Jupiter's Belle: Article

Learning Day from Night…
By: Judy Foreman

For more than 25 years now, Debra Brandon has been looking for better ways to take care of preemies - babies born weeks or even months before they are ready to leave the safety of the womb.

In her early days as a nurse, recalls Brandon, now an assistant professor of nursing at the Duke University School of Nursing in Durham, N.C., it was standard practice to leave bright lights on all the time in NICUs, or neonatal intensive care units, the better to attend to the preemies' urgent medical needs.

Over the years, as researchers found that constant light was stressful for preemies, many NICUs switched to near-darkness, the better to mimic the darkness of the womb.

Now, in a provocative study published in February in the Journal of Pediatrics, Brandon has found that the best approach may be cycled light, that is, normal indoor lighting during the day and darkness at night, the better to replicate the day/night rhythms of the real world.

Brandon took 62 babies born at least 10 weeks prematurely and weighing, on average, 2 pounds. She randomly assigned them to three groups with different lighting conditions. She found that those exposed to cycled light earlier grew faster – at least 23 grams more per week - than those who got cycled light near the end of their hospitalization.

Brandon's study is music to the ears of scientists who study circadian medicine, which could be defined as the still-uphill battle to get doctors and hospitals to recognize the importance of natural biological rhythms in everyday medicine.

Granted, some hospitals are trying. At Brigham and Women's Hospital in Boston, for instance, the staff does "take circadian rhythms very seriously," says spokeswoman Christine Baratta, noting that lights and noise are kept to a minimum at night whenever possible.

Still, the Duke study is "exciting," says Dr. Charles Czeisler, chief of the division of sleep medicine at Brigham and Women's, because many hospitals still act as though "circadian rhythms don't represent a biological need," either in the way they treat patients or the way they treat doctors in training, who are often required to work 30 consecutive hours every few days.

"Hospitals aren't organized to take into account the body's time structure," agrees Michael Smolensky, professor of environmental physiology at the University of Texas School of Public Health in Houston. "Studies like this are a wake-up call," says Smolensky, whose research includes the way the same drugs can have different side effects and different degrees of efficacy at different times of day and night.

Getting hospitals to respect the basic rhythms of the body is no easy task. Some patients still say that they are awakened in the wee hours for CT scans, not because of an emergency, but because that is when the busy machines are available. It's also routine to wake patients before dawn to draw blood, not because that's a good time for them but because it's convenient for doctors to know the results early in the morning. Moreover, hospitals often try to wean patients from ventilators in the early morning, just when the biological rhythms that support respiratory drive are at their lowest.

Things can be even worse in intensive care units, where patients obviously need the most monitoring - but also need their sleep.

Many hospitals do try to keep ICUs dark at night, says Maureen Harvey, a nurse who is president of the Society of Critical Care Medicine. Yet it's at 5 a.m. "that everything happens - patients get their EKGs, they get their labs drawn, X-rays, they get weighed, bathed...it's ridiculous." Even though deep, slow-wave sleep is important for healing because that is the time when the body secretes growth hormone, she says, "most patients don't sleep for more than five to 30 minutes at a time."

Scientists have known for years that circadian rhythms are a basic part of biology. Indeed, most creatures on earth, even single-celled organisms, have an internal "clock" that governs circadian (literally, "about-daily") rhythms. This suggests that since the early days of evolution, there has been a clear survival advantage to synchronizing an animal's internal, chemical life to the light-dark rhythms of the outside world.

"You can live without a 'clock'," the structure in the brain that controls circadian rhythms, says Dr. Stephen Reppert, professor of neurobiology at the University of Massachusetts Medical Center. And some laboratory animals that have had this part of the brain destroyed do fine in the lab where food is plentiful and predators are not. In the wild, however, losing circadian rhythms could be fatal.

In people, at least those who work during the day and sleep at night, body temperature fluctuates according to circadian rhythms - rising in the morning, decreasing at night. Hormonal secretions follow daily rhythms, too. Cortisol, a major stress hormone, kicks in dramatically at dawn to prepare the body for daytime activity and decreases to near zero in the evening. Other hormones, such as thyroid stimulating hormone, melatonin and prolactin kick in during sleep.

Medical conditions also show circadian patterns. Heart attacks and strokes are most common in the morning, when a person gets up and when blood pressure and heart rate begin to rise. Asthma is often worse at night, when airways tend to constrict. Diabetes tests using a measure called glucose tolerance are different from morning to afternoon, even when the patient has fasted for hours before each test.

In humans and many other animals, the job of keeping the body's natural rhythms in sync with night and day in the outside world falls to a small cluster of nerve cells called the SCN, or suprachiasmatic nucleus, which lies in a part of the brain called the hypothalamus.

The SCN functions as a master clock that, using chemical messengers and neural connections to other parts of the brain, keeps the body in harmony with night and day.

Details have been emerging rapidly in the last five years, and here's how scientists now think it all works. When light comes in through the eye and falls on the retina, a specialized pigment called melanopsin in photoreceptor cells is activated, says Fred Davis, a biologist who studies circadian rhythms at Northeastern University
in Boston.

