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REVIEW

Thomas C. Erren · Russel J. Reiter · Claus Piekarski

Light, timing of biological rhythms, and chronodisruption in man

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Abstract This paper reviews abundant evidence suggesting that causes and course of aging and cancers can be considered as being both light- and rhythm-related. We define chronodisruption as a relevant disturbance of orderly biological rhythms over days and seasons and years in man. Light is the primary external mediator and melatonin a primary internal intermediary of such disturbances, which can result in earlier deaths via premature aging and cancers. We conclude that experimental and epidemiological research can provide further insights into common denominators of these chronic processes and may offer novel and uniform targets for prevention.

Light—a binary environmental "switch"

Light can be defined as "visually effective radiant energy for human beings" (Stevens and Rea 2001). Another—more comprehensive—definition of light could be "visually *and* chronobiologically effective radiant energy for human beings" because in man—and in many other species—both support of vision *and* regulation of biological rhythms are mediated via electromagnetic radiation in the range of 10^{14}–10^{15} Hz. To account for the observation that vision and biological rhythms depend on the same spectrum of radiation, the following conjecture seems straightforward: from an evolutionary point of view, nature often starts from manageable simplicity and, in this case, no elements of complication needed to be added; the presence of external light of appropriate wavelength and intensity enabled vision and actions and the absence of external light impeded actions and led to physiological rest which is reinforced by internal biological clocks. In essence, the exclusive use of one signal "L" alone, i.e., the presence and absence of "L", to allow vision and activity, on the one hand, and to disallow vision and enforce rest and sleep, on the other, constitutes a very effective binary environmental "switch."

T. C. Erren (✉) · C. Piekarski
Institute and Polyclinic for Occupational and Social Medicine,
School of Medicine and Dentistry, University of Cologne,
Joseph-Stelzmann-Strasse 9, 50924 Cologne, Germany
e-mail: tim.erren@uni-koeln.de
Tel.: +49-478-5819
Fax: +49-478-5119

R. J. Reiter
The University of Texas Health Science Center,
San Antonio, Texas, USA

Timing of biological rhythms

Technically, rhythms constitute regularly recurring and therefore—within limits—predictable components of a time series. Biologically, rhythms can be characterized as regularly recurring components in biological processes or orderly biological events as a function of time. But how do biological rhythms serve species—including man—in the first place? And, what provides the principal timing of biological rhythms? One answer to the first question is that orderly sequences and hierarchies of biological processes have obvious advantages to prepare physiology for demands which change over time. In evolutionary terms, "natural selection, or the survival of the fittest" (Darwin 1859) meant those that could be expected to survive because of adaptations to their physical conditions of life and functional efficiency when compared with others. In this vein, species which developed and maintained biological rhythms which prepared them for changing environmental conditions and economized physiology along resulting activity–rest and sleep–wake cycles had a competitive edge.

If we now consider what constituted relevant physical changes in nature we arrive at an answer to the second question as well: the Earth's rotation and the tilt of our planet cause significant changes in sunlight conditions which lead to day and night and cycles of spring, summer, fall, and winter. For the timing of biological rhythms it is crucial that these changes in the physical environment were not random but could be "predicted." In fact, with the use of light information for the principal timing of biological rhythms, species could anticipate the light-

related environmental challenges and very appropriately prepare physiology for the latter. Rhythms can, of course, also be generated by self-sustained oscillators ("biological clocks") in the absence of external information (e.g., at the gene level in individual cells). However, the principal timing of rhythmic activities of cells, organs, and organisms is provided through visible electromagnetic radiation. With regard to evolution, a rhythmic adaptation of physiology to the light-related environmental periodicity provided—at first a few members of and eventually whole—species with increased relative success in reproduction and a survival advantage.

