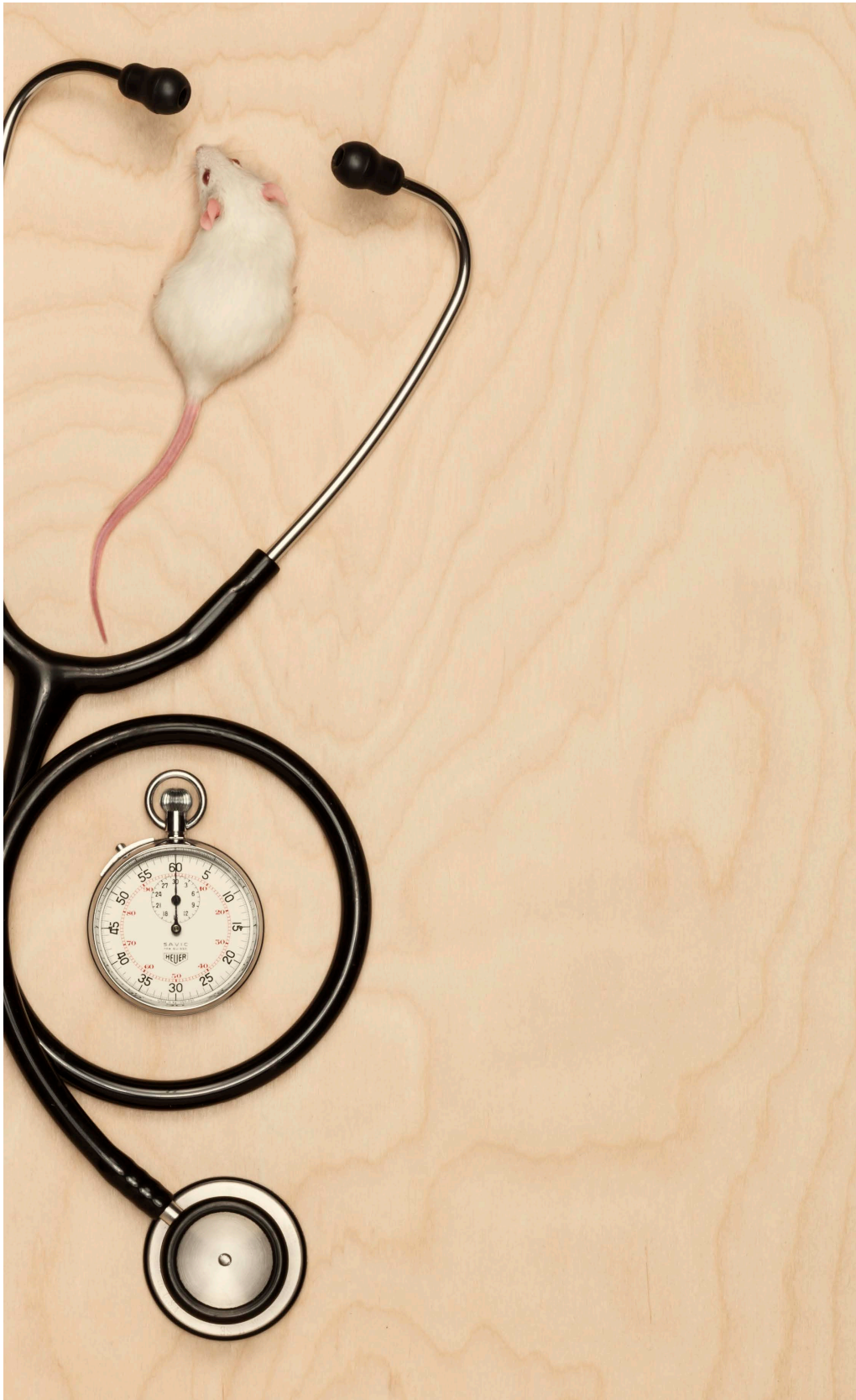
STANFORD MEDICINE

Spring 2015



special report

LIFE TIME
THE LONG AND SHORT OF IT

Body clocks
What makes us tick

Abraham Verghese, MD
'We don't make people immortal'

Days are long, years are short
A young surgeon's life at sunset

911
The chopper's on the way

How long can people live?
The biology of aging

plus

The Nobelist
Paul Berg's winning choice

Three times a baby
Saving the Luevanos triplets

STANFORD MEDICINE

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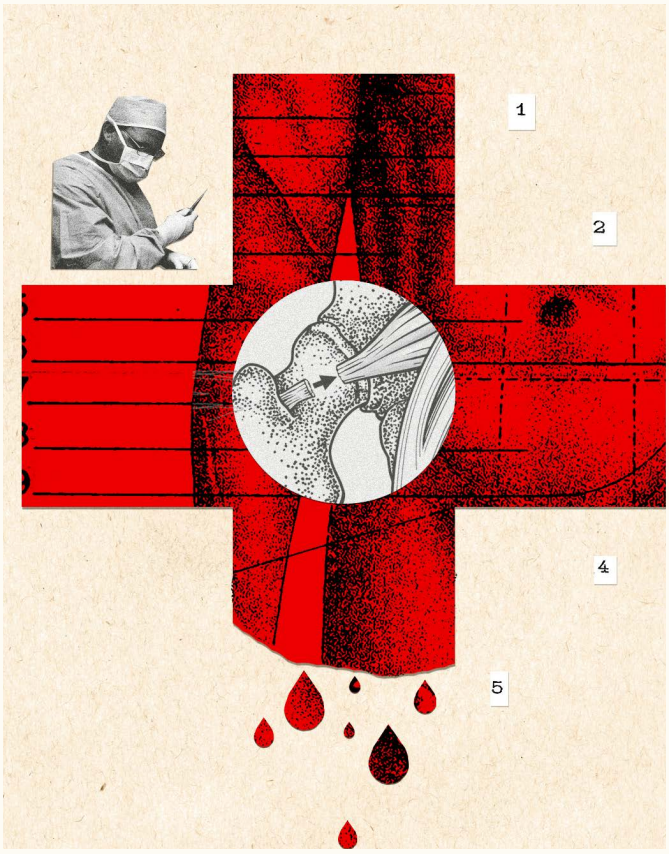
TRUE BLOOD

PREDICTING A SPEEDY RECOVERY

The millions of people who undergo major surgery each year have no way of knowing how long it will take them to recover from their operations. Some will feel better within days. Others won't for a month or more. Right now, doctors can't tell individual patients which category they'll fit into. But Stanford researchers have discovered that the activity level of a small set of immune cells during the first 24 hours after surgery provides hints about how quickly patients will bounce back from surgery-induced fatigue and pain, and be back on their feet again. • "We learned that within the first 24 hours after surgery you can find strong clues in blood that reveal what shape a particular patient is going to be in two weeks later," says Martin Angst, MD, professor of anesthesiology, pain and perioperative medicine, who shared senior co-authorship of the study with microbiology and immunology professor Garry Nolan, PhD.



The discovery could lead to the development of a blood test for predicting recovery after major surgery. Such a test could both help physicians optimize recovery regimens and let patients know what to expect. A full understanding of the molecular mechanisms identified in the study might even make it possible for clinicians to manipulate the immune system to foster faster recoveries.

In the study, published in *Science Translational Medicine*, the researchers analyzed blood samples drawn from 32 middle-aged to older patients undergoing a hip-replacement procedure. The highly sensitive technology used for the analysis — single-cell mass cytometry — simultaneously monitors large numbers of biochemical features on the surfaces of immune cells and within the cells. The researchers drew blood from the patients one hour before surgery, then at one, 24 and 72 hours post-surgery and again four to six weeks after surgery. They used the cytometry device, developed in Nolan's lab, to determine the identities and activities of the immune cells the samples contained. The Stanford team observed what Angst calls "a very well-orchestrated, cell-type- and time-specific pattern of immune response to surgery." The pattern consisted of a sequence of coordinated rises and falls in numbers of diverse immune-cell types, along with various changes in activity within each cell type.

"Amazingly, this post-surgical signature showed up in every single patient," Angst says. However, the magnitude of the various increases and decreases in cell numbers and activity varied from one patient to the next. In particular, activity patterns in one fairly rare subset of immune cells correlated strongly with patients' recovery times.

The Stanford group is now looking to see if they can identify a pre-operation immune signature that predicts the rate of recovery. That could help clinicians decide when, or if, a patient should have surgery. — BRUCE GOLDMAN

LINCOLN AGNEW

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Life time

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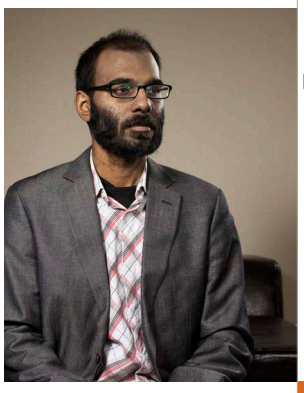

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Macular degeneration
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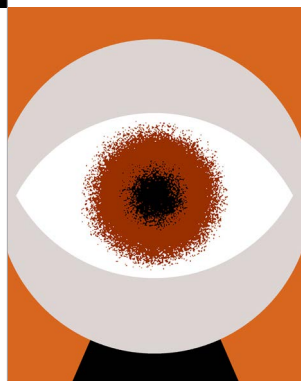


DEPARTMENTS

COVER: DAN WINTERS

letter from the dean

Time. Looking back over many years, time has always been my most precious commodity. I've never had a lack of things I wanted to do, and haven't yet experienced the curse of boredom.

As a physician in the clinic, I learned that patients appreciated the time I spent with them, and that I gained valuable knowledge by listening to them. It also became clear that the time I spent conducting research led to advances that helped them. One example of this was my description of a condition that explains an unusual set of symptoms arising from an inner ear anomaly, followed by the development of a treatment plan and surgical procedure to help patients with this debilitating condition. • As a surgeon, I learned that I shouldn't let an operation extend longer than necessary, but I also couldn't rush the procedure. And as a scientist, I learned that the time I spent delving into a problem, designing experiments to test hypotheses and looking at data from many vantages was the essential investment required for discovery. • It's not easy for physicians and scientists to figure out the best way to allot precious minutes. We juggle our time in the clinic, the operating room or the laboratory with many other tasks. Of course, working too much can lead to errors and burnout, which can take a toll not only on our mental health but also on the well-being of our trainees, our patients and our families. Clearly, time for relaxation and renewal as well as time for significant personal relationships is vital for anyone. A balance is essential for nurturing health, creativity and innovation. • I began to think seriously about managing time in 2003, when I became a department chair at Johns Hopkins. I didn't give up any of my responsibilities: I was still seeing patients, conducting research, and mentoring future scientists and clinicians. Nothing fell off my plate, but new tasks were added. I was recruiting professors, managing finances and working with the faculty to chart the department's course. Each day I had different situations to deal with and I had to adjust my priorities accordingly.

I found help then in David Allen's book *Getting Things Done*. His notion is that we all tend to keep too much in our heads, which prevents us from concentrating and focusing. I learned to use lists and structure. To this day, it allows me to be fully present during the task at hand and therefore much more productive.

