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THE POWER TO MAKE OR BREAK OUR HEALTH, FROM BIRTH TO ADULTHOOD AND EVER AFTER | BY ELAINE VITONE

SLEEPING'S BEAUTY

Pick a piece of your physiology, any piece. Heart health, lung health, kidney health. Appetite and metabolism. Or consider memory, learning, and emotion. Pain. Aging. The immune system. Neurological development. Fetal development. Heck, any cellular-level kick-starting or daily humming-along, period. Every single aspect of our health that's been measured so far has been directly linked to sleep. There are "clock genes" in every cell of our bodies. How we operate in our 24-hour rhythms is central not only to the quality of our lives but also how long we get to live. That could make for a pretty scary bedtime story, given that we live in a culture that tends to squeeze in shut-eye between the 11 o'clock news and breakfast.

"Measuring sleep is like measuring temperature and blood pressure," says David Kupfer, an MD and the Thomas Detre Professor of Psychiatry and a professor of neuroscience and of clinical and translational science in the University of Pittsburgh School of Medicine. (Kupfer served as chair of psychiatry when that department, with Western Psychiatric Institute and Clinic of UPMC, or WPIC, first became known as a preeminent research center.)

A sleep schedule gone askew can have devastating effects throughout the life cycle. Fortunately, sleep is a modifiable behavior.

ILLUSTRATIONS | CATHERINE LAZURE

When we lose step in our 24-hour rhythms and feel the inevitable effects, it's an outward sign that something's wrong, Kupfer says—or, many times, if sleep problems are left untreated, something will be.

A couple years ago, for the first time in its 30-plus-year history, *Healthy People*—the marching orders the U.S. Department of Health and Human Services (HHS) issues as benchmarks for better health—included an entire chapter on sleep. But the integral role of sleep in every aspect of medicine has been a mantra at Pitt for decades now.

It all started once upon a … okay, in 1973, when Kupfer came here from Yale as the first recruit of the late, great head of WPIC, Thomas Detre, to set up a chronobiology lab—one of the first four or five clinics of its kind in the country. Kupfer was among the first to look at sleep as a biological marker of depression, and those observations were among a few that prompted the biological revolution in psychiatry.

Sleep research at Pitt helped bring psychiatry into the realm of the biological science of the body. And ever since, Kupfer and Co. have urged Pitt's medical community to (so sorry) wake up to sleep.

"Now we have a third generation of sleep researchers here," says Kupfer, adding that Pitt has probably had more federal funding in this area than just about any other institution—and is beginning to train more people.

About five years ago, the 50-some-odd sleep researchers scattered across the University began to organize more formally under what's now called the Sleep Medicine Institute, which is based on the 11th floor of WPIC. It's a veritable Who's Who of sleep peeps: former presidents of the American Academy of Sleep Medicine and the Sleep Research Society, and authors of the sleep-disorders section of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM). (Kupfer mentee Charles Reynolds, UPMC Endowed Professor of Geriatric Psychiatry and director of the Pitt/UPMC Aging Institute, chairs the sleep-disorder group for the forthcoming DSM-5. Kupfer himself chairs the overall DSM-5 task force.)

At sleep-medicine conferences, it's hard not to notice Pitt people; their colleagues call Pittsburgh a "sleep mecca." On these pages is a sampling of what these scientists—with support from the National Institutes of Health, the Commonwealth of Pennsylvania, the Department of Defense, and Pitt's Clinical and Translational Science Institute, among others—are uncovering about sleep and human health.

They're finding that a sleep schedule gone askew can have devastating effects throughout the life cycle—but, fortunately, sleep is a modifiable human behavior. When we sleep better, we drift back to health, both in body and mind. Our zzz's can become the stuff of a Disney happy ending rather than a grizzly Grimm fairy tale.

DOWN WILL COME BABY

"There is absolutely no excuse for watching the 11 o'clock news," says Pitt's Timothy H. Monk, PhD, DSc professor of psychiatry. "I always say that when I'm interviewed on TV programs, and it ends up on the cutting room floor."

