



Light Hygiene: Time to make preventive use of insights – old and new – into the nexus of the drug light, melatonin, clocks, chronodisruption and public health

Thomas C. Erren^{a,*}, Russel J. Reiter^b

^aInstitute and Policlinic for Occupational and Social Medicine, University of Cologne, Kerpener Strasse 62, 50937 Köln, Lindenthal, Germany

^bDepartment of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229-3900, USA

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SUMMARY

Light is, clearly, a key to life on Earth and light, equally clearly, determines biological rhythmicity in organisms. Light does the latter by setting internal or endogenous clocks which allow a multitude of species, including man, to adjust their lives to changing external or environmental conditions. Critical changes over time occur from day to night and throughout the year. In this paper, we sum up how visible light provides electromagnetic information about environmental “time” via the ocular interface of newly discovered photoreceptive cells to a master clock in our brain, viz the suprachiasmatic nuclei [SCN], and how the SCN translate this input, with melatonin as a key biologic intermediary, into endogenous or biological time. We summarize experimental and epidemiological evidence suggesting how chronodisruption, a relevant disturbance of the temporal organization or order of physiology, endocrinology, metabolism and behaviour, is probably detrimental for human beings. On the basis of our synthesis, and in line with suggestions by other researchers voiced decades ago, light must, functionally, be considered as a drug equivalent. In this vein, the very timing, quality (wavelength), quantity (dose) and side effects, including chronodisruption, of light exposures can be critically important for health and disease in man. As a promising means to foster public health, we advocate an appropriate balance of exposures to the key *Zeitgeber* light in terms of “light hygiene”, implying strong and appropriate rather than weak and confusing temporal information. This focus on “light hygiene”, and thus on the key *Zeitgeber* light, does not mean to ignore that there are multiple entrainment pathways for our circadian clocks. Indeed, when dealing with light, chronodisruption and a multitude of adverse health effects, we ultimately need to consider *Zeitgeber* cues, and their possible interplay, beyond light alone. Confusions of the temporal programmes in humans can also stem from physical and social activities, stress and facets of food intake. And yet, since light possesses a rather unique and exclusive *Zeitgeber* role and in view of its ubiquitous nature, a specific, preventative focus on “light hygiene”, as a contribution to a general “*Zeitgeber* hygiene”, is warranted.

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Time to appreciate light as a drug to foster public health

Suppose we were to discover a new drug, treatment or therapy. Suppose also that we could be certain that the drug could mitigate and relieve a wide variety of chronic processes, including cancer, ageing, sleep disorders, depression, and a range of other conditions. Suppose finally, that the drug would be available at no or at a trivial cost when compared with most other public health interventions: would we rush to introduce such an ameliorative drug, treatment or therapy into medicine, would public health officials be interested to promote its use, would physicians be keen to work with it? The answer to all these questions is a surprising “no”. For, potentially, we have such a functional drug, treatment or therapy

at hand now, but it appears to be frequently abused rather than appropriately used by many who could benefit from it [1].¹

A drug, according to the FDA, “is defined as a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease”. Moreover, “a drug is defined as a substance (other than food) intended to affect the structure or any function of the body”. In terms of cause-and-effect relationships, we work here with the term exposure, rather than substance, when talking about drug or drug equivalent. With these premises, a causal exposure which is intended for use in treating or preventing disease and powerfully affects functions of our body should certainly qualify for a drug or drug equivalent.

¹ This paragraph follows David Horrobin, 2003. Nutrition Discussion Forum. Why do we not make more medical use of nutritional knowledge? How an inadvertent alliance between reductionist scientists, holistic dietitians and drug-oriented regulators and governments has blocked progress. *British Journal of Nutrition* (2003), 90, 233–238.

* Corresponding author. Tel.: +49 221 4784450; fax: +49 221 4785119.
E-mail address: tim.erren@uni-koeln.de (T.C. Erren).

Hygiene, deriving from the ancient Greek goddess of healthful living, named Hygeia, can be considered, in medical contexts, as the science of health and how to preserve it. More generally, hygiene denotes conditions or practices which promote health for the individual and the community and prevent disease. More specifically, if anyone thinks about hygiene, this approach to foster public health is hitherto considered to comprise, for instance, personal hygiene (cleanliness, food, clothing, exercise, sexual behaviour), public hygiene (control of water and air quality) and industrial hygiene (control of accidents and diseases at the workplace).