As dean, I know that where I direct my time and attention will determine where others in our organization will direct theirs. I focus a great deal on department chair and other leadership searches, seeking to create an evermore accomplished and diverse community. I spend time working with volunteers, donors and development professionals to ensure that we have the resources we need. I also spend time with our faculty and students, whose knowledge, insights and creativity are a constant source of inspiration. I devote time to our initiatives on clinical quality and value in health care — cornerstones in all our activities that involve patient care.

Figuring out my relationship with time has been a lifelong journey. It's always been my most valuable resource, though I didn't recognize it as such for many years. I've learned it needs to be planned and allocated just as anything else in my life — it dictates the books I read, the materials I prepare. And I've seen how I have benefited from the wisdom, dedication and time of those with whom I have had the privilege of working. I encourage all of us to reflect on ways we can harness time to enhance our lives.

Sincerely,

Lloyd B. Minor, MD

Carl and Elizabeth Naumann Dean of the School of Medicine

Professor of Otolaryngology-Head & Neck Surgery

GLENN MATSUMURA

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD UNIVERSITY MEDICAL CENTER

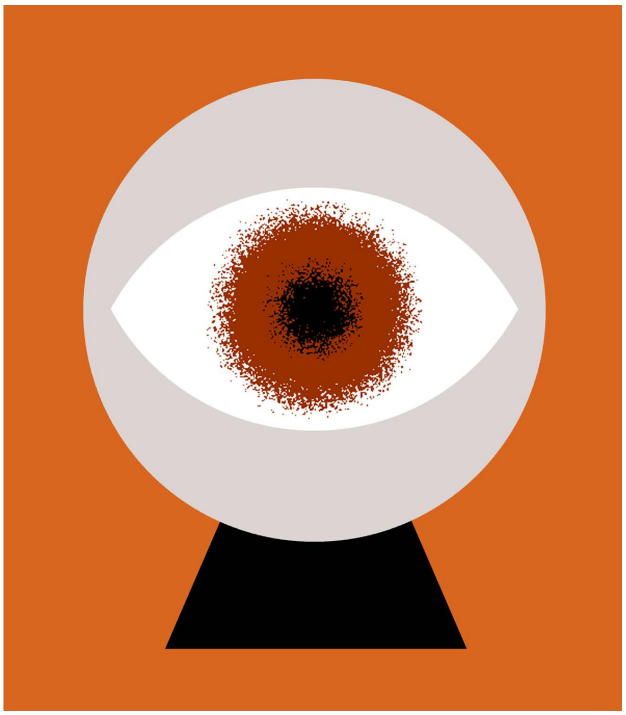
Eye spy

MEDICAL SCHOOL RESEARCHERS HAVE FOUND A WAY TO PREDICT which patients with age-related macular degeneration will progress to a stage of the disease that can quickly cause blindness if left untreated.

AMD is the leading cause of blindness and central-vision loss among adults older than 65. An estimated 10 million to 15 million people in the United States suffer from the disease, in which the macula — the key area of the retina responsible for vision — shows signs of deterioration.

Until now, there has been no way to tell which patients will progress to AMD's most advanced stage, in which abnormal blood vessels accumulate underneath the macula and leak blood and fluid, causing irreversible damage to the macula if not treated quickly. Only about one of every five people with AMD progress to this stage, but it accounts for 80-90 percent of all legal blindness associated with the disease.

Treatments typically involve injections directly into the eyeball, a painful prospect that makes treating people any sooner than absolutely necessary a non-starter. Doctors and patients have to hope the next office visit will be early enough to catch the advanced stage at its onset, before it takes too great a toll.



TERRY ALLEN

In a study published in *Investigative Ophthalmology & Visual Science*, a team led by Daniel Rubin, MD, assistant professor of radiology and of biomedical informatics, derived a method of accurately predicting whether — and, importantly, how soon — a patient with mild or intermediate AMD will progress to the most advanced stage. The new method, which employs imaging data that's already commonly collected in eye doctors' offices, will allow ophthalmologists to make smarter decisions about how soon to schedule an individual patient's next office visit to optimize the chances of detecting AMD progression before it causes blindness.

15%
of people with diabetes develop skin ulcers. More at http://stan.md/1J90RCh.

A family matter

"FOR A LONG TIME, PEOPLE blamed families for causing anorexia nervosa and thought they should be left out of treatment," says James Lock, MD, PhD, professor of psychiatry and behavioral sciences.

But a Stanford-led investigation of 164 patients found otherwise.

The study, published in *JAMA Psychiatry*, compared an approach that taught parents to help children eat normally at home with a therapy that addressed difficult family dynamics.

"This study suggests that, however you involve them, families can be useful," says Lock, who is a co-author.

Antibiotics: Salmonella's BFF?

About 80 percent of all antibiotics used in the United States are given to livestock because doing so increases the animals' growth rates. Experts worry that this practice contributes to the rise of drug-resistant pathogens. But a new study, published in the *Proceedings of the National Academy of Sciences*, highlights a different concern.

When Denise Monack, PhD, associate professor of microbiology and immunology, and her colleagues gave antibiotics to mice infected with the food-poisoning bacterium *Salmonella typhimurium*, a small minority — so-called "superspreaders" — that had been shedding high numbers of salmonella in their feces for weeks remained blithely asymptomatic. The rest of the mice got sicker instead of better and, oddly, started shedding like the superspreaders. The findings pose ominous questions about the widespread, routine use of sub-therapeutic doses of antibiotics in livestock.

"If this holds true for livestock as well — and I think it will — it would have obvious public health implications," says Monack. "We need to think about the possibility that we're not only selecting for antibiotic-resistant microbes, but also impairing the health of our livestock and increasing the spread of contagious pathogens among them and us."

The concern here is that antibiotic use in livestock will encourage, rather than impede, salmonella's spread in the animals (and through them, us) while sparing the superspreaders among them (and us) who are responsible for most of its transmission.

STENT DRUG IN A HAYSTACK

Four years ago, heart researchers at Stanford set out to find a better drug for coating the tubes, known as stents, used to prop open the blood vessels of people with coronary artery disease. Current coatings reduce the chances of vessels closing up again, but they can increase the risk of blood clots and heart attacks.

Using a "big data" approach, associate professor Euan Ashley, MD, and colleagues combined a text analysis of the whole medical literature with data from large-scale genetic studies in humans to build a theory that they then tested in mice. The result pinpoints the chemotherapy drug Crizotinib as a possible alternative for coating stents. The study was published in the *Journal of Clinical Investigation*.

Fighting flu while pregnant

PREGNANT WOMEN GET SICKER FROM THE FLU THAN OTHER HEALTHY ADULTS. Now researchers think they know why.

Expectant moms have an unusually strong immune response to influenza, a study published in *Proceedings of the National Academy of Sciences* found. This was a surprise; most immune responses are weakened by pregnancy to protect the fetus from rejection by mom's body.

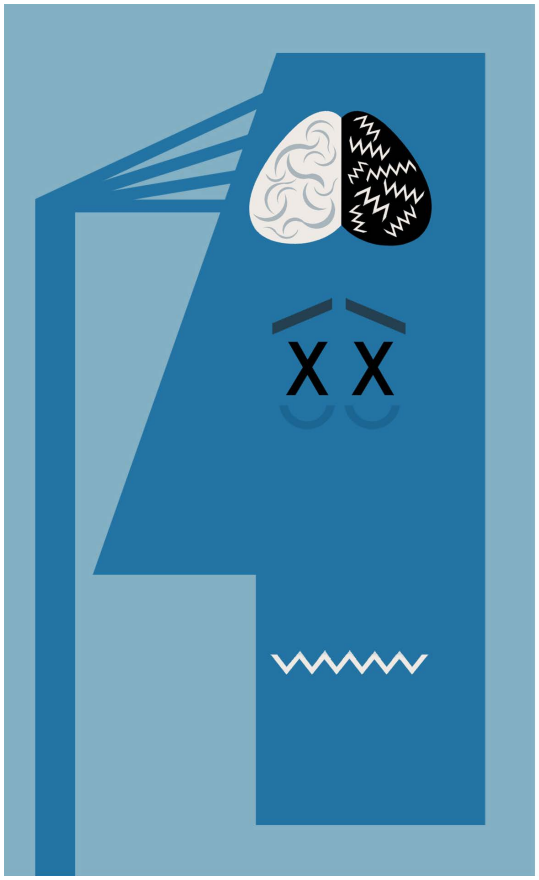
The study was the first to examine how immune cells taken from pregnant women react to influenza viruses, including the H1N1 strain that caused the 2009 flu pandemic. H1N1 made pregnant women's natural killer and T cells produce excess cytokines and chemokines. These molecules attract other immune cells to the site of an infection, which could be increasing the women's pneumonia risk.

"Too many immune cells are a bad thing in the lung, where you need air space," says Catherine Blish, MD, PhD, assistant professor of infectious diseases and the study's senior author.

"We now understand that severe influenza in pregnancy is a hyperinflammatory disease rather than a state of immunodeficiency," she adds. That means anti-inflammatory therapies may be added to the treatment arsenal.

Chronic fatigue marker

THE BRAINS OF PEOPLE WITH CHRONIC FATIGUE SYNDROME HAVE DISTINCT DIFFERENCES FROM THOSE OF HEALTHY PEOPLE. This new finding, published in *Radiology*, could lead to more definitive diagnoses of the syndrome and may point to an underlying mechanism in the disease process.



CFS affects between 1 million and 4 million Americans. Coming up with a more precise number of cases is tough, because it's difficult to actually diagnose the disease. While all CFS patients share a common symptom — crushing, unremitting fatigue that persists for six months or longer — other symptoms can vary widely, often overlapping with those of other conditions.

"If you don't understand the disease, you're throwing darts blindfolded," says Michael Zeineh, MD, PhD, assistant professor of radiology, who led the study.

Comparing brain images of healthy people with those of CFS patients, the Stanford investigators made three noteworthy observations. First, overall white-matter content of CFS patients' brains, compared with healthy subjects' brains, was reduced. ("White matter" denotes long, cable-like nerve tracts carrying signals among broadly dispersed concentrations of information-processing "gray matter.")

Second, the scientists found a consistent abnormality in a particular part of a white-matter tract in CFS patients' brains. The degree of abnormality closely tracked the severity of the patient's condition. Bolstering this observation was a third one: a thickening of gray matter at the two areas of the brain connected by that tract.

SEMEN WARNING

A STUDY OF MORE THAN 9,000 MEN WITH FERTILITY PROBLEMS, CONDUCTED BY INVESTIGATORS AT THE SCHOOL OF MEDICINE, links poor semen quality to a higher chance of having hypertension and other health conditions. The findings, published in *Fertility and Sterility*, may spur more-comprehensive approaches to treating male infertility.

"There are a lot of men who have hypertension, so understanding that correlation is of huge interest to us," says lead co-author Michael Eisenberg, MD, assistant professor of urology and director of male reproductive medicine and surgery.

Eisenberg notes that either high blood pressure itself or the treatment for it could be causing reproductive malfunction. He's actively exploring this now.

About 15 percent of all couples have fertility issues, and in half of those cases the male partner has semen deficiencies, he says. "We should be paying more attention to these millions of men. Infertility is a warning: Problems with reproduction may mean problems with overall health. That visit to a fertility clinic represents a big opportunity to improve their treatment for other conditions, which could actually help resolve the infertility they came in for in the first place."

