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Reflections in Mutation Research

# Electric light causes cancer? Surely you're joking, Mr. Stevens<sup>☆</sup>

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### ABSTRACT

Night is no longer dark in the modern world, and the Milky Way has disappeared. Electric light has benefits but there are also a few detriments. These are (1) loss of the night sky, (2) wasted energy, (3) harm to animal and plant life, (4) and perhaps increases in some severe human maladies such as cancers of breast and prostate. The science on phototransduction for the circadian system and on clock gene function is evolving rapidly, and it provides a rationale for the idea that circadian disruption from light at night could cause disease. Direct evidence from humans and rodent models has also accumulated to the point where the idea is no longer fanciful. Although it may seem logical now, the journey on the path from electric light to breast cancer has been a tortuous one, at least for me.

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*"When you're thinking about something that you don't understand, you have a terrible, uncomfortable feeling called confusion."* – Richard Feynman, 1963.

### 1. The mystery of breast cancer

In the mid-1980s I was among the many who were dismayed by the recent reports that dietary fat consumption was unrelated to risk of breast cancer in women. We had assumed that the large international differences in risk must be mainly a result of the high-fat Western diet. For example, the historically low risk in Japan has been increasing dramatically in recent decades as the intake of animal fat has correspondingly increased as well. The rodent model is very strong; if rats are fed a diet high in saturated fat, chemically induced tumor yield increases [1]; if polyunsaturated fatty acids (e.g., linoleic acid) are added as well, tumor yield increases even more [2]. And on a population level, there is a strong international correlation between estimates of per capita fat consumption and breast cancer incidence among countries [3]. Yet after decades of intense research, including many large prospective cohort studies, estimates of fat consumption for individual women and risk to those women are almost unrelated [4]. In fact there are virtually no consistent associations of risk with any dietary factors

in adulthood except for a modest effect of alcohol consumption [5]. The latest cohort study [6] and a large intervention trial [7] do both report a small impact of very high fat consumption of borderline statistical significance, yet the large effect of adult fat intake predicted long ago seems now to have been ruled out.

I got to the Pacific Northwest Laboratory (PNL) in Richland, Washington, in 1984 at a time when these first diet studies were hitting the press. (I came from the Institute for Cancer Research in Philadelphia, but that comes later.) Coincidentally, one of our sponsors at the Department of Energy, Bob Goldsmith, had a small amount of funding available for research on power frequency electromagnetic fields (EMF) and health. This was an issue of acrimonious public argument at the time, but the possibility of some adverse effects seemed worth investigating to me. Given my despair at the lack of a dietary explanation of breast cancer, I decided to find out whether a study of EMF and breast cancer would make sense. I asked Larry Anderson, a staff scientist and friend at PNL, if he knew of any biological effects of these very weak, power frequency fields. He told me that Bary Wilson had published a finding of reduced melatonin in rats after exposure [8]. I had no idea what that might mean so I asked a guy I knew at the Fred Hutchinson Cancer Research Center in Seattle, David Thomas, what he knew about melatonin. He gave me a paper by Cohen et al. that had appeared in the *Lancet* in 1978 [9]. This paper provided a fascinating entrée into a field I have been struggling to understand ever since. Cohen proposed that lower melatonin might lead to elevated estrogen and thereby increase breast cancer risk. The notion that lifetime exposure to estrogen was a major factor in causing breast cancer was just beginning to be widely appreciated [10]. On this basis, Cohen further proposed

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that international differences in prevalence of pineal calcification might therefore explain the differences among societies in their burden of disease.