Reception of light and environmental time

But how is the external light information conveyed within organisms and, ultimately, used to regulate biological processes? Environmental light influences circadian and seasonal rhythms in mammals, including man, via a nuclear complex in the anterior hypothalamus of the brain referred to as the suprachiasmatic nuclei (SCN); this nuclear group is widely accepted as providing the infrastructure for the biological clock or internal pacemaker ("master clock in the brain;" Reppert and Weaver 2002). The interface between visible radiation (i.e., light) and the biological clock are the retinas of the eyes. Interestingly, however, a series of studies indicates that it is not the classical rods and cones, which mediate vision, of the retina that detect the light which synchronizes the biological clock (Bellingham and Foster 2002). Rather, recently identified specialized retinal ganglion cells (Berson et al. 2002),which contain a unique opsin photopigment that has a peak sensitivity to 479 nm wavelength (Lucas et al. 2001)and which is operative in synchronizing the activity of the SCN. In our view, the extensive research to characterize the retinal sensory cell(s) responsible for non-image forming processes (Soni and Foster 1997; Soni et al. 1998; Provencio et al. 1998, 2000, 2002; Blackshaw and Snyder 1999; Freedman et al. 1999; Lucas et al. 1999, 2001, 2003; Brainard et al. 2001; Thapan et al. 2001; Hankins and Lucas 2002; Hattar et al. 2002; Berson et al. 2002; Ruby et al. 2002; Panda et al. 2002) is effectively a quest for *chronoreceptors* which initiate a cascade of temporal information transfer within mammals. This implies that the sense organ of the eye evolved both for the sense of sight and for the sense of biological time, or *chronosense*, which enables us to coordinate otherwise independent and less efficient biological rhythms (T.C. Erren et al., unpublished material). It can be expected that the receptors which primarily convey information about environmental time will be identified in the near future. This should also allow the characterization of the chemical nature of such pigment(s) sensitive to ambient light. Indeed, since 1997, a number of opsins [vertebrate ancient (VA) opsin (Soni and Foster 1997; Soni et al. 1998), encephalopsin (Blackshaw and Snyder 1999), and melanopsin (Provencio et al. 1998, 2000)] and cryptochrome (Miyamoto and Sancar 1998; Thresher et al. 1998) have been discussed as novel candidate photopigments. Lately, considerable focus has been placed on the key role of the retina's melanopsin (Provencio et al. 2000, 2002; Hattar et al. 2002; Berson et al. 2002) for the photoentrainment of mammalian systems over time (Ruby et al. 2002; Panda et al. 2002; Lucas et al. 2003).

Transduction of photic information into biological time

The photic information is transduced into a neural signal which projects, via the axons of the retinal ganglion cells, through the optic nerves to the SCN of the forebrain. The intrinsic neurons of the SCN are inherently rhythmic (Gillette and Tischkau 1999). Thus, when grown outside the body, neurons of the SCN exhibit alternating periods of quiescence and firing, with the duration of this quiescent/firing period usually being around 25 h, i.e., slightly longer than the 24-h light:dark cycle. Given that the intrinsic neurons do not have a period of 24 h, one function of the prevailing light:dark period is to synchronize the biological clock to 24 h via the pathways described above. The function of this aspect of the photoperiodic environment is apparent in a majority of humans who are profoundly blind (with no light perception). In these individuals the biological clock, in the absence of information regarding the prevailing light:dark cycle, runs with a period different from 24 h, i.e., it free runs. Thus, the bodily functions of these individuals are on about a 24.5-h rather than a 24-h cycle (Sack et al. 1992; Lockley et al. 1997)and they are described as not being synchronized with the photoperiodic environment, i.e., they are out of sync (Skene et al. 1999).

In sighted individuals—and also in some blind people with no conscious perception of light (Czeisler et al. 1995; Lockley et al. 1997; Klerman et al. 2002)—the 24-h light/dark cycle imposes a 24-h rhythm on the SCN. Light does this by inhibiting the firing of the neurons in the biological clock (Gillette and Tischkau 1999). Thus, during the day the neurons of the SCN are in a relatively quiescent state. Conversely, in the absence of light at night, the SCN neurons fire more-or-less freely. These alternating periods of reduced and elevated neuronal activity in the internal pacemaker, i.e., the SCN, eventually impart circadian information to the body as a whole, resulting in the synchronization of a variety of bodily functions to 24 h, e.g., the sleep/wake rhythm.

