Does Light Have a Dark Side?

Nighttime illumination might elevate cancer risk

By JANET RALOFF

Since life began, one pattern has dominated Earth's natural environment—a daily rhythm of intense sunlight alternating with nights of near-total darkness. As a source of heat and energy, sunlight powers a majority of the planet's biological activities. When that light disappears, much of the world rests.

Humans, the grand manipulators, have not been content to cede control of their activity cycle to the heavens, however. People have spent eons developing ever better means to artificially extend the day. Thanks to widespread electrification and color-corrected, high-watt lightbulbs, synthetic sunlight can now bombard city dwellers around-the-clock.

This attempt to erase the night—or at least to confine it to small, artificially defined windows—may come with a price. At a minimum, it can lead to a chronic lack of sleep, diminishing the effectiveness of the body's immune system. Some new studies, however, suggest the possibility of an even more worrisome threat.

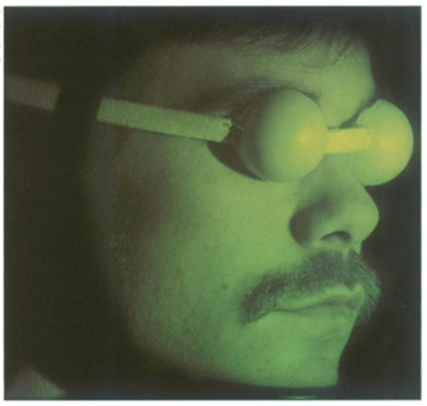
Exposure to light at night can disrupt the body's production of melatonin, a brain hormone best known for its daily role in resetting the body's biological clock (SN: 5/13/95, p. 300). Secreted primarily in the brain, and at night, melatonin triggers a host of biochemical activities, including a nocturnal reduction in the body's production of estrogen. Some researchers have speculated that chronically decreasing nocturnal melatonin production—as with light—might increase an individual's risk of developing estrogen-related malignancies, such as breast cancer.

Two studies in Nordic populations now offer tentative support for this idea.

According to neuroendocrinologist Russel J. Reiter of the University of Texas Health Science Center at San Antonio, the emerging science indicates that, functionally, "light is a drug"—and that "by abusing it, we risk imperiling our health."

Light entering the eye allows our brains to sense the shape, size, color, and motion of objects around us. It also summons, albeit imperceptibly, a cadre of other biological sentinels. These go on to trumpet light's presence to distant tissues—organs and cells lacking the means to detect illumination directly.

When these biochemical fanfares occur late at night, they can alter the timing of melatonin's peak output, as a landmark study in 1980 showed. Alfred J. Lewy and his colleagues at the National Institute of Mental Health in Bethesda, Md., shut down melatonin production in men by waking and exposing them to 2,500 lux of white light at 2 a.m., when synthesis of the hormone was at its peak. (For perspective, 100 lux may be found in a comfortably dim living room, whereas sunlight at high noon on a cloudless day can blast the eyes with 100,000 lux.) At the Oregon Health Sciences University in Portland, 8 years later, Lewy and George C. Brainard, now at Thomas Jefferson University in Philadelphia, found that just 50 lux could do the same trick—if it is green light.



Brainard

Not all light is equally effective at suppressing nighttime melatonin production. The shade of green depicted in this test has proved especially potent.

At about the time this work was going on, Richard G. Stevens of the Energy Department's Pacific Northwest National Laboratory in Richland, Wash., was developing a controversial theory now known as the melatonin hypothesis. It holds that long-term environmental perturbations in natural rhythms of melatonin secretion—by exposure to electromagnetic fields (SN: 1/10/98, p. 29) or to light at night—might increase cancer risk, especially in the breast, by increasing estrogen exposure.

Since the theory's debut, researchers have shown in animals that melatonin also functions as an antioxidant (SN: 8/14/93, p. 109) and an anticarcinogen. Some rodent studies have also demonstrated that certain nascent cancers grow more rapidly when the animals encounter even low levels of light at night (see sidebar).