Monk, who has a sense of humor about just about everything except the importance of a healthy sleep rhythm, has been studying the body clock since 1974, back when people wouldn't even use the term *circadian rhythm* without putting quotes around it. He investigates what happens to sleep, performance, and mood when the biological clock is disrupted—by jet lag, space travel, depression, age, what have you. Monk wrote some of the first studies showing disruptions in circadian rhythms experienced by night nurses, astronauts, depressed patients, and octogenarians. He also developed widely used tools for measuring sleep rhythmicity.

Most of Monk's work has focused on late adulthood, but in recent years, he has learned that a botched circadian cycle can be detrimental even in infancy ("something a million miles from your thoughts," he says with a laugh, gesturing to this writer's then-very-pregnant belly).

Collaborating with researchers at the University of Wisconsin in the early '90s, Monk enlisted new parents in a study of their 1-month-old babies' daily routines, charting out their sleep times as well as their time spent feeding, playing, diaper-changing, and cuddling-up for comfort. Monk's Wisconsin colleagues then revisited these families several times throughout the tykes' school-age years.

A bad night's sleep can turn even the most amiable among us into monsters the next day. Can poor sleep patterns impair the ability to regulate our emotions in the longer term?

The team found that the babies with irregular sleep and lifestyle routines were significantly more likely to grow up to have anxiety in early adolescence.

Monk believes that, among other factors, more regular routines for Baby make for a more predictable set of demands on Mom and Dad, which in turn makes the parents more cued into their kids' cues. When these things line up, parents are all the more confident in their parenting skills. And a confident parent who's attuned to a baby's needs is exactly the sort of parent to turn out children who can regulate their emotions.

So what's his advice for new parents? Is there anything we can do? Are the circadian rhythms of kiddos set by nature or nurture? "Both. So you help it along," says Monk, adding that letting the sun shine into the room during the daytime and darkening the bedroom at night certainly help. But mostly, it's about tending to an infant differently at night than you do the rest of the day. "At night, you're talking quietly, you're soothing her. But in the morning, it's, *Hey, Baby!*"

MONSTER UNDER THE BEDHEAD

Sleep and emotion have all sorts of interesting intersections (which David Kupfer, Charles Reynolds, and others at Pitt have helped to uncover, by the way): People with insomnia often have problems with emotion regulation. Depression is more severe and resistant to treatment in people who have poor sleep, and it's often preceded by poor sleep. And then, of course, even for those of us who don't suffer from either malady, an all-nighter—or even a bad night's sleep—can turn the most amiable among us into monsters.

So, Peter Franzen, Pitt assistant professor of psychiatry, wondered: Is this more than just coincidence? We all have our own anecdotal evidence along these lines, but is this something you can measure in a lab? And what is the cumulative effect? Over time, can poor sleep actually

sabotage our emotional health?

Franzen did a pilot study of teens in their all-too-typical state—way more sleep deprived than their still-developing brains ought to be. He showed them photographs of emotionally charged scenes and played for them recordings of disturbing verbal exchanges, then asked the teens to control their emotional reactions to these stimuli. Meanwhile, Franzen's team measured the teens' pupil-dilation responses: "It's sort of an old-school measure [of emotional regulation]," he says, "but it's cheap and easy to do, and it's noninvasive." (Pupil dilation also coincides with cognitive function. So, just to be sure that wasn't what was behind any changes in their peepers, Franzen also observed the kids discussing conflict with their friends and measured signs of emotional regulation or lack thereof.)

Sure enough, when Franzen compared the sleep-deprived adolescents to controls, pupils were about twice as big when the sleepy kids were exposed to negative stimuli. (Their interactions with their friends hinted at a similar pattern—dominance, aggression, general short-fusedness.)

With a new National Institutes of Health Research Project Grant (a.k.a. R01 grant) in hand, this summer Franzen is launching a full investigation of these pilot-study results, hoping to finally arrive at the first objective measures of impaired emotional control related to sleep deprivation. He's comparing the results of the teen studies to his previous work with young adults, probing the question of whether or not adolescents are more vulnerable to the ill effects of sleep loss. And further down the road, he plans to tease out how exactly neural circuitry changes when people, especially adolescents, don't get enough sleep.

