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The rhythm of everything

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Dawn triggers basic biological changes in the waking human body. As the sun rises, so does heart rate, blood pressure and body temperature. The liver, the kidneys and many natural processes also begin shifting from idle into high gear. Then as daylight wanes and darkness descends, these processes likewise begin to subside, returning to their lowest levels again as we sleep.

These internal biological patterns are tightly linked to an external cosmic pattern: the earth's rotation around the sun once every 24 hours. This endless loop of light and darkness and the corresponding synchrony of internal and external clocks, are called circadian rhythms, from "circa diem," Latin for "approximately a day." Circadian rhythms influence almost all living organisms, from bacteria to algae, insects, birds and, as is increasingly understood by science, humans beings.

Researchers are learning that these endless patterns also have profound effects on human health. "Circadian rhythms regulate almost every biological process in our body, especially hormone-related processes," says Yong Zhu, associate professor in the Department of Environmental Health Sciences at the Yale School of Public Health. He has traced the consequences of disrupting circadian rhythms right down to changes at the molecular level. His research is on the frontier where circadian rhythms and one's work schedule intersect with public health.

A collaboration is born

To understand Zhu's work, some background is helpful. Circadian rhythms are ancient. The pattern was established about 3 billion years ago, and life on earth evolved in accordance with it. Yet many aspects of circadian rhythms and their influences remain mysterious. Scientists partially understand how the synchronicity of internal and external clocks governs such things as migrating birds, hibernating bears and the navigational sun-bearings communicated by honey bees to their hivemates. Scientists also understand some of the links between circadian rhythms and human health. These rhythms, or disturbances of them, help explain such physiological phenomena as jet lag, winter blues (seasonal affective disorder), chronic insomnia and habitual fatigue among adolescents.

But it is only in recent years that researchers have turned their attention to the long-term health effects of disrupted circadian rhythms. About 25 years ago a cancer epidemiologist at the University of Connecticut Health Center named Richard G. Stevens wondered why breast cancer rates were so high, and highest of all in industrial societies. He suggested a possible link between breast cancer and a modern invention that constantly disturbed circadian rhythms—electric lights. Following this logic, he also postulated that female night shift workers would have higher rates of cancer than female workers on the day shift.

"People thought I was nuts," Stevens says today. "But this lighting of the night is new in human evolution. We figured out how to use fire probably a million and a half years ago, and we got candles about 5,000 years ago, but we weren't lighting the whole night. Electricity really changed things, with bright lights that can stay on all night. Our circadian system, which is ancient, is confused. The issue is getting a lot of attention now—things have been accumulating rapidly in the last 10 years—but it took a while."

This is where Zhu enters the picture. When he arrived at Yale a decade ago as a molecular epidemiologist, he happened to attend a lecture by Stevens at the school about the possible links between breast cancer and the circadian disruptions that result from modern life. Zhu, excited and intrigued, talked to Stevens afterward about applying his molecular expertise to Stevens' theory. "I realized that circadian rhythms probably have a tremendous impact on public health," says Zhu, "but people weren't paying enough attention." The two researchers started a collaboration that continues to this day.

Several core circadian genes—sometimes called clock genes—were identified in animals in the late 1990s. Zhu and Stevens decided to explore what Zhu calls the circadian gene hypothesis. "I wondered whether we could provide genetic evidence—that's the key issue—linking mutations in circadian-related genes to breast cancer risk."

Growing evidence

According to Stevens, two of their recent papers, for which Zhu was lead author, have pushed Zhu to the forefront of molecular researchers in this area. The first paper appeared in *Cancer Epidemiology, Biomarkers & Prevention* in 2005. Using cases drawn mostly from Yale-New Haven Hospital, the researchers identified a structural genetic mutation in the Period3 gene that was significantly associated with breast cancer. They further examined all 10 human circadian genes, particularly the core circadian gene called CLOCK, which the authors describe as "the heart of the molecular autoregulatory feedback loop," responsible for "maintaining the circadian cycle." These findings provided the first genetic evidence linking breast cancer with circadian genes. Zhu and his colleagues also found evidence linking mutations in circadian genes to prostate cancer and non-Hodgkin's lymphoma.

Further, they discovered that CLOCK regulates many other genes, including some associated with hormone production. In other words, circadian rhythms are deeply and systemically influential at the molecular level. Researchers call regulatory genes like CLOCK "transcriptional activators," which are also known as oncogenes or tumor suppressors—genes that can affect cancer development. The paper's clear implication is that when something knocks CLOCK out of sync with the universal circadian rhythm, the health consequences can be grave.

"Then we went one step farther," says Zhu. By that point, a number of studies had confirmed Stevens' hunch about the relationship between breast cancer and disrupted circadian rhythms. Studies in Denmark, Norway and the United States had shown that women of varying occupations who worked at night for long periods—nurses, caterers, flight attendants and others—had higher rates of breast cancer. Women who worked irregular rotating shifts suffered the highest rates, probably because their circadian rhythms were maximally disrupted. "Taking all studies into account," says Zhu, "the consensus is about a 50 percent increased risk of breast cancer." (In a fascinating corollary study, Stevens and others found that visually impaired women had a lower risk of breast cancer, with the lowest risk among blind women. "They don't perceive light at night," says Stevens, "so their circadian rhythm is robust.")

By 2007, the link between breast cancer and night shift work was so well-accepted that a panel of experts assembled that year by the International Agency for Research on Cancer concluded that "shift work involving circadian disruption is probably carcinogenic to humans." The biological causes, however, remained unknown.

"So we asked the question," says Zhu, "what exactly happens at the molecular level?" Using data from a landmark Danish study of female shift workers, Zhu and colleagues discovered the missing molecular link: in women who worked at night for at least 10 years and had breast cancer, the disruption of their circadian rhythms was detectable at the level of DNA, in epigenetic changes—that is, genetic changes caused by external influences. This breakthrough paper was published in late 2011 in *Chronobiology International*.