How the SCN notifies such a variety of systems of its rhythmic instructions has not yet been clarified. Obviously, there are neurons in the SCN whose axons project to many other nuclear groups in the brain which impose on them timing information. Specifically, however, how this information is transferred (what neurotransmitters, etc.) and used to induce periods of rest and activity and the expression of other rhythms is in the realm of conjecture. Unquestionably, many of the cyclic bodily functions are influenced by messages received from the SCN. That the SCN plays a central role in the proper

synchronization of these cycles is obvious in animals in which the pacemaker neurons are experimentally destroyed. Under these conditions animals exhibit free running cycles, i.e., non-24-h rhythms.

Melatonin and biological rhythms

One of the major output signals of the SCN regulates the pineal melatonin synthesis cycle (Reiter 1991). This is accomplished by a chain of neurons that connect the central circadian pacemaker to the pineal gland. The pathway is well defined and includes axons of SCN neurons that project to the paraventricular nuclei of the hypothalamus whose fibers descend to the upper thoracic cord where they terminate on preganglionic sympathetic cell bodies. The axons of these neurons exit the spinal cord and synapse on parikarya of postganglionic sympathetic cells in the superior cervical ganglia; axons of these neurons ultimately innervate the pineal gland where they control the cyclic production of melatonin (Zeitzer et al. 2000).

Melatonin, the major secretory product of the pineal gland, is uniquely synthesized and released in darkness. More generally, the primary production and secretion of this indole is inversely proportional to ambient light exposures: The presence of light of sufficient duration and intensity inhibits, and the absence stimulates, the synthesis of melatonin, which was therefore described as the chemical expression of darkness (Reiter 1991). More specifically, the rhythmic production of melatonin is influenced by the environmental photoperiod in at least two ways. First, the regular cycle of melatonin synthesis is adjusted to a 24-h period by environmental day/night variations and, secondly, the imposition of light during darkness acutely suppresses melatonin production. Since the environment's light conditions change over time, the internal melatonin production as a hormonal blueprint also changes and, as a consequence, both clock and calendar information to organisms is provided (Reiter 1993). Once released from the pineal, melatonin distributes, via the blood and cerebrospinal fluid, throughout the body. A major target of melatonin is the SCN itself, i.e., the central pacemaker. Here melatonin acts to phase-shift the firing rates of the intrinsic neurons and thereby phase-shift biological rhythms generally.

One crucial rhythm that melatonin influences is the sleep/wake cycle (Zisapel 2001). While melatonin has been promoted as a sleep-inducing substance, the precise mechanisms by which it influences sleep remain unexplained. It is generally agreed that melatonin per se is not a soporific agent. Rather, melatonin only when given at the proper circadian time phase-shifts the underlying rhythms which promote sleepiness; this has been referred to as "opening the sleep gate." Thus, melatonin's efficacy in inducing sleep is time-dependent and relates to its ability to phase-shift the circadian pacemaker rather than to any direct soporific activity. Melatonin also slightly reduces core body temperature, which presumably contributes to its ability to promote sleep.

Chronodisruption

It is suggestive that health can be promoted by a physiologic balance of biological rhythms. While it may take many years to understand details, it seems likely that such a physiologic balance of rhythms can be crudely characterized by an appropriate balance—or order—of activity and rest and of wake and sleep states. A major public health objective would then be to identify and promote those activity–rest and sleep–wake cycles which enable a maximized life span.

The increasingly used terms "circadian disruption" or "disruption of circadian rhythms" suggest that rhythms over 24 h can become desynchronized and that this may have adverse health effects. Since biologically relevant disruptions of rhythms are likely to occur over days and seasons and years, we suggest to use the more general term chronodisturbance for modulations of rhythms over time. It can be expected that the effects of many modulations of rhythms can be physiologically compensated so that they do not necessarily lead to manifest chronic processes. To explicitly describe relevant effects of chronodisturbance beyond some homeostatic threshold to chronicity, we choose to work in this paper with the term chronodisruption: in fact—with aging and cancer—we are going to turn now to overt chronic processes over many years and decades. We suggest to investigate the causes and course of aging and cancers from the perspective of being both light- and rhythm-related. This approach may appeal to scientists from various disciplines because it implies that aging and cancers may have common denominators. Of course, aging and cancer are multifaceted processes, but a focus on aging and cancer as belonging to one light- and rhythm-related effect entity seems warranted for two reasons: first, insights into a common etiology are conceivable and, second, this approach may offer novel and uniform targets for prevention.

