Comments on the International Symposium on

Light, Endocrine Systems and Cancer

Christopher J. Portier, Ph.D.

Environmental Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709 USA

Correspondence to:

Dr. Christopher Portier
NIEHS
PO Box 12233
Mail Drop A3-06
Research Triangle Park, North Carolina USA 27709
Phone: +1 919/541-3802
Fax: +1 919/541-1479
E-mail: portier@niehs.nih.gov

OBJECTIVE: A conference was held at the University of Cologne on May 2-3, 2003, to discuss the strength-of-the-evidence supporting a linkage between light, endocrine systems and cancer. This overview of the conference is intended to summarize some of the key elements of the conference and to indicate both conclusions and research gaps identified by this reviewer.

Introduction

If I had to pick a theme song for this conference it would be "I Got Rhythm"[1] which asks the rhetorical question, "Who could ask for anything more?" From the keynote address by Russ Reiter to the closing comments by Charles Poole, this conference focused on the "rhythm" that evolution has provided to most organisms on this planet through regular light-dark cycles. The recognition that these cycles may play an important role in cancer incidence through changes in levels of critical endocrine hormones is beginning to gain considerable scientific support and is the key focus of this conference. In my summary, I will discuss some of the research presented at the workshop and provide opinion on where critical data gaps exist and new research opportunities are emerging. In the final summary, I will discuss the general question of whether changes in the light-dark cycle should be considered a human carcinogen.

Clocks, Physics and Epidemiology

The most striking aspect of this conference was the broad expertise assembled to discuss the role of light on cancer risks in human populations. From presentations on the basic physics of light through the molecular biology of clock genes to epidemiology, this conference covered every aspect of light, endocrine systems and cancer. To review the presentations of the conference, I'll begin with the basic stimulus, light, and work my way through human response and epidemiology.

Sidney Perkowitz noted that light is essential for life on earth. But not all light is created equal when it comes to the potential for harmful effects in humans. In a talk ranging from the Big Bang to modern life, we learned of the scientific breakthroughs that lead to the discovery of light

as waves and the identification of the pineal gland as a target of light's effects on human beings. But it was clear from his presentation that electromagnetic radiation, of which visible and ultraviolet light are just one component, covers a very broad spectrum with differing effects on human health ranging from direct cellular damage (ionizing radiation) to breaking chemical bonds (some frequencies of ultraviolet photons). Karin Scharffetter-Kochanek and Roland Böni expanded upon these observations by giving a thorough review of skin cancer and the role of solar radiation in initiating the onset of melanomas. The findings for skin cancer clearly indicate the presence of genetically sensitive subpopulations in humans that are extremely sensitive to the effects of solar radiation.

Not all types of light have similar effects, even on vision and there are distinct differences in the spectrum of solar radiation, incandescent light, fluorescent light and mercury vapor lamps. Many of the presenters noted that scientists interested in studying the effects on light on living systems must know exactly what their light sources are and how they might interact with cellular targets. George Brainard demonstrated the right way to do studies of light focusing on the activation of the suprachiasmic nucleus and the frequency spectrum needed to stimulate melatonin synthesis in the pineal gland. His extremely thoughtful and careful experiments were able to suggest the presence of a new type of photo-receptor with a peak at 464 nanometers that did not correlate with any known photoreceptors and is likely to be the peak frequency for stimulation of the pineal response in humans. He also clearly demonstrated the need for careful analysis using Hill equations to support his observation of a new photoreceptor. These observations and similar ones made by Thomas Erren demonstrate the difficulty facing epidemiologists in studying human subjects with very diverse exposures to light. It was clear that minor fluctuations in light sources can alter biological responses and our interpretation of studies lacking clear analyses of the light sources will be extremely difficult.