"It's a small study that has to be replicated," says Stevens, "but if it turns out to be true, it's absolutely dynamite, because then we have an environmental connection to heritable changes in the expression of genes."

The exact nature of the biological mechanism, however, remains unclear. That's Zhu's next target. He suspects that the disruption of circadian rhythms caused by night shift work suppresses the production of melatonin. Darkness triggers the release of this crucial hormone, which in turn signals certain biological processes to decelerate and helps us to sleep. Some research has suggested that when melatonin is suppressed, estrogen levels jump—a known cause of breast cancer.

Women who work at night under bright lights are habitually blocking the production of melatonin and perhaps increasing their risk of breast cancer. The obverse may also be true: melatonin has been shown to suppress mammary tumors in rodents. In his cell line work, Zhu has found that adding melatonin to cells helps them resist cancer and reduce its damage.

Worldwide, an estimated 15 percent to 20 percent of the female labor force works at night, but Zhu points out that many of these women probably are not susceptible to the risk factors he has studied, just as many smokers don't develop lung cancer. No one knows how much disruption of circadian rhythms is necessary to bring on problems; Zhu believes that this varies from person to person. He also expects the future to bring genetic tests that identify people who are biologically vulnerable to disruptions of their circadian rhythms.

In the last 30 years, the incidence of breast cancer in the United States has risen from 100 to about 135 per 100,000, according to the U.S. National Cancer Institute's SEER database. Disruption of circadian rhythms is one of many possible risk factors, but how large a role it plays remains unclear, partly because researchers don't yet know all the ways that circadian genes interact and combine with other risk factors. "For example," says Zhu, "premenopausal women who carry certain genetic mutations in a circadian gene are more likely to develop breast cancer, and some genetic associations between circadian genes and breast cancer risk have been detected among women with a particular ER/PR [estrogen receptor/progesterone receptor] status."

Future directions

The group at risk from circadian disruption includes males as well as females, across many occupations—police officers, airline pilots, firefighters, factory workers, business people who frequently cross many time zones and others. And the potential health risks extend far beyond breast cancer. Zhu's work, for instance, has implicated circadian rhythms in prostate cancer. Weaker evidence links circadian disruption to ovarian and colon cancers. Zhu expects this list of cancers to grow, especially hormone-related cancers. Research also has linked disturbed circadian rhythms to obesity, diabetes and chronic inflammatory diseases. That list, too, is likely to lengthen as scientists continue to unlock the mechanisms of circadian genes.

Zhu intends to be one of the lock pickers. He plans to replicate his results in bigger studies and to corroborate epigenetic changes among people who work at night or flout circadian rhythms by not getting enough sleep. "DNA repair gets triggered during sleep and works to fix all the genetic damage that happens during the day," he points out. Unrepaired cells are at greater risk cancerous changes. Similarly, circadian genes are directly engaged in regulating cell division, much of which occurs during evening or nighttime hours—probably because ultraviolet light can cause mutations and cells are more susceptible to mutation while dividing. All this means that people who work at night or have erratic sleep patterns may be more vulnerable to attack from cancer and other health problems.

Zhu hopes to collaborate on a new project soon with Mary A. Carskadon, director of Chronobiology and Sleep Research at Bradley Hospital in Riverside, R.I., and professor of psychiatry and human behavior at Brown University. Carskadon is a pioneering researcher on sleep and circadian rhythms in children and adolescents. Last spring while visiting Yale to lecture, she had a conversation with Zhu about his new epigenetic work. "In 20 minutes he taught me a huge amount," she says, "and he made one comment out of the blue that was so inspirational it changed one of my projects." The two now hope to collaborate on research about epigenetic phenomena.

"Basically his point was that, yes, you have a genetic background," says Carskadon, "but do experience and environment change your genes in a way that might either mitigate or accentuate your response to that environment? There have been epidemiological signals about shift work and cancer, but Yong has taken it to the next level with his work on CLOCK genes and epigenetics. It gives us a sense of the next steps to take, because it's fundamental research that could lead to clinical interventions by identifying people at greater risk."

Researchers are also looking for ways to work with circadian rhythms to improve health. Some medications, for instance, are more effective if given at certain points in the circadian cycle. Heart attacks and strokes are more common early in the morning, when heart rate and blood pressure increase to meet the day. That's why blood pressure medication should be taken first thing in the morning. Conversely, asthma attacks are most common at night, so preventive medication works best before sleep. Preliminary research suggests that some cancer chemotherapies are significantly more effective and cause fewer side effects when given at the optimal time of day.

Much of this remains experimental and outside of mainstream health care, though that is slowly changing, thanks to researchers such as Zhu, Stevens and Carskadon. Last June the American Medical Association adopted recommendations about the adverse health effects of nighttime lighting, based on a report by Stevens. In January of this year the Centers for Disease Control and Prevention issued a warning about the health risks associated with sleepy drivers, specifically night shift workers and people who don't get enough rest because of lifestyle or sleep disorders. Such people, said the CDC, are less attentive, slower to react and more likely to make poor decisions—consequences of ignoring circadian rhythms. These potential effects have led some medical schools, including Yale's, to alter the long hours and rotating shifts typically worked by medical residents.

"Circadian rhythms and sleep are central components of our biological systems," says Carskadon. "This is part of how life has been regulated forever. And yet we fly around the globe or work around the clock and ignore these signals. But we mess with these things at our peril. The implications span all of public health, from tumors to automobile accidents."

Zhu puts it more simply. "Every single species on earth evolved and adapted to this cycle," he says. "Any changes in it will impact our bodies."

Provided by Yale University

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