Aging and cancer

To date, the relationship of chronodisruption to the processes of aging have not been completely defined although there is general agreement that repeated disturbances of circadian rhythms contribute to the general deterioration of the organism (Armstrong and Redman 1991). This seems evolutionarily rational considering that most organisms evolved over eons in an environment which provided a regular and repeating light:dark cycle as determined by the rising and setting sun. With the advent of artificial light sources, however, the timing of the circadian pacemaker was disrupted, i.e., exposure to light during the normal dark period changed the electrical activity of the SCN as well as phase-shifted (or phase-

advanced) downstream cyclic events. Considering that regular cyclic events within organisms undoubtedly evolved to benefit those organisms, their persistent disruptions would seem to be inherently negative and tax the organisms in terms of energy expenditure. The long-term consequences of this chronodisruption are presumed to accelerate the processes of aging, although this has not been unequivocally documented. First experimental evidence to support the notion that the temporal organization of biological rhythms may affect aging and provide adaptive advantages for the longevity of an organism was suggested in 1998 (Hurd and Ralph 1998). Indeed, the authors indicated that longevity in hamsters was decreased when the rhythmicity of circadian systems was noninvasively disrupted. Moreover, longevity of that species was increased when grafts of fetal SCN into older animals restored higher amplitude rhythms.

With specific regard to the relationship of chronodisruption to the processes of cancer, numerous experimental studies over many and epidemiological studies over few years provide more evidence for possibly causal links. The pineal secretory product, melatonin, can be considered as an oncostatic agent (for a recent review see Sanchez-Barcelo et al. 2003) and it has been even argued that "Lack of melatonin can reasonably be anticipated to be a human carcinogen" (Portier 2000, p 313). Melatonin may accomplish oncostatic effects via several different means. Indeed, melatonin prevents damage to DNA that results when toxic reactants are generated as by-products of oxygen in aerobic organisms. Damaged DNA, if it goes unrepaired, can mutate and initiate cancer. Once established, melatonin also inhibits cancer growth (progression) via mechanisms that involve melatonin receptors on at least a variety of cancer cells (Blask et al. 2002a, b). Considering the above-mentioned effects of melatonin on cancer initiation and promotion, exposure to light at night (which suppresses endogenous melatonin production) may predispose individuals to cancer initiation, via increased damage to DNA, and to increased cancer growth due to the loss of a normal oncostatic agent (Glickman et al. 2002).

Experimental studies

There are a plethora of experimental studies in animals which document the ability of light to exacerbate and what could be called the antithesis of light, i.e., melatonin, to suppress both DNA damage (Reiter 2002), a factor that predisposes cells to become cancerous, and the actual growth of established tumors (Blask et al. 2002b). As one example, ionizing radiation, a known carcinogen, mutilates DNA via several mechanisms including by the generation of the devastatingly toxic hydroxyl radical (Agrawal et al. 2001), and this damage is exaggerated when melatonin levels are low (as occurs during light exposure at night). Conversely, when either physiological or pharmacological levels of melatonin are given, the genomic destruction mediated by ionizing radiation is attenuated (Karbownik and Reiter 2000; Vijayalaxmi et al. 2002). An obvious implication of these studies is that light exposure at night, a factor that deprives an individual of elevated nocturnal melatonin levels, increases the likelihood that nuclear DNA will be damaged by ionizing radiation (Karbownik and Reiter 2000; Vijayalaxmi et al. 2002) as well as chemical carcinogens (Karbownik et al. 2001) and, as a result, increased cancer incidence would be expected.