As we will develop now, the promising drug or treatment to which we referred in our first paragraph is visible “light”, both from natural and from anthropogenic sources. And, as we shall demonstrate, the evidence of light’s value for public health when considering crucial aspects of light hygiene is considerable. Indeed, we seem to be approaching a golden age of “light research”, when many aspects of the nexus between light exposures, ocular photoreception, phototransduction and circadian biology have been or are indeed likely to be identified in a nearer future. But, as with almost any other drug, there can be severe “side effects” of light exposures. Indeed, if we ignore principles of light hygiene, such as the appropriate timing and dosing of light, this can lead to chronodisruption [2], “a critical loss of time order, i.e., a disorder or chaos of an otherwise physiological timing at different organizational levels, including the gene expression levels in individual cells” [3]. Importantly, as a relevant disturbance of the temporal organization or order of physiology, endocrinology, metabolism and behaviour, chronodisruption can possibly lead to severe chronic processes, including premature ageing and cancers [4,5].

Light, melatonin, clocks and rhythms

The cyclic production of melatonin in and its release from the pineal gland, with elevated levels of both parameters at night, have been used to gauge the activity of the master biological clock, the suprachiasmatic nuclei [SCN], for decades. Moreover, it has been tacitly assumed that molecular alterations induced by light energy within photoreceptive retinal rods and cones were essential for the synchronization of circadian rhythms at the level of the SCN.

Knowledge related to the detection of light which subserves the regulation of circadian rhythmicity, however, has undergone a revolution within the last decade with the discovery of a new photoreceptive cell and a novel photopigment in the retina. Years earlier it was noted that albino rats with extensive destruction of their retinal rods and cones still responded to even low light exposures at night with melatonin suppression [6]. Subsequently, Czeisler et al. [7] reported that similarly in profoundly blind humans, light exposure also suppressed high circulating melatonin concentrations. The results of this animal and human study suggested that some cell other than the classic retinal photoreceptors mediated the disruptive effects of visible electromagnetic radiation on circadian rhythmicity and, consequently, on circulating melatonin concentrations.

Intensive research by many excellent scientists within the last decade has now clarified some of the remarkable processes whereby phototransduced photic energy alters circadian rhythmicity [8,9]. These changes involve an opsin/vitamin A-based photopigment, melanopsin, which is present in a small subset (<2%) of intrinsically photoreceptive retinal ganglion cells (ipRGC) [10]. During light exposure, melanopsin transduces light energy into an electrical signal which is sent via the retinohypothalamic tract to the SCN in the basal anterior hypothalamus [11]. Besides the small number of ipRGC involved, it is also a selective set of wavelengths that reconfigure melanopsin and initiate the signal required to alter the function of the SCN and thereby disturb circadian rhythms and suppress melatonin production in the pineal

gland. Hence, it is specifically blue wavelengths of light (roughly in the range of 458–484 nm) that are most capable of disturbing the function of the master clock [12]. Sunlight and most artificial light sources possess these critical wavelengths and, as a result, when the brightness is adequate, man-made light exposure at night excites melanopsin in ipRGC which can lead to chronodisruption and melatonin suppression. Pineal melatonin synthesis and release is a result of light inhibition of the SCN which then interrupts the discharge of the neurotransmitter norepinephrine from postganglionic neurons which terminate on the melatonin-producing cells in the pineal gland, the pinealocytes [13].

The ocular interface between the external and internal environments involves ipRGC which project to the SCN. Via this pathway non-photosensitive internal organs are provided information about environmental time with the waxing and waning of the melatonin rhythm imparting information to the body regarding the prevailing light:dark status. With the advent of artificial light exposure after darkness onset, both the activity of the master clock and the melatonin-forming system are corrupted, possibly leading to chronodisruption and the pathophysiological consequences thereof.

Chronodisruption: experimental and epidemiological insights

Disturbances of biological rhythms and melatonin suppression have been at least provisionally linked to a variety of human maladies including sleep inefficiency [14], mood disorders [15] and cancer [16,17]. Within the last decade, especially the elevated risk of certain cancer types has piqued the interest of epidemiologists [2]. This has also led to more thorough tests on the relationship of chronodisruption and/or melatonin suppression to cancer cell biology in experimental animals.

