Sleep Biology:
Circadian Rhythms and Mother Nature

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Circadian Rhythms and Shiftwork:

- Circadian physiology
- The circadian clock
- Molecular function of the clock
- Circadian rhythms and shift work
- The problems
- Potential solutions
An Early Clock
Biological Rhythms:

- **400 B.C.:** Alexander the Great observed that the tamarind tree opened its leaves in the day and closed them at night. 
  Interpretation: Sun Worship

- **1729:** Jean-Jacques de Mairan observed that a mimosa plant placed in a dark room continued its pattern of raising and lowering its leaves. 
  Interpretation: Presence of an internal clock.
Biological Rhythms:

• 1754: Linnaeus designed a “clock garden” with flowers opening from 6 AM to 6 PM.

• 1919: Richter observes circadian behavior in rats and introduces science of chronobiology.

• Last ~ 80 years: Multiple experiments have shown genetic inner clock rhythms, continuation of circadian patterns in animals and plants kept at the South Pole and in NASA Space Shuttles.
**Definition:**

Circadian =

\( \textit{circa} = \text{about} \)

\( \textit{dian} = \text{day} \)
Other period lengths:

- **Ultradian:** < 24-hour period
  - infant sleep/wake periods
  - hormonal rhythms

- **Infradian:** > 24-hour period
  - Circannual: hibernation, migration
  - Capistrano phenomenon (March 19)
    - Cicadas that emerge from mud cocoons every 17 years.
    - Chinese bamboo “Sleeping Beauty” blooms every 125 years.
THE BEST OF TIMES

12 MIDNIGHT
- Sexual intercourse most frequent
- Melatonin secretion starts

11
- Alcohol best tolerated
- Skin repair peaks

10
- Track & swimming performance best
- Natural childbirth most common

9
- Body temperature peaks
- Body temperature lowest

8
- Taste most acute
- Cortisol secretion greatest

7
- Breathing easiest in lung diseases
- Height greatest

6 EVENING
- Lung & heart efficiency maximum
- Blood pressure & pulse surge

5
- Best training time for most sports
- Testosterone highest in men

4
- Reaction time best
- Melatonin secretion turns off

3
- Best time for power nap
- Bowel movement most common

2
- Eye-hand coordination best
- Body weight lowest

1 NOON
- Mood high
- Mental alertness & arousal high
THE WORST OF TIMES

Restless leg syndrome worst
Skin irritability & itching peaks
Highest reactivity to asthma triggers
Snacking adds most weight
Menopausal hot flashes most frequent
Children's growing pains peak
Backache pain worst
Colic most frequent
Blood pressure highest
Cholesterol levels increase
MS fatigue worst
Fibromyalgia pain intense
Osteoarthritis pain worst
Intestinal ulcer rupture most frequent
Tension headaches peak
"Post-lunch" dip in alertness & arousal
Stomach ulcer rupture most frequent

Gout attacks worst
Gallbladder attacks flare
Periodic limb movements most frequent
Heartburn & peptic ulcer attacks flare
Congestive heart failure symptoms peak
SIDS deaths peak
Bone breakdown peaks
Nightwork errors peak
Cluster & migraine headaches start
Peak risk of auto & truck crashes
Asthma attacks peak
Toothaches start
Greatest likelihood of dying from any cause
Hay fever symptoms worst
Cold & flu symptoms worst
Rheumatoid arthritis pain peaks
Nosebleeds most common
Depression worst
Heart attacks & strokes peak
Angina pectoris & sudden heart deaths peak
The Circadian Clock: Where is it?
The Circadian Clock:

• **1960’s**: Richter discovered that the generator of body rhythms was located in the hypothalamus.

• **1972**: Stephan/Zucker (Berkeley) and Moore/Eichler (Chicago) found the suprachiasmatic nucleus – the body’s master clock.
The SCN

Location of section

Cerebrum
Lateral ventricles

Anterior commissure
Hypothalamus
Third ventricle
Optic chiasm
Suprachiasmatic nuclei
The SCN
The Circadian Clock:

• Circadian rhythms in mammals are generated by the suprachiasmatic nucleus (SCN) of the hypothalamus.