Even as kids are waking up early for the 8 a.m. school bell, they're burning the midnight oil—because that's what they're hardwired to do, says Franzen. "At puberty, the desire to stay awake at night is not just social—there are biological influences, too."

The teen years are such a vulnerable time—"when kids are increasing their risk for development of substance abuse and depression," says Franzen. He hopes that by showing neural circuitry shifts at work, eventually he can make a case for screening kids in the clinic and flagging the ones who may be headed for trouble. "Adolescence is perhaps a unique opportunity to prevent a problem from happening in the first place," he says.

SNORING: THE CINDERELLA OF SLEEP

Though still underdiagnosed, sleep apnea has gained attention as a serious public-health risk. The evidence continues to pour in. For example, Patrick Strollo—professor of medicine and of clinical and translational science, medical director of the UPMC Sleep Medicine Center, and codirector of the Sleep Medicine Institute—found a whole new reason these patients have such poor outcomes: They have higher levels of a particularly bad form of artery-hardening cholesterol called LDL subclass B.

But snoring? It's the other sister, just sort of *there*, like background noise. We've always taken for granted that, yes, people who report snoring tend to have health problems, but that's just because they have sleep apnea, right? In five decades of research on sleep disturbances and their devastating effect on cardiovascular health, we've never really monitored snoring.

But a few years ago, when Tom Rice (Fel '11) began working with Kim Sutton-Tyrrell, a cardiovascular epidemiologist in Pitt's Graduate School of Public Health, he read an Australian study with a small sample of snorers verses nonsnorers. It suggested that sawing logs—or rather, the resulting vibrations in the neck that rattle the carotid artery—might actually do damage, independent of sleep apnea.

Piggy-backing on a cardiovascular-risk study of Sutton-Tyrrell's, Rice studied young adults who were overweight but who had not developed cardiovascular disease, measuring the vibrations in the air flow in their noses as well as their carotid artery wear and tear over time. The results were more impressive than he'd expected: Nonsnorers in the study had healthy, thin carotid walls. People with sleep apnea, as it's long been known, have thick carotid artery walls. But the snorers in Rice's study were somewhere in the middle.

Snoring, it seems, could be part of a gradual progression to heart attacks and strokes.

"We don't know all the reasons sleep apnea leads to cardiovascular disease," says Rice, who's now assistant professor of medicine. He adds that fragmented sleep and lack of oxygen explain some, but not all, of it. "[Perhaps] snoring damages the arteries in the neck and then makes them more susceptible to the damage from the low oxygen level."

Rice presented the findings from his ongoing, now-NIH-funded study at the International Symposium on Sleep and Breathing in Barcelona last spring.

Assistant Professor of Psychiatry Wendy Troxel (PhD '05), another one of the many Pitt people who trained here in sleep medicine and stayed to join the faculty, has also made surprising discoveries regarding this Cinderella of sleep disturbances. In the journal *Sleep* in 2010, Troxel published the first prospective study showing that people who report snoring and insomnia complaints had greater risk of developing metabolic syndrome, a cluster of factors that increase the odds of getting heart disease. These findings are the first to show that commonly reported sleep problems, including snoring and difficulty falling asleep, can predict the onset of metabolic syndrome over a three-year follow-up period.

Some 40 to 50 percent of the U.S. adult population snores, and those are just the ones we know about. If you sleep alone, or if your better half is sleeping soundly, you could be a snorer and be none the wiser.

Sawing logs—all in a night's work? Evidence suggests that snoring may be part of a progression to cardiovascular disease.

MOTHER'S SLUMBER, SPOILED, SPELLS TROUBLE

Michele Okun (Fel '07) knows her preggos. She can even guess the exact gestational stage of a *Pitt Med* writer just by looking at her (33 weeks at the time I waddled into her office). "Glad I haven't lost my touch," she says. "I haven't worked with third-trimester women in a long time."

For 10 years, Okun, a PhD assistant professor of psychiatry and psychology and a psychoneuroimmunologist, has studied the impact of disturbed sleep on women's health. The past few years her focus has been on weeks 10 to 20 of pregnancy. This is when cells within the uterus begin to expand and remodel to conjure up that most crucial cauldron of baby-making magic: the placenta.