Although they made no mention of light-at-night (LAN) or electricity, Cohen et al. did allude to early laboratory experiments in which constant light in the animal rooms affected mammary tumorigenesis in rodents. I was curious about this for no good reason but tracked down some of these studies nonetheless. It began with pioneering work by Jöchle [11] and by Khaetski ([12]; described in [13]) in the 1960s. The tumor outcomes of experiments from a dozen labs over the years since then have been mixed, but one study from which I learned much was described in a marvelous paper by Shah et al. [14] in which constant light not only increased chemically-induced tumor yield but also altered the normal development and differentiation of the mammary tissue in rats. A few years earlier, Lewy and co-workers [15] had made the seminal observation that bright light in the middle of the night suppressed melatonin production in humans, the first such observation. I was enduring the anguish of trying to make sense of a new area of science when, some months into this journey of confusion, I found myself fretting about being awake in the middle of the night in my apartment. I suddenly realized I could almost read a newspaper by the street light shining through the shades on my window. Like a light bulb going on, it occurred to me that maybe it was the light bulb going on that accounted for some of the breast cancer pandemic. (I now know that midnight awakening is normal and healthy as long as you stay quietly in the dark [16].)

There have been a couple dozen epidemiological studies of EMF and breast cancer with mixed results but that on balance do not support any obvious association. There were also a couple of groups that conducted toxicological studies using rats exposed to power-frequency magnetic fields with conflicting results. One group in Germany headed by Wolfgang Löscher, however, has pursued this with startling results including increased tumor yield, and a strong suggestion of a genetic component to detection of the fields. Their results are fascinating scientifically, whether or not they have application to human disease (e.g., [17]). It is astonishing that the work of Löscher and his co-workers, published in major journals for over 10 years, has not gained the attention of other labs and funding agencies.

To this day it remains highly contentious whether EMF has any meaningful physiological effects on humans at all, much less in any way that could affect cancer risk. For light at night, however, there is no question that there are many physiological effects, some of which may well have bearing on cancer risk, including suppression of melatonin. So, I put one and one together (I'm bright, but I'm no Feynman), and published a paper in 1987 proposing that electric power (EMF and/or electric lighting at night) might increase risk of breast cancer [18].

Almost immediately, I became somewhat deflated because I realized that breast cancer risk in Japan, though rising, was still much lower than in the U.S., yet Japan has been heavily industrial for a long time. I wondered whether the typical household in Japan used as much electricity as the typical household in the U.S. so I called an expert at Lawrence Berkeley Lab; he sent me a paper [19] which estimated that indeed annual Japanese household electricity consumption in 1973 was much lower than in the U.S. (1.9 MW h vs. 8.2 MW h), but was rising very fast, over 50% by 1983. I became inflated again, and this is what I have pursued with increasing vigor for the past 25 years.

## 2. Evolution and electric power

We, life on the planet, have evolved for several billion years with a reliable cycle of bright broad-spectrum light (the Sun) and dark. This fundamental aspect of the environment has, not

surprisingly, had a profound impact on the organization of our metabolic, cellular, and organismal processes. Suddenly (in evolutionary time), the bulk of humanity began to be exposed to light during the night after the introduction of electric power, and to dim, spectrum-restricted light during the day inside buildings. Everything changed, and not all for the good.

I wanted to have a meeting about all of this, so I called Les Reinlib at the National Institute of Environmental Health Sciences (NIEHS). Much to my pleasure, Les was very supportive and we got a healthy budget for the meeting, which Dave Blask and I co-chaired. It was an ambitious endeavor because we wanted top researchers for all aspects of the subject. I sent an email to Susan Golden who had done elegant work [20] on the clock gene mechanism in cyanobacteria (a.k.a. 'pond scum'). She returned an email asking why in the heck would a basic scientist like her, studying bacteria, be invited to a meeting about breast cancer. I told her that we need new directions and perspectives in the pursuit of understanding breast cancer, and I told her why clock genes in cyanobacteria matter to a breast cancer researcher like me. She emailed back that she would be there.

