Light and Dark and Human Health

– Joan E. Roberts, Ph.D.

Professor of Chemistry, Department of Natural Sciences,
Fordham University
113 West 60th Street
New York City NY 10023
jroberts@fordham.edu

Humans evolved under both a light and dark night cycle. Therefore, it is not surprising that modifying natural, cyclical daylight and dark exposure would lead to severe health risks. It must be emphasized that the dark periods are equally important as the light period for proper human health and well-being.

Cyclic daylight and dark night exposure controls the fluctuation of the body's production of various hormones; this is known as the circadian rhythm with about a 24-hour period. The human circadian system is regulated by both environmental stimuli and endogenous (internal) clocks. Visible light between 460 – 500 nm (Gaddy *et al.*, 1993) received by the human eye is one of the regulators of the circadian response in humans (Figure 1). The photosensitive molecule (chromophore) that receives this circadian light is melanopsin, which is located in the neural retina in the intrinsic photosensitive Retinal Ganglion Cells (ipRGC)

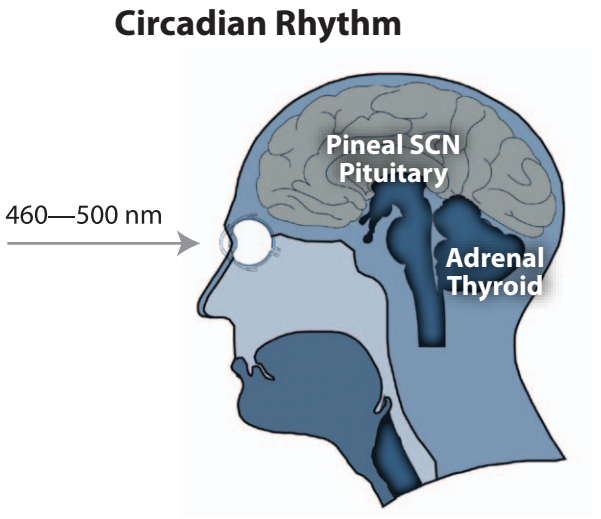

Figure 1 — The most powerful external regulator of the circadian response in humans is visible light, which is transmitted through the eye. When visible light impinges on the retina (intrinsically photosensitive Retinal Ganglion Cells), it sends a signal to the suprachiasmatic nucleus (SCN) in the hypothalamus leading to a cascade of hormonal changes in the pituitary, pineal, adrenal, and thyroid glands.

Table 1

Circadian Blue Light 460 – 500 nm, Morning 6 – 10 am

Neurotransmitters	
Cortisol	stress response
Serotonin	impulse control, carbohydrate craving
Dopamine	pleasure, alertness, muscle coordination
Neurohormones	
CRF	stress
Gastrin Releasing Peptide	hunger
Neuropeptide Y	hunger
FSH	reproduction
TSH	metabolism

(Berson 2003). When circadian light impinges on the retina, it sends a signal to the suprachiasmatic nucleus (SCN) (Brainard *et al.*, 2001) in the hypothalamus and from the hypothalamus, to the pituitary, pineal, adrenal, and thyroid glands to produce a specific set of hormones. Circadian blue-light exposure in the morning (Table 1) increases the hormones: cortisol [for stress], serotonin [for impulse control], gamma amino butyric acid (GABA) [for calm] and dopamine [for alertness] levels, and it modifies the synthesis of follicle-stimulating hormone (FSH) [for reproduction], gastrin-releasing peptide (GRP), neuropeptide Y (NPY) [for hunger], and thyroid-stimulating hormone (TSH) [for metabolism] (Brewerton *et al.*, 1995; Roberts, 1995; Wehr *et al.*, 2001; Cardinali and Esquifino, 2005; Veitch *et al.*, 2004; Praschak-Rieder *et al.*, 2008; Sookoian, 2007; Van Someren and Riemersma-vander Leka, 2007; Werken *et al.*, 2010).

