PIERLUIGI LONGO

BLUE ALERT

Our body clocks can be messed with in ways we are only now waking up to, says **David C. Holzman**

"THESE people aren't really blind, they are lying." So stated one journal editor when confronted by an experiment whose results seemed impossible.

The experiment involved clocks. Body clocks. Our internal clocks tend to run a little fast or slow, so if we are deprived of any clues to what time it is, we soon get out of sync with the day-night cycle. It used to be thought that our everyday activities kept our clocks on time, but a series of studies in the 1980s revealed that light is the key. The clincher came in 1986, when Charles Czeisler showed that light could be used to reset people's clocks in the same way that one might reset a watch.

The findings helped explain why many blind people suffer periodic sleep disturbances. Because they cannot detect light, their body clocks go in and out of sync with the day-night cycle. But Czeisler, of Harvard Medical School, knew that the clocks of a few blind individuals ran on time. How was this possible?

Czeisler showed that their clocks were also set by light – and that their eyes were somehow detecting it even though these individuals had no conscious awareness of light. That suggested that our eyes have special light receptors that are quite separate from those we see with, and that must have been overlooked despite centuries of research. "That just blew us away," he says.

After 20 rejections over five years and numerous additional tests to rule out other explanations, Czeisler's paper was published in 1995. Other researchers soon identified the mechanism behind what he had found. We now know there are specialised light-detecting cells in the retina whose signals go to the master clock in the brain, rather than to the visual cortex. In some blind people this system remains unaffected by whatever caused their blindness, allowing their clocks to stay on time.

These discoveries are turning out to have profound implications. It is becoming clear that even dim lights can affect our body clocks, meaning simply having the lights on late at night or staring at a computer screen can disrupt our internal rhythms. What's more, it turns out that blue light has the greatest power to change our clocks, and modern lighting is getting bluer. The potential effects go far beyond the unpleasant, jet-lagged feeling that body-clock disruption can cause. There is growing evidence that continual disruption is linked in the long term to serious illnesses including cancer, heart disease and diabetes. It can even alter the wiring of our brains.

It is not all bad news. Bright light during the day has, of course, long been known to mitigate the depressive effect of long dark winters on people who suffer from seasonal affective disorder, and recent research has demonstrated more general benefits. For example, elderly nursing-home residents exposed to very bright indoor light (around 1000 lux – roughly equivalent to outdoor light on an overcast day) for an hour in the morning were less likely to show signs of depression, according to a 2008 study (*Journal of the American Medical Association*, vol 299, p 2642).

Part of the reason for this is that our central clocks control levels of the hormone melatonin. When it gets dark, our melatonin levels rise, making us sleepy, while bright light turns off melatonin production and makes us more alert.

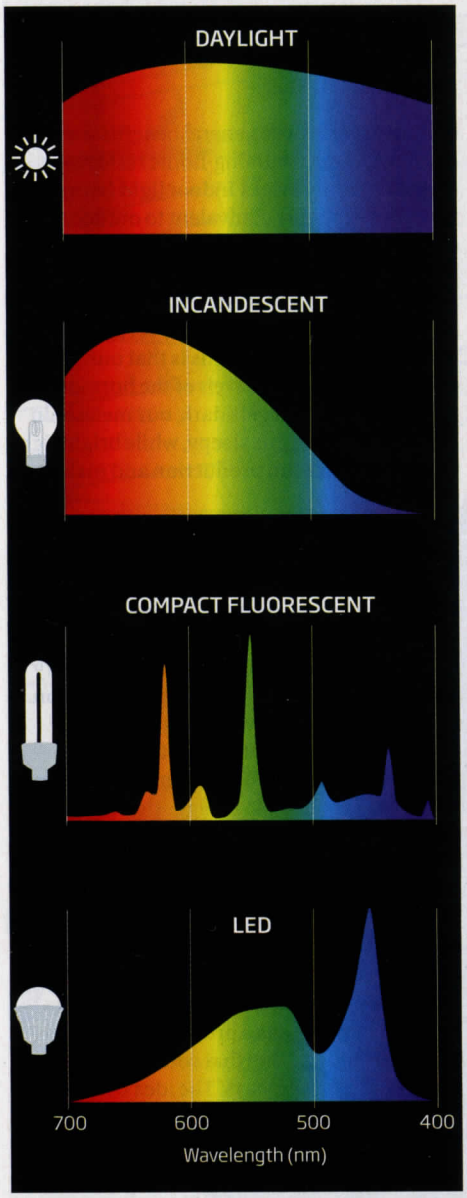
So light at night actually has two distinct effects. It can reset our internal clocks, as Czeisler showed, and it can also suppress the production of melatonin. The first to suspect the suppression of melatonin could affect our health was Richard Stevens at the University of Connecticut Health Center in Farmington. During the 1980s, he was investigating the causes of breast cancer, rates of which are much higher in developed countries. Stevens came across studies that suggested that too much light could alter the development of breast tissue and suppress melatonin secretion, and that lower melatonin might boost oestrogen levels.