We also invited, among other notables, David Berson [21] who had helped find the new photoreceptive cell for the circadian system in the retina (ipRGC) which Science Magazine called one of the Top 10 breakthroughs for 2002 (it is actually much more than that), Iggy Provencio [22] who found the photopigment for these new cells (melanopsin), Chris Bradfield [23] who discovered one of the core clock genes in mammals (he called it 'MOP3' only to have it renamed 'BMAL1' against his will by the Borg Collective), and Mark Rea, Director of the Lighting Research Center and editor of the Lighting Handbook [24], essential reading for the architectural lighting community worldwide. There were no refusals, even though the workshop was in a crummy hotel in DC; all these people had done that too many times in the past on various study sections, yet for this meeting they came again to DC. The result of the meeting was published [25], and although breast cancer was the original topic, we describe potential importance of circadian disruption to certain other cancers, such as prostate, and, believe it or not, to other chronic diseases such as obesity and diabetes as well.

## 3. Predictions of the Light-at-Night (LAN) theory

The Light-at-Night (LAN) theory for breast cancer is easy to state: increasing use of electricity to light the night leads to circadian disruption which accounts for part of the breast cancer burden in the modern world and rising risk in developing countries. But how to test it? Virtually no-one in industrialized societies does not use electricity to illuminate part of the daily dark period, be it at the end of day into the night, or at the beginning before sunrise. One prediction that occurred to me was that shift working women should be at higher risk due to an even higher exposure to light at night than day-workers.

So, in 1987, I wrote a letter to Walt Willett at Harvard suggesting a question be added to the ongoing Nurses' Health Study (NHS I). To my astonishment Walt did add a question to the 1988 NHS I biennial questionnaire. He also put the same question in the inaugural 1989 questionnaire for a new Nurses' Cohort II (NHS II) that he was just starting. At about the same time I was working with Scott Davis, an early comrade in the electric power struggle, on a grant application to NIH for a case-control study. Scott gets more done before breakfast than I do all day; among many other honors, he is the only American scientist I know of who was elected to the Russian Academy of Medical Sciences for his monumental efforts to study health effects of Chernobyl. As PI, he wrote a beautiful grant that was funded in 1992. I checked every so often on progress of the NHS studies, but nothing happened for a

long time. Meanwhile, Scott, Dana Mirick, and I finished a paper showing a significantly increased risk of breast cancer in women with a history of night work; we submitted it to the Journal of the National Cancer Institute (JNCI) on May 3, 2001. A couple weeks later I received a paper to review from JNCI submitted by the NHS I reporting increased risk in nurses with a long history of rotating shift work. It had been submitted May 8. It was amazing that after a dozen years these two studies were submitted to the same journal within a week of each other. I recommended to JNCI that the NHS I paper be accepted. (I was mildly perturbed that I was not mentioned in the acknowledgments in the paper for suggesting the idea, although I did not complain in my anonymous review; fortunately, this was corrected by Sue Hankinson in the NHS II paper several years later [26]; this study also found elevated risk in rotating shift workers).

It was a coincidence that the two papers were published in the same issue of JNCI in 2001 [27,28]; a very nice coincidence because their publication was the turning point for the LAN/breast cancer topic. Despite the date of publication, October 17, 2001, during the peak worries about anthrax after 9/11, it got a lot of media attention. Actually, Johnni Hansen had scooped us with a strong study from Denmark published earlier in the year [29]. Johnni wrote an excellent editorial for JNCI that accompanied the two papers [30]. Much other evidence has accumulated, and it resulted in the International Agency for Research on Cancer (IARC) concluding that “shift-work that involves circadian disruption is probably carcinogenic to humans (Group 2A)” [31].

