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COMMISSION INTERNATIONALE DE L'ECLAIRAGE
INTERNATIONAL COMMISSION ON ILLUMINATION
INTERNATIONALE BELEUCHTUNGSKOMMISSION

TECHNICAL REPORT

OCULAR LIGHTING EFFECTS ON HUMAN PHYSIOLOGY AND BEHAVIOUR

CIE 158:2009 (including Erratum 1)

UDC: 612.014.481-06

Descriptor: Optical radiation effects on human

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The International Commission on Illumination (CIE) is an organisation devoted to international co-operation and exchange of information among its member countries on all matters relating to the art and science of lighting. Its membership consists of the National Committees in 37 countries and one geographical area and of 5 associate members.

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1. De constituer un centre d'étude international pour toute matière relevant de la science, de la technologie et de l'art de la lumière et de l'éclairage et pour l'échange entre pays d'informations dans ces domaines.
2. D'élaborer des normes et des méthodes de base pour la métrologie dans les domaines de la lumière et de l'éclairage.
3. De donner des directives pour l'application des principes et des méthodes d'élaboration de normes internationales et nationales dans les domaines de la lumière et de l'éclairage.
4. De préparer et publier des normes, rapports et autres textes, concernant toutes matières relatives à la science, la technologie et l'art dans les domaines de la lumière et de l'éclairage.
5. De maintenir une liaison et une collaboration technique avec les autres organisations internationales concernées par des sujets relatifs à la science, la technologie, la normalisation et l'art dans les domaines de la lumière et de l'éclairage.

Les travaux de la CIE sont effectués par 7 Divisions, ayant chacune environ 20 Comités Techniques. Les sujets d'études s'étendent des questions fondamentales, à tous les types d'applications de l'éclairage. Les normes et les rapports techniques élaborés par ces Divisions Internationales de la CIE sont reconnus dans le monde entier.

Tous les quatre ans, une Session plénière passe en revue le travail des Divisions et des Comités Techniques, en fait rapport et établit les projets de travaux pour l'avenir. La CIE est reconnue comme la plus haute autorité en ce qui concerne tous les aspects de la lumière et de l'éclairage. Elle occupe comme telle une position importante parmi les organisations internationales.

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1. Ein internationaler Mittelpunkt für Diskussionen aller Fragen auf dem Gebiet der Wissenschaft, Technik und Kunst der Lichttechnik und für den Informationsaustausch auf diesen Gebieten zwischen den einzelnen Ländern zu sein.
2. Grundnormen und Verfahren der Meßtechnik auf dem Gebiet der Lichttechnik zu entwickeln.
3. Richtlinien für die Anwendung von Prinzipien und Vorgängen in der Entwicklung internationaler und nationaler Normen auf dem Gebiet der Lichttechnik zu erstellen.
4. Normen, Berichte und andere Publikationen zu erstellen und zu veröffentlichen, die alle Fragen auf dem Gebiet der Wissenschaft, Technik und Kunst der Lichttechnik betreffen.
5. Liaison und technische Zusammenarbeit mit anderen internationalen Organisationen zu unterhalten, die mit Fragen der Wissenschaft, Technik, Normung und Kunst auf dem Gebiet der Lichttechnik zu tun haben.

Die Arbeit der CIE wird in 7 Divisionen, jede mit etwa 20 Technischen Komitees, geleistet. Diese Arbeit betrifft Gebiete mit grundlegendem Inhalt bis zu allen Arten der Lichtenwendung. Die Normen und Technischen Berichte, die von diesen international zusammengesetzten Divisionen ausgearbeitet werden, sind von der ganzen Welt anerkannt.

Tagungen werden alle vier Jahre abgehalten, in der die Arbeiten der Divisionen überprüft und berichtet und neue Pläne für die Zukunft ausgearbeitet werden. Die CIE wird als höchste Autorität für alle Aspekte des Lichtes und der Beleuchtung angesehen. Auf diese Weise unterhält sie eine bedeutende Stellung unter den internationalen Organisationen.

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This Technical Report has been prepared by CIE Technical Committee 6-11 of Division 6 "Photobiology and Photochemistry" and has been approved by the Board of Administration of the Commission Internationale de l'Eclairage for study and application. The document reports on current knowledge and experience within the specific field of light and lighting described, and is intended to be used by the CIE membership and other interested parties. It should be noted, however, that the status of this document is advisory and not mandatory. The latest CIE proceedings or CIE NEWS should be consulted regarding possible subsequent amendments.

Ce rapport technique a été élaboré par le Comité Technique CIE 6-11 de la Division 6 "Photobiologie et Photochimie" et a été approuvé par le Bureau de la Commission Internationale de l'Eclairage, pour étude et emploi. Le document expose les connaissances et l'expérience courantes dans le domaine particulier de la lumière et de l'éclairage décrit ici. Il est destiné à être utilisé par les membres de la CIE et par tout les intéressés. Il faut cependant noter que ce document est indicatif et non obligatoire. Il faut consulter les plus récents comptes rendus de la CIE, ou le CIE NEWS, en ce qui concerne des amendements nouveaux éventuels.

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OCULAR LIGHTING EFFECTS ON HUMAN PHYSIOLOGY AND BEHAVIOUR

SUMMARY

The nonvisual biological and behavioural effects of light in animals and humans are mediated by specific neuroanatomical pathways. Controlled empirical studies have shown that light can be used to treat some clinical disorders and may have broader, nonclinical applications for problems of shift work and jet lag. Studies are testing how lighting may be incorporated into architectural designs that are optimal for vision as well as physiological and behavioural stimulation.

CONSEQUENCES DE L'ECLAIREMENT DE L'OEIL SUR LA PHYSIOLOGIE ET LE COMPORTEMENT HUMAINS

RESUME

Les effets, non visuels, biologiques et comportementaux de la lumière chez les animaux et les humains sont acheminés par des voies neuro-anatomiques spécifiques. Des études empiriques, contrôlées, ont montré que la lumière peut être utilisée pour traiter des pathologies et peut avoir de plus larges applications, non médicales, pour les problèmes posés par le décalage horaire et les travaux décalés dans le temps. Les études évaluent comment l'éclairage peut être introduit dans les réalisations architecturales, optimisées pour la vision comme pour les stimulations comportementale et physiologique.