The morning production of the hormones serotonin, dopamine, and GABA are essential for mental health. Insufficient serotonin and dopamine results in sadness, decreased energy and libido, increased need for sleep, and strong cravings for carbohydrates, while the deprivation of sufficient GABA leads to anxiety. Unusual food cravings are a result of the circadian imbalance in the hunger hormone GRP and NPY and thyroid TSH imbalance. These symptoms are a result of a lack of circadian blue light or daylight in the morning. They are most common in the winter [Seasonal Affective Disorder (SAD)] (Glickman *et al.*, 2006) or when crossing several time zones [Jet Lag] (Cho, 2001; Eastman *et al.*, 2005) and Shift Work Dysfunction (Arendt 2010)

Some hormones are made only in the dark (or red light) (Table 2), for instance melatonin [for sleep], vasointestinal peptide (VIP) [that lowers blood pressure], and growth hormone (GH) [for metabolism and repair]. Staying up at night and sleeping during the day will disturb this nighttime dark hormonal production. The "dark" hormones, melatonin, VIP, and GH are primarily produced during deep delta "restorative" sleep. The state of sleep has two components: REM (rapid

Table 2

Circadian Dark Response – above 600 nm
No circadian blue after 10 pm

Neurotransmitters	
Melatonin	sleep
Vasoactive Intestinal Peptide	blood pressure
Growth Hormone	decreased body fat

eye movement) and SW (slow-wave sleep). With REM sleep, the brain, eye, and body muscles are active and we dream; slow-wave sleep is when the brain's activity is slowed down. Slow-wave sleep is further classified as delta (deep sleep) or theta (light, drowsiness). (Table 3) During deep-delta "restorative" sleep, stress-related hormones and blood pressure decreases while the anti-aging growth hormone increases. Imbalance in these dark hormones leads to high blood pressure, and abnormal weight gain (Spiegel *et al.*, 2005; DiLorenzo, 2003; Arendt, 2010).

Delta (restorative sleep) cannot be attained without the presence of the sleep hormone melatonin. Under normal nighttime darkness, melatonin is produced between 10 p.m. and 4 a.m. As the dawn (6 a.m. – 10 a.m.) brings exposure to blue circadian light, melatonin is converted to serotonin. Melatonin production is blocked if there is ocular exposure to visible light at night instead of darkness. The slightest blue or white visible light (2 lux blue light or 24 lux white light that is emitted from the flicker of the bathroom light, a night-light, computer screen, TV, or cell phones, is sufficient to disrupt the production of melatonin and therefore interfere with deep restorative sleep (Gooley *et al.*, 2010). Even with proper darkness, only 15% of a good night's sleep is delta sleep and this percentage naturally decreases with age. Furthermore, a nap during the day will only reach about 5% total delta sleep.

Insufficient circadian blue light in the morning and/or visible light in the evening will result in mood swings, confusion, irritability, depression (AMA 2012; Stevens *et al.*, 2007) due to the lack of or decreased production of important neurotransmitters and neurohormones. [Table 1 and 2]
It is not only mood that is disturbed by circadian rhythm disruption but overall health. There is an increased risk for

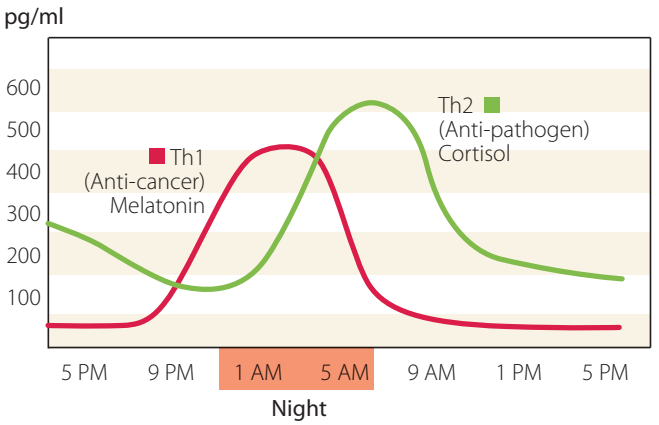

Figure 2 — The human immune response is circadian. Th1— involves cytotoxic T-Cells and N-Killer cells. These anti-tumor cells are activated in the evening (in the dark, in the absence of circadian blue light) by the presence of melatonin. Th2—involves B Cells. These anti-pathogen cells are activated in the morning in response to circadian blue light (480 nm) by the presence of cortisol and other neurotransmitters. (Adapted from Cutolo, M., Maestroni, G.J. et al.,*" 2005)*

cancer and infectious disease if one is exposed to insufficient daylight in the morning or darkness in the evening. How is this possible? This is because the human immune system is circadian.