Okun explains that throughout pregnancy, the immune system churns in a delicate balance, its demands constantly changing. Too little inflammation at the onset, and the blastocyst can't implant properly. Too much immune response at various points thereafter, and the woman's body rejects the fetus.

When the placenta is developing is the most precarious time. The most dangerous outcomes of pregnancy—low birth weight, preterm birth, preeclampsia, you name it—are associated with heightened levels of cytokines, messenger cells that signal immune responses, during this critical interval.

And what's one common cause of climbing cytokine levels? Sleep loss, of course.

Okun says that in common lore as well as in ob/gyn literature, everyone assumes women are supposed to be cursed with crummy sleep pretty much the whole way through pregnancy. But in Okun's ongoing, four-year study, which was funded by a K99/R00 grant from the NIH, she has found that this is, first of all, not true. (In fact, in the first trimester, about 30 percent sleep very well, and another 30 percent sleep poorly.) And secondly, it is a potentially pretty dangerous assumption. As she follows the outcomes of the women in her study, she's finding that those who sleep poorly between weeks 10 and 20 are indeed having more complications. Eventually, Okun hopes her work will inform a new set of primer questions that ob/gyns can use to screen for problems from the get-go—an idea that's pregnant with potential.

HAUNTING

Sleep affects health, which affects sleep. It's a complicated mess to sort out, which is why most academic medical centers' sleep programs have single-disease foci. But Pitt's sleep think tank is different, says Martica Hall, associate professor of psychiatry and psychology and of clinical and translational science. "I think it's fair to say in Pittsburgh we've created the most diverse set of studies investigating the bidirectional relationship between sleep and health."

Hall, who came to Pitt for her PhD in biopsychology in 1995, was the first of Pitt's sleep peeps to study physical health, and she's proud to have fostered what's now a very big interest in this giant, sprawling family of researchers. "It's a big sandbox, and we're having a lot of fun."

Hall's particular interest is how stress affects sleep, which, in turn, affects stress, and how that whole ugly cycle has a way of throwing our health for a loop. She's studied how acute and chronic stress stymie sleep and health in a number of populations: adolescents, young adults, parents of sick children, people with insomnia or depression, caregivers, elders in bereavement. In measuring heart-rate variability—a sign of a healthy ticker capable of adapting to a changing environment—Hall has shown that everyone, even healthy young college kids, do worse by this measure when they're introduced to acute stress before they hit the hay. "I call it haunting," she says.

As principal investigator on the ancillary sleep study to the NIH's Study of Women's Health Across the Nation, Hall conducted the first multisite study to understand who develops sleep disturbances during menopause and why. So far, she and her collaborators have published numerous papers to this end, on everything from the intricate dance between hormones, hot flashes, and brain activity during sleep to how factors like marriage affect sleep.

One factor that's clearly accounting for significant differences is race. African American women have the highest risk for persistent sleep disturbances, she's found—even when you control for stress level, hot flashes, health complaints, medication, environment, depression, worries about money, and more.

However, there's something "very intriguing" going on that doesn't yet add up, she says.

"If you look at brain waves in African American women, they do not sleep as deeply as white women, but their periphery tells a different story. Their heart rate variability during sleep is more ideal than that seen in whites. So now we are taking a step back to try and better understand more about race differences in nocturnal physiology. Because we actually know very little."

A team of researchers is trying to understand who develops sleep problems during menopause and why.

TURNING THE PAGE

Imagine a truck lumbering down a dusty desert road. Out of nowhere, there's an explosion, an ambush, a threat that's audible with terrifying clarity, but you can't see it. The person in the seat beside you is hurt, but you can't tell how badly. You are scared, out of breath, and utterly helpless. And then you wake up.

This scenario is all too typical among the nearly 2 million who have served in the wars in Iraq and Afghanistan. For 90 percent of people with post-traumatic stress disorder (PTSD), the brain has a terrible habit of replaying nightmares night after night. The lack of sleep only compounds what they're going through: feeling anxious, irritable, depressed, and frustrated as they struggle to reenter school, family, friendships, and work environments. Concentration suffers. Tempers rise. Isolation, despair, and alcohol and substance abuse often follow.