TERRY ALLEN

Read more about lymphedema, a frequently ignored disease, at http://stan.md/153952b.

Swell solution

HOME TREATMENT FOR lymphedema — a painful cancer-related condition that causes tissues to swell — cuts costs and controls symptoms, a new study has found. But unfortunately, insurers reimburse this type of therapy poorly, says Stanley Rockson, MD, senior author of the study and professor of cardiovascular medicine. Rockson and his co-authors examined the impact on symptoms and costs of compression sleeves. Based on the claims submitted to a national private health insurer from 2007 to 2013, they found that lymphedema patients who used the compression device cut their annual health-care cost of $62,190 to $50,000. "This is clearly a compelling argument for increased coverage of similar home-care devices to reduce costs," Rockson says. The research was published in *PLOS ONE*.

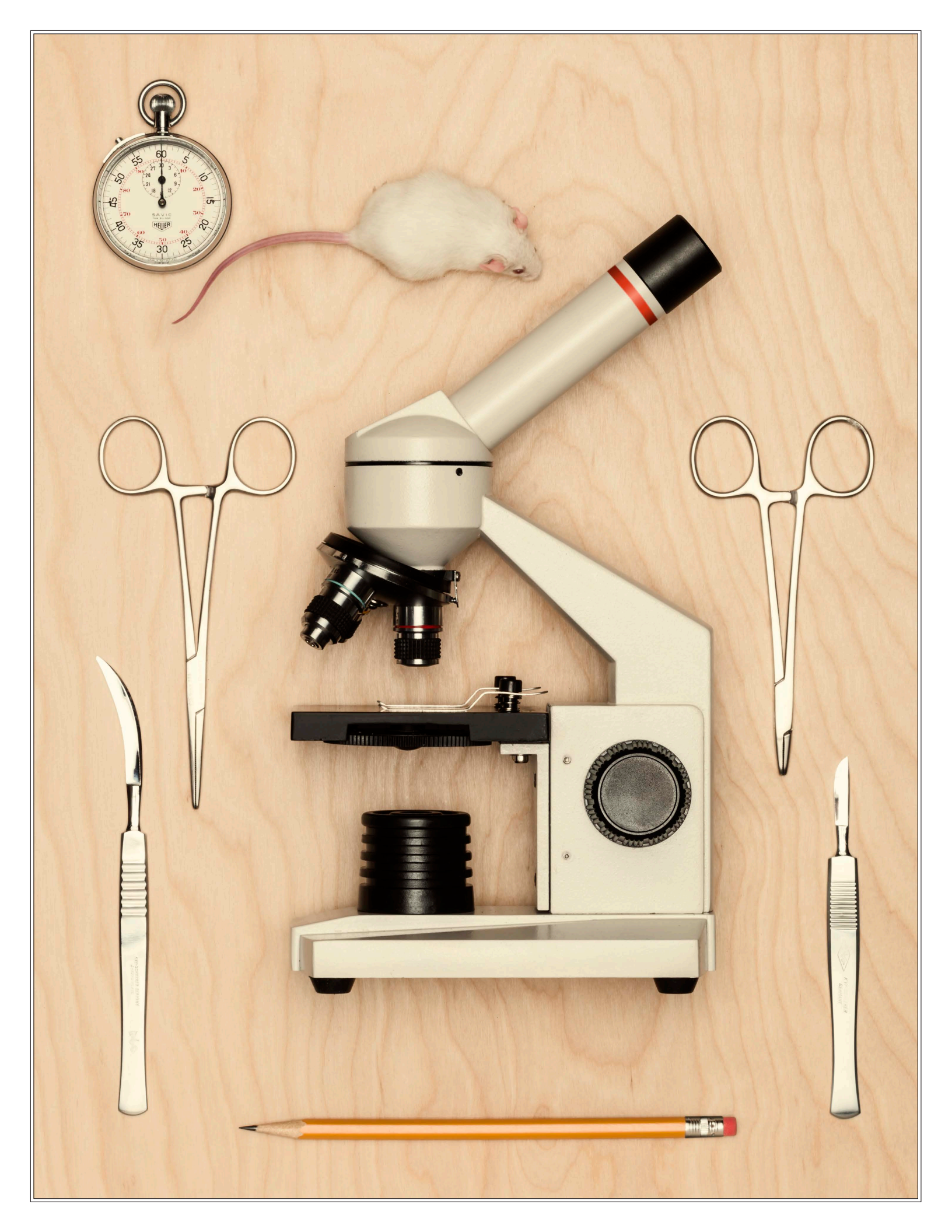
as time goes by

THE HUMAN ORGANISM ON THE CLOCK

Time's passage is "a stubbornly persistent illusion," Albert Einstein said. Yet in the realm of human health, time is the bottom line; it's as real as it gets. Each human being has a limited cache of moments, and when our mortality takes center stage — after diagnosis with a terminal illness, for example — those moments become exceedingly precious.

Time heals many, though unfortunately not all, wounds. • In health care, time is often an adversary. Emergency crews race against it, rushing patients to the hospital before irreparable damage is done. Physicians barrel through their schedules because "time is money": Primary care visits these days are down to 15 minutes per patient. • There's more to time than its scarcity, though. • If you stop and think about it, the simple fact that our body keeps time seems miraculous. How is it that our cells divide regularly, with different types cleaving at their own characteristic paces? And what keeps our large-scale loops on track — from our obvious cycles like sleeping and waking to the subtler circuits followed by our immune cells? • By learning more about our bodies' timekeepers, researchers are discovering how to schedule surgeries and therapies to maximize their effectiveness, and how to reset our internal clocks to improve our health. • As you'll read in these pages, time is a tyrant, but it's also a tool — one that we're only beginning to understand.

PHOTO-ILLUSTRATION BY DAN WINTERS


SAVIC
HEUER

hacking the biological clock

HOW CO-OPTING THE BODY'S TIMEKEEPERS MIGHT IMPROVE HEALTH

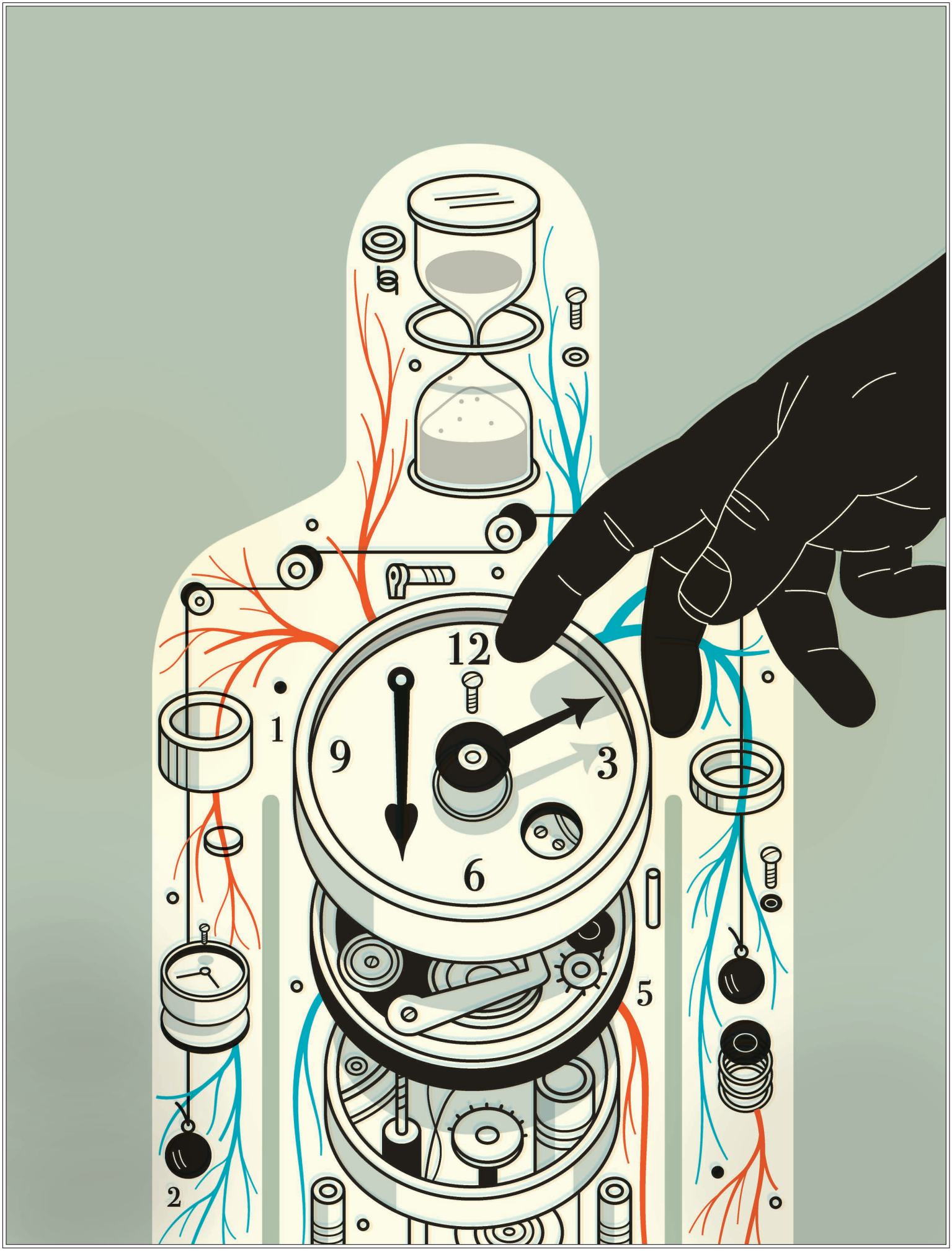
Ancient Egyptians used water clocks to measure the passage of time. Mechanical clocks started ticking away in 14th-century Europe; and pocket watches, in the 17th century. Timex was founded in 1854 and Rolex in 1905. Today, you might use a smartphone to follow your schedule.

But before all these timers, there were living cells — themselves impeccable timekeepers.

Cells in the human body follow cycles that repeat anywhere from once a second, in the case of a heartbeat, to once a month, for the female reproductive cycle. Living organisms have biological cycles that span all sorts of other time frames — the fastest-replicating bacterial cells duplicate every 15 minutes, bears hibernate annually, some cicada species emerge from the ground only once every 17 years, and many bamboo plants go for more than 60 years without flowering. • Scientists have watched these cycles with awe, asking what keeps these clocks ticking. Slowly, they've revealed many of the molecular gears that let cells stay on schedule. And even among disparate species — and between cycles with drastically different periods — they have uncovered commonalities. • "All these cycles are driven by clocks," says James Ferrell, MD, PhD, a Stanford professor of chemical and systems biology and of biochemistry. "There's almost nothing in common between each clock when it comes to the exact genes and proteins involved. But at a fundamental level each type of circuit is the same." • With that knowledge in mind, scientists have now turned to a new type of

By Sarah C.P. Williams

ILLUSTRATION BY HARRY CAMPBELL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question: How can we take advantage of what we know about the clock? Some researchers are exploring how to combat jet lag or treat narcolepsy and insomnia by altering sleep cycles. Some are probing how to administer different medications — from vaccines to drugs that enhance memory — by giving them at the time of day when they're most effective. And others are working to stall tumor growth by slowing the clock that controls how fast cancer cells divide. At Stanford and in time zones around the globe, scientists are learning not just how to take a clock apart and see its insides, but to reassemble that clock the way they want, prevent it from getting off-kilter or get it back on track when it's lost track of time.