OKULARE WIRKUNGEN DER BELEUCHTUNG AUF PHYSIOLOGIE UND VERHALTEN DES MENSCHEN

ZUSAMMENFASSUNG

Die nicht-visuellen biologischen Wirkungen von Licht und seine Auswirkung auf das Verhalten bei Tieren und Menschen werden über spezifische neuroanatomische Bahnen vermittelt. Kontrollierte empirische Untersuchungen haben gezeigt, dass Licht zur Behandlung bestimmter klinischer Störungen verwendet werden kann und auch in nichtklinischen Bereichen (Probleme durch Schichtarbeit und Jetlag) Anwendung finden kann. In Studien wird untersucht, wie Beleuchtung in die architektonische Gestaltung integriert werden kann, sodass sie sowohl für das Sehen als auch für die Stimulierung von physiologischen Vorgängen und Verhalten optimal ist.

OCULAR LIGHTING EFFECTS ON HUMAN PHYSIOLOGY, MOOD, AND BEHAVIOUR (CIE 158:2004)

ERRATUM (2009-Jan-21)

The committee wishes to correct two errors in the original report, as follows:

Page 4, figure 3, should be as follows:

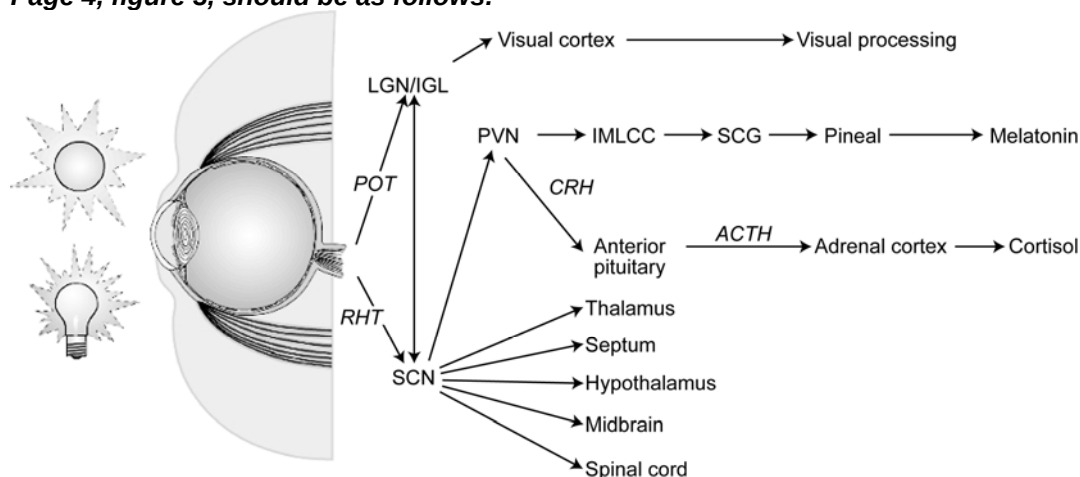


Figure 3: Simplified schematic diagram of two eye-brain pathways. Light received by the eye is converted to neural signals that pass via the optic nerve to these visual and non-visual pathways. POT = Primary optic tract. RHT = Retino-hypothalamic tract. LGN/IGL = Lateral geniculate nucleus / Intergeniculate leaflet. SCN = Suprachiasmatic nucleus of the hypothalamus. PVN = Paraventricular nucleus of the hypothalamus. IMLCC = Intermediolateral cell column of the spinal cord. SCG = Superior cervical ganglion. CRH = Corticotropin releasing hormone. ACTH = adrenocorticotrophic hormone.

Page 7, paragraph 3, should read:

2.4 Cortisol

Cortisol is secreted principally by the cortex of the adrenal gland, at the end of a sequence of neurohormonal events. A current model for its circadian regulation holds that the SCN signals to cells in the paraventricular nucleus (PVN) of the hypothalamus to secrete corticotropin releasing hormone, which in turn stimulates the anterior pituitary to release adrenocorticotrophic releasing hormone, which acts on the adrenal cortex to secrete cortisol (Buijs et al., 1998). Cortisol secretion shows a marked circadian pattern, peaking close to habitual waketime (~08h00) and reaching its trough close to habitual bedtime (~midnight) (Figure 2), superimposed on a distinct pulsatile (ultradian) profile. The amplitude of this rhythm might differ in people who report morning versus evening chronotypes ("larks" versus "owls") (Bailey & Heitkemper, 2001), and for people with some mental disorders (American Psychiatric Association, 1994). Cortisol is also secreted, however, in pulses over the day, and acutely in response to strong external stimulation (Baum & Grunberg, 1997). Cortisol's principal functions are to regulate glucose production from protein and to facilitate fat metabolism (Baum & Grunberg, 1997). Thus, its secretion in response to stressful events helps to release the energy needed to respond to threat. Its daily rhythm corresponds to the usual patterns of daily activity in humans.

CIE 158:2009

1. INTRODUCTION

1.1 Biological, psychological and architectural issues

In the late 1990s, CIE began to shift its emphasis from lighting for visibility to a more broad definition of *lighting quality*, encompassing human needs, architectural integration, and economic constraints (including energy) (Veitch, 1998; Veitch, Julian, & Slater, 1998) (Figure 1). Human needs, as defined here, include lighting that is appropriate to maintain good health, as well as lighting for visibility, task performance, interpersonal communication, and aesthetic appreciation.

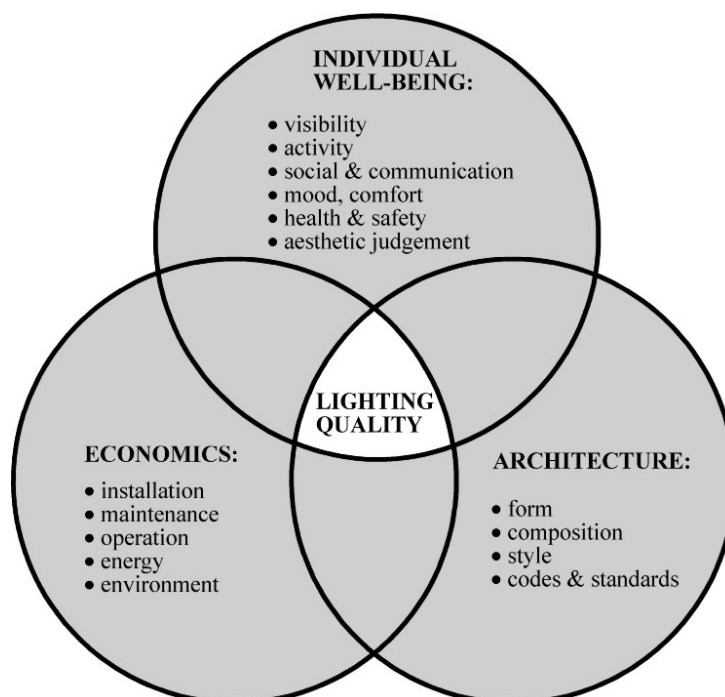


Figure 1. Lighting quality model. From Veitch (1998), courtesy of the National Research Council of Canada.