Poor sleep is a risk factor for PTSD, depression, and substance abuse. But this newest generation of foreign-war veterans has given researchers the chance to, for the first time, study—and, more importantly, screen and intervene for—those returning from combat zones before a long descent into illness. "If we can fix this one aspect, sleep, we may have a broad impact on mental health," says Pitt's Anne Germain, PhD associate professor of psychiatry.

"And it's one that people want. They want to sleep well." In

addition, for many veterans, help with a sleep disorder—one mental health complaint that doesn't carry a stigma—is a gateway treatment to addressing other difficulties they may have.

Germain teaches veterans how to stop replaying their nightmares, which have become involuntary habits, default modes for their sleeping minds. Through writing and visualizing exercises that she's developed, Germain trains veterans to finally turn the page and dream about something else by focusing on a whole new set of images of their choosing.

She's also fine-tuning and packaging the treatment so that it's easy for primary care providers, nurses, social workers—any number of people with even minimal training in mental health—to provide the treatment, as well.

Germain is pressing on and digging deeper, trying to understand what happens in the sleeping brain of a person who's been exposed to traumatic events, in hopes of finding better treatments. In the past six years, she has studied some 400 veterans; one additional year's work will complete the data-analysis portion of this U.S. Department of Defense–funded project.

In imaging studies, Germain is showing that, in both waking and REM/dream-sleeping, the brains of veterans who have PTSD light up in regions of emotional reaction and alertness: the amygdala, the hippocampus, the medial cortex, and the arousal regions of the brain stem.

"Your brain is saying, 'Something's going on—better be ready.' You get stuck in this state of hypervigilance of threat, and you never get a chance to get out."

Germain is studying veterans before and after a successful course of treatment. She's also looking at veterans with PTSD who do not have sleep problems in hopes of figuring out what makes their sleep so resilient. These insights, she says, could be useful in helping veterans and civilians alike.

"These are people who are already more resistant to stress—I don't know about you, but I don't think I could get through boot camp—and they still aren't immune to the impact [trauma] has on sleep or mental health. If we can understand how to treat combat-exposed military veterans, we can generalize to anyone who's exposed to not just traumatic events, but milder stressors, too, and still have a big impact on sleep."

PRECUNEUS AND CURIOUSER

Trying—and failing—to fall asleep all night is exhausting. Typically, people with insomnia will sleep late whenever they get a chance. Their circadian rhythms get so out of whack that their bodies have no idea when it's time to settle down for the night.

But usually, people with insomnia find that their sleep improves once they learn a few basic principles: restrict the time you spend in bed; establish a regular waking-up time; put off going to bed until you're actually sleepy; and, if you find yourself stuck, wide awake, get out of bed and go do something else until you're tired.

"It sounds pretty obvious," says Daniel Buysse (Fel '89, Res '87), "but I can tell you, when you present these to people with insomnia, their jaws often drop in amazement. They've often been doing exactly the opposite."

Buysse, professor of psychiatry and of clinical and translational science, director of the Neuroscience Clinical and Translational Research Center, and codirector of the Sleep Medicine Institute, is one of the world's leading experts on insomnia. (In the late '90s, he spearheaded the now widely used Pittsburgh Sleep Quality Index.) He explains that sleep scientists have shown again and again that behavioral treatments are more effective than going down the rabbit hole with sleeping pills, the side effects of which often prove to be too much for people. Here's the problem: Behavioral treatments typically take eight weeks of one-hour sessions with highly trained clinical psychologists. "The prevalence of insomnia far outstrips supply of this treatment," Buysse says. "I ran into this in my clinic. I just don't have the time."

So starting in 2003, Buysse adapted and distilled the treatment to a one-month course of two in-office counseling sessions and two follow-ups over the phone that teach patients to realign their body clocks. They restrict their sleep at the onset, among other changes in their routines. They build sleep pressure so that when they finally hit the pillow, sleep comes quickly, and at the appropriate time.