Some of the most compelling findings related to chronodisruption and experimental cancer growth in animals are the studies of Filipinski et al. [18,19] who utilized repeated phase advances of the light:dark cycle to disturb the biological rhythms and undoubtedly the melatonin cycle as well (although this latter parameter was not actually evaluated) in mice bearing Glasgow osteosarcoma xenografts. In these studies, the light:dark cycle to which the mice were exposed was phase advanced by eight hours every two days. The locomotor activity of the mice as well and rhythms of clock gene expression in peripheral organs were severely disrupted in the animals exposed to this unconventional photoperiod. Moreover, the Glasgow osteosarcoma cells proliferated more rapidly and the tumors grew faster than those in mice kept under a stable light:dark cycle. These findings provide strong evidence that chronodisruption and/or melatonin suppression predisposes tumors to a more rapid growth rate. Whereas there are only a few studies on the role of chronodisruption and its effects on cancer cell proliferation in animals, the data from the two reports summarized above provide seemingly unequivocal data regarding the dangers of disturbing biological rhythmicity when cancer cells are present. In contrast to chronodisruption, melatonin has been widely tested for its ability to impact the initiation and progression of tumors [20,21]; in these cases, melatonin is always considered inhibitory.

Melatonin has been known as an endogenous oncostatic agent for more than three decades. Dozens of reports have documented the ability of both physiological and pharmacological levels of melatonin to curtail the growth of a wide variety of cancer cell types in both *in vitro* and *in vivo* studies [22,23]. That nocturnal human blood melatonin concentrations (roughly 1 nM) are sufficient to markedly restrain the growth of human MCF-7 breast cancer and rat hematoma cell growth in animals was recently shown by Blask and co-workers [16] who infused daytime and nighttime collected blood into rats bearing these tumors. Only the blood collected at night contained sufficiently high levels of melatonin (roughly four

times higher than daytime blood melatonin concentrations) to inhibit all parameters of tumor growth that were investigated. Importantly, when the blood donors were exposed to light at night, which reduced their circulating melatonin concentrations, blood samples were no longer capable of reducing tumor growth. These findings have direct application to the issue of chronodisruption, melatonin suppression and cancer risk in humans and are consistent with the idea that any perturbation that interferes with the nighttime rise in circulating melatonin levels compromises the cancer-fighting activity of humans.

In 2003, we suggested that cancer, but also ageing, can be considered as being both light- and rhythm-associated chronic processes [4]. Five years later, we proposed that epidemiological studies which explicitly or implicitly pursued the validity of the hypothesis that diminished function of the pineal gland may promote the development of breast cancer [24], of the so-called “melatonin-hypothesis” [25] or of associated corollaries should be conceptualized under “A generalized theory of carcinogenesis due to chronodisruption” [2]. Intriguingly, that light exposures, and melatonin as light’s antithesis [4], can be critical for the suspected, biologically-plausible links to cancer is compatible with an increasing number of epidemiological studies.

When four epidemiologic investigations examined breast cancer incidence in blind individuals [26–29], these studies pursued the rationale that a presumed lack of light reception would critically affect the melatonin-axis. Indeed, suspected “uninhibited”, abundant melatonin levels could be one explanation for an observed pattern of cancer deficits in the blind (in one study, cancer risks actually tended to be increased; [28]). Mechanistically, the suggested protection against malignant neoplasms may be attributed to the excess melatonin’s effects on one or more of the hallmarks of cancer [30–32]. However, there are considerations that complicate interpretation of the observational studies. In fact, quite a few “blind” individuals do have a free-running cycle which in itself could be associated with some chronodisruption and might pose some risk. That a subset of blind people is in fact entrained to the rhythmic change from light to darkness during day and night [7] can actually be explained today by the aforementioned new(ly discovered) melanopsin-based photoreception system. Thus, there may be individuals who are visually blind but not in a chronobiological sense, i.e., they may still possess circadian vision [9]. In any case, while it appears likely that light plays a role in cancer risks of blind persons it is not yet evident what the magnitude, let alone what the direction is in individual cases. Some blind persons may have abundant melatonin, i.e., uninhibited by light, but there may be a trade-off with some chronodisruption because their free-running cycles would favour “25-h-rhythmicity” in 24-h societies.

With regard to differential ambient light exposures depending on latitude it was proposed that winter darkness in the Arctic should increase residents’ melatonin levels and this was indeed supported by a series of small and scattered investigations [33,34; an overview of 9 empirical studies in Arctic residents in 35]. In addition, it was predicted that hormone-dependent cancers should therefore occur less frequently in people living north rather than south of the Arctic Circle [34,36]. While this rationale was supported by epidemiological data, it was emphasized that the ecologic nature of the observations severely limited both the scope and the methodological weight of the investigation. Importantly, the prediction was extended in 2001 [37] when it was proposed that melatonin levels and rhythms should vary between people who are differentially exposed to light by virtue of variations in ambient photoperiods. So far, this “light dosimetry by geography” approach has not been systematically pursued. And yet, the proposed research for a biomarker study of healthy general populations in a wide range of latitudes would be “...essential research that will characterize light exposures, melatonin cycles, and circadian rhythms from the Arctic

to the Mediterranean, in a systematic and comprehensive way, to supplement what now exists primarily as a scattered set of small studies and isolated reports. It will not answer any questions about cancer and light, but solid research to answer those questions will not be able to be designed sensibly without the information this crucial baseline study will produce” [38]. Recently, it was again emphasized that polar regions with their extreme light conditions offer promising leads for research into light- and rhythm-associated diseases, including cancers and seasonal affective disorders (SAD) [36].