BASIC MACHINERY

Just as the same underlying principles of electronic circuits are used to design machines from calculators and radios to cars and cellphones, all biological clocks are governed by the same basic patterns of molecular switches. But unlike electronic circuits that are composed of wires and metals and silicon, cellular circuits are made of molecules that work together in a big game of tag, turning each other on and off.

To understand the molecular circuits that underlie biological clocks, Ferrell studies one of life's most integral timers: the cell cycle. All living cells on Earth — from bacteria to stem cells — go through a similar cell cycle, which includes getting larger, copying genetic material, divvying it up and forming two new cells. The cell cycle is how an embryo develops, how skin cells are constantly replaced and why you can't get your hair and fingernails to stop growing.

"You can think of the cell cycle as being driven by a clock in the same way you think of heart rate or sleep patterns being driven by clocks," says Ferrell.

Human cells go through a cell cycle every 24 hours on average. But many organisms have faster cell cycles: Yeast cells divide every few hours, frog embryos cycle every 25 minutes and bacteria multiply even faster.

Recently, researchers started hypothesizing how sets of molecules might control this timing. One idea, says Ferrell, was that it's driven by a positive feedback cycle. That would mean that a set of molecules switch each other on in brief pulses, like people passing a hand squeeze around in a circle. If it took a fixed amount of time for the signal to get back to the start of the circle, then a clock — or, in more technical terms, an oscillator — would be born. Every time the signal would hit one molecule in the cycle, it could spur some other biological process, be it cell division or hunger for lunch.

But when Ferrell and others started running computer simulations on how a positive molecular feedback loop could keep a biological clock ticking, their results didn't click. "It makes complete sense that positive feedback should be able to work as an oscillator," says Ferrell. "But it just doesn't work. It turns out that the circuit will either eventually fade out to nothing, or end up with everything turned on all the time. The balancing point between these is just too fine a knife blade."

Instead, biological clocks seem to always be driven by a negative feedback loop. In retrospect, Ferrell says, although it wasn't the intuitive answer, this fits with what modeling and theories have been suggesting for a few decades; in fact, mathematician René Thomas conjectured in 1981 that all complex oscillators must contain a negative feedback loop.

Ferrell's lab has spent the past few decades studying the negative feedback loop that controls the cell cycle. Like a positive feedback loop, a negative feedback loop involves molecules passing a signal in a circle. But in this case, they don't just turn each other on in pulses: They alternately turn each other on and off. The cell cycle, though, isn't just a simple loop — it also has all sorts of checkpoints. These ensure, for instance, that a cell doesn't start copying its genetic material if it hasn't grown large enough.

But the cell cycle — like many other biological clocks — can be complicated by the fact that it sometimes speeds up or slows down. In some cases, this is OK; cells in frog embryos, for instance, begin dividing slowly and speed up as they grow larger. But in other cases, this can lead to disease: Cells that progress through many fast cell cycles in a row can form a cancerous tumor. So, understanding how cells control the pace of the cell cycle is key to understanding one of the most fundamental properties of cancer.

"Every cell type in the body does the cycle a little bit differently; they're very idiosyncratic," Ferrell says. "And even within one population of cells, the cycle can speed up and slow down." And then there are cancer cells: the fastest-dividing cells of them all. Cancers cells march through the cell cycle at a faster pace than other cells, and that's what makes tumors grow so aggressively. "The hope is that if we understand the cell cycle better, we can design more effective therapies for cancer," he says.

Ferrell's group has turned to frog embryos, because of their unusually reliable cell cycle length, to learn in more detail what proteins and genes control the speed of this clock. Using frog eggs, he's shown why the first division cycle of the embryo is long, about 80 minutes, while those following are less than half an hour. The difference, he found, is

'THE VIEW NOW IS THAT HEALTHY SLEEP IS AS IMPORTANT AS DIET AND EXERCISE TO OVERALL HEALTH.'

due to the ratio of two proteins: Having more of one protein leads to the longer cycle. The lesson isn't directly applicable to cancer cells — tumors don't contain those same two proteins — but gives scientists hints about how cancer cell cycles might be sped up. Already, researchers have found that many tumor suppressor genes and oncogenes are directly involved in cell cycle checkpoints. Drugs targeting these pathways — and therefore restoring the cell cycle to its normal pace — are in clinical trials.

SLEEP'S CONCERT CONDUCTOR

As cells tick tock through the cell cycle, other rhythms in the human body are progressing at their own paces. For anyone who has ever flown halfway around the globe only to spend days like a zombie and nights wide awake, the steady beat of one clock is obvious: the sleep cycle. Most of us find our bodies sticking to a 24-hour pattern of sleep; we get drowsy around the same time each night.

At the Stanford Center for Narcolepsy, sleep doctor and researcher Emmanuel Mignot, MD, PhD, is using findings he's made on the human sleep cycle over the past few decades to develop new treatments for sleep disorders, including narcolepsy. Patients with narcolepsy have severe disturbances in their sleep-wake cycles, often characterized by sudden bouts of extreme fatigue during the day. At the end of the 1990s, Mignot and his colleagues identified the first narcolepsy gene, hypocretin receptor 2, in dogs. Since then, they've uncovered how a lack of the protein hypocretin in mammals, including humans, can cause narcolepsy. In most people, hypocretin levels peak during the day, when the protein promotes wakefulness and blocks sleep, Mignot has shown. In many people with narcolepsy, hypocretin is missing — or is found at very low levels in the brain — so the sleep pathways aren't blocked during the day.

But even uncovering hypocretin hasn't answered some of the most basic questions on why most of us have a regular pattern of alertness and fatigue and what other molecules wax and wane in tune with the sleep cycle. "The hypocretin system is like an orchestra director," Mignot says. "It's controlling the music — sleep and wake — but not making it. Right now we don't even know who's in the orchestra or what music is being played during sleep or wake."

There's another interesting cycle linked to narcolepsy, though, that's leading to unexpected findings — an annual cycle. "There are always a lot more new cases of narcolepsy during the spring and summer," Mignot explains. "And there was a huge rise in the number of narcolepsy cases in 2010 just after the winter of the swine flu."

Mignot's latest research looks at this intersection between this seasonal cycle and the sleep cycle. The onset of narcolepsy, he's shown, can likely be triggered by a case of the flu, which may be asymptomatic and tends to happen over the winter. A few months later, narcolepsy appears. Mignot has been among the scientists who have shown over the past decade that most narcoleptics have an overactive immune system that attacks the cells that produce hypocretin, causing the lack of hypocretins. This problem, he thinks, may be triggered by the body's production of immune cells produced to fight specific strains of influenza.

"It's turning out to be quite an interesting journey looking at this," says Mignot.

Through this research, Mignot is illuminating not only ways to treat narcolepsy, but other sleep disorders, like insomnia; an insomnia drug related to the hypocretin system is hitting the market soon.

"The view now is that healthy sleep is as important as diet or exercise to overall health," Mignot says. "And sleep disorders of any kind are really an important societal problem."

CYCLES OF LEARNING

If anyone knows how surprisingly different the body can be at different points in its rhythmic cycles, it's biologist Craig Heller, PhD, who co-directs the Stanford Down Syndrome Research Center. Mice with the genetic mutation that causes Down syndrome in people usually have trouble learning and on memory tests. They quickly forget objects they've seen and can't remember how to complete a maze. But when Heller gives these mice a dose of pentylenetetrazole each day as the sun rises, before these nocturnal animals go to sleep, he can reverse their deficits. For months after receiving a two-week morning regimen of PTZ, the

CONTINUES ON PAGE 38

the time of your life

Cells hold clues to a healthy old age

By Krista Conger

PHOTOGRAPHY BY GREGG SEGAL

The small, silvery-yet-colorful fish paused in patrolling his tank for a moment to eyeball me, perhaps assessing a threat. After a split second of scrutiny, he resumed his patrol of the tank. Around him, row upon row of similar tanks, stacked 10 feet high, hold similar fish, doing similar fishy things. The dim lighting and sounds of bubbling, flowing, fresh water hint at a spalike atmosphere curiously in sync with the real purpose behind the tanks: to understand — and perhaps even slow (or stop?) — human aging. • If you feel like you've stumbled into a science fiction tale, don't be alarmed. Immortality is a concept both alluring and frightening. And yet some animals seem to have achieved the impossible. The "immortal jellyfish," for example, responds to aging or injury by rewinding time, reverting to an immature polyp state and then re-maturing to generate new, healthy medusas wafting gracefully on the

Anne Brunet

HER LAB STUDIES GENES THAT CONTROL AGING.

ocean currents. Barring predation by hungry tuna, turtles or sharks, a single individual could conceivably continue this stately cycle of not-quite-death followed by triumphant rebirth for, well, forever.

These animals have conquered the passage of time in ways that make our heads spin and our souls hopeful. Could we someday stop the aging clock and achieve the same fate?

It's a question humans have struggled with since the dawn of recorded history but, unlike our now-deceased predecessors, our generation is closer to grabbing the golden ring than ever before.

"Ways of prolonging human life span are now within the realm of possibility," says professor of genetics and newbie fish keeper Anne Brunet, PhD. Brunet, who is an associate director of Stanford's Paul F. Glenn Center for the Biology of Aging, focuses her research on genes that control the aging process in animals such as the minnowlike African killifish I'd watched fiercely guarding his territory.

The killifish is especially important to researchers like Brunet because it has an extremely variable, albeit short, life span. One strain from eastern Zimbabwe completes its entire life cycle — birth, maturity, reproduction and death — within about three to four months. Another strain can live up to nine months.

It's also a vertebrate, meaning it belongs to the same branch of the evolutionary tree as humans. This gives it a backbone up over more squishy models of aging like fruit flies or roundworms — translucent, 1-millimeter-long earth dwellers you could probably find in your compost pile if you felt like digging.

The killifish is a relative newcomer on the aging scene, however. Brunet and her colleagues are working to sequence the fish's genome and to learn more about why some strains live longer than others by comparing their genomes. They'd also like to devise ways to swap out specific genes to create designer strains for study.

"We'd like to identify genes specific to vertebrates that regulate life span," says Brunet. "These fish are so like us, and they breed and develop much more quickly than other laboratory animals like mice. Worms and flies have been revolutionary in moving the field forward, but they lack key tissues, organs and systems that are critical to human life. They don't have bones, or the same type of blood or an adaptive immune system. We are really in love with this fish because it will allow us to quickly test some fundamental concepts of aging."

Learning how our cells and tissues change with the passage of time, and how these changes compare with those seen in other species, may help us identify crucial genes or pathways that could be tweaked to prolong our lives, and our health. That's because aging is the single biggest risk factor for the development of chronic diseases from diabetes to cancer to heart disease. Interfering or modulating the natural aging process may be one way to reduce our risk of many devastating, life-shortening conditions.