Another prediction of the LAN theory is that blind women should be at lower risk. Robert Hahn published this idea and the first data in 1991 [32]. The evidence to date is not as strong as for shift work, but a half dozen other studies have also reported lower risk in blind women. Very recently studies have reported an inverse association of sleep duration and risk of breast cancer. This was based on the idea that reported sleep duration could be a surrogate for hours of dark [33]. It would be very crude, but that is what epidemiology usually must deal with. We published a paper in 2005 [34] reporting the predicted inverse association in Finland. The association was quite strong so we felt smug. The Nurses' Health Study immediately checked their data and found no such inverse relationship, and even a suggestion of the reverse [35]. Now we felt considerably less smug than before. Then, with the publication of two more good prospective studies supporting our inverse finding [36,37], we are again feeling smug, though not cocky because one never knows.

#### 4. Basic biology and Dave's experiment

Two areas of rapidly evolving basic biology have excited many of us, both for their inherent scientific interest and for their impact on the LAN theory for breast cancer causation. One is the mechanism of phototransduction for the circadian system, and the other is the molecular genetics of circadian rhythm generation. For the clock gene mechanism there are many implications, one of which would be a connection to cell cycle regulatory genes such as cyclin D1 [38] which could provide a direct rationale for a breast cancer effect [39]. For phototransduction the story has advanced greatly as described below.

Bud Brainard at Jefferson Medical College had been working furiously for years to define the precise wavelengths of light that maximally suppress melatonin, as a marker of circadian rhythmicity, in the middle of the night. This spectral response function was critical to figuring out the phototransduction mechanism for the circadian system. By the late 1990s accumulating evidence was suggesting that the primary mechanism was not vision *per se*, although the retina appeared to be required; some of this evidence was from blind persons [40] and from retinally degenerate mice

[41]. In 2001, Bud published his spectral response [42] and later an important extension of it to phase resetting in a study led by Steve Lockley, a very talented chronobiologist in Czesler's lab [43]. The melatonin response spectrum required hundreds of arduous individual experiments in which volunteers were in the lab over night and exposed to one of many combinations of monochromatic light of a specific wavelength and a specific photon flux density. It took over 5 years to do it right. The peak sensitivity turns out to be at about 480 nm, which is the wavelength of that beautiful blue we see in the sky on a clear day at mid-morning. It is probably no coincidence from an evolutionary perspective that the system for telling our inner self whether it is day or not is finely tuned to that wavelength. The new photoreceptive cell found in the retina, called the intrinsically photoreceptive retinal ganglion cell (ipRGC), also responds maximally to this wavelength [44].

Meanwhile, Dave Blask at the Bassett Research Institute had for years been conducting serious experiments on the mechanism by which melatonin was oncostatic to breast cancer e.g., [45,46]. (Dave would strongly insist that this work be attributed not only to him but also to his many co-workers over the years.) Dave had an idea that was inspired; he suggested to Bud that he recruit young women in Philadelphia into an experiment in which Bud would take blood under three different conditions: during the day, at night in the dark, at night after light exposure. Bud would send the blood to Dave's lab in Cooperstown, where Bob Dauchy would infuse the blood into xenografts of a human-derived breast cancer (MCF7) growing in nude rats. (Bob invented this remarkable surgical technique [47].) As predicted, blood taken during the night in the dark stopped the growth of the tumors, whereas blood taken during the day or at night after a light exposure did not slow the growing cancers at all. This experiment [48] is as close as ethically possible to a direct test of whether LAN influences breast cancer growth in women.

#### 5. Mechanisms of carcinogenesis and the Jedi Knight

The historical paradigm for defining a carcinogen is that it is either genotoxic or mitogenic. In general under this paradigm, the larger the dose, the greater the cancer yield. For a long time, thought about causes of cancer was confined to initiation and promotion, in which an agent caused a heritable genetic alteration predisposing to malignant transformation and/or increased turnover of 'intermediate' cells, thus increasing the probability that a heterozygous genetic alteration would become homozygous [49,50]. It turns out that it is a little more complicated than that [51–53]. In particular, agents or environmental factors that increase cell turnover and differentiation in normal tissue could have a large impact on breast cancer risk and be neither initiators nor promoters; they could actually have effects pre-initiation [54]. Increased risk of breast cancer for a woman who had an early age at menarche may be an example of that. Conversely, agents or exposures that increase the chance that a fully transformed cell or colony (very small cancer) would survive to ever be diagnosed as cancer could also have a large impact on cancer risk. The evidence that the recent reduction in use of hormone replacement therapy (HRT) by post-menopausal women in the last few years has already had a noticeable impact on breast cancer incidence may be an example of that [55].