That all came together for him one night as a street light shone into his apartment. He realised that the introduction of bright artificial lighting was a profound change in our environment, one that could be affecting our health in many ways. The idea became known as the light-at-night hypothesis, and there is growing evidence in support of it.

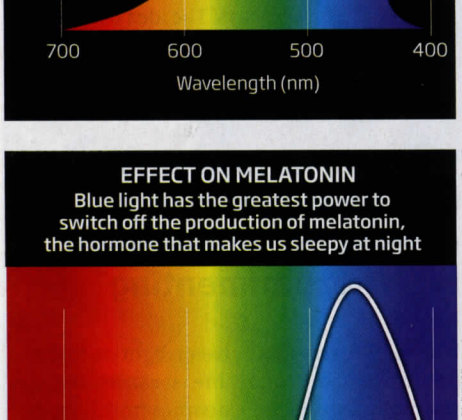
Several epidemiological studies suggest there is indeed a link between light-at-night and cancer, particularly breast cancer. Perhaps the most direct evidence comes from a study by David Blask of Tulane University School of Medicine, New Orleans, and collaborators. They implanted human breast tumours into female rats and pumped the tumours with blood from healthy women. The blood had been collected either in daylight, or at night after the women experienced 2 hours of ›

"We have no idea what low-level light at night does as the whole world is self-experimenting"

True colours
While the spectra of different makes of light bulb varies greatly, white low-energy fluorescent and LED bulbs typically produce much more blue light than conventional white incandescent bulbs



EFFECT ON MELATONIN
Blue light has the greatest power to switch off the production of melatonin, the hormone that makes us sleepy at night



SOURCE: JOURNAL OF NEUROSCIENCE, VOL 21, P 6405

complete darkness, or at night following 90 minutes under bright fluorescent light.

The melatonin-rich blood taken from subjects in total darkness severely slowed the tumours' growth, they found. Conversely, tumours grew much faster after receiving melatonin-depleted blood from women exposed to light (*Cancer Research*, vol 65, p 22274). "We can manipulate light and melatonin levels, and thus cancer growth rates, almost like a dimmer switch," says Blask.

Tumours also grow faster in mice made to follow schedules mimicking shift work or jet lag, says Steven Lockley of Harvard Medical School in Boston. The evidence implicating shift work in breast cancer is so extensive that in 2007 the World Health Organization categorised shift work as a probable cause of cancer.

If melatonin is the key, it is plausible that anything that suppresses melatonin could increase the risk of cancer. Lockley points out that totally blind women – with no functioning light receptors at all in their eyes – have a breast cancer risk half that of their sighted counterparts. "The totally blind women never have their melatonin perturbed, which may be the reason why their cancer risk is less," he says.

Besides cancer, disruption of our body clock and melatonin suppression have been linked to obesity, diabetes and cardiovascular disease. Studies show that night-shift workers have higher rates of heart attack and stroke than those on day schedules, for instance, and that the difference grows with the number of years spent doing the job.

Impaired thinking

Animal studies show that disrupted routines can even alter the wiring of the brain, impairing cognitive function, it was reported earlier this year (*Proceedings of the National Academy of Sciences*, vol 108, p 1657). Ilia Karatsoreos of The Rockefeller University in New York found that mice kept on an unnatural cycle of 10 hours of light followed by 10 hours of darkness lost neuronal complexity in the prelimbic prefrontal cortex, an executive part of the brain. Karatsoreos thinks the results are relevant to people. "I think this study is proof in principle that disrupting the clock by changing the light cycle can result in changes in the brain, behaviour and physiology," he says.

However, imposing a 20-hour cycle is like "hitting the system over the head with a hammer", he cautions. It remains to be seen if milder disruptions also have these effects.

"Disrupting the body clock by changing the light cycle can affect the brain, behaviour and physiology"

Meanwhile, studies have been showing that the blue wavelengths are by far the most powerful in shifting rhythms and suppressing melatonin. In 2001, George Brainard of Thomas Jefferson University in Philadelphia, Pennsylvania, and collaborators found that melatonin secretion was most powerfully suppressed when volunteers were exposed to very bright light at around 2 am, at wavelengths from 450 to 480 nanometres – squarely in the blue part of the spectrum (*Journal of Neuroscience*, vol 21, p 6405).

The findings suggested that the special receptor cells in our retinas contain a light-sensitive protein distinct from those we see with, and that it responds mainly to blue light. Sure enough, the cells were shown to contain a protein called melanopsin the following year.