It may also help answer one of the biggest biological questions of all, and one that's recently incited keen interest among savvy investors.

"We don't really know what aging is," says Thomas Rando, MD, PhD, professor of neurology and director of the Glenn Center. "We don't know what it really means to 'die from old age.' We understand development as a biological program — how we are conceived, develop and mature — but aging remains, fundamentally, a biological mystery. But the interest in the private sector in this research is almost unimaginable compared to just 10 years ago."

AGING IS INHERENTLY interesting, because we're all doing it. Like it or not, our bodies are slowly winding down as time passes. But what actually happens in our tissues and cells? It's clear that we are subject to a plethora of depressing outcomes, including sagging tissues (hello, wrinkles), reduced cognitive capacity (where did I put my car keys?) and a slowing metabolism that (tragically) favors belly padding over muscle building.

Inside our cells, the situation looks even more dire. DNA mutations begin to accumulate, our cells' energy factories begin to wind down, and proteins policing gene expression appear to "forget" how to place the chemical tags on DNA that serve as runway lights for the appropriate production of proteins.

The protein production, transportation and degradation network that cells depend on to deliver these molecular workhorses to all parts of the cell at exactly the right times also falls into disarray. Proteins are degraded too soon, or begin to clump together in awkward bundles that interfere with cellular processes. These events have obvious, previously inescapable, outcomes.

"As we age, time becomes compressed and we tend to develop many chronic diseases or health problems simultaneously," says Brunet. "Many elderly people are dealing with a constellation of health conditions. We'd like to imagine ways to stretch out the healthy period of our lives, so it comprises more of the totality. This is something we call 'health span,' and it would be tremendously advantageous to stretch out that portion of our lives."

THE GLENN CENTER was created in 2011 with a $5 million grant to Rando from the Glenn Foundation for Medical Research. He and his colleagues are hardly alone in wondering whether it's possible to slow or stop the aging clock. Nationwide, both public and private efforts have been launched to better understand and prolong our golden years. In 2012, the National Institutes of Health created the Geroscience Interest Group to bring together experts from across the agency to create a framework to advance aging research. In 2013, tech industry giant Google backed the creation of an independent research and development company called Calico (short for California Life Company) to investigate the basic biology of aging, and in 2014 Calico joined forces with research pharmaceutical company AbbVie to tackle age-related diseases, such as cancer and neurodegeneration, to the tune of at least $500 million.

Human genomics pioneer Craig Venter, PhD, threw his hat into the ring in early 2014 with La Jolla, Calif.-based Human Longevity Inc., which secured $70 million in initial funding for its plans to sequence up to 40,000 human genomes each year to learn more about cancer, the microbiome and possible stem cell therapies for the diseases of aging.

Nonprofit efforts have also sprung up during the past few years, such as the SENS Research Foundation (SENS stands for the Strategies for Engineered Negligible Senescence, or preventing or reversing cellular aging). Founded in 2009 in part by gerontologist Aubrey De Grey, PhD, SENS funds research at universities around the world as well as at its own facility in Mountain View, Calif.

Even NIH director Francis Collins, MD, PhD, has a particular interest. His research focuses on understanding a genetic condition called progeria, in which children age extremely rapidly, often dying of apparent old age in their early teens. Progeria is caused by a mutation in a single gene called lamin A that makes a protein that stabilizes the structure of a cell's nucleus. It's thought that when the nucleus deforms it causes a cascade of changes that leads to premature aging.

Associated with the growth in funding is an expansion in laboratory research that suggests the possibility of intervening in the aging process and extending the human health span, says Rando, who is also a practicing neurologist. "It may one day be possible to avoid chronic diseases, living into old age free from dementia, diabetes and heart disease. Our tissues will still age, but we may be able to delay or prevent the onset of the decline in function that comes with passing years."

'It may one day be possible to avoid chronic diseases, living into old age free from dementia, diabetes and heart disease. Our tissues will still age, but we may be able to delay or prevent the onset of the decline in function that comes with passing years.'

SO WHAT'S CHANGED? Humans have grappled with mortality for hundreds, if not thousands, of years. Ancient humans propounded myriad ways to live longer, from a subsistence-only diet to bathing in or drinking magical water (the Fountain of Youth, anyone?) to alchemy or transfusions with the blood of children. Longevity has been sometimes associated with devout spirituality, or with capacious sexual appetites. Geographic location and climate were viewed as critical; both mild and stringent weather were at times considered beneficial. In short, if you can think of it, humans have likely tried it.

We can chuckle at some of these suggestions. Others, however, are somewhat unnervingly close to promising paths of current research. Calorie restriction has been shown to increase the lives of mice and other lab animals, and Rando, together with neuroscientist Tony Wyss-Coray, PhD, are among several researchers who have shown that the blood of young mice contains factors that help the muscles and brains of aging mice perform better.

"It's clear that, as we age, our cells and tissues change," says Rando. "The fundamental question is 'To what extent are these changes reversible?' This research shows that it's possible to drive cells from an old state to a young state with factors that circulate in the blood."

Researchers have also identified geographic locations they've termed blue zones that harbor more than their fair share of centenarians (the Italian island of Sardinia, for one, and the Okinawa region of Japan). Stuart Kim, PhD, professor of developmental biology and of genetics, recently sequenced the whole genomes of 17 "supercentenarians" (individuals at least 110 years old) to identify longevity-associated genes. The participants in the study were unusually healthy for their advanced age, and only one had cancer, diabetes or another age-related disease.

The study was unable to pinpoint with certainty any reasons these people were so long lived, perhaps because there are simply too few individuals to study. It's also possible that their good fortune is due to a plethora of influences. In other words, winning the longevity lottery requires a rare, felicitous combination of environment, genes and simple good luck.

"The process of aging is very complex," says professor of medicine Steven Artandi, MD, PhD, who, with Brunet, is also an associate director of the Glenn Center. "It seems like there's no single cellular variable that is changing with time that is the main trigger for aging. But starting at about ages 30 or 40, we experience a gradual physiological decline. The ends of our chromosomes shorten, the proteins in our cells begin to clump, our cells' energy factories begin to become dysfunctional and we begin to accrue damage to our DNA. We begin to exhibit cognitive, metabolic and respiratory decline."

If that's not insult enough, there's proof that, at least in some ways, aging is an active, deliberate process.

Individual human chromosomes are made of single DNA strands that are tens or hundreds of millions of nucleotides long. At each end is a protective cap called a telomere, which in humans is only about 8,000 nucleotides. Every time a cell divides, it loses a tiny snippet of DNA from the ends of the telomeres. This loss appears to act as a cellular clock, restricting any one cell to a limited number of cell divisions. When the telomeres become too short, the cell stops dividing.

The telomere may be an internal timekeeper, but recent research suggests its length is also affected by external factors. In the past few years, researchers have associated shortened telomeres with a huge variety of environmental influences, from consuming sugary soft drinks to depression in young girls to the perception of race discrimination by African-American men. Conversely, other research has suggested that a reduction in stress acts to slow telomere shortening.

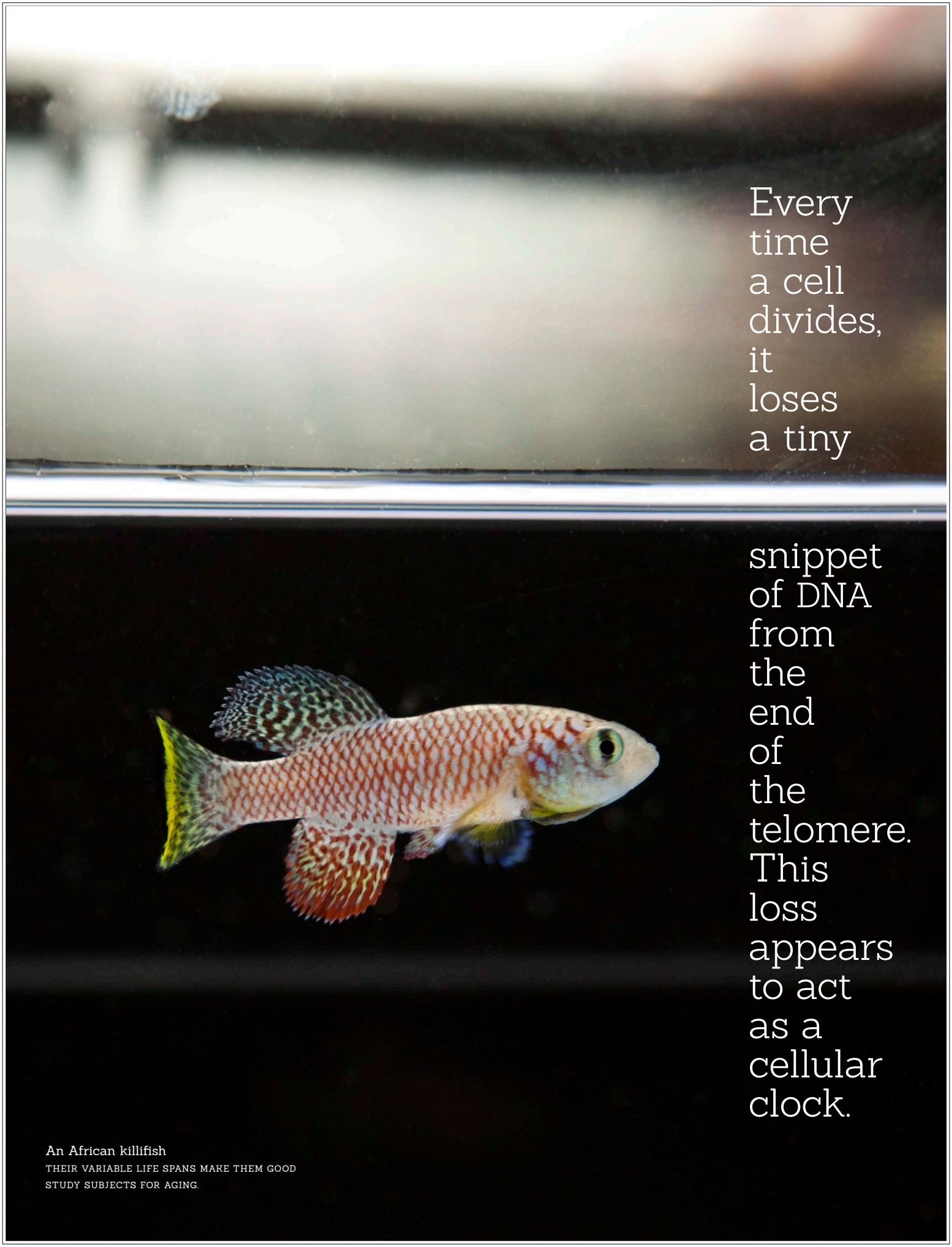
All this hasn't escaped the notice of the biotech industry, which has spawned several companies offering to measure people's telomeres and make predictions about their future health. But Artandi cautions that much still needs to be learned about the association.

"The average telomere length varies dramatically among individuals," he says. "A 30-year-old person could have the same telomere length as a 50-year-old person, with no identifiable effects on his or her health. What might be more interesting would be to track the rate of shortening over time in an individual. Rapid shortening could indicate more rapid aging, and an increased likelihood of developing diseases of aging such as heart disease and cancer. But much more research remains to be done."