Among other developments, this definition reflects the many demonstrations that there are nonvisual, systemic effects of light in humans. Specifically, controlled laboratory and clinical studies have demonstrated that light processed through the eye can influence human physiology, mood and behaviour (Aschoff, 1981; Lam, 1998; Society for Research on Biological Rhythms, 1988; Society for Research on Biological Rhythms, 1995; Wetterberg, 1993; Wurtman, Baum & Potts, 1985). These findings may provide the basis for major changes in future architectural lighting strategies.

These effects are evoked by wavelengths within the region of the electromagnetic spectrum that provides the stimulus for vision (380-780 nm). Therefore, this report uses the word “light” to refer to this physical stimulus. At least five characteristics of light are known to be implicated in these effects: spectrum, intensity, timing, duration, and temporal pattern of exposure. Much of what is known about spectral effects concerns photodetection, and is discussed under that heading (Section 3.2). The spectral response data reported since 2001 suggests that photopic photometry is a poor measurement system for some of the nonvisual effects of light. These findings have serious implications for measurement, which are discussed in section 6. The effects of varying light intensities are discussed throughout, using the units reported by the original authors of cited studies, usually illuminance in lux.¹ The

¹ This allows a valid comparison of relative light intensity when applied to illuminants having the same spectral power distribution, but will result in inaccurate estimations when applied to comparisons of different light sources. Unfortunately most of the published literature does not include enough detail to resolve this problem (see section 6).

importance of timing is underscored in this report by treating daytime and night-time exposures separately. Duration and the temporal pattern of exposure (also sometimes called "exposure history" or "light history") are discussed in sections where relevant findings exist, but few conclusive results are yet available concerning these aspects.

1.2 Terms of reference

Interest in the biological and psychological effects of light, apart from vision, has dramatically increased since the 1980s (Lavie, 2001). This interest both stimulated the formation of several CIE technical committees concerned with such topics, and complicated the task of writing definitive reports. The science continues to evolve. When, after many years of existence, the committee had not completed its work because of the rapid development in the field of photobiology, this technical committee set a more modest goal. The following terms of reference were adopted at the 1995 CIE Session in New Delhi, India:

TERMS OF REFERENCE: Provide the CIE with a concise summary document on the systemic effects of ocularly detected optical radiation with the relevant, key scientific references. Specifically the document will introduce the controlled laboratory and clinical studies on the effects of light on human physiology, mood and behaviour. Studies on use of ocular light therapy for clinical disorders as well as for improving human adaptation to shift work and intercontinental jet travel will be discussed. How these new findings may change future architectural lighting strategies will be considered.

The report is based on an invited address by Brainard and Bernecker at the CIE session in New Delhi (Brainard & Bernecker, 1996), updated and expanded in some areas. For example, expansion of interest in the new area of photoimmunology (Roberts, 1995; Roberts, 2000) has led the committee to add this area to its report. This report is based on published work up to February 2002, when it was written.

Another CIE technical committee report that relates to this topic is TC 6-16, "Psychobiological effects of lighting", which has produced an extensive annotated bibliography (CIE, 2001a). CIE Technical Committee TC 3-16, "Psychological Aspects of Lighting" also concerns related research. At time of writing this committee had produced a draft report but had not completed final editing or division balloting, and it is not known when the report will be publicly available. These reports should be read together for a complete picture of the state of knowledge in this area as of the late 1990s/early 2000s.

2. NEUROPHYSIOLOGY OF LIGHT AND DARK

2.1 Rhythms of activity

Many biological functions are rhythmic, increasing and decreasing in level following a constant cyclic pattern. Different processes cycle at different rates, characterised by the frequency with which they complete a cycle (i.e., the period of the oscillation, for example from peak to peak). Four rhythms have specific definitions in terms of their frequency, as follows:

- *ultradian*: a rhythm with a period shorter than one day, but longer than one hour (e.g., the non-rapid eye movement (NREM) – rapid eye movement (REM) sleep cycle occurs approximately every 90 minutes during sleep),
- *circadian*: a rhythm with a period of approximately 24 hours (e.g., hormonal melatonin rhythm, core body temperature, sleeping and waking - discussed further below),
- *infradian*: a rhythm with a period longer than a day (e.g., menstrual cycles occur approximately every four weeks),
- *circannual*: a rhythm with a period of approximately one year [e.g., seasonal changes in hormone secretion (e.g., Wehr, 1991)].

Biological rhythms also differ in amplitude, or the degree of difference between the peak level and the mesor (the midpoint of the range of levels). Some show dramatic changes over the period of the cycle; a well-known example is the infradian rhythm of estrogen secretion in adult women. Circannual changes in hormone secretion in humans, by contrast, have low amplitude.

2.2 Circadian rhythms

For the purposes of this report, the major focus is on circadian rhythms. In general, the circadian system is responsible for controlling daily rhythms such as sleep and wakefulness, body temperature, hormonal secretion, and other physiological parameters including cognitive function and immune responses. The human circadian rhythm has an average period close to 24 h (24,2), with a range in sighted, healthy subjects from ~23,9 to 24,5 h (Czeisler et al., 1999). Light detected by the eyes is the primary environmental stimulus for regulating the circadian system, although other external stimuli such as sound, temperature, social cues, caffeine, and meal times may also influence the body's timing functions (Aschoff, 1981; Binkley, 1990; Klein, Moore & Reppert, 1991; Klerman et al., 1998; Lakin-Thomas, 1997; Wetterberg, 1993). Age might modify circadian amplitude (Arendt, 1998a; Jean-Louis et al., 2000) but does not appear to change the period of the cycle (Czeisler, Duffy et al., 1999).