In similar experiments involving extended nocturnal exposure to light, Brainard, Czeisler and Lockley showed that pure blue light of 460 nm suppressed melatonin for roughly twice as long as green light of 555 nm (*Journal of Clinical Endocrinology & Metabolism*, vol 88, p 4502). The blue light also reset people's internal clocks by 3 hours on average, compared with just an hour and a half for green light. Resetting clocks in this way means people find it hard to get to sleep the following night, and then feel tired in the morning.

More evidence comes from a study led by Leonid Kayumov at the University of Toronto, Canada. He asked some volunteers to wear goggles designed to filter out blue light. When volunteers did simulated shift work under bright indoor light (800 lux), melatonin production was suppressed in those not using the goggles, whereas those wearing goggles had melatonin secretion profiles similar to those of subjects exposed to dim light (*Journal of Clinical Endocrinology & Metabolism*, vol 90, p 2755). This suggests the use of such goggles could minimise the impact on shift workers or people staying up late (see "Use light right", right).

While blue light is worst in terms of affecting our body clocks at night, it is also the best kind

RYAN MCVAY/GETTY

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Light from televisions and phones could be disrupting our clocks

of light to have by day. Dieter Kunz of the Clinical Chronobiology Research Group at Charité University of Medicine in Berlin, Germany, waxes lyrical about the benefits of blue. "Bright blue in the morning is incredible. Throw away the pills," he jokes. Blue light also has the greatest power to keep us alert. Lockley has shown that people exposed to pure blue light responded faster in tests and made fewer mistakes than those exposed to pure green light (*Sleep*, vol 29, p 161).

So blue wavelengths appear to have the greatest influence on human physiology, day or night. There have been claims that full-spectrum lighting, which contains a mixture of all visible wavelengths and resembles natural daylight, is best for working environments, but the level of blue matters most as far as alertness is concerned.

These findings suggest that if light at night is a serious issue, it could be getting worse. Low-energy fluorescent bulbs and LED-based lighting usually produce much more blue light than the old-fashioned tungsten light bulbs they are replacing (see "True colours", left).

What's more, while most studies into the effects of night-time light have involved intense illumination over extended periods, recent studies are showing that normal home lighting and even dim light may be disruptive to human physiology. A study published earlier this year, for instance, found that for people exposed to normal room lighting in the late evening – less than 200 lux – melatonin levels rose later than in people subjected to dim lighting, and then remained high for about 90 minutes less (*Journal of Clinical Endocrinology & Metabolism*, vol 96, p 463). "One hundred lux gives 50 per cent of the maximal response under very bright light, and melatonin suppression can be measured at much lower light levels," says Lockley.

Besides suppressing melatonin, even relatively dim light sources such as table lamps and computer monitors can set back our internal clocks. "Our lab has shown that less than 8 lux is capable of entraining the circadian clock," says Lockely. The team speculates that this might explain the high prevalence of delayed sleep phase disorder, in which people have trouble getting to sleep and then wake up feeling tired. So how serious is this problem? "We have no idea what chronic low-light exposure does as the entire world is self-experimenting on using electric light at night," he says.

The degree of harm is likely to depend on the degree of disruption, Lockley says, but it would take a very large study to prove this. However, there is already plenty of evidence linking short sleep duration to increased risks of cardiovascular disease, stroke, high blood presssure, diabetes and depression.

It is a problem people can do something about. While researchers remain reluctant to provide specific guidelines for night-time lighting, we can get a glimpse of the latest thinking in this area from NASA. It recently reduced the upper limit of illumination in the general sleeping areas of spacecraft, where some astronauts might be active as their colleagues doze, from 20 lux to 1 lux (a lux is roughly equivalent to full moonlight). For dedicated sleeping areas, the upper limit is 0.02 lux (equivalent to a quarter moon).

Manufacturers could also help by selling lights for use at night that produce less blue. In fact, one newly launched kind of low-energy lighting, called ESL, has a spectrum more like that of incandescent bulbs.

Changing light bulbs is relatively easy. The hard part will be persuading people to turn off their TVs and put down their iPads well before they go to sleep. ■

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Use light right

BE ALERT IN THE DAY, SLEEP WELL AT NIGHT

- Get lots of bright light during the day, especially in the morning. It will make you more alert and happier, and help you sleep at night.
- As you get older, you will need more light during the day. The lens of the eye lets less light through as you age: in particular, it lets through less blue light, which is most important for setting your clock.
- Dim the lights well before your bedtime. That means no bright screens, either – including televisions, computers and smartphones.
- Maintain a consistent bedtime and wake time from day to day.
- Time spent in the dark makes your body clock more sensitive to light. If you have to get up during the night, use a dim red light to minimise any disruption.
- Avoid caffeine late in the day and develop a relaxing bedtime routine.
- If, despite doing all the above, you still struggle to sleep, try wearing amber-coloured goggles in the hours before bed. They are commercially available and designed to filter out blue wavelengths.