• SCN cells can keep time *in vitro.*
SCN cells transplanted from one animal to another cause the recipient to adopt the donor’s circadian rhythm.
The Circadian Clock:

• The role of the SCN is to synchronize body rhythms with environmental light-dark cycles.

• Light reaches the SCN from the eyes, through the retino-hypothalamic tract.

• Light is the most potent stimulus for shifting the phase of the circadian cycle.
Photosensitive retinal ganglion cells
Circadian Rhythms in Humans:

• Long considered to be under voluntary control.

• 1980: Lewy discovered that light inhibits melatonin production.
Circadian Rhythms

• Control of circadian rhythms is not voluntary – it occurs at the molecular level.
MORNING

Cytoplasm

Nucleus

Clock  BMAL-1

Per and Cry genes

mRNA
DAY

Cytoplasm

Nucleus

Clock  BMAL-1

Per 1
Per 2
Per 3

CRY 1
CRY 2

mRNA
DAY – (later)

Cytoplasm

Nucleus

Clock BMAL-1

PER CRY

mRNA
EVENING

Cytoplasm

Nucleus

Cytoplasm

Clock  BMAL-1

PER  CRY

mRNA
NIGHT

Cytoplasm

Nucleus
EARLY MORNING

Cytoplasm

Nucleus

mRNA
Effects of light on mRNA production in the SCN
What is the normal human circadian period?

Estimates: Close to 24.2-24.5 hours

(Creisler et al., Science 284:2177-2181, 1999)
The CLOCK gene:

- A semi-dominant mutation was found to lengthen circadian period and abolish rhythmicity in mice.  
  (Vitaterna et al., Science 264:719-725, 1994)

- CLOCK gene mutations also affect the length of the circadian rhythm.  
The CLOCK gene:

- In humans, a single nucleotide polymorphism in the 3’ region of the human CLOCK gene correlates with morning/night diurnal preferences.

(Katzenberg et al., Sleep 21:569-576, 1998)
Delayed Sleep Phase Syndrome: (Frequently seen in teenagers)
### Advanced Sleep Phase Syndrome:
(Frequently seen in older people)

<table>
<thead>
<tr>
<th></th>
<th>PM</th>
<th>Midnight</th>
<th>AM</th>
<th>Noon</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
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<td>11</td>
<td>12</td>
<td>1</td>
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<tr>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Sun**
  - 12 → 6
- **Mon**
  - 12 → 6
- **Tues**
  - 12 → 6
- **Wed**
  - 12 → 6
- **Thu**
  - 12 → 6
- **Fri**
  - 12 → 6
- **Sat**
  - 12 → 6

**X** = lights out and trying to sleep,

- **←→** = asleep,
- **↓** = in bed,
- **↑** = out of bed
Advanced Sleep Phase Syndrome:

Familial trait:

- Described in 3 families (Northern European)
- High-penetrance autosomal dominant trait
- Youngest affected subject: 8 years old
- Shortened endogenous circadian period (23.3 hours)

(Jones et al., Nature Medicine 5:1062, 1999)
Pedigrees of 3 families with ASPS:
Sleep Duration:

- Genetically determined in many cases.
- High degree of variability in humans.
- Reports: 67 min to >14 hours/24-hr period

Leonardo da Vinci: Slept 15 min/4 hours (total of 90 min/24 hours)
A short sleeper:
Margaret Thatcher = 4 hours
A short sleeper:
Bill Clinton = 3-4 hours
A short sleeper: Bill Clinton
Short sleeper: Michelangelo = 4 hours
Short sleeper: Mozart = 2 hours + “cat naps”
Short sleeper: Leonardo daVinci = 15 minutes/4 hours
Short sleeper: Napoleon = 3 - 4 hours
Short sleeper:
Vincent Van Gogh = 1-2 hours at a time
A Long Sleeper:
Shift Work Sleep Disorder:

- Definition: Difficulty with insomnia or excessive sleepiness related to a work period which is scheduled during the desired sleep phase.