Telomeres shorten with each cell division, except when they don't. An enzyme called telomerase lovingly repairs telomeres in embryonic stem cells and sperm cells to keep them in tip-top shape. As far as their chromosomal ends go, those cells don't appear to age at all.

"Nature knows how to solve the problem of telomere shortening," says Artandi. (Without this attention, we'd age across generations as our children inherited progressively shortened telomeres.) "But it chooses not to do so in most tissues. We don't know why this is."

The short-lived killifish may offer clues. Unlike labora-



Every time a cell divides, it loses a tiny snippet of DNA from the end of the telomere. This loss appears to act as a cellular clock.

An African killifish
THEIR VARIABLE LIFE SPANS MAKE THEM GOOD STUDY SUBJECTS FOR AGING.

Time in a bottle?

LIFE EXTENSION GETS REAL

LONGEVITY RESEARCH IS GAINING MOMENTUM, BUT HOW SOON CAN YOU EXPECT TO SEE SOMETHING IN YOUR MEDICINE CABINET THAT MIGHT TURN BACK TIME? Surprisingly, a few prospects are already generating a buzz. Some of these anti-aging contenders are drugs that have already been approved for treating medical conditions such as diabetes, Parkinson's or Huntington's disease, or to combat organ rejection. And as Christopher Scott, PhD, and Laura DeFrancesco, PhD, point out in a recent feature in *Nature Biotechnology*, nearly all influence cell energetics — the pathways involved in metabolism, insulin signaling and response to metabolic stress or genetic damage. Here are a few attracting the attention of researchers worldwide:

RAPAMYCIN This compound was first isolated from bacteria discovered in the soil of Easter Island, and is now the darling of the kidney transplant world. In that capacity, it functions to tamp down a patient's immune response to a foreign tissue. But it also boosts immune response in other situations, like when older people are vaccinated against influenza. Most intriguingly, it increases the life span of organisms ranging from budding yeast to fruit flies to roundworms to our mammalian laboratory buddy, the mouse. It functions by inhibiting a protein called mTOR, which serves as a kind of molecular funnel, gathering diverse data about amino acid and nutrient levels. The downside? Rapamycin treatment comes with a variety of fairly nasty side effects, such as low platelet levels, anemia and elevated cholesterol, that would likely limit any long-term use.

METFORMIN This widely prescribed oral drug for treating type-2 diabetes works by lowering blood sugar levels, which it accomplishes by increasing insulin sensitivity and suppressing glucose production by the liver. Diabetics receiving the drug appear to have a slightly reduced rate of developing a variety of tumors, and laboratory mice experience a small uptick in longevity.

RESVERATROL This naturally occurring substance has made headlines over the past nine years as a potential anti-aging compound present in small amounts in red wine. It functions to increase the expression of a class of proteins called sirtuins, which have been shown to influence longevity in yeast, worms, flies and mice. Sirtuins are highly conserved among species, and appear to be involved in nutrient sensing. Calorie restriction has also been shown to increase sirtuin levels and lead to lower levels of IGF-1 (a hormone with a structure similar to insulin) and blood glucose in humans. Although a clinical trial testing the effect of resveratrol in humans has recently been suspended, another testing a similar molecule called SRT3205 is ongoing.

YOUNG BLOOD This last item is one you're unlikely to ever store in your medicine cabinet (one would hope!). But researchers including Stanford professors of neurology Thomas Rando, MD, PhD, and Tony Wyss-Coray, PhD, have shown that infusing the blood of young mice into old mice can rejuvenate muscles, activate neuron growth and improve memory and learning in the older animals. Researchers are now trying to identify the components in the blood that provide these benefits (oxytocin, the hormone that stimulates labor in pregnant women and appears to play a role in social bonding, is an intriguing contender). In the meantime, however, a clinical trial was launched in September 2014 by Alkahest (a Menlo Park-based company founded by Wyss-Coray) to test whether regular infusions of blood from donors under the age of 30 can help people recently diagnosed with Alzheimer's stave off memory loss and reduce other disease-related symptoms.

tory mice, which have extremely long telomeres (about 100,000 nucleotides), the fish sport telomeres that are comparable in size to those of humans, making them more amenable to study.

The indomitable fish could also shed light with their ability to stop the clock for months at a time. They can survive for months or years as embryos in a kind of suspended, seemingly ageless, animation called diapause when their puddly playgrounds evaporate in the hot African sun. The tactic allows them to leapfrog into the next generation without missing a beat when the rains come again. Cell growth and development largely stops during this time and, intriguingly, those individuals that emerge after years of diapause live just as long, and appear just as healthy, as those that were out of commission for only a few short weeks.

"These fish can live almost four times their normal adult life span in diapause," says Brunet. "We don't really know how organisms survive in this kind of suspended animation, or exactly how they choose to enter and exit. Could understanding this better teach us something about immortality?"

JUST AS KILLIFISH EMBRYOS respond to seasonal rains by emerging from diapause, the health of humans is also affected by the environment. Smoking, chronic disease and obesity have all been shown to exacerbate aging-related damage in our cells. Conversely, diets in which calorie intake is severely restricted have been shown not just to reduce telomere shortening and cellular senescence, but to also significantly increase life span in a variety of laboratory

animals, including the killifish. (No second helpings of fish flakes for you!) The cells and tissues of these animals continue to look like those of their younger counterparts even as the months and years pile on — indicating that the animals are experiencing not just an increase in life span, but also in the health span coveted by scientists and laypersons alike.

Researchers are also still grappling with the fact that different species of animals, and even plants, exhibit vastly different life spans. Killifish are the most short-lived of all the vertebrates that can be bred in captivity, but other organisms live for decades or even centuries. The Methuselah tree, a bristlecone pine in the mountains of eastern California, is thought to be about 5,000 years old; a colony of quaking aspen trees in Utah may have originated as many as 80,000 years ago.

"We really don't understand why some organisms evolved to have extremely long lives, while others are very short," says Artandi, "just like we don't understand why some people age very well, and others don't."

"There is something across the entire spectrum of the animal kingdom that puts the 'stopping point,' or maximum life span, in vastly different places," says Rando. "We'd like to know why this is. But this is a very interesting, and difficult, question. We are not even sure where this stopping point is in humans." The oldest human with a reliably recorded age was Jeanne Calment, who died in France in 1997 at the age of 122; many researchers believe the maximum human life span to be around 120 years.

Part of the trouble in identifying a maximum life span in humans lies in the difficulty of separating aging itself from the diseases that accompany it. Do we get diseases because we age? The winding down of the body's clock clearly affects many biological processes, including our ability to fight off infection or to regenerate healthy muscle. However, some conditions, such as chronic inflammation, actually increase the accumulation of age-associated changes in our cells — having a disease can actually age us. It seems like a no-win situation. But we're getting better at staving off some of the more preventable causes of death.

"Average life expectancy doubled during the past thousand years, and doubled again during the past hundred," says Rando. At the end of 2014, researchers at the Global Burden of Disease Study announced that the average human life expectancy had reached 71.5 years — a number that would have been nearly unthinkable just a few decades ago. With continued improvement, will we eventually find ourselves bouncing off an internal maximum life span that has yet to be defined? And if so, what then?

In October 2013, the trans-NIH Geroscience Interest Group held a summit to identify ways in which researchers from many different disciplines could work together to identify the molecular causes of aging and the relationship between aging and chronic disease, and to investigate approaches to attack root causes that could not only prolong life, but improve health. Many of the suggestions involved new ideas such as studying the development of chronic diseases in aging, rather than young, laboratory mice; to use genetically diverse, rather than identical, laboratory animals; and to pay closer attention to companion animals like dogs to learn more about how our shared environment affects aging. In November 2014, the group published its recommendations in a commentary in *Cell*.

"We have high hopes that our research strategy will help move collaborative efforts to the next level," said Brian Kennedy, PhD, president and CEO of the Buck Institute and the lead author of the commentary in an accompanying press release. "What has come out of our work is a keen understanding that the factors driving aging are highly intertwined and that in order to extend health span we need an integrated approach to health and disease with the understanding that biological systems change with age."

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'Average life expectancy doubled during the past thousand years, and doubled again during the past hundred.'

tick tock

A CHILD'S LIFE IN DANGER

By Ruthann Richter

ILLUSTRATION BY LINCOLN AGNEW

It's nap time at a Fremont, Calif., preschool when a 50-pound cabinet shears away from the wall and comes tumbling down onto the head of a sleeping 3-year-old girl. On the other side of San Francisco Bay, Stanford flight nurse Shara Griffis, RN, leaps to her feet and bolts out the door the moment the call comes in, at 3:39 p.m. She bounds up the stairs and is off at a near-run down the corridor at Stanford Hospital with her colleague, Jonathan Gardner, RN. • At this point, the nurses have no idea who they are being called upon to rescue, or that a toddler with significant head trauma awaits them some 23 miles away in southern Fremont. They know only that someone's life might depend on them, and they must make every moment count. In their world, time is everything. • Evan Toolajian, a veteran U.S. Navy pilot, is already in the cockpit of the aircraft when the nurses arrive at the rooftop, home to Life Flight, Stanford's air ambulance service. They snap on big yellow helmets, then head out the double doors of the flight room in their red Nomex jumpsuits. Their goal is to make it safely from call to takeoff in 7-10 minutes. • Toolajian motions them to stop, then gives the go-ahead as the nurses duck into the side doors of the red, white and blue EC 145. Gardner stations himself in front with the pilot, Griffis in the treatment area in the back. • They've agreed to let me fly along to see them in action, seating me next to Griffis. I'm facing the back of the aircraft, my heavy, padded helmet making my head feel as if it's underwater; I hook it into the radio system, which allows me to eavesdrop on conversations between the flight crew and emergency ground personnel. • I scan the 50-square-foot aircraft, which is better equipped than many emergency rooms and serves as a kind of intensive care unit in the sky. Depending on the mission, it might carry an intraortic balloon pump to support heart function, an ECMO (extracorporeal membrane oxygenation) machine for heart and lung assistance, a sophisticated ventilator and a cardiac monitor, in addition to a full pharmacy of medicines — from narcotics to heart drugs to anesthetics for help inserting a breathing tube in patients who are seriously compromised.


N145SU
LIFE FLIGHT

3:49 p.m. The blades whirling, the helicopter rises as its twin engines grind and roar, heading into the mottled sky of a waning Friday afternoon in November. It skirts the towering cranes at the Stanford University Medical Center Renewal Project and glides east at about 120 miles an hour over Palo Alto's green, tree-pocketed neighborhoods and a wide expanse of brown — the wetlands and brackish water of south San Francisco Bay. It rises to 1,200 feet, and a blast of cold air whooshes into the warm cabin.

The radio is crackling with information from firefighters and paramedics at the scene. There are two injured children, not one, at the Fremont preschool. The flight nurses are the face of calm, but their minds now are buzzing with dozens of questions as they anticipate the needs of a critically ill 3-year-old.

"I'm thinking about the right drug doses, the right size of equipment," Gardner says later. "Where am I going to take the patient? Are we taking two patients? Can we handle two really critical pediatric patients? How are we going to reconfigure the aircraft?"

