switzerland

**Conclusions:** We provide first evidence that humans homozygous for the PER3 S/S allele are particularly sensitive to blue-enriched light, as indexed by the suppression of endogenous melatonin and waking theta activity. Light sensitivity in humans may be modulated by a clock gene polymorphism implicated in the sleep-wake regulation. (*J Clin Endocrinol Metab 97: E433–E437, 2012*)
Analysis of circadian properties and healthy levels of blue light from smartphones at night

Ji Hye Oh, Heeyeon Yoo, Hoo Keun Park & Young Rag Do

Received: 29 January 2015
Accepted: 13 May 2015
Published: 18 June 2015
Wright camping study
(Current Biology, August 19, 2013)

8 subjects: one week in city, one week camping
Disentangling sleep disruption from circadian disruption

- complex design; 26 subjects in Lab
  - two groups: one with circadian alignment, one without
  - DI, a marker of diabetes risk
  - C-reactive protein, a marker of inflammation and heart disease risk

- sleep restriction

- “Circadian misalignment that occurs in shift work may increase diabetes risk and inflammation, independently of sleep loss.”

Leproult, Holmbäck, van Cauter. Diabetes, June 2014
shift work meta-analyses

- **Jia Y et al.** *(Cancer Epidemiol 2013)*
  - RR = 1.4 (1.13-1.73) high quality studies

- **Ijaz S et al.** *(SJWEH 2013)*
  - RR = 1.04 (1.0-1.1) 300 night shifts

- **Kamdar B et al.** *(Breast Can Res Treat 2013)*
  - RR = 1.21 (1.0-1.5) ever/never

- **Wang F et al.** *(Ann Oncol 2013)*
  - RR = 1.19 (1.05-1.35) ever/never

- **He C et al.** *(Int Arch Occ Env Health 2014)*
  - RR = 1.19 (1.08-1.32) ever/never
three more recent studies
(two breast cancer, one prostate cancer)

- **Wang, Sleep Medicine, 2015**
  - case-control; ~700 of each
  - ever/never night work: OR = 1.34 (1.05-1.72)

- **Åkerstedt, BMJ, 2015**
  - cohort; 463 cases over ~8 years followup
  - ever/never OR=0.96; 21-45 years, OR=1.92

- **Papantoniou, Int J Cancer, 2015**
  - case/control (prostate); ~1,000 of each
  - ever/never OR=1.14 (NS); >27 years OR=1.38 (1.05-1.81)
two possibilities

- **truth: no effect**
  - the small relative risks are due to bias and/or residual confounding

- **truth: shift work increases risk due to circadian disruption from electric light exposure**
  - the estimated relative risks are an underestimate because day-workers also exposed
### Table S2. Information about participant groups

Night duration is from sunset to sunrise, clock time and times relative to these, and ambient conditions (wt data).  

<table>
<thead>
<tr>
<th>GROUP/MIDPOINT OF RECORDING</th>
<th>LATITUDE (degrees)</th>
<th>LONGITUDE (degrees)</th>
<th>NIGHT DURATION h</th>
<th>SLEEP TIME h</th>
<th>WASO (wake after sleep onset)</th>
<th>SLEEP EFFICIENCY =sleep time/time in “bed”</th>
<th>ENVIRONMENTAL TEMPERATURE RANGE</th>
<th>AGE</th>
<th>BMI</th>
<th>PARTICIPANTS</th>
<th>TOTAL DAYS</th>
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<tbody>
<tr>
<td>HADZA</td>
<td>-3.7315</td>
<td>35.1946</td>
<td>12.1</td>
<td>6.3±0.63</td>
<td>81±25</td>
<td>82±5.8</td>
<td>12-29</td>
<td>36.6±11.8</td>
<td>21.4±2.5</td>
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<td>60</td>
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<td>TSIMANE</td>
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<tr>
<td>8/18/13-W</td>
<td>-14.875</td>
<td>-66.7282</td>
<td>12.4</td>
<td>6.6±0.93</td>
<td>82±17</td>
<td>83±6.0</td>
<td>14-29</td>
<td>38.0±10.7</td>
<td>26.1±3.9</td>
<td>9</td>
<td>63</td>
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<td>-66.7282</td>
<td>12.2</td>
<td>6.4±1.03</td>
<td>92±16</td>
<td>81±4.6</td>
<td>15-33</td>
<td>35.2±14.3</td>
<td>22.8±3.3</td>
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<td>63</td>
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<td>85±5.54</td>
<td>18-28</td>
<td>32.2±10.7</td>
<td>26.2±3.5</td>
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<tr>
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<td>-66.7282</td>
<td>11.5</td>
<td>6.5±0.32</td>
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<td>22-31</td>
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<td>8/14-W</td>
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<td>11.0</td>
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<td>72±10</td>
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<td>38.5±14.0</td>
<td>18.3±2.2</td>
<td>15</td>
<td>420</td>
</tr>
</tbody>
</table>