- May occur with night shifts, rotating shifts, or early AM shifts.

- Normal circadian rhythms, including biochemistry patterns and 24-hour temperature patterns are lost.
Shift Work Sleep Disorder: Diagnostic Criteria

• A primary complaint of insomnia or excessive somnolence.
• Symptoms are temporally associated with a work period that occurs during the habitual sleep phase.
• There is evidence of a disturbed circadian rhythm by demonstration of loss of the normal sleep-wake pattern.
• The absence of another disorder that could account for the symptoms.
Three Mile Island:
March 28, 1979 (4:00 AM)
Chernobyl: April 26, 1986 (1:23 AM)
Probability of Errors During Shift Work

Percentage Change

Time of Day

8 am 12 pm 4 pm 8 pm 12 am 4 am 8 am

(24-Hr. Average)

12:04 A.M. Exxon Valdez
12:40 A.M. Bhopal
1:23 A.M. Chernobyl
4:00 A.M. Three Mile Island
1986: Challenger takeoff
Escalating occurrence across the night shift from 0000 to 0800 hours
<table>
<thead>
<tr>
<th>Sleep loss (time in bed)</th>
<th>Equivalent US beers*</th>
<th>Alcohol dose (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 h (8 h)</td>
<td>10 - 11</td>
<td>0.190</td>
</tr>
<tr>
<td>6 h (2 h)</td>
<td>7 - 8</td>
<td>0.102</td>
</tr>
<tr>
<td>4 h (4 h)</td>
<td>5 - 6</td>
<td>0.095</td>
</tr>
<tr>
<td>2 h (6 h)</td>
<td>2 - 3</td>
<td>0.045</td>
</tr>
</tbody>
</table>

*Given 14.22 g of ethanol in a 12-oz beer.
†Approximate breath ethanol concentration at peak.
American vs. European school schedules:

- American schools: 6:50 AM (zero hour)
  7:40 AM (regular start)
  3:15 PM (dismissal)

- European schools: 9:30 AM (regular start)
  5:00 PM (dismissal)
Sleep patterns in American high school students: (Hansen et al., Pediatrics 115: 2005)

- Students sleep 2 hours less per school night compared with vacation schedule.
- Weekend sleep is only 30 minutes longer, compared with vacation schedule.
- Early start times contribute to sleep deprivation.
- Students perform better in the afternoon.
- Difficulty with concentration and alertness in morning classes.
Teenagers, grades, and sleep schedules:  
(Wolfson et al., Child Dev 69, 1998)

N= 3120 high school students  
Correlation between grades and sleep time

<table>
<thead>
<tr>
<th>GPA</th>
<th>&gt;/= 3.0</th>
<th>vs.</th>
<th>&lt; /= 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep time</strong> (hrs)</td>
<td>&gt; 8:15</td>
<td></td>
<td>&lt; 6:45  (p&lt;.001)</td>
</tr>
<tr>
<td><strong>Bedtime</strong></td>
<td>&gt; 40 minutes earlier</td>
<td></td>
<td>(p&lt;.001)</td>
</tr>
<tr>
<td><strong>Weekend bedtimes compared to school nights</strong></td>
<td>&lt; 1 hour</td>
<td></td>
<td>&gt; 2 hours (p&lt;.05)</td>
</tr>
</tbody>
</table>
The Controversy: Should schools let teenagers sleep later?

No!

- Athletics: No time for practice, difficulty with game scheduling.
- Bus schedules: 2-tiered system would be affected.
- After-school jobs: New schedules needed, students get home even later.

(Hsu E., The Record, March 8 2007)
The Controversy: Should schools let teenagers sleep later?

Yes!