Figure 2 shows four important circadian rhythms schematically, to illustrate the concurrent biological rhythms over each day. It shows two full cycles (48 hours) of peaks and nadirs. Alertness is shown peaking at approximately 13H00, with its nadir at approximately 04H00. Conversely, secretion of the hormone melatonin is lowest during the day, and peaks when alertness is lowest. Core body temperature peaks ahead of melatonin secretion and reaches its nadir shortly after the melatonin peak. Secretion of cortisol, another endocrine hormone, peaks approximately four hours after melatonin. Later sections discuss these patterns and hormones in greater detail.

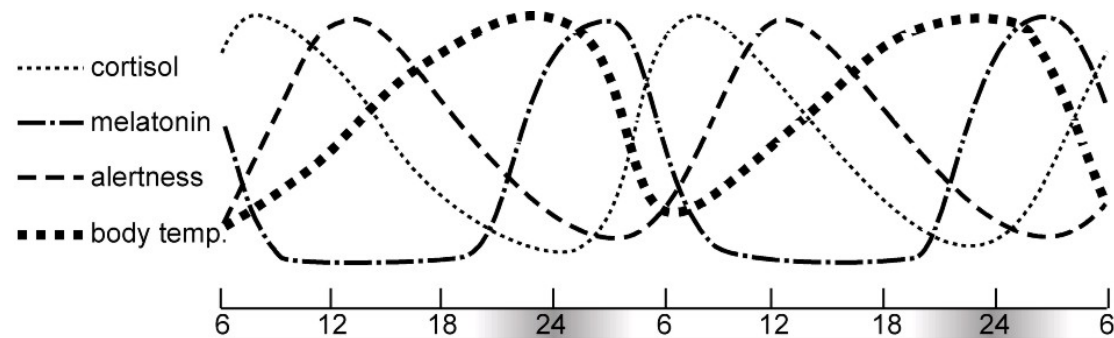


Figure 2. Schematic diagram of four circadian rhythms shows the rise and fall of alertness and core body temperature, and the secretion rates of two hormones, cortisol and melatonin. The diagram does not show absolute levels, but illustrates the differences in the timing of peaks and valleys against clock time and the different shapes of the rhythms. © Philips Lighting, ALC, 2001, courtesy of Philips Lighting.

2.2.1 Brain structures controlling circadian rhythms

As shown in Figure 3, a neural pathway called the retinohypothalamic tract (RHT) projects from the retina into a non-visual part of the brain called the hypothalamus (Aschoff, 1981; Card, 1994; Klein et al., 1991; Klein et al., 1983; Moore & Lenn, 1972; Pickard & Silverman, 1981). The hypothalamus is a complex neural region that controls many basic functions of the body including hormonal secretion, core temperature, metabolism and reproduction as well as higher neural functions such as memory and emotion (Morgane & Panksepp, 1979). A pair of specific hypothalamic nuclei, the suprachiasmatic nuclei (SCN), are the principal termination of the RHT (Klein et al., 1991; Moore & Lenn, 1972; Pickard & Silverman, 1981). These bilateral nuclei are considered to be fundamental parts of the "biological clock", or circadian system, which regulates the body's physiological rhythms (Aschoff, 1981). Advances in genetics have begun to unravel the circadian clock mechanism in the SCN at the molecular level (Devlin & Kay, 2001; Reppert & Weaver, 2001).

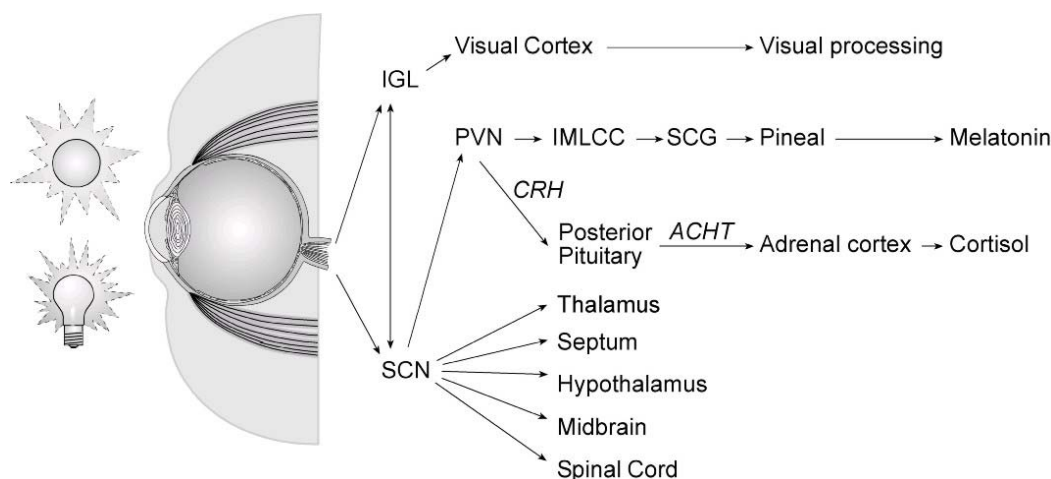


Figure 3. Schematic diagram of eye-brain pathways. Light received by the eye is converted to neural signals that pass via the optic nerve to two pathways, one visual and one non-visual. RHT = Retino-hypothalamic tract. IGL = Intergeniculate leaflet. SCN = Suprachiasmatic nucleus of the hypothalamus. PVN = Paraventricular nucleus of the hypothalamus. IMLCC = Intermediolateral cell column. SCG = Superior cervical ganglion. CRH = Corticotrophic releasing hormone. ACTH = adrenocorticotrophic hormone.

The SCN relay photic and non-photoc information to various control centres in the nervous system including other hypothalamic nuclei, the septal nuclei, the thalamus, the midbrain and the spinal cord (Klein et al., 1991). These systems regulate the production of almost all hormones, including cortisol, thyroid-stimulating hormone, and melatonin (which have large-amplitude circadian rhythms), and insulin, growth hormone, prolactin and luteinizing hormone (which have smaller-amplitude daily rhythms, some of which differ between men and women) (Czeisler & Klerman, 1999; Wehr, 1998). Thus, light exposure influences a wide variety of physiological functions, in relationships that are not entirely well-understood as yet but that are under active investigation (Buijs, Hermes & Kalsbeek, 1998; Morin, 1999; Partonen, 2000).