He turns on the suction machine, in case he needs to clear vomit or other obstructions from a patient's throat. He's calculating the right dose of the calming drug Ativan in case a child suffers a seizure, and figuring out what size breathing tube will fit the throat of the average 3-year-old. "Pretty much it's always thinking three steps ahead," he says.

Gardner, 38, is, like all of Stanford's 13 flight nurses, a highly trained clinician, with skills that go beyond those of a paramedic or the average nurse or even some physicians. He can thread a line into a patient's artery to monitor blood pressure second by second, or insert a breathing tube in a patient with burns or face trauma. Tall, blond, with an intense look, he is a former police officer, paramedic and emergency nurse now acquiring specialized training in anesthesiology while still working full-time. "We're all overachievers," he says with a grin.

His partner, Griffis, 40, also works as a critical care nurse at the Veterans Affairs Palo Alto Health Care System to keep her skills up and is studying to become an instructor in mindfulness-based meditation, which can be useful in crises like these. Petite, with a raft of long, black curls, she throbs with energy while in the hospital, but like her partner, her expression remains neutral throughout the call and her movements are carefully measured, not betraying the urgency of the situation.

The nurses are essentially on their own, making second-by-second decisions about patient care. "The flight nurses don't need a lot of physician input, though we have that available," says Michael Baulch, RN, JD, Life Flight's program manager. "They are independent decision-makers. Mostly, they are very calm, which is one of the most important ingredients. We have some very chaotic situations. They're very good at establishing presence at a scene."

3:55 p.m. Just six minutes after takeoff, the pilot, guided by GPS and coordinates provided by emergency ground crews, says he now has the school in his sights. He is maneuvering his way through some birds, who could get caught in the rotors and bring the aircraft down. The school is situated midway between two major freeways, Highways 680 and 880, in a densely populated area with lots of air traffic, and there are hazards to navigate — high-voltage power lines that can easily snag a rotor, fences and debris on the ground and a horde of bystanders next to four emergency vehicles with flashing lights.

"If you see anything unsafe, call us off," the pilot tells the ground crew, as he takes an extra few minutes to hover over the area and reconnoiter. It's precious time lost, but safety comes first. Every year, air ambulances around the country go down in the course of their missions, making medical flight work one of the most dangerous jobs in the United States.

"One thing that goes through my mind every day is how many of our colleagues die," Gardner says. "Every time we show up to work, it's not 100 percent guaranteed. I'm at the pilot's mercy.

'I'm thinking about the right drug doses, the right size of equipment. Where am I going to take the patient? Are we taking two patients? Can we handle two really critical pediatric patients?'

But that's why we have awesome pilots here…. In an industry like this, you can't have one moment of complacency."

Fortunately Stanford Life Flight, California's oldest air ambulance service, has never suffered a crash in its 30-year history, says Geralyn Martinez, RN, who has been a flight nurse with the service for 23 years.

4:02 p.m. The pilot makes a gentle landing in a dirt- and weed-filled field behind the school, as emergency crews rush forward with a gurney. There is the tiny face of a girl, her neck supported by a brace, peeking out from a welter of wires and blankets. Fremont Fire Department battalion chief Tom Mulvihill briefs the flight nurses: The girl has vomited twice. Her throat has been cleared and she's on oxygen. She's been going in and out of consciousness. She's been very lethargic. They've put her in a cervical spine brace, as they don't know if there is an injury there, which could lead to paralysis.

But time has been lost. The accident happened around 2:30 p.m., according to Fremont fire officials, who said school officials failed to call 911. They only alerted the child's mother, Avani Bhatt, that her daughter had a "bump" on her head, Bhatt says. With no hint that the situation was urgent, Bhatt, a pharmacist at a Fremont drug store, waited for a co-worker to take over before she headed to the school. When she arrived 45 minutes later, she was stunned: Her injured little girl, Aeshna, was propped up in a chair in the corner alone, obviously unwell.

"She was throwing up, and when I called to her, 'Aeshna,' her eyes were rolling, and soon she passed out," the mother recalls. There was blood on the girl's shirt and on her bedclothes. "I was really upset and worried about the whole situation…. My biggest concern was to get her the care she needed. The moment I saw her, I knew she was showing signs of head injury — passing out, not answering questions, throwing up. There were obvious signs that something was wrong."

Aeshna is usually a noisy, active, restless child, who loves to run around and do somersaults and resists sleep, her mother says. She is a terrible tease, often playing tricks on her 7-year-old brother. But there she was, sitting motionless in the chair, nodding in and out of consciousness.

Bhatt called 911 at 3:13 p.m., and Fremont paramedic/firefighter Daniel Viscarra was among the first to arrive, five minutes later. He found a spectral, dazed little girl in the chair, vomit on her shirt. She was unusually quiet and failed to react when he tugged on her arm to check her blood pressure, he says.

"Three-year-olds don't let you do vital signs. They will cry. They are scared and will push you away," he says. But Aeshna didn't resist.

Another child, he discovered, had also been injured in the accident, with a big bump on his forehead, but he was crying and answering questions and behaving like a normal 3-year-old. He was taken by ambulance to a nearby community hospital, where he was treated and released later that day.

Meanwhile, Viscarra tended to Aeshna, clearing her throat, giving her high-flow oxygen through a mask and attaching the cervical brace, in case there was injury to the upper spine. He decided to summon Life Flight, as the girl needed to get to a trauma center as soon as possible.

"Time already had lapsed. If she had a head bleed, it could be significant by that time. The survival rate goes down after an hour," he says, referring to the crucial "golden hour" after which trauma victims can quickly deteriorate.

Particularly in cases of severe head trauma, time is of the essence. One of the biggest concerns is bleeding in the brain, either from a large vein or artery or from brain tissue itself, says Greg Hammer, MD, a professor of anesthesia and of pediatrics who later treats Aeshna at Lucile Packard Children's Hospital Stanford. If a bleed is not recognized and treated promptly, it can press on the brain and lead to a cascade of calamitous events, as tissues may die for lack of oxygen, leading to irreversible brain injury, he says.

4:12 p.m. Aeshna is loaded on a gurney into the helicopter and secured in place next to a heart and blood pressure monitor, which tracks her moment-to-moment status. Because she was injured in Alameda County, county protocol dictates that she be brought to Children's Hospital Oakland, unless the family prefers otherwise. Her mother opts for Stanford.

Gardner, the flight nurse, makes a split-second decision to offer Bhatt a front seat in the helicopter, though family members are rarely allowed to ride along in these situations. They can be too much of a distraction, and critical minutes may be lost in getting them situated, Griffis says. And if the little girl deteriorates along the way and the mother hears crisis chatter on the radio, she may panic.

"I have someone I don't know in the front seat of the helicopter, and I don't know what they will do," says Griffis, who can't recall another instance in her seven years with Life Flight when a family member rode along on a 911 call.

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BEFORE I GO

TIME WARPS FOR A YOUNG SURGEON WITH METASTATIC LUNG CANCER

In residency, there's a saying: *The days are long, but the years are short*. In neurosurgical training, the day usually began a little before 6 a.m., and lasted until the operating was done, which depended, in part, on how quick you were in the OR. A resident's surgical skill is judged by his technique and his speed. You can't be sloppy and you can't be slow. From your first wound closure onward, spend too much time being precise and the scrub tech will

By Paul Kalanithi
PHOTOGRAPHY BY GREGG SEGAL

Paul Kalanithi
TIME AT HOME, TIME WELL SPENT

announce, "Looks like we've got a plastic surgeon on our hands!" Or say: "I get your strategy — by the time you finish sewing the top half of the wound, the bottom will have healed on its own. Half the work — smart!" A chief resident will advise a junior: "Learn to be fast now — you can learn to be good later." Everyone's eyes are always on the clock. For the patient's sake: How long has the patient been under anesthesia? During long procedures, nerves can get damaged, muscles can break down, even causing kidney failure. For everyone else's sake: What time are we getting out of here tonight?

THERE ARE TWO STRATEGIES to cutting the time short, like the tortoise and the hare. The hare moves as fast as possible, hands a blur, instruments clattering, falling to the floor; the skin slips open like a curtain, the skull flap is on the tray before the bone dust settles. But the opening might need to be expanded a centimeter here or there because it's not optimally placed. The tortoise proceeds deliberately, with no wasted movements, measuring twice, cutting once. No step of the operation needs revisiting; everything proceeds in orderly fashion. If the hare makes too many minor missteps and has to keep adjusting, the tortoise wins. If the tortoise spends too much time planning each step, the hare wins.

The funny thing about time in the OR, whether you frenetically race or steadily proceed, is that you have no sense of it passing. If boredom is, as Heidegger argued, the awareness of time passing, this is the opposite: The intense focus makes the arms of the clock seem arbitrarily placed. Two hours can feel like a minute. Once the final stitch is placed and the wound is dressed, normal time suddenly restarts. You can almost hear an audible whoosh. Then you start wondering: How long till the patient wakes up? How long till the next case gets started? How many patients do I need to see before then? What time will I get home tonight?

It's not until the last case finishes that you feel the length of the day, the drag in your step. Those last few administrative tasks before leaving the hospital, however far post-meridian you stood, felt like anvils. Could they wait till tomorrow? No. A sigh, and Earth continued to rotate back toward the sun.

But the years did, as promised, fly by. Six years passed in a flash, but then, heading into chief residency, I developed a classic constellation of symptoms — weight loss, fevers, night sweats, unremitting back pain, cough — indicating a diagnosis quickly confirmed: metastatic lung cancer. The gears of time ground down. While able to limp through the end of residency on treatment, I relapsed, underwent chemo and endured a prolonged hospitalization.

I emerged from the hospital weakened, with thin limbs and thinned hair. Now unable to work, I was left at home to convalesce. Getting up from a chair or lifting a glass of water took concentration and effort. If time dilates when one moves at high speeds, does it contract when one moves barely at all? It must: The day shortened considerably. A full day's activity might be a medical appointment, or a visit from a friend. The rest of the time was rest.

With little to distinguish one day from the next, time began to feel static. In Eng-

PAUL KALANITHI SAVORS MOMENTS WITH HIS DAUGHTER, CADY

Yet there is

DYNAMISM IN OUR HOUSE. OUR DAUGHTER WAS BORN DAYS

after I was released from the hospital. Week to week, she blossoms:
a first grasp, a first smile, a first laugh. Her pediatrician regularly records her growth on charts,
tick marks of her progress over time..

lish, we use the word time in different ways, "the time is 2:45" versus "I'm going through a tough time." Time began to feel less like the ticking clock, and more like the state of being. Languor settled in. Focused in the OR, the position of the clock's hands might seem arbitrary, but never meaningless. Now the time of day meant nothing, the day of the week scarcely more so.

Verb conjugation became muddled. Which was correct? "I am a neurosurgeon," "I was a neurosurgeon," "I had been a neurosurgeon before and will be again"? Graham Greene felt life was lived in the first 20 years and the remainder was just reflection. What tense was I living in? Had I proceeded, like a burned-out Greene character, beyond the present tense and into the past perfect? The future tense seemed vacant and, on others' lips, jarring. I recently celebrated my 15th college reunion; it seemed rude to respond to parting promises from old friends, "We'll see you at the 25th!" with "Probably not!"