Buysse and his sleep-medicine cronies on the 11th floor of Western Psychiatric Institute and Clinic of UPMC have used this treatment, dubbed BBTI (Brief Behavioral Treatment for Insomnia), with great success for years. And clearly, it's working—they just don't know why. That is, they don't know what makes the brain of a person with insomnia different from the rest of the waking-when-we're-supposed-to world, or what happens biologically to help people with insomnia snap out of it.

Buysse may be closing in on the reason, though—and it has to do with a particularly curious puzzle when it comes to people with insomnia. They complain not just of sleeping too

little, but also that the sleep they do get is lousy, like they were never really asleep at all. And yet when you bring them into the sleep lab and measure their brain waves, they seem to snooze no differently than the rest of us.

Using a brain-imaging technique called ^{18}F-FDG PET imaging, in conjunction with EEG sleep studies—a technique that was developed in the '90s by Pitt's own Eric Nofzinger (Res '91, Fel '93), professor of psychiatry—Buysse measured metabolism in the brains of people with insomnia. Buysse found that, both in sleep and wakefulness, these patients had unusually high levels of activity in regions called the precuneus and the posterior cingulate. These sites take over, essentially, when you put your brain in neutral—when you daydream, tease out your what-ifs, and let your mind wander to the other side of the looking glass.

But after sleep restriction (similar to what's used during BBTI), it's a totally different story. In Buysse's preliminary studies, he's found that the precuneus actually pipes down, allowing the person to sleep more deeply.

Buysse laughs, a Cheshire Cat grinning over the possibilities. "Behavioral treatments often cause the person to have less sleep, yet people say that they're feeling better. It just does not make sense! But maybe the thing we need to do with our treatments is not to increase sleep, but to decrease the activity in this self-monitoring center of the brain during sleep. It could be that all this sleep monitoring we've been doing with EEG may be a huge red herring. EEG tells us what the brain is doing globally, but insomnia may be something that happens locally in specific brain regions.

"This is potentially really cool. If it really holds up, it could be a pretty fundamental change in what we think of as insomnia."

PEOPLE WHO GO BUMP IN THE NIGHT

Say your grandpa falls asleep in his La-Z-Boy while watching a preprime-time episode of *Wheel of Fortune*. By the witching hour, he's already gotten most of the sleep he needs for the night, so naturally, by 2 a.m., he's wide awake. This becomes his habit, so he goes to the doctor and says he has insomnia. The doc then may prescribe a bottle of sedatives—potentially dangerous stuff to have onboard when Grandpa inevitably gets up in the middle of the night to empty his bladder.

Up to 10 percent of seniors have serious insomnia, and for this population, it's more than a nuisance. The wee-hour puttering of an elderly family member going bump in the night can be very disruptive to the other family members, who have work and school and a 6 a.m. alarm to worry about. And knowing that is distressing for Grandpa, too.

It all comes back to circadian rhythms, says Pitt's Timothy Monk, who directs the Human Chronobiology Research Program at WPIC. "The circadian signal isn't as strong as people get older," he says, though some people fare better than others. To discover exactly why—and how the strengths of the superior snoozers might inform better treatments for seniors with insomnia—he's leading Pitt's sleep dream team in AgeWise, a large, five-year study funded by the National Institute on Aging. It's an all-encompassing look at the role of seniors' circadian rhythms, sleep strength, stress reactivity, functional brain neuroanatomy, and genetics in these folks' responses to a standard behavioral treatment of insomnia. (So far, a good portion of the seniors in the study are responding well.)

If more and better therapies became available for seniors, the potential public-health impacts could be huge. Between the stress of disturbing the family's sleep and the very real threat of a hip-snapping trip over the cat, sleep problems are among the biggest reasons people transition to nursing homes.

Sleep makes or breaks us all, from cradle to La-Z-Boy. And it's worth the investment of our time, says Monk.

"You've got to think of sleep as something you do. It's not something that just fills the time when you're not doing things. It's something you do." ■

Pitt's sleep researchers are always looking for participants to volunteer for their studies. Call 412-246-6413.