The first preliminary evidence linking light to cancer in people emerged 8 years ago in a report by Robert A. Hahn of the Centers for Disease Control and Prevention in Atlanta. After combing statistics from a national survey on women who had been hospitalized between 1979 and 1987—including some 11,700 with breast cancer—he computed the incidence of this malignancy in blind and sighted women. If light alters cancer risk through some disruptive effect on melatonin, the epidemiologist reasoned, people whose eyes can't detect light should prove resistant. As a further test, he looked at heart-disease incidence, where melatonin should play no role.

In the May 1991 EPIDEMIOLOGY, Hahn reported that although the profoundly blind women proved as likely as the sighted women to get heart disease, they appeared only half as prone to develop breast cancer.

Probing this idea in more detail, Maria Feychting and her colleagues at the Karolinska Institute in Stockholm have just compared cancer incidence in 1,600 profoundly blind men and women with that in 13,000 people having severe visual impairment. Because members of the second group could still perceive light, Feychting explains, they should resemble sighted people in terms of any light effects on melatonin.

In the September EPIDEMIOLOGY, her team now reports finding that, as predicted, cancer incidence among the visually impaired individuals was virtually identical to that in Sweden's general population. People who were unable to detect light faced only 70 percent of that cancer risk.

Among profoundly blind men, the lower incidence showed up largely in cancers of the prostate, stomach, colon, rectum, skin, and lung. Among profoundly blind women, less cancer occurred in the breast, ovaries, and stomach.

The variety of cancers affected was unexpected. Feychting had anticipated that any change in cancer rates would trace to melatonin's influence on the body's production of estrogen (SN: 7/3/93, p. 10). High lifetime exposure to estrogen can spur the development of certain cancers, notably breast cancer. Instead, she now observes, melatonin may have a more general cancer-suppressing role.

A new Finnish study also compares cancer incidence among profoundly blind

people with rates in visually impaired men and women. Slated for publication in the November CANCER CAUSES AND CONTROL, the study found an even more sharply reduced incidence of breast cancer among people unable to perceive light than was seen in the Swedish study. It also found that cancer incidence rates in people with minor visual impairment "were rather close to those in the general population," notes Eero Pukkala, an epidemiologist with the Finnish Cancer Registry in Helsinki and one of the report's authors.

"Throughout the visual categories, we also see a nice trend of decreasing breast cancer risk with decreasing vision," he says. Indeed, this would make sense, argues Stevens, if the eyes of the more visually impaired individuals actually take in or sense less light—as occurs in many eye diseases.

However, in sharp contrast to the Swedish analysis, Pukkala notes, profoundly blind individuals in his study showed no reduction in cancer risk for sites other than the breast. Because the Finnish study analyzed the same types of data as the Swedish study, and in a group of comparable size, he is perplexed by the dissimilarity in their findings for sites other than the breast.

Although the findings of both studies are consistent with the premise that melatonin disruption by light promotes at least breast cancer in humans, Feychting and Pukkala acknowledge that both analyses fall far short of proving it. Their new studies are merely an initial probe of the potential link. Pukkala now plans a larger analysis, pooling data on blind and visually impaired individuals throughout the Nordic countries. He's hoping it will at least home in on the reasons for the discrepancies between the current studies—which he suspects trace to "differences in life habits" between Swedes and Finns such as nutrition, medical care, or social factors.

Such discrepancies also might arise because some blind people may respond to light—even though they did not perceive it—by altering their melatonin-production cycles. Similarly, some sighted people may have abnormal rhythms. Neither Nordic study had the resources to measure each participant's daily cycle of melatonin production—a lengthy and cumbersome procedure that requires frequent, round-the-clock sampling of blood or urine.

Steven W. Lockley, a chronobiologist at the University of Surrey in England, and his colleagues have made such measurements. And in the November 1997 JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, they noted that melatonin cycles in the blind are anything but predictable.

His group recruited 49 legally blind individuals to participate in a roughly month-long trial. Each collected his or her urine over a 48-hour span each week. The scientists then measured a melatonin byproduct in the urine.

