Research into the chronodisruption-cancer theory:
The imperative for causal clarification and the danger of causal reductionism

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Submitted: 2009-12-09 Accepted: 2009-12-10 Published online: 2010-02-16

Key words: **biological rhythmicity; disruption; disease**

Neuroendocrinol Lett 2010; **31**(1):1–3 **PMID:** 20150863 NEL310110L01

COMMENTARY

"MAKE EVERYTHING AS SIMPLE AS POSSIBLE BUT NOT SIMPLER"
Attributed to Einstein

A cascade of investigations into the validity of the chronodisruption-cancer theory (CD-CT), proposed 2008 in Neuroendocrinology Letters as a synthesis of abundant experimental and tantalizing – but still limited – epidemiological data, can be expected in coming years. In view of the possible public health relevance of the suggested links between chronodisruption, defined as the disruption of the temporal organization or order of biological rhythmicity over days and seasons, and the development of disease, including cancer, we provide practical aspects which should be considered for the planning, conduct and the very interpretation of such studies. The interrelated considerations address two facets: first, the critical necessity of causal clarification can be evinced appropriately by Poole's earlier contribution to the Journal. Researchers into the validity of the CD-CT should certainly consider Poole's 2002 illustration via causal graphs for shift work, light at night and breast cancer of the subtleties that can arise in the use of exposure surrogates of different kinds. Second, we emphasize the importance of considering the Zeitgeber multiplicity to avoid causal reductionism in epidemiologic – but also other – chronodisruption research.

THE NEED FOR CAUSAL CLARIFICATION

Light exposures at unusual times such as during the biological night continue to be a key – but not the exclusively relevant – determinant of chronodisruption, a critical "disruption of the temporal organization or order of biological rhythmicity over days and seasons" (Erren *et al.* 2003). That it is important to clarify the role of light-at-night (LAN) as a suggested "cause" of cancer within the rationale of the chronodisruption-cancer theory (CD-CT; Erren and Reiter, 2008 and 2009a) can be evinced systematically by Charles Poole's executive summary (Poole 2002) of the Cologne Symposium 2002 "Light, Endocrine Systems and Cancer". Intriguingly, the epidemiologist, using Pearl's formalized system of causal graph notation (Pearl 2000; Greenland *et al.* 1999) to systematize the traditional "confounding triangle" for light-at-night, shift-work and breast cancer, illustrated

some of the subtle effects, and substantial difficulties for interpretation, which may arise if we use exposure surrogates of different kinds, such as employing shift work as a surrogate for light-at-night rather than measuring the exposure-in-question (Poole 2002).

Currently, the research field involving "chronodisruption and cancer" is characterized by using exposure surrogates for unmeasured light such as shiftwork, blindness, time-zone travel, latitude, sleep length (an overview in Erren and Reiter 2008) to approximate the possible public health relevance of intriguing experimental data from rodent toxicology and basic human biology. Importantly, among other possibilities, Poole illustrated lucidly, that "a measured variable that serves as a surrogate for an unmeasured exposure can be

- a causal intermediate between the exposure and disease,
- an extraneous effect of the exposure,
- an effect of a cause of the exposure, or
- a cause of the exposure, among other possibilities.

Epidemiologists tend to be satisfied with the mere presumption that a surrogate is associated with the exposure of interest, without drawing explicit distinctions among these, and other, ways in which those associations may come about". Moreover, Poole anticipated a further complication "concerning the evolution from studying shift work as a surrogate for unmeasured light at night exposure to studying shift work as a source (and potential confounder) of measured light at night exposure. That is the presently ill-defined relationship between sleep disruption and exposure to light at night. The two are obviously correlated in free-range human populations" (Poole 2002).