So how can exposure to light fit into a model of carcinogenesis? The concept of 'dose' probably needs a different definition than that for ionizing radiation or a toxic chemical.

I learned about mechanisms of carcinogenesis at the Institute for Cancer Research (ICR) in Philadelphia. I had come there from graduate school in Seattle in 1977 as the research assistant to Suresh Moolgavkar who had accepted a position. At the time there were about 50 faculty members at ICR, five of whom were

members of the National Academy of Sciences (Bob Perry, Tom Anderson, Beatrice Mintz, Barry Blumberg, and Ernie Rose). Barry had received a Nobel Prize for his work on Hepatitis B virus, and years later, in 2004, Ernie got his for work he was doing on ubiquitin while I was at ICR. (As my PhD advisor, Barry taught me a lot about how to formulate a hypothesis, gather reliable data, and communicate the results coherently; he also sent me to Taiwan and to the Solomon Islands to do this [56]) Not much later a sixth ICR scientist, Al Knudson, was elected to NAS.

Part of the ICR culture was 'tea time' every day at 3:30. A wealthy benefactor included in her considerable endowment to ICR a provision for a tea time, and she expressly forbade coffee. So every day, Suresh and I would go down to tea time and talk with this amazing collection of scientists. Tom Anderson, a pioneer of electron microscopy, was particularly accessible to the younglings like me, and a wonderful guy with a great sense of science and how it is done. In the early 1980s ICR was subsumed into the Fox Chase Cancer Center. The place has grown at least 5-fold in staff and funding, although there have been no new members elected to NAS. Sometimes bigger is not necessarily better.

My luck in mentors has been great, but Suresh had the most impact in guiding my progression through the rank of Padawan. He treated me like a colleague, though I was excessively insecure and had a morbid fear of public speaking. We published many papers together on analysis of vital data, while he was also gaining wide respect for his work on casting biological models of carcinogenesis into mathematical terms, particularly the two-stage model [57]. Very generously he included me in some of that work as well [54]. Part of what was new here was incorporating growth kinetics of both normal and 'intermediate' cells into the mechanism of transformation.

My thinking about how LAN and circadian disruption could 'cause' cancer, has been greatly influenced by this early experience with Suresh. Initiation and promotion can be interpreted as processes that included mutations that render a cell fully transformed. Further mutation may be required to confer metastatic potential. Dave Blask's brilliant work addresses what would be called 'progression' – melatonin preventing the growth or survival of a small colony of fully transformed cells, cells that if released from melatonin's oncostatic action could then grow and flourish to become a clinically detectable cancer. But there are many other possibilities.

At the other end of the carcinogenic process could be an effect of LAN on normal mammary tissue development. Based on Dimitrios Trichopoulos's [58] intriguing idea that early life experience, even beginning *in utero*, affects lifetime risk of breast cancer, a prediction is that LAN during these critical developmental periods could also affect lifetime risk [59]. This possibility could have serious implications for light exposure to pregnant women (e.g. shift work) and for the lighted environment of children. There has been a very limited and indirect look at this important possibility. Shah et al. [14], in their experiment described above, used light exposure beginning *in utero*. My buddies at PNL and I tried to replicate this but started constant light exposure at age 26 days [60]. Much to our surprise (and dismay) we found that this exposure lowered tumor yield apparently by speeding differentiation of the breast; Jim Morris, an astute observer, noticed at terminal necropsy that the majority of the exposed rats (constant light) were lactating despite being virgin whereas he saw this in none of the control rats (on a 12 h light:12 h dark schedule). This is an understudied area.