This has been experimentally documented in animal studies. When rats were given a chemical carcinogen (safrole) either during the day (when endogenous melatonin levels are low) or at night (when endogenous melatonin is high), the quantities of damaged DNA in the liver were dramatically different; thus, during the day the carcinogen induced significantly more molecular genomic destruction compared with its nighttime administration (Tan et al. 1993). When nighttime melatonin values were low, such as occurs after nocturnal light exposure, the carcinogen again induced massive DNA damage. Clearly, the nighttime endogenous rise in melatonin is sufficient to thwart the ability of a highly toxic chemical carcinogen to attack and damage DNA, damage that is a prelude to the initiation of cancer (Reiter 1999). The outcome of this study has obvious implications for the elderly, who typically have a greatly attenuated nocturnal melatonin rise (Sack et al. 1986; Skene and Swaab 2003). Since old humans are relatively melatonin deficient, their exposure to a carcinogen, either physical or chemical, would generate more genomic damage than would occur in a young individual with a robust nocturnal melatonin increase. As a consequence, the likelihood of cancer initiation would rise proportionally. In this vein, light suppression of melatonin (like aging) has been speculated to increase the possibility of cancer development (Coleman and Reiter 1992).

In addition to cancer initiation, the possibility of accelerated growth of already established tumors is likely also to be a consequence of excessive light exposure at night. This was emphasized by a study in which rats received a transplantable tumor (hepatoma) and were then placed in a photoperiodic environment which provided a regular light:dark cycle or a light:dark cycle where the dark was contaminated with low intensity light (sufficient to reduce the nighttime rise in melatonin). In the rats living in the photoperiodic cycle where the night was contaminated with light, the transplanted tumors grew significantly faster and tumor metabolism was likewise accelerated (Dauchy et al. 1997). Thus, light exposure at night that is sufficiently bright to compromise the nighttime melatonin rise also permits the more rapid growth of established tumors.

In addition to the examples cited above, there is a vast published literature on the inhibitory effects of both physiological and pharmacological concentrations of melatonin limiting the growth and metabolism of cancer (Blask 1997, 2001; Blask et al. 2002a, b). What these findings mean in terms of excessive light exposure at night seems obvious. Thus, curtailing the nocturnal rise in

Table 1 The melatonin hypothesis, corollaries, predictions and epidemiologic investigations

Hypothesis and corrolaries	Predictions	1st author and year of publication	Are study results compatible with the predictions?
Light at night inhibits melatonin synthesis and can increase breast cancer risks	1		
	Female shift-workers have higher risks	Tynes 1996	yes
		Hansen 2001a, 2001b	yes
		Davis 2001	yes
		Schernhammer 2001	yes
	Female shift-workers have higher risks of colorectal cancers	Schernhammer 2003	yes
Darkness, i.e., absence of light, stimulates melatonin synthesis and can decrease breast cancer risks in particular and cancer risks in general	2		
	Blind people have lower risks	Hahn 1991	yes
		Feychting 1998	yes
		Pukkala 1999	no
		Verkasalo 1999	yes
		Kliukiene 2001	yes
	3		
	Arctic residents have lower risks	Erren 1999	yes
Light can increase the risk of some diseases, e.g., cancer, and decrease the risk of other diseases, e.g., depression	4		
	Light co-determines the geographical distribution of health and disease	Erren 2001, 2002	–

melatonin with unusual light exposure during darkness, with the alterations caused by light in terms of basic circadian rhythmicity, may be detrimental in terms of cancer and aging, both of which seem to involve the accumulation of free-radical-damaged intracellular molecules.

Epidemiologic studies

On the basis of extensive laboratory and very limited epidemiologic evidence, a melatonin-mediated effect of electric power on breast cancer risks was suggested some 15 years ago (Stevens 1987; Stevens et al. 1992). In the context of this review, it is noteworthy that the so-called "melatonin hypothesis" specified that light exposures at night may disrupt the function of the pineal gland and thus increase breast cancer risks. In principle, this hypothesis provided a biological rationale for epidemiologic studies to interpret any association between light and breast cancer as reflecting a cause and effect phenomenon (Erren 2001). In practice, the hypothesized causal link between ubiquitous light and cancer poses a significant challenge to epidemiologists. On the one hand, epidemiology is a discipline which can crucially contribute to the often needed in vivo verification of experimental findings. In other words, epidemiology may contribute to answering the question whether what we find in experiments is really relevant to humans and public health. On the other hand, if universal exposures lead to homogeneous exposure patterns in populations, any true effect of light on human health will be underestimated and may even be undetectable. Epidemiologists therefore need to identify populations who are differentially exposed to light, i.e., they need to recruit individuals who are more (or less) exposed than others and compare the groups. On the basis of the melatonin hypothesis, corollaries and associated predictions, different study populations have been identified in the past 12 years. Table 1 summarizes the strategies and indicates what studies have been conducted to date.