Clock genes have become one of the most exciting research areas in molecular biology and Alexander Lerchl gave an excellent overview of their function. The clock genes can be reset by exposure to light and stay reset for a considerable period of time even after the light-dark cycle is severely altered. While it is clear that, *in-vitro*, melatonin can reset these clock genes, it is not clear if this is the active mechanism in humans and considerable work is needed to understand the relationship between these clock genes and light. In addition, the function of these clock genes, beyond a few biochemical processes such as nitrogen fixation, is unknown and could play a large role in cancer risks, especially if the suggested relationship between the clock genes and cell-cycle regulatory genes can be firmly established. One area discussed at the meeting was the possible problems which might arise when the biological rhythms set by the clock genes differ dramatically from the usual 24 hour light-dark cycle. In addition, while Russ Reiter notes the clear beneficial effects of melatonin in protecting against DNA damage from hydroxyl radicals, it is not clear what impact external doses of melatonin may have on the inherent biological rhythm set by the clock genes.

Two talks (Günter Vollmer and myself) focused on some of the known endocrine pathways which, when disrupted, have been shown to lead to increased cancer risk. Most notable amongst these was the linkage between circulating estrogen and progesterone and the risks of breast, uterine and endometrial cancer. For melatonin, light of sufficient intensity and adequate frequency regulates the synthesis and release of the hormone and it was clearly demonstrated that changes in other endocrine pathways at the organ controlling production of the key hormones can increase cancer risk. Several presenters, most notably George Brainard and Richard Stevens, discussed Richard Stevens' original melatonin hypothesis in detail and expanded on the role of melatonin in breast cancer based upon the recent literature. Key to all of these discussions is a better understanding of the linkage between the many endocrine

systems in the body and the pineal-melatonin system. Other targets for endocrine disruption such as receptor antagonists, cofactors and stimulators of enzyme activity were briefly discussed by several speakers and in comments from Meike Mevissen and Christian Bartsch; these are likely to play an important role in our understanding of differences across test species in cancer response and may explain some of the variability seen in human populations.

The animal evidence showing a direct linkage between changes in light-dark cycles and cancer risk were reviewed by Vladimir Anisimov and David Blask. The literature provides considerable evidence that melatonin can affect tumor incidence through initiation, promotion and progression of tumors. A number of signaling pathways associated with cellular replication appear to be affected by the available levels of melatonin in the system which can explain at least some of these responses. Considering the consistency of the estrus cycle in laboratory animals held under controlled light-dark cycles, the results presented here strongly support a role of melatonin in the incidence of mammary cancer in rodents and may explain a significant fraction of human breast cancers. Since breast cancers occur the most frequently of all first cancers in women (at least in the US), these findings could have significant public health impact and warrant aggressive additional research efforts.

The epidemiological and clinical evidence supporting the effects of changes in light-dark cycles and changes in endocrine hormones is fairly strong. However, the linkage between these changes or changes in light-dark cycles and cancers in human populations is not well established. As noted by Richard Stevens, Thomas Erren and Charles Poole, there is a clear need for carefully designed epidemiological studies to address these issues. If the animal evidence continues in the direction of current research, it will be imperative to establish this relationship in humans to begin to consider methods through which people can alter their behaviour and their environment to reduce their cancer risks. Considerable discussion at the end of the

workshop focused on the possible confounders in any epidemiological study of light-dark effects on cancer, many of which are obvious from the animal evidence. One issue was clear; as many biomarkers as possible should be obtained on the individuals in such a study with special emphasis on circulating hormones already associated with cancer risks such as estrogen.

Conclusion

The evidence is growing the disruptions in the light-dark cycle in humans plays a role in the overall tumor burden on this planet. The exact nature of the mechanisms involved are still being investigated and are so complex that a definitive answer may be many years in coming. Conferences, like this one in Cologne, should be more frequent so that scientists in the diverse fields associated with this research have a forum for sharing their ideas and forming the necessary collaborations.

As for me, I'll pay a bit more attention to my personal "rhythm" after listening to the scientists in Cologne; the alternative could be an increased cancer risk and I'm not very good at "singing the blues".

Reference

1. Gershwin G, Gershwin I, Bolton G, McGowan J. I Got Rhythm. From the musical "Girl Crazy" Opened on October 14, 1930 at the Alvin Theatre New York City, 1930.