Among the 30 people unable to perceive light, 57 percent had a free-running rhythm—a cycle longer or shorter than 24 hours. "This included every single subject that we've studied who has had their eyes removed," he notes. Another 23 percent had a normally cycling clock, with melatonin reliably peaking at night. The remainder had abnormal or unclassifiable cycles.

Even among the 19 people in the study who could perceive light, 26 percent exhibited abnormal rhythms, with melatonin production peaking at times other than the middle of the night.

"So one can't assume that the melatonin rhythm in all blind people . . . is free-running—or that its peaks in light-sensitive individuals will be normal," observes neuroendocrinologist David E. Blask of the Mary Imogene Bassett Research Institute in Cooperstown, N.Y.

Blask's studies of rats suggest that an abnormal timing of melatonin peaks can have a powerful effect on cancer.

He administered cancer-causing chemicals to rats and then over subsequent weeks injected the animals daily with melatonin. The injections were timed to produce peaks during daylight hours, when melatonin concentrations should have been negligible.

When those injections occurred midmorning, tumors grew at the same rates seen in animals not receiving injections. However, in animals that received the hormone during the afternoon, "we see an inhibitory effect of the hormone on tumor growth, not only in liver cancers, but also in breast cancers."

The findings suggest "that there is a rhythm of sensitivity within tumor tissues or in cells susceptible to becoming tumors," he told SCIENCE NEWS. "And maybe in people who can't perceive light, the oscillating cycle of their biological clock causes their melatonin peaks to coincide with the inhibitory period of tumor cells more often than they do in light-sensitive people."

The growing body of data on melatonin, light, and cancer suggests that certain populations, such as shift workers or others who regularly work in bright light at night, could face unusual risks, Blask argues. Certainly, he says, "the data are suggestive enough to raise eyebrows and prompt further serious study."

William S. Baldwin and J. Carl Barrett of the National Institute of Environmental Health Sciences in Research Triangle Park, N.C., agree that such theories should be tested—by probing the most likely mechanisms of

light's effects. "When the melatonin hypothesis was first presented," the pair notes, "no putative melatonin receptors [on cells] were known." Since then, three types have been identified.

In the March MOLECULAR CARCINOGENESIS, they lay out the molecular basis for concerns that light at night might prove an endocrine disrupter with the potential to increase cancer risk. They note that recent findings in several laboratories working with cells and with tissues removed from animals indicate that a reduction of melatonin can alter the production of other hormones, may suppress the immune system's ability to recognize and respond to newly emerging cancers, and appears to spur the growth of at least some tumor tissues.

By studying which cells possess melatonin receptors and how cells use them to respond to the hormone—as Barrett's team and others are now doing—science may resolve whether nighttime illumination truly threatens health, and if so, how much and in whom.

Studies now under way are also testing which wavelengths—or colors—are most biologically active. For instance, blue and green light appear especially effective at inhibiting melatonin synthesis in healthy young men, according to studies by Brainard. Indeed, he notes that for some colors, "17 lux was sufficient to produce strong melatonin suppression in these men—and some had full suppression with exposure to as little as 5 lux." The latter "is a little more illumination than what you'd have with full moonlight."

Brainard notes that the payoff for finding out what wavelengths are most hormonally disruptive could be insights on how "to tailor nighttime lighting to provide good vision without interfering with the melatonin rhythm." He says that "it may also help us develop more effective lights for use in treating winter depression and sleep disorders." □

How much light is too much?

At least in rats, a little light throughout the night can have a dramatic impact on cancer, observes David E. Blask of the Mary Imogene Bassett Research Institute in Cooperstown, N.Y.

Tumors can grow especially rapidly in rodents exposed to constant light, he notes—presumably because of a near-total suppression of their melatonin. To test just how much light was necessary to enhance tumor growth, he implanted liver-cancer cells into rats.