In 1992, it was suggested that shift work may increase breast cancer risks (Stevens et al. 1992). The underlying rationale implied that regular work at night can not only reduce endogenously produced melatonin but also disrupts the activity of the circadian pacemaker. To find out empirically whether prediction 1 may be valid, four targeted studies were conducted in women. All these studies in Norway, Denmark and in the USA evinced higher breast cancer risks in female shift workers (Tynes et al. 1996; Hansen 2001a; Davis et al. 2001; Schernhammer et al. 2001; Hansen 2001b) but other factors than light exposures must also be considered as possible explanations for the findings. Furthermore, the suggestion that melatonin may have antiproliferative effects on cancer in general led to a study of night-shift work and the risk of colorectal cancer in women (Schernhammer et al. 2003). Compatible with the prediction, the authors of this study concluded that nurses who worked rotating night shifts for 15 or more years may have an increased risk of colorectal cancer. In the near future, additional studies of diverse cancer endpoints are likely to follow in female shift workers. Moreover, the possible links between light exposures and hormone-dependent cancers such as prostate cancer in particular and cancer in general may be also investigated in male shift workers. Interestingly, a comprehensive study of male airline pilots from Denmark, Finland, Iceland, Norway and Sweden showed that the risk of prostate cancer increased with the number of flight hours in long-distance aircraft (Pukkala et al. 2002). With regard to flight attendants, it was suggested earlier that their common work at night and their extensive travel across time zones could lead to chronic disturbances in biological rhythms in general and mela-

tonin secretion in particular (Mawson 1998; Härma et al. 1994). In this vein, the authors of the Nordic study of airline pilots concluded that their findings could be related to circadian hormonal disturbances, i.e., chronodisturbances and chronodisruption in the context of this paper. Until recently, cosmic radiation was the primary concern in flight personnel investigations and interpretations of cancer findings [for a review see Boice et al. (2000); combined analyses are available in Ballard et al. (2000), and in Lynge (2001), and a pooled analysis of European studies is planned; (Auvinen et al. 1999)] are difficult. For instance, with regard to suspected breast cancer risks in female flight attendants, occupational factors such as electromagnetic fields from cockpit instruments and even DDT (Wartenberg and Stapleton 1995), reproductive factors such as age at first birth and nulliparity and lifestyle factors such as hormone use and alcohol consumption have been considered beyond cosmic radiation. Since the large study from the Nordic countries showed no marked risk of cancer attributable to cosmic radiation (Pukkala et al. 2002), further studies of male pilots and aircrew are warranted which also focus on a possible link between the suggestive dose-response patterns in prostate cancer and chronodisruption.

With regard to prediction 2 that blind people who perceive less or no light visually have higher melatonin levels and lower breast cancer risks in particular (Hahn 1991; Coleman and Reiter 1992) and lower cancer risks in general than the sighted, five studies were conducted. Compatible with the prediction, results from studies in the USA (Hahn 1991), Sweden (Feychting et al. 1998) and Norway (Kliukiene et al. 2001) suggested reduced risks of breast cancer in particular and cancer in general. Two further studies were conducted in Finland: one (Pukkala et al. 1999) showed higher risks for several cancer sites among visually impaired, another (Verkasalo et al. 1999) indicated that breast cancer risks decreased with increased degrees of visual impairment. In any case, caution is warranted when we interpret these studies of the blind. More generally, explanations beyond light exposures must also be considered in all these investigations to explain the findings. More specifically, we noted earlier that light can induce nocturnal melatonin suppression in some blind people with no conscious perception of light (Czeisler et al. 1995; Lockley et al. 1997; Klerman et al. 2002). Furthermore, first empirical evidence from some blind adults exposed to light suggested that they do not have a longer duration of melatonin secretion than healthy sighted individuals (Klerman et al. 2001). To find out to what degree the underlying assumption of prediction 2 is valid, i.e., to answer the question how many blind people do have higher melatonin levels than the sighted, we shall need more research. That some blind individuals share the melatonin patterns of the sighted could imply that the risk reduction in blind individuals who do not react to light exposures with altered melatonin synthesis may be more pronounced than estimated in the epidemiologic studies to date. And yet, individuals with intact light–melatonin regulation who are otherwise totally blind are perhaps less likely to experience the same light exposures as sighted people so that they may nevertheless produce more melatonin (Erren 2002).