The neural pathway responsible for vision is anatomically separate from the pathway responsible for circadian regulation. There is, however, a functional connection between the primary visual pathway and the circadian neuroanatomy by way of the intergeniculate leaflets (IGL) (Horvath, 1998; Morin, 1994). Although the retinohypothalamic tract has its densest projection in or around the suprachiasmatic nuclei, this pathway has diffuse projections to other hypothalamic nuclei (preoptic nuclei, anterior and lateral hypothalamic areas, retrochiasmatic area and dorsal nuclei) as well as nuclei outside the hypothalamus (thalamic IGL, midbrain periaqueductal grey) (Card, 1994; Klein et al., 1991). The functional roles of these and other nonvisual projections from the retina are under active investigation.

2.2.2 Light and circadian rhythms

Numerous studies on biological responses of humans to bright artificial light have confirmed that light entering the eyes is a potent stimulus for controlling circadian rhythms (Brainard et al., 1988; Czeisler et al., 1986; Czeisler et al., 1990; Lam, 1998; Lewy et al., 1987; Minors, Waterhouse & Wirz-Justice, 1991; Shanahan & Czeisler, 1991; Wetterberg, 1993; Wurtman et al., 1985). The effect of light exposure differs depending on the timing in relation to the endogenous circadian phase (Czeisler et al., 1986; Czeisler et al., 1989; Jewett, Kronauer & Czeisler, 1994; Jewett et al., 1997; Minors et al., 1991; Shanahan & Czeisler, 1991). Light exposure after the nadir of the body temperature cycle (i.e., in the morning) advances the phase of the body temperature cycle and the melatonin rhythm (so that the new cycles peak earlier); light exposure in the evening delays both the body temperature and melatonin cycles (so that these cycles peak later than they would have) (Czeisler & Klerman, 1999). Light exposure close to the core body temperature minimum may also directly suppress circadian amplitude (Jewett et al., 1994).

The general principles of phase-shifting are well accepted, but the molecular mechanism underlying this physiology is under intensive investigation (Czeisler & Klerman,

1999; Lakin-Thomas, 1997; Menaker, 1997; Reppert & Weaver, 2001). Much of our knowledge about light input to the circadian system comes from studies of acute melatonin suppression during night-time exposures, which are discussed below.

2.3 Melatonin

2.3.1 Melatonin circadian rhythms

In all vertebrate species studied to date, including humans, high levels of melatonin are secreted during the dark phase of the photoperiod (night) and low levels are secreted during the light phase (day) (Aschoff, 1981; Wetterberg, 1993; Wurtman et al., 1985). Melatonin is synthesised from tryptophan, an amino acid, in a series of four enzymatic steps that include the neurotransmitter serotonin as an intermediate step (Wiechmann, 1986). The activity of the rate-limiting enzyme in the chain is higher at night than during the day, in response to neural information about external light stimulation (Klein et al., 1997). The activity of the enzymes at each step varies depending on the state of the circadian clock mechanism (Gillette & Tischkau, 1999). Thus, the system regulates rhythmic activity both by directly relaying information about the state of external stimulation and by circadian changes in sensitivity to incoming external signals.

Melatonin's main role is to reflect environmental photoperiod via its secretion profile and can be considered a humoral signal of darkness. This function of melatonin persists regardless of whether the species are diurnal or nocturnal, making inferences for a direct physiological role of melatonin difficult. Endogenous melatonin may help to modulate circadian rhythmicity through feedback mechanisms via melatonin receptors on the SCN. It has been proposed to influence sleep-wake timing and thermoregulation based mainly on extrapolation from studies of exogenous melatonin administration, although there is little direct evidence for an endogenous role in circadian regulation (Arendt, 1998b; Arendt et al., 1999; Czeisler, 1997; Korf, Schomerus & Stehle, 1998). Melatonin also synchronizes the responses of fetus and mother to environmental conditions (Menaker, 1997). Its most well-defined physiological role is the control of seasonal reproduction in some species, in which the critical photoperiods controlling reproductive development and function are signalled humorally through the melatonin profile (Arendt, 1998b; Menaker, 1997; Wehr, 1991). Pinealectomy abolished such responses.

Melatonin is present in the gastrointestinal tract (Huether, 1993), retina (Gern & Ralph, 1979), ciliary body of the eye (Martin et al., 1992) and in the aqueous humour which bathes the iris of the eye (Abramson et al., 1993; Martin et al., 1992). However, the principal source of circulating melatonin is its secretion by the pineal gland (Arendt, 1998b). As shown in Figure 3, one well-defined neural pathway that carries non-visual information about light extends from the SCN to the pineal gland via a multisynaptic pathway with connections being made sequentially in the paraventricular hypothalamus, the upper thoracic intermediolateral cell column, and the superior cervical ganglion (Card, 1994; Klein et al., 1991; Klein et al., 1983; Moore & Lenn, 1972; Pickard & Silverman, 1981). By way of this neuroanatomy, cycles of light and darkness which are perceived through the eyes entrain SCN neural activity which, in turn, entrains the rhythmic production and secretion of melatonin from the pineal gland. Confirmation of this pathway in humans has been demonstrated in para- and tetraplegic patients (Zeitzer, Ayas, Shea et al., 2000).

2.3.2 Acute light suppression

Light can have an acute suppressive effect on high levels of melatonin during the night. This acute light-induced suppression of nocturnal melatonin synthesis was first observed in rats (Klein & Weller, 1972) and has been used in numerous animal studies to help determine the neural and biochemical mechanisms of melatonin regulation (Brainard et al., 1994; Brainard, Rollag & Hanifin, 1997; Bronstein et al., 1987; Nelson & Takahashi, 1991). In 1980, it was demonstrated that exposure of the eyes of normal human volunteers to 2500 lux of white light during the night induced a strong decrease in circulating melatonin within one hour. In contrast, volunteers exposed to 500 lux of white light appeared to exhibit no significant melatonin suppression (Lewy et al., 1980).