Epidemiological studies of shift-workers, and their results of increased risks of breast and prostate cancers [2], colorectal [39] and of endometrial cancers [40], could all be “explained” by exposures to artificial light at unusual times which provide the light-dependent central circadian pacemaker, aggravated additionally by unconventionally timed Zeitgeber cues via food intake [41,42] and activities at unusual times, with inappropriate and confusing entrainment information. Once again, this certainly leads to melatonin disturbances and chronodisruption.

Flight-personnel experience additional chronodisruption insofar as they can be exposed both to shift-work plus extended transmeridian, i.e., time-zone-travel. There is no doubt that the regular and important photoperiodic synchronization of biological rhythms, viz by light exposures at regular, anticipatable times, is very significantly disrupted in flight-personnel. While future studies must investigate whether chronodisruption and/or other factors are critical, observations to-date show what seem to be unequivocally increased prostate and breast cancer risks by some 40–70 per cent in male and female flight personnel, respectively [2].

That sleep – both length and quality – could be a factor in cancer development can also be expected [35]. Indeed, a light-deprived sleep – empirically it takes some 2000 lux to affect the melatonin-axis when eyelids are closed [43,44] – should not only allow melatonin production and secretion to occur but also constitutes in itself the chronobiological equivalent of rest, recovery and a host of repair processes which have a cyclic nature. Recent examples include the fact that nucleotide excision repair activity in the mouse cortex is highest during their biological nights and is at its lowest during their biological days [45]. In a similar vein, exogenous melatonin administration preliminarily has been shown to hasten DNA repair in cultured peripheral blood lymphocytes [46].

Epidemiological evidence regarding possible associations between the very length of sleep and cancer risks are still very scarce and, in part, equivocal but, overall, lend some support to the notion that long sleepers might have lower breast cancer risks [47–52].

Finally, please note that all epidemiological predictions investigated so far are certainly – albeit to a varying degree – simplifications of the complex light and timing issues described in experimental detail and context above. But note also that the observation of increased cancer risks in crude epidemiological studies implies that the real effects of light exposures could be very strong [53]. In particular, because light is an ubiquitous exposure and because hitherto we do not know alternative risk factors which explain the high incidence of epidemic cancer like the ones of the breast and the prostate. Under these premises, from a public health point of view, light exposures at inappropriate times could be an important cause of breast and prostate cancer because the ubiquitous nature of visible radiation implies the possibility that even small risk elevations could lead to many cases and contribute to a substantial proportion of the total population burden.

Light is a functional drug

The key role of light as a functional drug was acknowledged decades ago. Intriguingly, as in other instances, core science elucidated in the course of meticulous work what conventional

wisdom knew all along, viz light powerfully affects species, including man, during day and night and from season to season. In an early synthesis 22 years ago, Wirz-Justice [54] summarized some of the complex issues under 'light and dark as a "drug"'.

The qualification of light as a drug seems imperative for several reasons: because it is, functionally, one and because this very labeling could bring about the necessary awareness for both its beneficial working but also for its possible detrimental side effects. Indeed, the qualification "drug" and the postulate to pay attention to and foster light hygiene should, at the very least, make everyone aware of – and thus be prepared for – the power or force of light.

Importantly, such awareness should lead to require – as is true for any potent drug – the realization that dose and timing should be understood and regulations as to its proper use developed and followed appropriately. This could be a means to two ends: to allow light's benefits on the one hand and to disallow its adverse side effects, including those that lie on chains of causation which may lead to cancer and premature ageing, on the other.

Novel endpoints are on the chronobiological radar, no longer classical candidates like seasonal affective disorder, depression and sleep disturbances alone but cancers and ageing processes as well. Importantly, while caution in the extrapolation [55] between species and between laboratory and field conditions is certainly warranted, the abundance of experimental insights and epidemiological suggestions justifies, in our view, precautionary steps and, indeed, prudent avoidance of light at unusual times in order to achieve a reduction in chronodisruption.