Finally, the emerging understanding of the role of clock genes in expression of so many other genes [61] has led to ideas of how these could affect DNA damage [62–64], apoptosis [65], and cell cycle regulation [66,67], all of which have direct implications for cancer causation.

## 6. Past and future

As often happens, I stumbled into a new area while pursuing another: into the circadian rhythm arena while searching for answers to the mystery of why breast cancer is so common in the modern world. Early on, when I told my mentors and senior colleagues about electric power, they reacted with sympathy and compassion for my mental state and warned me off this path. At the time, I was a hot young science stud publishing in big journals with big co-authors. My Ph.D. advisor was a Nobel Prize winner, Barry, and I had a real career going. Fortunately, I never heard the word 'career' growing up in the home of two artists, Bob and June, in Berkeley during the 1950s and 1960s. To them all that mattered was one's work. So I stuck with the electric power topic through the 1980s and 1990s, despite it being an oddity and not advancing much, and my 'career' looking odd and not advancing much either.

But in fact, by the mid-1990s I was getting scared. What if this electric power stuff really was junk science as some prominent physicists were saying publicly and aggressively? Funding from DOE was drying up, and I did not have much else going on anymore. I had never taught students, and I had no NIH grants, so a new job at a University seemed unlikely. Then, in late 1995, I received a letter from Sydney Weinhouse. He wrote that as Cover Editor for the journal *Cancer Research* he wanted to put my picture and work on the cover. Dr. Weinhouse was past Editor-in-Chief of the journal, member of the National Academy of Sciences, and renowned as a real gentleman. I was astounded that he would want my picture for the cover of that prestigious journal. How in the heck did a person like Sidney Weinhouse notice this work and actually take it seriously? The cover appeared on the July 15, 1996, issue and was a psychological lifeline that got me through the rest of the 1990s, saving me from a life of crime.

Then in the early 2000s the dam broke and good evidence began to be published from many research groups. Reports appeared that shift working women were at higher risk, blind women at lower risk, sleep duration inversely related to risk. And startling new reports appeared showing associations with prostate cancer in men which had been predicted many years before [68]. The LAN/circadian disruption idea suddenly became legitimate. As also often happens, once an idea becomes attractive, credit for it gains value, and so there were some publications which minimized or denied my role in the genesis of the theory [69,70], to which I realized I must respond promptly [71,72]. In the long run, it makes no difference who thought of what, but in the short term, it matters very much to the principals involved. Accurate attribution of ideas matters. Too many universities and research institutions assess a scientist's productivity on numbers of grants and data papers, ignoring or undervaluing ideas. For any younglings who might be reading this, stick with what you love. That is the end of the rant for now.

Presently I am involved with a couple of excellent younger colleagues who have addressed some of the other implications of a potential impact of LAN and circadian disruption on breast cancer (with each passing year, more and more people are younger than me including for the first time our President). At the basic biology level, Yong Zhu at Yale has attacked the logical idea that polymorphisms in clock genes might confer different levels of risk of breast cancer, and he was the first to publish such a study [73]. His work is moving fast, and he has extended these ideas greatly including epigenetics. At the macro level, Itai Kloog at Haifa University has published the first assessment of whether, and to what extent, LAN and breast cancer incidence co-distribute in the population at large [74]. As predicted, there was a strong association among Israeli communities of nighttime light level and breast cancer incidence, but not lung cancer incidence which had been chosen as a test of the specificity of the method. This is a

necessary, but not sufficient condition for there to be a large effect of LAN on risk. He too is moving fast on this important topic.

Now I work at UConn – not the Yukon in northern Canada where huskies pull sleds but the other UConn in central Connecticut where Huskies shoot hoops – teaching and researching and staring out the window. At the moment, I'm having fun.

### Conflicts of interest

None.

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