**AVERAGES** | **6.4** | **80.3** | **83** | **36.5** | **TOTALS** | **94** | **1165**
Biphasic Sleep?

- A good night’s sleep in modern societies is supposed to be the oft-repeated ‘8-hours’ at one stretch.
- Given our evolutionary past, is this really right for everyone?
- If you awake in the middle of the night, are you abnormal?
- Thomas Wehr’s experiments
before electricity

now days

dusk
first sleep
awake
maybe dim fire
capture dreams
second sleep
~12 hours
dawn

lights out

one sleep
7 or 8 hours
dreams lost

lights on
Genetics & Epigenetics
The Circadian Clock: clock-controlled genes

- Cell cycle regulation crucial to normal and malignant cell growth (e.g., cyclin D1)
- 5-10% of all mammalian genes are clock controlled
- Among these are genes for the key regulators of cell-cycle progression and apoptosis (e.g., cyclins and caspases)
- Light-dark cycle strongest circadian cue
- Per3 variant and breast cancer in young women - Yong Zhu et al. Cancer Epidemiol Biomark Prev, 14:268, 2005
Circadian Loop

Positive (transcriptional activators?): CLOCK (or NPAS2) and BMAL1 are basic helix-loop-helix PAS-domain containing transcription factors that activate transcription of the Per and Cry genes.

Negative (transcriptional repressors?): The resulting PER and CRY proteins heterodimerize, translocate to the nucleus and interact with the CLOCK–BMAL1 complex to inhibit their own transcription. After a period of time, the PER–CRY repressor complex is degraded and CLOCK–BMAL1 can then activate a new cycle of transcription.

The entire cycle takes approximately 24 hours to complete

Takahashi et al., *Nat Rev: Genet*, October, 2008
We surmised that maybe:

Clock is “oncogene”? 

CRY2 is “tumor suppressor”?
“CLOCK in Breast Tumorigenesis”
(Hoffman et al., Cancer Research, 2010;70:1459-68)

- case-control study in CT (441 cases)
- 80 cases before adjuvant therapy
- hypomethylation strongly associated with risk
methylation in night workers
(Yong Zhu, et al., Chronobiol Int. 2011 Dec;28(10):852-61)

- Danish members of the ‘Diet, Cancer, and Health’ cohort, enrolled 1993 to 1997
- 19 long term night workers, 98 day workers, all disease free at blood draw
CLOCK and CRY2

![Bar chart showing the percentage of population for CLOCK and CRY2 with OR=0.36, 95% CI: 0.13-1.00 for Low and Mid/High, OR=0.32, 95% CI: 0.11-0.93 for High and Mid/Low. Day Workers are represented by blue bars, and Long Term Shift Workers are represented by red bars.](image-url)
Elements of a Circadian System

- **Environmental input**
  - phototransduction to entrain the clock

- **Molecular mechanism of the clock itself**
  - clock genes and feedback loops

- **Physiological output**
  - transduce ‘molecular time’ of the endogenous 24-hour clock into behavioral changes in the cell and organism
  - e.g., rhythms of gene expression
  - timing of hormone production and release

Mammals

- Mammals exhibit an endogenous 24-hour circadian rhythm
  - melatonin production
  - core body temperature
- Suprachiasmatic nucleus is master circadian pacemaker
- Light can reset the circadian rhythm
- **CLOCK** gene polymorphisms
Melatonin

- monoamine hormone
  - pineal gland
  - strong daily rhythm
    - low during day
    - high at night
- mood & depression
- reproductive physiology – antigonadotrophic?
- fights breast cancer?
  - inhibits breast cancer in rats
  - slows human breast cancer cells in culture
Intervention and mitigation: is there sufficient evidence?

- recommendations to the public
  - e.g., ?
- legislation and regulation
  - e.g., ?
- find alternatives
  - e.g., ?
interventions?

- evening exposure in home
- iPads?
- genetic tests for light exposure?
- change lighting - Boeing Dreamliner
- lighting for truckers - Hebert
- funny glasses - ‘notching’
Melatonin Rhythm


Plasma Melatonin (pg/ml)

- Depressed
- Euthymic

200 lux light

Phototransduction (retina) 
Opsins (vitamin A) 
Cryptochromes (B$_2$)

Neuronal signaling retina to SCN, pineal, pituitary

Cell proliferation & tissue morphological change
Altered potential for malignant transformation

Spectrum  Timing  Intensity  Duration

Neuroendocrine transduction hormone production & release
Melatonin
Estrogen
Prolactin

mammary tissue
cellular CLOCK effects on cell cycle regulatory genes
Light at Night
U.S. - the Present