With regard to prediction 3, it was suggested that residents in the Arctic have lower hormone-dependent cancer risks because they may have higher melatonin levels over the year (Erren and Piekarski 1999). In particular it was assumed that extended darkness-at-day in winter months at the extremes of latitude may lead to increased yearly averages of net melatonin levels and to different seasonal melatonin secretion patterns which can be very relevant for the development of cancer (Panzer and Viljoen 1997). With regard to the latter assumption, additional considerations are in order. The obvious question is: does complementary lightness during summer nights inhibit melatonin production which then counterbalances a stimulation of melatonin secretion via winter darkness? To arrive at an answer, studies with melatonin measurements in residents at or North of 60°N were identified in the peer-reviewed literature: All the empirical investigations (Beck-Friis et al. 1984; Martikainen et al. 1985; Kauppila et al. 1987; Kivelä et al. 1988; Levine et al. 1994; Stokkan and Reiter 1994; Laakso et al. 1994; Weydahl et al. 1998; Wetterberg et al. 1993, 1999a, 1999b) evinced that shorter photoperiods in winter, i.e. decreased ratios between the day's and night's length, may significantly increase yearly averages of melatonin levels in healthy individuals who live at or north of 60°N latitude. As possible explanations it was assumed that Arctic residents will assure some light protection at time of bed rest during the summer ("anthropogenic shield"), on the one hand, and that closed eyelids can be effective shields against light exposures. With regard to the latter, human evidence from laboratory studies does indeed indicate that closed eyelids can shield against light and thus prevent melatonin suppression ("natural shield") (Hatonen et al. 1999; Jean-Louis et al. 2000). Interestingly, large population-group data from the Arctic do suggest the predicted low hormone-dependent cancer risks (Erren and Piekarski 1999) but such ecologic observations—on their own—are insufficient for making causal inferences.

Finally, the rationale for prediction 3 leads to prediction 4, that there can be risk gradients from North to South depending on geographical latitude and the associated ambient light exposures. If there are diseases other than cancer that are more likely to occur when melatonin levels are relatively high, then the prediction would be that the risk of these diseases (e.g., mood disorders: Brzezinski 1997; depression: Panzer and Viljoen 1997) should be higher in the Arctic than at lower latitudes (Erren et al. 2001; Erren 2002). Whether light can really co-determine the geographical distribution of health and disease in man has not been investigated. Likewise, there is no epidemiologic study to date which has focused on the possible relationships between light, biological rhythms, and aging.

Common denominators for aging and cancer

Clearly, the epidemiologic evidence for a possible link between light, melatonin levels and the activity of our circadian pacemaker and chronic health effects is limited but tantalizing and, equally clearly, the experimental evidence is abundant and suggestive. In our view, there can be no doubt that the intentional or inadvertent manipulation of the biological clock by exposure to light at unusual times, i.e., particularly at night, has physiological consequences for organisms. As a result, more research is needed to define how important what is referred to as the "misuse of light" is in terms of pathological processes generally and cancer and aging in particular. In the latter vein, the above material suggests that the processes of aging and cancer often have a common causative feature, i.e., accumulated molecular debris that is a consequence of radical attacks. It is widely accepted that free-radical mutilation of essential molecules on a daily basis throughout the life of an organism contributes to the deteriorative changes of aging, a concept known as the free-radical theory of aging (Harman 1992) of which there are a number of permutations. Similarly, as noted above and elsewhere (Halliwell and Aruoma 1993), the persistent assault on DNA by oxygen and nitrogen-based reactants, many of which are free radicals, unequivocally contributes to the likelihood of cancer. Thus, excessive light exposure, the resulting melatonin suppression, and the increased molecular destruction of the genome by free radicals are common denominators for two life-altering processes, i.e., aging and cancer development.