The human immune response consists of two major pathways: Th1 (T helper 1) [cell-mediated immunity], which uses N-Killer (NK) cells and cytotoxic T cells to destroy viruses and cancer, and Th2 (T helper 2) [humoral or antibody-mediated immunity], which enlists B cells to produce specific antibodies to help eradicate bacteria, parasites, and toxins (Figure 2). The Th1 immune response is most active in the evening, at least partly in response to the nocturnal production of melatonin, while the Th2 immune response is activated in the morning, in response to the production of cortisol and other morning neurotransmitters. An imbalance of Th1/Th2 immune responses can trigger an autoimmune response. Autoimmune diseases (asthma, rheumatoid arthritis) are more prevalent in the morning, while light at night prevents the nocturnal melatonin production, preventing the activation of the anti-cancer N-Killer (NK) cells and cytotoxic T cells. Night workers have a particular risk for breast and prostate cancer because of the disrupted production of melatonin. Exposure to

Table 3

Alertness and sleepiness may be quantitatively measured by noting the changes in the electroencephalographic (EEG) power spectrum. In general, the lower the number (Hz) the slower the brain pattern.

Slow Wave Sleep			12 – 14 REM Sleep	
Delta	**Theta**	**Alpha**	**Sigma**	**Beta**
0.5 – 4 Hz	4 – 7 Hz	8 – 13 Hz	11 – 15 Hz	13 – 40 Hz
deep	Light	alert	focused	vigilant

visible light at night also deregulates the circadian gene, Per2 (Chen *et al.*, 2005; Fu *et al.*, 2002), which is involved in human breast and endometrial cancer development. For this reason, when the natural circadian immune cycle is disrupted, there is an increase risk of cancer, autoimmune, and infectious diseases (Roberts, 2000, 2008; Cutolo *et al.*, 2005; Baldwin and Barrett, 1998; Levi, 2000; Blask *et al.*, 2005; Blask, 2009; Dimitrov *et al.*, 2004; Erren and Reiter, 2008; Spiegel *et al.*, 2005; Hu *et al.*, 2011; Maestroni, 2003).

There have been numerous clinical trials studying the affect of appropriate and inappropriate lighting on circadian dysfunction and human health. They involve varying lighting regimens, including enhanced circadian blue light in the morning to increase alertness and red light at night to enhance sleep. For shift workers, blue-blocking glasses in the morning were used to prevent circadian stimulation, and enhanced daytime darkness and/or melatonin to aid in restorative deep (delta) sleep. Dark/light control of the human circadian response has been directly applied to treating sleep disorders and other circadian disorders (Arendt *et al.*, 2008; Arendt 2010; Gooley *et al.*, 2012; Burkhart & Phelps 2009; Glickman *et al.*, 2006; Kent *et al.*, 2009; Lockley *et al.*, 2003; Lieverse *et al.*, 2008; Levi & Schibler 2007; Scheer *et al.*, 2009; Werken *et al.*, 2010; Pechacek *et al.*, 2008). Modifying diet at specific times of day has also been found to help overcome jet lag and rebalance shift work circadian disruption (Wurtman *et al.*, 2003; Mendoza, 2007). For instance, eating tyrosine- (the precursor for dopamine) containing foods increases alertness, and eating tryptophan- (precursor of serotonin and melatonin) containing foods enhances serenity and sleep.

These studies are only valid if precise measurements have been made that involve age of recipient, the definition, spectrum, intensity, the time of day of exposure, and direction of the light source (Portaluppi *et al.*, 2008; Van Someren, 2011). It is particularly important that the report includes a detailed description of the spectral properties of the light source and the total irradiance at the action spectra of non-visual photoreception (460-500 nm). Terms such as "Bright Light" and "Dim Light" or continuous light (LL) and continuous dark (DD) are biologically irrelevant and not reproducible.