Early attempts to suppress melatonin in humans failed when investigators used typical indoor light levels reported to be between 100 and 800 lux (Jimerson et al., 1977; Lynch et al., 1978; Vaughan et al., 1976; Wetterberg, 1978). At first, it appeared to take much more light to suppress melatonin in humans than is required for human vision. However, on closer examination, these findings were the result of poor experimental controls (discussed below). Further evidence for differences between the sensitivities of the circadian and visual systems was shown in the demonstration of acute melatonin suppression in three totally blind patients (Czeisler et al., 1995). At its extreme, under experimental conditions, dose-dependent melatonin suppression and phase shifts in humans has been observed at much lower illuminance levels (Boivin et al., 1996; Brainard et al., 1988; Wright et al., 2001). In one study, a single exposure to a simulated dawn signal (from 0,01 lx to 1000 lx over 90 min in the early morning) resulted in a small shift of circadian rhythm, as marked by the timing of dim light melatonin secretion the following night (Danilenko et al., 2000).

Zeitzer, Dijk, Kronauer, Brown and Czeisler (2000) found a non-linear relationship in which response to a single 6,5-hr episode of 100 lx in the early biological night resulted in 50% of the maximal response compared to 9000 lx, both in terms of circadian phase shifting and melatonin secretion. It now appears that the circadian system is very sensitive to light exposure. However, the same study found that melatonin secretion and melatonin circadian phase-shifting responses do not show identical responses to interior light. Melatonin suppression saturated (90% of maximal response) at 200 lx; melatonin circadian phase shifting saturated at 550 lx. Thus, even modest changes in interior light exposures might have profound influences on circadian regulation and melatonin secretion, and light as dim as candle light may be adequate to maintain entrainment to 24 hours in combination with weak non-photoc time cues (Wright et al., 2001). However, there remains much to be learned about the effects of timing of exposure and the contrast of light exposure against background light.

Melatonin's influence on sleep is complex (Arendt et al., 1999). The best sleep occurs when core body temperature is dropping and melatonin production is rising (Arendt, 1998a); propensity for sleep (the "sleep gate") has been associated with onset of melatonin production. Blind individuals with free-running circadian rhythms (Lockley, Skene, Arendt et al., 1997) note the greatest sleep propensity around the peak of melatonin secretion and the trough of core body temperature (Arendt et al., 1999; Lockley et al., 1999; Lockley, Skene, Tabandeh et al., 1997; Sack et al., 1992). However, melatonin alone does not control sleep; it is possible to sleep out of phase with melatonin secretion, and whether or not one experiences sleepiness following a dose of exogenous melatonin depends on posture and activity (Arendt et al., 1999) and environmental lighting (Roberts, 2001).

Conversely, suppression of night-time melatonin secretion by bright light exposure is coincident with increased self-reported alertness and increased cortical arousal [as assessed by electroencephalograph (EEG) readings] (Badia et al., 1991; Cajochen et al., 1998; Cajochen et al., 2000; Daurat et al., 1993; French, Hannon & Brainard, 1990), although a causal relation has not been established. Cajochen et al. (2000) found that these effects followed the expected logarithmic dose-response curve. Two experiments found that bright light at night suppressed melatonin but did not influence concurrent self-reported sleepiness (Dollins et al., 1993; Leproult et al., 1997). Methodological differences might explain the null findings: In the case of Leproult et al. (1997), the onset times for light exposure varied, which one would expect to add to the variability in sleepiness scores immediately following the exposure, whereas the initial sleep-wake states of the participants in Dollins et al. (1993) appear not to have been controlled. In both cases the sensitivity of self-report measures of sleepiness would be reduced. (The effects of behavioural consequences not directly linked to melatonin are discussed below.)

2.3.3 Health and melatonin cycles

Wehr (1991; 1997; 1998; Wehr et al., 1995) published data suggesting that urban environments offer biological darkness by day (in interiors with relatively low illuminances) and unnatural brightness by night (electric lighting extending apparent day length, producing apparently constant day length over the seasons), with unknown health consequences. One consequence of the apparently longer day is a decrease in the total melatonin release because of melatonin suppression during light exposure. Another possibility is that daytime light exposures (which are relatively low) might influence subsequent melatonin release, as

was observed in the laboratory by Wehr (1991). Total melatonin production is unknown for any population, but the possibility of systematic reductions, in quantity or cyclic amplitude, concerns some scientists.

For example, studies show that physiological nocturnal levels of melatonin inhibit MCF-7 human breast cancer growth *in vitro* by suppressing the estrogen response pathway (Hill & Blask, 1988; Hill et al., 1992; Molis, Walters & Hill, 1993). There is also *in vitro* evidence that physiological nocturnal melatonin concentrations inhibit the growth of melanoma cells through mechanisms that remain uncertain (Hu, McCormick & Roberts, 1998; Roberts, Wiechmann & Hu, 2000), raising the possibility that reduced melatonin levels in Western societies could contribute to both breast and skin cancer development.

Evidence is mounting that melatonin suppression might increase cancer risk, and in particular, breast cancer (Hansen, 2001; Stevens, Wilson & Anderson, 1997). The causal chain in this hypothesis is light exposure at night and the consequent suppression of melatonin. Among the indicators cited in the development of this hypothesis is the observation that breast cancer incidence is highest in developed countries, where electric lighting is ubiquitous (Brainard, Kavet & Kheifets, 1999). Breast cancer is associated with high estrogen levels. Although the nocturnal melatonin signal inhibits estrogen production in certain seasonally-breeding species, there is no evidence linking nocturnal melatonin levels with a suppression of estrogen production in humans (Reiter, 1998). Furthermore, no acute changes in circulating estrogen levels are associated with light-induced suppression of nocturnal melatonin in healthy women at any menstrual cycle stage (Graham et al., 2001). However, nocturnal melatonin concentrations block the ability of estrogen to stimulate the growth of MCF-7 human breast cancer cells *in vitro* (Hill et al., 1992). Dim light (0,25 lx) at night suppressed melatonin release by the pineal gland and increased tumour growth in a strain of rats with transplanted liver tumours (Dauchy et al., 1999; Dauchy et al., 1997). Removing the pineal gland also stimulated tumour growth (Blask et al., 1999). In addition, three epidemiological studies with differing methodologies have observed increased breast cancer risk among women who work at night or who have other light exposure at night (Davis, Mirick & Stevens, 2001; Hansen, 2001; Schernhammer et al., 2001), although these investigations could not entirely exclude other possible risk factors (e.g., sleep disruption, diet, other toxic exposures). Despite this logical evidentiary sequence, much remains unknown, particularly as regards the intensity, spectrum and timing of light exposures that might lead to a higher incidence of breast and other cancers in humans.