- Minneapolis school district (12,000 high school students): High school start time changed to 8:40 AM (previously 7:15 AM)

- Results: (Wahstrom et al., University of Minnesota Education Dept.)
  1. Improved school attendance
  2. Decreased tardiness
  3. Decreased student depression assessment scores
  4. Less sleeping in class

(Hsu E., The Record, March 8 2007)
N = 452

PDS, Pediatric Daytime Sleepiness; significant linear trend P < .01.
Kinder residency hours
Four Days with an International Flight Crew

Day 1
- Crew's time: 1:10 am
- Local time: 6:10 am
- Norita to Bangkok
  - Flight time: 7 hrs.
- Crew's time: 8:10 am
- Local time: 4:10 pm
- 7 hrs. 50 mins. between flights

Day 2
- Crew's time: 12:55 am
- Local time: 5:55 pm
- Norita to Hong Kong
  - Flight time: 4 hrs. 55 mins.
- Crew's time: 5:50 am
- Local time: 9:50 pm
- 15 hrs. 20 mins. between flights

Day 3
- Flight time: 11 hrs. 35 mins.
- Crew's time: 8:45 am
- Local time: 8:45 am

Day 4
- Crew's time: 9:10 pm
- Local time: 1:10 am
- Hong Kong to Seattle
  - Flight time: 3 hrs. 10 mins. between flights

Legend:
- ■ In Flight
- □ Between Flight
Shift Work Sleep Disorder:

Measures that improve sleep after a night shift:

- Avoid exposure to light on the way home.
- Keep bedroom dark.
- Determine optimal sleep pattern and use it consistently.
- “Anchor sleeping”: Reserve a block of time during the day for sleeping and take a nap during that time, even on days off.
Shift Work Sleep Disorder:

What Might Help:
Measures to promote alertness on the job

• Forward shift rotation (mornings to evenings to nights).
• Cross-training of repetitive tasks to avoid sleepiness.
• Exercise facilities for use during breaks.
• On-site sleeping facilities.
Circadian Effects of Exercise

- Exercise can shift circadian rhythms independently of light exposure.
- Nighttime exercise is associated with phase delays of melatonin and TSH rhythms.
- The magnitude of phase delay is directly proportional to the intensity of exercise.
- These effects are worst when exercise occurs before the circadian bedtime, and least when exercise occurs in the early morning.
Age and Shiftwork:

- “The older you get, the harder it is!”
- Increased difficulty with recovery sleep.
- Increased fatigue, hypersomnolence.
- Self-selection
Age and Shiftwork: A Local Experiment

- N = 11 radiologists
- Ages = 33 to 62
- M/F = 9/2
- 12-hour night shift for 7 nights every 9 weeks

- Ages <= 45: “Reasonable” tolerance for shift changes, adequate recovery sleep.

- Ages > 45: “I hate this! I want to quit! I’m too old! I feel sick! I can’t sleep! I’m afraid I’ll miss something!”
Shift Work Sleep Disorder:

Light therapy
The effect of light:

• Exposure to bright light in the early morning results in a phase advance...AVOID in shift work sleep disorder.

• Exposure to light in evening resulted in a phase delay in the temperature cycle.  
  
  (J Am Geriatr Soc 41:829, 1993)

• Outside daylight or special indoor lighting (>2500 Lux) is required.
(A) Sleep pattern before light treatment

(B) Sleep pattern after light treatment
NASA protocol for circadian shift-work adjustment
Conclusions:

• Human circadian rhythms are complex and control occurs at the cellular level.

• Some circadian patterns are genetically determined.

• These genetic variations can make us become “morning” or “night” people and can determine our sleep requirements.
Conclusions:

• Despite our best efforts, our parents, through their DNA, continue to influence our bedtimes...
Conclusions:

• Can we fool Mother Nature when our innate circadian rhythms are different from our shift work schedules?

**YES**

• With the proper combination of sleep periods, appropriate timing of light avoidance or exposure, and pharmacologic assistance, it is possible to trick Mother Nature and maintain a reasonable degree of comfort despite shift work.
Mont St. Michel: Prisoner of an extreme circadian rhythm