In summary, exposure to the appropriate spectrum of light during the day and evening enhances human health and well-being, immune response, and productivity (Figure 3). Because of these hormonal changes, the circadian dark/light cycle controls and modifies the sleep/wake cycle, blood pressure, metabolism, reproduction, and the immune response. Removal of circadian blue light exposure at night allows for an appropriate circadian response. However, exposure to light sources that do not match the natural solar

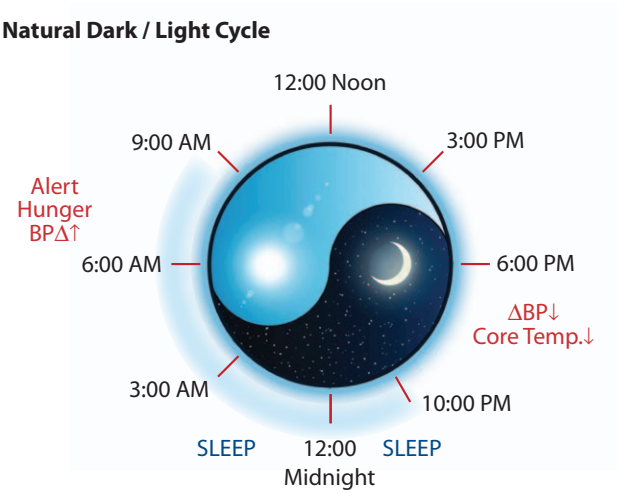

Figure 3 — The circadian dark/light cycle controls hormonal change, which modifies the sleep/wake cycle, blood pressure, sleep, and other physiological functions.

spectrum to the time of day or evening is hazardous to human mental and physical health.

Acknowledgements

Special thanks for the graphics designed and created by David Green, NIEHS Multi-Media Services, North Carolina.

References

Arendt, J. (2010). Shift work: coping with the biological clock. *Occup Med*, *60*, 10-20.

Arendt, J., Van Someren, E.J., Appleton, R., Skene, D.J., & Akerstedt, T. (2008). Clinical update: melatonin and sleep disorders. *Clin Med*, *8(4)*, 381-383.

Baldwin, W.S. & Barrett, J.C. (1998). Melatonin: receptor-mediated events that may affect breast and other steroid hormone-dependent cancers. *Mol Carcinog*, *2*, 149-155.

Berson, D.M. (2003). Strange vision:ganglion cells as circadian photoreceptors. *Trends Neurosci*, *26(6)*, 314-320.

Burkhart, K. & Phelps, J.R. (2009). Amber lenses to block blue light and improve sleep: A randomized trial. *Chronobiol Int*, *26*, 1602-1612.

Blask, D.E. (2009). Melatonin, sleep disturbance and cancer risk. *Sleep Med Rev*, *13*, 257-264.

Blask, D.E., Brainard, G.C., Dauchy, R.T., Hanifin, J.P., Davidson, L.K., Krause, J.A., Sauer, L.A., Rivera-Bermudez, M.A., Dubocovich, M.L., Jasser, S.A., Lynch, D.T., Rollag, M.D., & Zalatan, F. (2005). Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Res*, *65(23)*, 11174-11184.

Brainard, G.C., Hanifin, J.P., Greeson, J.M., Byrne, B., Glickman, G., Gerner, E., & Rollag, M.D. (2001). Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci*, *21(16)*,6405-6412.

Brewerton, T.D., Lydiard, R.B., Johnson, M., Ballenger, J.C., Fossey, M.D., Zealberg, J.J., Roberts, J.E. (1995) CSF Serotonin: diagnostic and seasonal differences. *Biol Psych*, 37, 655.