2.4 Cortisol

Cortisol is secreted principally by the cortex of the adrenal gland, at the end of a sequence of neurohormonal events. A current model for its circadian regulation holds that the SCN signals to cells in the paraventricular nucleus (PVN) of the hypothalamus to secrete corticotrophic releasing hormone, which in turn stimulates the posterior pituitary to release adrenocorticotrophic releasing hormone, which acts on the adrenal cortex to secrete cortisol (Buijs et al., 1998). Cortisol secretion shows a marked circadian pattern, peaking close to habitual waketime (~08h00) and reaching its trough close to habitual bedtime (~midnight) (Figure 2), superimposed on a distinct pulsatile (ultradian) profile. The amplitude of this rhythm might differ in people who report morning versus evening chronotypes ("larks" versus "owls") (Bailey & Heitkemper, 2001), and for people with some mental disorders (American Psychiatric Association, 1994). However, cortisol is also secreted in pulses over the day, and acutely in response to strong external stimulation (Baum & Grunberg, 1997). Cortisol's principal functions are to regulate glucose production from protein and to facilitate fat metabolism (Baum & Grunberg, 1997). Thus, its secretion in response to stressful events helps to release the energy needed to respond to threat. Its daily rhythm corresponds to the usual patterns of daily activity in humans.

Because of its association to sleep-wake cycles and activity, and strong circadian rhythmicity, cortisol has been a target of photobiologists interested in determining which circadian rhythms respond to light. Two studies have found that morning light exposure can influence cortisol secretion, whereas evening light has no effect on cortisol levels (Lemmer et al., 1994; Scheer & Buijs, 1999). Lemmer et al. (1994) found that six days of bright light exposure in the morning, before the daily cortisol peak, advanced the phase of the cortisol rhythm, whereas six days of bright light exposure in the evening, before the daily cortisol

nadir, had no effect on cortisol circadian rhythms. Scheer and Buijs (1999) found an acute increase in salivary cortisol following morning light exposure, but no acute effect following evening light exposure.

2.5 Other biological functions

Many biological functions show circadian rhythms and are the targets of photobiological research, although melatonin, core body temperature, and (to a lesser extent) cortisol dominate research efforts at present, as they are considered to be the strongest endogenous outputs or markers of the circadian system. Control of the circadian rhythm of heart rate is among the other functions actively under investigation. There exists a circadian rhythm for heart rate independent of sleep, in which heart rate peaks around midday and is lowest around midnight (Scheer, van Doornen & Buijs, 1999), with an amplitude of approximately 6,5 beats per minute. Heart rate increased in a dose-dependent manner in response to acute bright light exposure during the night and early morning, but not during the day. This pattern of results suggests that one pathway for influencing heart rate is via the nonvisual receptor pathway and the SCN.

Reproductive hormones such as prolactin and luteinizing hormone also show circadian rhythms (Waldstreicher et al., 1996; Wehr, 1998). Studies of these hormones' circadian patterns have been complicated by the strong influence of sleep on their secretion (Czeisler & Klerman, 1999) and by the fact that these hormones differ in level and secretion pattern between the sexes. The seasonal patterns that have been observed in these hormones are believed to be responses to changes in day length; both men and women respond to changes in apparent day length with changes in both the amplitude and pattern of hormone production (Wehr, 1998).

A complete catalogue of all known SCN-controlled circadian rhythms is beyond the scope of this report. The inter-relationships between hormones and neurotransmitters, and their circadian, infradian, and circannual rhythms, are likely to be the target of future reports as our knowledge increases.

2.6 Photoimmune responses

Among the physiological processes that the pineal gland mediates, immune response has attracted attention because of its obvious relation to disease processes. However, these mechanisms are poorly understood as yet, and there is recognition that the neurohormonal mechanisms involved are complex and interactive (Brainard, Hanifin, Barker et al., 2001; Maestroni, 1999; Maestroni, 1993; Roberts, 1995; Roberts, 2000). The operation of the immune system shows its own circadian rhythms (Levi et al., 1991), with parameters relating to fighting the initial exposure to a pathogen being more active when the organism is active (i.e., during the day for diurnal animals, and nocturnally for animals active at night), and more energetic infection-fighting mechanisms being more active when the animal is at rest (Plytycz & Seljelid, 1997). Circannual rhythms of immunity are also known; for instance, seasonal changes in immune function might be a marker for Seasonal Affective Disorder (Avissar et al., 1999). As our knowledge of these rhythms expands, it might become possible to optimise the effectiveness of drug administration and medical treatment by linking it to circadian or circannual phase states, although at present such protocols are in their infancy.

Melatonin, produced by the pineal gland, influences the activity of several components of the immune system (Cardinali et al., 1999; Maestroni, 1993; Molinero et al., 2000; Park & Tokura, 1999). For example, following exposure to 5000 lx of white light during the day, night-time melatonin secretion increased in comparison to secretion levels following 200 lx during the day (the bright light exposure, in effect, increased the amplitude of the circadian rhythm) (Park & Tokura, 1999). During the daytime hours, secretion of salivary immunoglobulin A, an antibody, increased in bright light in comparison to dim. The overall melatonin secretion correlated highly with the overall salivary immunoglobulin A secretion. Circadian rhythms, apparently mediated by melatonin, were observed to influence blood concentrations of some cytokines, which are chemicals released by immune cells that regulate immune cell interactions (Lissoni et al., 1998). Melatonin activity on the thymus gland also appears to contribute to the regulation of immune functions (Molinero et al., 2000).

One challenge to this area of research is the separation between correlation and causation. Current knowledge offers few certainties but this: Researchers working in this realm will continue to provide insight into this complex system for many years to come.

3. OCULAR ANATOMY AND PHYSIOLOGY

3.1 The visual system

Scientists have generally agreed that separate systems process light information for vision and light detection for co-ordinating physiological responses to environmental conditions (Devlin & Kay, 2001; Foster, 1998; Moore, Speh & Card, 1995). However, the two systems share a common anatomical starting point: the eye. The eye is a complex organ consisting of optical structures for admitting and focusing light onto the receptor tissue, the retina (Figure 4).