THE DANGER OF CAUSAL REDUCTIONISM

While light certainly has a key role for chronobiology, it appears important to emphasize once again that focusing on "light-at-night alone" would be a reductionist approach and a likely scientific dead-end. In fact, determinants of the central link in the "probable" chain of causation between shift-work and cancer which IARC experts identified in 2007 (Straif *et al.* 2007), namely circadian or chronodisruption (CD), can be a variety of exposures which include light but also other chronodisruptors (Erren and Reiter 2009a). CD, we suggested in 2003, is "a relevant disturbance of the temporal organization of physiology, endocrinology, metabolism and behaviour, which links light, biological rhythms and the development of cancers (Erren *et al.* 2003), with melatonin being a key biological intermediary". In principle, whatever allows to establish temporal organizational order in organisms should also be capable of disrupting such order or temporal programme when present or applied in excess or deficit and, importantly, at unusual and inappropriate times. In practical terms, with these premises, one key exogenous or external chronodisruptor certainly is LAN. A second example is melatonin which, when administered at unusual times (Wirz-Justice *et al.* 2004), can also powerfully disrupt the circadian and seasonal rhythmicity of our biology, thus leading to CD. Notably, therefore, we are looking at a Zeitgeber multiplicity and interaction which allows fine-tuning of biological rhythms to changing challenges from the environment and disallows simplified causal analyses of what exactly happens when the physiological order, or sequence, of biological rhythms is disrupted. To provide yet another example for a relevant Zeitgeber, in recent months, a long-suspected food-dependent master clock was suggested to have been located in a distinct area of the hypothalamus (Fuller *et al.* 2008), albeit considerable dispute regarding the "findings" has been voiced since (Mistlberger *et al.* 2008; Mistlberger *et al.* 2009). In any case, since researchers expect that food provision can play a critical Zeitgeber role in the entrainment of workers' biological 24-hour rhythms to shiftwork conditions (Stokkan *et al.* 2001), future epidemiologic studies into chronodisruption and disease should certainly begin to consider information as to what shiftworkers eat and when (Erren *et al.* 2008). Yet one further conceivable chronodisruptor to look at, not appreciated previously, in particular in – but not confined to – shiftworkers, could be "noise". Indeed, ambient noise at unusual times such as during biological nights could cause and contribute to chronodisruption and to adverse health effects, including internal cancers, for instance in residents exposed to unanticipated intermittent noise generated by airport, railroad or road traffic.

Against this very complex background, we have emphasized elsewhere that, while light is a key Zeitgeber and, if applied at "wrong", i.e., unanticipated environmental times, a key chronodisruptor, blocking light at unusual times alone while maintaining work and leisure activities and unusual eating is unlikely to prevent chronodisruption, and possibly associated adverse health effects, including a biologically plausible development of cancers in shiftworkers (Erren and Reiter 2009b).

A further note is in order to the observation that melatonin suppression by light exposures at night is affected by the intensity of prior exposures to – outdoor and indoor – light. On empirical grounds, therefore, a further variable to consider, and possibly control for, shall be the individuals' "light memory" in future studies. As one practical consequence, this could imply that me must consider, and possibly adjust for, latitude as well (Erren and Reiter 2008). Indeed, the latter could be a *conditio sine qua non* to be able to compare and merge data from different studies at different geographical locations with different ambient light exposures at the time of the year(s) when a study is conducted and when light exposures and melatonin levels are measured at the workplaces.

Last, but by no means least, what Poole – and others – suggested with regard to the possible relevance of "sleep" adds further complexity to research. Intriguingly, beyond the critical role of melatonin, being produced primarily during sufficient darkness and thus, in most individuals while at sleep, a recent experimental study provides distinct mechanistic evidence for the importance, and integrity, of the biological night. Remarkably, nucleotide excision repair activity in the mouse cortex is highest during their biological nights and is at its lowest during their biological days (Kang *et al.* 2009).

Overall, there can be no doubt that research into possibly important causal relationships between Zeitgebers such as light exposures at unusual times, such as the night, on the one hand and melanopsin, melatonin, chronodisruption and downstream adverse health effects, including cancers and conceivable ageing processes, on the other, can be (very) important for public health. In any case, diligent epidemiologic – and other – research must avoid over-simplification of very complex interrelationships of a number of chronodisruptor candidates, including light, noise, work, leisure activities or eating at biologically unusual times. To this end, epidemiologists who will conduct the series of observational studies lying ahead of us shall certainly benefit from Poole's 2002 thoughtful advice regarding the subtleties and problems of interpretation when exposure surrogates of different kinds are used.

In summary, we can't put our conclusions too strongly: research into the validity of the chronodisruption-cancer theory must be based on clear causal terminology on the one hand and must avoid reductionist research in this complex field of chronobiology, chronodisruption and health and disease, including the possible development of cancers, on the other.

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