This in turn causes nerves to fire, transmitting a signal to the SCN, which lies just at the point where optic nerves from the two eyes cross. The SCN then releases a chemical signal (glutamate) which acts on one or more "clock" genes in the nucleus of SCN cells.

So far, scientists have found at least eight such genes, giving them names like "clock" and "period." Through a complicated feedback system, the "period" gene, for instance, turns itself on and off rhythmically over the course of 24 hours, even in the absence of light, Davis notes. But when it's in its "off" cycle, if light triggers the SCN, the cycle is speeded up. Light, in essence, re-sets the SCN clock so that biological rhythms are in sync with the light/dark rhythms of the outside world.

The fact that nature has gone to such trouble to keep the body's cells and organs in sync with day and night strongly suggests that doctors and hospitals should, too.

For one thing, drugs can have different effects at different times of day and night, notes Smolensky of Texas. In studies of rodents and people, for instance, the antibiotic gentamicin has been shown to have more adverse effects on hearing and kidney function at night.

On the other hand, chemotherapy drugs for colon cancer such as 5-FU (fluorouracil) and leucovorin cause fewer side effects if given during the night. Some blood pressure lowering drugs have different effects depending on whether they are taken in the morning or at night. Some cholesterol lowering drugs must be taken in the evening for maximum effect.

Basic sleep/wake cycles can become disturbed, too, when hospital schedules disrupt circadian rhythms. It's been known for decades, for instance, that ICU patients can become confused when they don't get normal light/dark signals, a major reason why many states now have guidelines for ICU construction stipulating that ICU rooms have access to windows and outside light.

Even when it's impossible to put a window in an ICU room, there are ways to help boost patients' awareness of day/night rhythms, says Donald Axon, an architect in Laguna Niguel, California who designs ICUs and is working with the Society of Critical Care Medicine to update its guidelines. Some hospitals, for instance, install special lighting on nature scene pictures for patients' walls so that the light in the picture gets brighter during the day and dimmer at night.

The bottom line? Many routines in hospitals can't easily be changed, especially in ICUs for adults and preemies, the sickest and most fragile of patients. But the more patients can be kept on normal day/night cycles, the better, says Brandon of Duke. Lighting, she says, is "the most practical time-of-day cue we can provide."

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SIDEBAR

The first few months of a baby's life are a fascinating period in terms of circadian rhythms. Circadian rhythms control when natural labor starts. Indeed, birth is more common between midnight and 6 a.m., presumably because evolution determined that this is the safest time.

When an infant is first born, his circadian clock is in sync with his mother's clock, particularly her rest/activity cycle. Even though the infant's own circadian clock is active at birth, however, it doesn't become fully operational until three months, when the rest/activity pattern and secretions of hormones fall more solidly into a day/night cycle.

Many people assume that because it's dark in the womb, a developing fetus has no circadian rhythms. That's not true, says Dr. Scott Rivkees, a pediatric endocrinologist at the Yale University School of Medicine.

In the womb, the fetal clock is already functioning and day/night rhythms in clock activity can be detected. But instead of being re-set every 24 hours by daylight and darkness in the outside world, the fetus's rhythms are controlled by chemical signals that cross the placenta from the mother.

Melatonin, for instance, a hormone secreted in the pineal gland in the brain during darkness, can cross the placenta, and there are receptors in the fetal brain "clock" for melatonin. The timing of the mother's feeding also seems to send signals to the fetal clock. Another hormone called dopamine, secreted by the fetal clock, may also help keep the fetus and mother in sync.

Once a baby is born, however, his circadian clock often falls out of sync with that of the mother and the light/dark cycle of the outside world unless he is exposed to regular light/dark cycles.

It can take about three months for day/night rhythms in sleep and hormone production to kick in, says Rivkees, who is conducting a large study of preemies, and, like the Duke University researchers, is comparing their behavior and development under conditions of constant near-darkness and cycled light.

It's not clear, Rivkees adds, why babies exposed to cycled light would grow faster, as the Duke team found. But even if cycled light does not spur growth per se, it may have other advantages. His hypothesis is that cycled light may help babies get back in sync with the world, and more important, their mothers. And that this in turn can make for better maternal-infant bonding, with all the positive effects that holds.

Ultimately, what may really matter most, especially in neonatal intensive care units is to tailor care to a baby's individual needs and rhythms, says psychologist Heidelise Als, director of neurobehavioral infant and child studies at Children's Hospital in Boston.

This means minimizing the degree to which lights in the unit are suddenly switched on or off, watching for subtle signs of distress - like rigid, jerky movements or a panicked, glassy-eyed look - and making extra efforts to let stressed-out preemies sleep on a parent's chest in a dim, quiet room.

For more information, you might want to read:

- "The Body Clock Guide to Better Health," by Michael Smolensky and Lynne Lamberg.
- You can also check out:
    - www.bodyclocks.com and
    - www.ammcc.org the American Association of Medical Chronobiology and Chronotherapeutics).