His team housed one group of caged animals in a room illuminated around-the-clock with about 850 lux of white light, which is roughly equivalent to an office with medium lighting. A second group of animals spent their days in 850 lux but their nights in total darkness. A third group encountered almost the same light-dark cycle. The only difference: 0.2 lux leaked in at the bottom of the door to their room from a hallway outside—illumination well below that typical of a moonless night, he says.

In the October 1997 LABORATORY ANIMAL SCIENCE, Blask's team reported that tumors in animals exposed to the crack of light coming under the room's door grew almost twice as fast as those in animals getting a night of total darkness. Indeed, he says, "animals exposed to the low-level light contamination had a tumor-growth rate virtually identical to that in the animals exposed to bright, constant light." He has just replicated the findings in an experiment in which the lighting was more rigorously controlled. —*J.R.*

Biology

Diabetes drug stirs cancer confusion

New research has offered hope that troglitazone, a widely prescribed diabetes drug, could become a new colon cancer therapy, but some scientists also express concern that the drug may trigger the cancer in genetically susceptible people.

This seemingly contradictory story emerges from several studies in the September NATURE MEDICINE. In one, Bruce M. Spiegelman of the Dana-Farber Cancer Institute in Boston and his colleagues report that troglitazone and other compounds that activate an intracellular protein called PPAR-gamma can transform colon cancer cells into nonmalignant cells in test-tube experiments. The drug also inhibited growth of tumors formed from human colon cancer cells implanted into mice.

PPAR-gamma normally regulates cell proliferation and specialization. Spiegelman and his colleagues hope soon to test whether troglitazone can help patients with colon cancer. The drug has already shown some promise in people with liposarcoma, a different cancer, says Spiegelman.

Curiously, however, two research groups have found that PPAR-gamma activators increase the incidence of cancer in certain mutant strains of mice. One group, led by Ronald M. Evans, a Howard Hughes Medical Institute investigator at the Salk Institute for Biological Studies in La Jolla, Calif., tested such compounds on mice with mutations in a tumor-suppressor gene called *APC*. These animals are generally predisposed to cancer of the small intestine. People with *APC* mutations almost invariably develop cancer of the colon.

The scientists had hoped that the PPAR-gamma activators might reduce cancer risk, but treated mice developed many more precancerous polyps in the colon than untreated ones. "What we found was exactly opposite what we had expected," says Evans. Yet normal mice receiving the PPAR-gamma activators had no greater incidence of cancer. Similar results have emerged from studies conducted on *APC* mutant mice by a group led by Johan Auwerx of the Pasteur Institute in Lille, France.

Since fats can activate PPAR-gamma, these studies may explain the finding that diets high in fat increase a person's risk of colon cancer. Evans also warns that people with diabetes who take troglitazone, especially those with a family history of colon cancer, should be carefully monitored for any signs of the disease. Spiegelman, however, notes that the mice may not reflect how colon cancer develops in people and that only those with *APC* mutations may face an increased cancer risk. "There's no evidence that [troglitazone] induces polyps in normal people or mice," he says. —*J.T.*

Rats have too much on their minds

Students cramming for an exam sometimes feel as if their brains can't absorb any more information. That overloaded feeling is shared by rodents studied by Edvard I. Moser of the Norwegian University of Science and Technology in Trondheim and his colleagues. The scientists used electrodes to stimulate memory-forming regions of rat brains. The stimulated animals fared poorly on a spatial-learning task that involves swimming for a hidden platform in a water tank, the researchers report in the Sept. 25 SCIENCE.

The overstimulation seems to prevent a strengthening of the connections between brain cells, known as synapses, that occurs after repeated stimulation. Many neuroscientists now believe that this strengthening, called long-term potentiation or LTP, is the primary mechanism by which animals form memories. The overstimulation experiments confirm that LTP can strengthen the synaptic connections between brain cells only so much. Moreover, if a brain reaches maximum stimulation, any learning is difficult if not impossible. "People are now focusing on how such changes in synaptic strength allow memories to form. That's the next issue, and it's a formidable question," says Moser. —*J.T.*