Light hygiene

Relationships between light exposures and some diseases, including SAD, depression and sleep disturbances are not new. In fact, for decades physicians and researchers have tested respective propositions and rhythm hypotheses have been put forward, and were critically examined, as summarized by Wirz-Justice [54]. What can be considered novel beyond successful light therapy for some individuals affected by those diseases and disorders is the rationale to employ light to prevent rather than treat on the one hand and the growing understanding that there are intricate links between light and further rhythm-associated chronic processes on the other, including ageing and cancer developments.

To advocate a focus on "light hygiene" as an appropriate balance of exposures to the key Zeitgeber light does not mean to ignore the multiple entrainment pathways for our circadian clocks [56]. Indeed, when dealing with light, chronodisruption and a multitude of adverse health effects, we ultimately need to consider Zeitgeber cues, and their possible interplay, beyond light alone. Clearly, confusions of the temporal programmes in humans can also stem from physical and social activities, stress and facets of food intake – a long-suspected food-dependent circadian master clock appears to have been localized in the dorsomedial hypothalamus [42], although conclusive evidence remains elusive [57,58]. And yet, since light possesses a rather unique and exclusive Zeitgeber role and in view of its ubiquitous nature, a specific focus on "light hygiene", as a key contribution to a general "Zeitgeber hygiene", is certainly warranted.

What to do exactly, i.e., how to best pursue light hygiene, must be scrutinized in future research. Indeed, at this stage, there are many open questions. Just recall the different epidemiological angles referred to above which may all be important with regard to differential light exposures and will certainly occur in some combination (for instance, effects of shift-work, sleep, food and latitude may have to be considered together). To take the example of shift-work, which affects as many as 20 per cent of workers in developed countries, note some specific gaps of knowledge: For

instance, could there be ways to identify shift-workers' susceptibility to light exposures at unusual times and chronodisruption? Such insights may actually provide a basis to possibly disallow or dissuade "doomed" shift-work careers in the first place. However, a further complication to consider is the fact that shift-work tolerance changes – in many individuals – with age. Intriguingly, despite decades of abundant shift-work research worldwide, with regard to shift-regimes, it is not even unambiguously settled whether forward or backward rotation of shifts is less harmful in terms of chronodisruption [59]. Moreover, some researchers recommend fast forward rotating shifts with a maximum of 3 night shifts to rather avoid entrainment to an "unnatural" night rhythm. And yet, it may be better to adjust as fast as possible to a night rhythm in order to alleviate chronodisruption and its effects.

What certainly holds promise as a means to achieve light hygiene, implying strong and appropriate rather than weak and confusing information about environmental time, is to seek strong time cues in terms of "light showers", for instance during a walk outdoors at specific times of the day. Indeed, we know that the circadian system of many, if not the majority of individuals, benefits from unequivocal, strong time, i.e., light, cues. Recall that many of us work in offices with 500–1000 lux exposures while during Summer and in Winter days we can experience as much as 100,000 and 20,000 lux intensities outdoors, respectively. Other considerations include the development of light sources that are devoid of the critical wavelengths of light (458–484 nm) that alter circadian rhythms and lead to melatonin suppression. Alternatively, goggles or lenses which filter these critical wavelengths may be of value [4,5]. Overall, though, that blocking light exposures alone would decrease cancer occurrence caused by chronodisruption is an unlikely expectation in our view [56]. In any case, whatever the precise strategy, given the potentially serious and pervasive nature of the problem, it seems imperative to be imaginative when approaching the "light challenge".

Conclusions and perspectives

Overall, we feel that light hygiene concepts should be systematically investigated and applied to promote public health and to prevent disease. Indeed, provided that our synthesis of abundant experimental insights and epidemiological suggestions is appropriate, "light hygiene" could produce substantial health returns for minimal expenditure and action.

So let us be practical and give much more attention to aspects and prospects of light hygiene. In line with Sir Bradford Hill

"All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time" [60]

we may already have most of the knowledge required to produce or work on considerable improvements for public health.

In conclusion, the public should be informed and know that there are critical issues involving the drug light theme. Scientists should determine what quality and quantity of light and what timing of the latter "makes the poison" on the one hand and what can be considered beneficial, on the other.

Finally, if the development of cancer is in fact proven to be unequivocally linked to excessive or unconventional light exposure, then it seems likely that the problem is more serious than currently appreciated. Indeed, cancer is a manifestation of alterations in fundamental cellular metabolism. This being the case, then other diseases may likewise be more common in individuals who experience frequent chronodisruption and melatonin suppression.

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