Cardinali, D.P., & Esquifino, A.I. (2005). Biological rhythms in neuroendocrinology. In: D.P. Cardinali & S.R. Pandi-Perumal (Eds.), *Neuroendocrine Correlates of Sleep/Wakefulness* (Chapter 4, pp 59-86). New York, NY: Springer Publishing

Chen, S.T., Choo, K.B., Hou, M.F., Yeh, K.T., Kuo, S.J., & Chang, J.G. (2005). Deregulated expression of the PER1, PER2 and PER3 genes in breast cancers. *Carcinogenesis*, *26*, 1241-1246.

Cho, K. (2001). Chronic 'jet lag' produces temporal lobe atrophy and spatial cognitive deficits. *Nature Neurosci*, *4*, 567-568.

Cutolo, M., Maestroni, G.J., Otsa, K., Aakre, O., Villaggio, B., Capellino, S., Montagna, P., Fazzuoli, L., Veldi, T., Peets, T., Hertens, E., & Sulli, A. (2005). Circadian melatonin and cortisol levels in rheumatoid arthritis patients in winter time: a north and south Europe comparison. *Ann Rheum Dis*, *64*, 212-216.

DiLorenzo, L., De Pergola, G., Zocchetti, C., L'Abbate, N., Basso, A., Pannacciulli, N., Cignarelli, M., Giorgino, R., & Soleo, L. (2003). Effect of shift work on body mass index. *Int J Obesity*, *27*, 1353-1358.

Dimitrov, S., Lange, T., Tieken, S., Fehm, H.L., & Born, J. (2004). Sleep associated regulation of T helper 1/T helper 2 cytokine balance in humans. *Brain Behav Immun 18*, 341-48.

Eastman, C.I., Gazda, C.J., Burgess, H.J., Crowley, S.J., & Fogg, L.F. (2005) Advancing circadian rhythms before eastward flight: a strategy to prevent or reduce jet lag. *Sleep 28,* 33-44.

Erren, T.C. & Reiter, R.J. (2008). A generalized theory of carcinogenesis due to chronodisruption. *Neuroendocrin Lett*, *29(6)*, 815-821.

Fu, L., Pelicano, H., Liu, J., Huang, P., & Lee, C.C. (2002). The circadian gene Period2 plays an important role in tumor suppression and DNA damage response in vivo. *Cell 111*, 41-50.

Gaddy, J.R., Rollag, M.D., & Brainard, G.C. (1993). Pupil size regulation of threshold of light-induced melatonin suppression. *J Clin Endocrine Metab*, *77*, 1398-1401.

Glickman, G., Byrne, B., Pineda, C., Hauck, W.W., & Brainard, G.C. (2006). Light therapy for seasonal affective disorder with blue narrowband light-emitting diodes (LEDs). *Biol Psych 59(6)*, 502-507.

Gooley, J.J., Rajaratnam, M.W., Brainard, G.C., Kronauer, R.E., Czeisler, C.A. & Lockley SW. (2010) Spectral Resonses of the Human Circadian System depend on the irradiance and duration of exposure to light. *Sci Transl Med*, *2(2) 31ra33*, 1-9.

Hu, D.N., Roberts, J.E. & Wiechmann, A.F. (2011). Melatonin and Melanoma. In R.R. Watson (Ed.), *Melatonin in the Promotion of Health* (2nd edition, Chapter 27, pp.421-431). London, UK: Taylor and Francis.

Kent, S.T., McClure, L.A., Crosson, W.L., Arnett, D.K., Wadley, V.G., & Sathiakumar, N. (2009). Effect of sunlight exposure on cognitive function among depressed and non-depressed participants: a REGARDS cross-sectional study. *Environ Health 8*, 34-48.

Levi. F. (2000). Therapeutic implications of circadian rhythms in cancer patients. *Novartis Found Symp*, *227*,119-136.

Levi, F. & Schibler, U. (2007). Circadian rhythms: mechanism and therapeutic implications. *Annu Rev Pharmacol*, *47*, 493-528.

Lieverse, R., Nielen, M.A.M., Veltman, D.J., Uitdehaag, B.M.J., Van Someren, E.J.W., Smit, J.H., & Hoogendijk, W.J.G. (2008). Bright light in elderly subjects with nonseasonal major depressive disorder: a double blind randomized clinical trial using early morning bright blue light comparing dim red light treatment. *Trials*, *9*, 48-58.