Detailed descriptions of the visual system are available from a lighting perspective in several sources [e.g., Illuminating Engineering Society of North America (IESNA), 2000]. Light falling on the retina is detected by two types of visual photoreceptors, rods and cones. Cones, which predominate at the centre of the retina (the fovea), are responsible for the detection of fine detail and colour vision. They are most sensitive at relatively high light levels. The overall spectral sensitivity of cones leads to the $V(\lambda)$ curve, established by the CIE as the photopic sensitivity function (Figure 5) (CIE, 1978). Rods are most numerous in the peripheral areas of the retina. They are less able to detect fine detail but are most active at low light levels. The rod spectral sensitivity function is known as $V'(\lambda)$, the scotopic sensitivity function (Figure 5) (CIE, 1978). Both types of photoreceptors contain photopigments that convert light energy to electrochemical signals. Photoreceptor cells provide input to bipolar and ganglion cells, which sum information from overlapping circular receptive fields before transmitting the information, through the optic nerve, to the visual cortex.

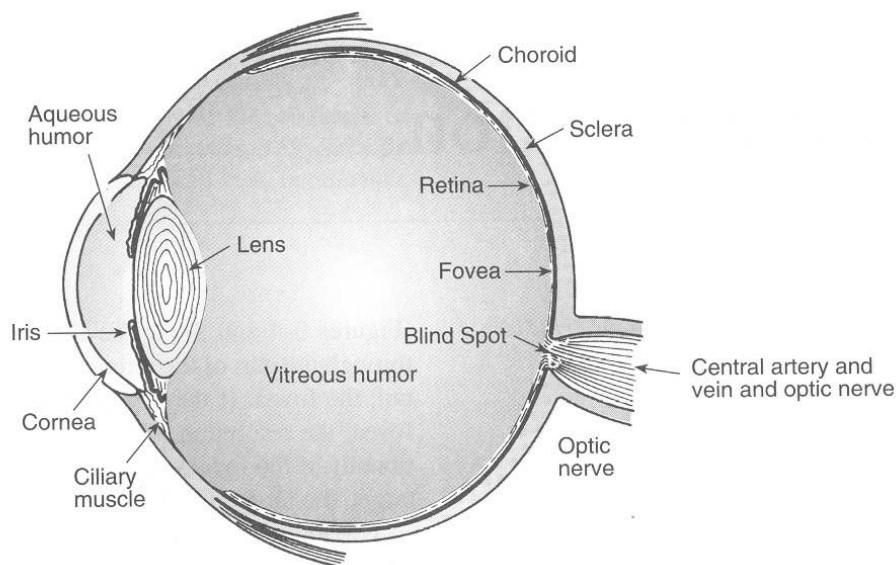


Figure 4. A section of the eye, showing major structures. Source: IESNA Lighting Handbook, 9th Edition, 2000, courtesy of the Illuminating Engineering Society of North America.

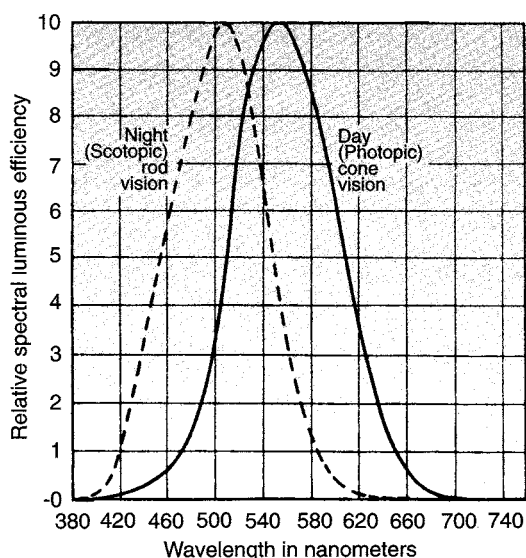


Figure 5. The photopic $V(\lambda)$ and scotopic $V'(\lambda)$ visual sensitivity functions. Source: IESNA Lighting Handbook, 9th Edition, 2000, courtesy of the Illuminating Engineering Society of North America.

3.2 Nonvisual photoperception

3.2.1 Location of nonvisual photoreceptors

There is considerable evidence from human and animal studies that the biological, behavioural and therapeutic effects of light apart from vision are mediated via a photoreceptive mechanism in the eye as opposed to a photoreceptive mechanism in the skin or some other part of the body (Aschoff, 1981; Binkley, 1990; Klein et al., 1991; Wehr et al., 1987; Wetterberg, 1993). Nonetheless, the possibility that mammals might also exhibit nonocular photodetection remains controversial. One study found that congenitally anophthalmic rats exhibited entrained circadian rhythms of pineal gland activity, which suggests a non-ocular mechanism of some kind (Jagota et al., 1999). Mole rats also show this ability (Pevet et al., 1984). In some humans with complete visual blindness, melatonin suppression can be induced by exposing the eyes to bright white light (Czeisler et al., 1995). In that study, blind subjects with loss of pupillary reflex, no conscious perception of the light stimuli, and no outer retinal functioning as determined by electroretinographic testing, still exhibited neuroendocrine sensitivity to light.

Campbell and Murphy (1998) elicited great interest with observations that light exposure to the popliteal region (behind the knee) caused circadian phase shifts. However, this finding has been challenged on methodological and theoretical grounds (Czeisler & Klerman, 1999; Foster, 1998), and has failed attempts at independent replication (Eastman, Martin & Hebert, 2000; Hebert, Martin & Eastman, 1999; Koorengevel et al., 2001; Lockley et al., 1998). In a comparison of blind subjects with some light perception, no light perception, or whose eyes had been removed altogether (Skene et al., 1999), the subjects without light perception had abnormal circadian rhythms compared to those who had some light perception, and those without eyes had free-running circadian rhythms for melatonin and cortisol. One hypothesis that can be ruled out is an influence of internal mental representations of light on circadian rhythms (Byrne et al., 2000).

3.2.2 Ocular photoreceptors

Data from animal and human studies raise the possibility that neither the rods nor the cones used for vision participate in regulating the circadian and neuroendocrine systems. For example, rats with total or near-total destruction of retinal photoreceptors due to prolonged constant light exposure still entrain their melatonin rhythms normally to the ambient light:dark cycle and exhibit acute light-induced suppression of nocturnal melatonin (Webb et al., 1985).