Retrospectives and perspectives

Biomedical research during the past decades as summarized in this paper can point to an important biological duality of light. Some billion years ago, life arose on Earth, presumably energized by sunlight, and ever since then light has maintained and affected life on our planet. For some decades now, we know that sunlight is a major risk factor for the most common cancer worldwide, i.e., skin cancer, and evidence is accumulating that light contributes significantly to aging processes (Reiter 2002; Reiter et al. 2002). Furthermore, numerous experimental studies of light and hormones and cancer in many species, limited clinical studies in man, and circumstantial epidemiological evidence suggest the possibility that ubiquitous light may be a significant risk factor for the leading noncutaneous malignancies worldwide; namely breast cancer in women and prostate cancer in men (Erren 2002). Clearly, important questions regarding the dual biological effects of light arise.

To what extent may light limit our life on Earth?

The answer to the question "does light both allow and limit our life on Earth?" seems to be an obvious "yes" because we know that the Sun's light is responsible for a substantial number of skin cancers which can lead to premature deaths. However, the answer to the related question "to what extent does light limit human life on Earth" requires more detailed considerations. Beyond causing skin cancers, light may limit life much more substantially than has been appreciated so far. Indeed, the Sun's light may also be responsible—in part—for a so-called background incidence of internal cancers for which we have not yet identified the cause(s). Moreover, natural light may be an important component cause (Rothman 1976) of premature aging and thus earlier termination of life. That man evolved by virtue of the Sun's light does not necessarily imply that light is an exclusively beneficial form of radiation. Note as an analogy that, while oxygen is necessary for us to live, it also leads to oxidative damage which is believed itself to be a major contributor to aging and cancer. Furthermore, man has been ubiquitously exposed to artificial light ever since light bulbs became widely used little more than a century ago. Without doubt, anthropogenic light has brought humans many advantages but it appears possible—if not probable—that the benefits may come at some price.

In principle, the ubiquitous nature of visible radiation implies the possibility that even small risk elevations could lead to many cases and to a substantial population burden. To zero in on a number of cases which may be attributed to light exposures and the resulting chronodisruption, a first computation has been made on the basis of epidemiologic studies of the blind and on the assumption that causality were established between light and the development of breast cancers (Stevens 2002). These caseload estimates were criticized on several grounds, in particular because there appeared to be no way to reduce exposures to light, i.e., to intervent (Poole 2002). However, preventive measures to "eliminate" the exposure in question could be available. In fact, one aspect which makes research into light and chronodisruption appealing is the fact that light would be much easier to modify than other possible determinants of the chronic processes of cancer and aging, e.g., genetic, nutritional or lifestyle factors. Indeed, to prevent chronodisruption through light, exposures may be modified insofar as endocrinologically relevant wavelengths could be reduced or blocked completely: Promising options include specifically designed artificial lighting or glasses and contact lenses with appropriate filters.

To convincingly show that causal links between light, cancer, and aging exist, and to assess the possible public health impact of chronodisruption will require much more research. With regard to the relationships between light, biological rhythms, and cancer, a number of promising options for both epidemiological and experimental studies have been suggested, discussed (Poole 2002; Portier

2002) and, at this writing, targeted investigations are on their way or being planned.

Light, order and life

A central point of this paper is that many species, including man, have developed biological rhythms which prepared physiology for the challenges of an environment that changes regularly through light. These ground-rooted notions regarding light's key role for orderly processes in nature are actually in line with more abstract considerations that "life seems to be orderly and lawful behaviour of matter .... based partly on existing order that is kept up" (Schroedinger 1948, p 69). Having linked life with "order" or "orderliness," Schroedinger continued that " .... the device by which an organism maintains itself stationary at a fairy high level of orderliness .... really consists in continually sucking orderliness from its environment" (Schroedinger 1948, p 75). Along this rationale, we suggest more generally that organisms in most of the Earth's biosphere extract "order" as one basis for the maintenance and evolution of life from the environment through light. More specifically, in animals, including man, light is a principal environmental source for internal order which is realized via biological rhythms.

Conspectus

We conclude that targeted epidemiological and experimental research into the causes and effects of chronodisruption are warranted in order to further elucidate the etiology of aging and cancer. From a preventive point of view, it seems promising to identify chronodisruption in individuals and populations as a basis for restoring physiologic order of biological rhythms by the use of appropriate lighting.

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