Lockley, S.W., Brainard,G.C., & Czeisler, C.A. (2003). High sensitivity of the human circadian melatonin rhythm to resetting by short wave length light. J *Clin Endocrinol Metab*, 88, 4502-4505.

Maestroni, G.J. (1993). The immunoneuroendocrine role of melatonin. *J Pineal Res*, *14*, 1-10.

Mendoza, J. (2007). Circadian clocks: setting time by food. *J Neuroendocrinol 19*(2), 127-137.

Pechacek, C.S., Andersen, M., & Lockley, S.W. (2008). Preliminary method for prospective analysis of the circadian efficacy of (day)light with applications to healthcare architecture. *Leukos*, 5, 1-26.

Portaluppi, F., Touitou, Y., & Smolensky, M.H. (2008). Ethical and methodological standards for laboratory and medical biological rhythm research. *Chronobiol Int*, *25*, 999-1016.

Praschak-Rieder, N., Willeit, M., Wilson, A.A., Houle, S., & Meyer, J.H. (2008). Seasonal variation in human brain serotonin transporter binding. *Arch Gen Psych, 65* (9), 1072-1078.

Roberts, J.E. (1995). Visible light induced changes in the immune response through an eye-brain mechanism (*Photoneuroimmunology*). *J Photochem Photobiol B:Biol*, *29*, 3-15.

Roberts, J.E. (2000). Light and Immunomodulation. *NY Acad Sci*, *917*, 435-445.

Roberts, J.E. (2008). The effects of visible and near infrared light in humans. In P.U. Giacomoni (Ed.), *Biophysical and Physiological Effects of Solar Radiation on Human Skin*, (Chapter 8, pp 209-223). Cambridge, UK:Royal Society of Chemistry Publishing.

Scheer, F.A.J.L., Hiltona, M., Mantzoros, C.S., & Shea, S.A. (2009). Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci*, *106 (11)*, 4453-4458.

Sookoian, S., Gemma, C., Gianotti, T.F., Burgueño, A., Alvarez, A., González, C.D., & Pirola, C.J. (2007). Serotonin and serotonin transporter gene variant in rotating shift workers. *Sleep*, *30(8)*, 1049-1053.

Spiegel, K., Knutson, K., Leproult, R., Tasali, E., & Cauter, E.V. (2005). Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *J Appl Physiol*, *99*, 2008-2019.

Stevens, R.G., Blask, D.E., Brainard, G.C., Hansen, J., Lockley, S., Provencio, I., Rea, M.S., & Reinlib, L. (2007). Meeting Report: The role of environmental lighting and circadian disruption in cancer and other diseases. *Environ Health Perspect*, *115*, 1357-1362.

Van De Werken, M., Giménez, M.C., De Vries, B., Beersma, D.G., Van Someren, E.J., & Gordijn, M.C. (2010). Effects of artificial dawn on sleep inertia, skin temperature, and the awakening cortisol response. *J Sleep Res*, *19*(3), 425-435.

Van Someren, E.J., & Riemersma-Van Der Leka, R.F. (2007). Live to the rhythm, slave to the rhythm. *Sleep Medicine Reviews*, *11*, 465–484.

Van Someren, E.J. (2011). Actigraphic monitoring of sleep and circadian rhythms. *Handb Clin Neurol*, *98*, 55-63.

Veitch, J.A., Van den Beld, G., Brainard, G., & Roberts, J.E. (2004). Ocular lighting effects on human physiology and behaviour. *CIE Publication 158* Vienna, Austria.

Wehr, T.A., Aeschbach, D., & Duncan, W.C. Jr., (2001). Evidence for a biological dawn and dusk in the human circadian timing system. *J Physiol*, *535 (3)*, 937-951.

Wurtman, R.J., Wurtman, J.J., Regan, M.M., McDermott, J.M., Tsay, R.H., & Breu, J.J. (2003). Effects of normal meals rich in carbohydrates or proteins on plasma tryptophan and tyrosine ratios. *Am J Clin Nutr*, *77*,128-32.