Yet there is dynamism in our house. Our daughter was born days after I was released from the hospital. Week to week, she blossoms: a first grasp, a first smile, a first laugh. Her pediatrician regularly records her growth on charts, tick marks of her progress over time. A brightening newness surrounds her. As she sits in my lap smiling, enthralled by my tuneless singing, an incandescence lights the room.

Time for me is double-edged: Every day brings me further from the low of my last cancer relapse, but every day also brings me closer to the next cancer recurrence — and eventually, death. Perhaps later than I think, but certainly sooner than I desire. There are, I imagine, two responses to that realization. The most obvious might be an impulse to frantic activity: to "live life to its fullest," to travel, to dine, to achieve a host of neglected ambitions. Part of the cruelty of cancer, though, is not only that it limits your time, it also limits your energy, vastly reducing the amount you can squeeze into a day. It is a tired hare who now races. But even if I had the energy, I prefer a more tortoiselike approach. I plod, I ponder, some days I simply persist.

WEB EXTRAS

Video and
a conversation with
Paul Kalanithi at
http://stan.md/1KR4Sis

EVERYONE SUCCUMBS TO FINITUDE. I suspect I am not the only one who reaches this pluperfect state. Most ambitions are either achieved or abandoned; either way, they belong to the past. The future, instead of the ladder toward the goals of life, flattens out into a perpetual present. Money, status, all the vanities the preacher of Ecclesiastes described, hold so little interest: a chasing after wind, indeed.

Yet one thing cannot be robbed of her futurity: my daughter, Cady. I hope I'll live long enough that she has some memory of me. Words have a longevity I do not. I had thought I could leave her a series of letters — but what would they really say? I don't know what this girl will be like when she is 15; I don't even know if she'll take to the nickname we've given her. There is perhaps only one thing to say to this infant, who is all future, overlapping briefly with me, whose life, barring the improbable, is all but past.

That message is simple: When you come to one of the many moments in life when you must give an account of yourself, provide a ledger of what you have been, and done, and meant to the world, do not, I pray, discount that you filled a dying man's days with a sated joy, a joy unknown to me in all my prior years, a joy that does not hunger for more and more, but rests, satisfied. In this time, right now, that is an enormous thing. **SM**

Contact Paul Kalanithi at http://paulkalanithi.com

time lines

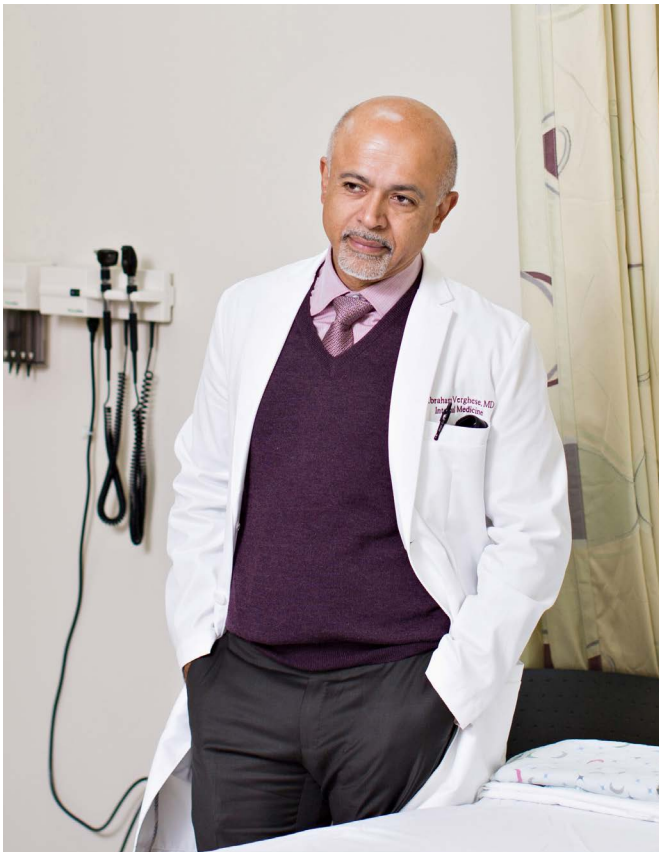
A simple dignity envelopes writer Abraham Verghese, MD.

A calm quietness about this Stanford professor of medicine conveys both strength and vulnerability. You have a sense as soon as you meet him, and especially when you get to know him, that there's great depth here.

He's written two searing works of nonfiction: *My Own Country*, a paean to the men he treated for HIV/AIDS as a young physician in eastern Tennessee, and *The Tennis Partner*, a lyrical eulogy to a fellow physician and best friend whose life went off the rails and skidded into the abyss.

His third book, the novel *Cutting for Stone*, found a huge new audience and the response was rhapsodic. Its first page jolts you. A Roman Catholic nun gives birth to twins and dies on the operating table in a hospital in Ethiopia. From that point on you are swept into a beautifully detailed world that comes alive through Verghese's skills as a physician and a writer. Novelist John Irving said of the book, "That Abraham Verghese is a doctor and writer is already established; the miracle of this novel is how organically the two are entwined. I've not read a novel wherein medicine, the practice of it, is made as germane to the storytelling process, to the overall narrative, as the author manages to make it happen here."

As the School of Medicine's commencement speaker last spring, Verghese talked about the timeless qualities of practicing medicine. Here he continues this line of thought in a discussion with *Stanford Medicine* executive editor Paul Costello.



JASON HENRY

PAUL COSTELLO: In your first book, *My Own Country*, you wrote so eloquently about HIV as an illness that takes people before their time.

ABRAHAM VERGHESE: That was certainly true of HIV in that era, but of course there are many diseases like that. Still, at that time, that one disease dominated my experience and affected young men, in most cases, who had every reason to think they had plenty of time left. Instead, they found themselves in this crucible, where there was only so much enzyme and substrate left before the whole thing ground to a halt. It made them acutely conscious of time and the fact that it was running out. I remember taking my kids to memorial services for my patients. I wanted my children to understand the fact that *this*, our time here, is not guaranteed and that time is precious. John Irving says in one of his books, "life is a terminal condition." It's about to run out on all of us. But it's a shock when you learn it will run out sooner. And there are no exceptions to the fact that it all ends. I think in a way that's what makes life poignant and beautiful ... and sad.

COSTELLO: As you are crafting narrative and characters, do you often think about time?

VERGHESE: It's hard not to think about it, but especially in fiction, time is almost like a character. In *Cutting for Stone*, I experimented with time in so many ways, ultimately settling on the idea of the narrator being an older individual looking back at the moment of his birth. The great power of a novel is that you can leap 10 years in the course of a page. At the end of one chapter, you've left one character. In the next chapter they are 10 years older — or 100 years older. I love that. One hopes that a good novel also distorts the reader's sense of time: You hope to pull the reader into your story and by page two make them suspend disbelief, make them forget they're reading words on a page but instead have them enter a new world, one you created, and you allow them to live vicariously through several lives playing out over several generations, hundreds of years going by, and when they come to the last page they look up and realize, wow, it's only Tuesday. I was always attracted to a novel that could do that, and it was my ambition to write like that.

COSTELLO: How has time changed you as a physician?

VERGHESE: I remember as a young physician feeling almost immune, as if there were a contract we had just made: In return for my hard work and acquiring all this huge knowledge, I would be spared these ghastly things that I saw every day. As you get older you begin to realize, first of all, you're not immune, and secondly, only the grace of God and tremendous luck spares you from being in that bed, and being the one looking up and speaking to the grisly crew around your bed. I think it just takes the passage of time to arrive at the perspective of one's own vulnerability and the fact that you are not immune. I get impatient with physician essays that revolve around a physician encountering medicine as a patient, often for the first time. And with it comes suddenly this epiphany about life and the nature of medicine. And I always think, "*Really*? It took that experience for you to understand this? All those years of watching the suffering weren't enough?" I am sure I am being unfair, because it is hard to be in someone's shoes till you are, but still.

COSTELLO: When you cross that threshold and enter a patient's room with physicians in training, what are you telling them is important?

VERGHESE: I am not sure I say anything. I think I am mostly trying to model a kind of interaction. I make rounds with third-year medical students on Wednesdays and Fridays at Stanford and at the Palo Alto VA hospital. And in each case I want to convey to them, without saying anything per se, a sense of this being hallowed ground. You're entering sacred space and given the great privilege to see people in distress and to treat. I try to teach students concrete and simple things: such as the fact that the two most important buttons in medicine are not the left and right mouse button but the button to raise the bed up so that you can do a decent job of examining the patient; and secondly, the task light button (which is often hidden or out of sight) so that you can see and study the patient. A mechanic does that for a motor, so it is the least we can do for our patients. I'm also trying to convey the skill of a quick exam and the need to read the body as a text. Why open a book if we can't read the words, and the patient's body abounds with words. If I'm lucky, I'll connect with the patient in a particular way that makes them forthcoming. I'll bring out stories from them. I'll tell them stories. And in the process I am hoping that students will see there is this great privilege and satisfaction in these interactions — and joy in teaching and modeling it and seeing the student respond.

WEB EXTRA
Hear the conversation at http://stan.md/1J9HJ7f

COSTELLO: I know you're not a Luddite when it comes to technology in medicine, yet you are concerned that technology often overrides spending time focused on the patient.

VERGHESE: Do we think we can deliver good patient care by spending all of our time in front of a computer screen, hours and hours and hours away from the patient? All of this perverse clicking we do: It's estimated we click about 4,000 times a day. A great percentage of that has to do with billing. But I'm an eternal optimist. And I am also sensing that we have a different breed of students today. They are incredibly motivated. I have great hopes that today's students will be the ones to set it all straight. I think they're in medicine for all the right reasons. I think they are more altruistic than ever before. I also think they have the knowledge and skills to solve this present dilemma we're in. I am not against technology by any means. But the reams of data that are in the computer and that we understand very well, a symphony of facts and theories, mean nothing if the patient only registers that people rarely come by. We are dealing with humans, not data points.

COSTELLO: Why do you think it's important for young physicians to understand the lineage of medicine?

VERGHESE: It's to help understand time. The lineage is a sense of connection. The technology isn't timeless, the understanding of disease isn't timeless — it changes logarithmically. But the desire of humans to serve the sick is timeless; the sense of vulnerability one feels when ill is timeless. So, in that sense, there is a lineage whose function is constant, and that is "to love the sick, each and every one of them as if our bodies were at stake," to quote Galen. I think to understand that lineage — and you can go back to Hippocrates, Galen, Paracelsus and Harvey, and in America go to Osler, and at Stanford to Shumway, Kaplan — the sense of sacredness emerges when you realize that you are the latest iteration of a long, long tradition. It makes the everyday, the humdrum bearable to know that. It does for me.

COSTELLO: What have you taken away from your patients as you've watched them face significant illnesses?

VERGHESE: Early on in my career I had a hemophiliac

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NOBEL BEGINNINGS

A FLEDGLING BIOCHEMIST IN A PREDICAMENT

Paul Berg was in for a shock when he arrived at Western Reserve University in Cleveland. He had moved there from Pennsylvania with his wife, Millie, to start graduate school in 1948. Berg, now the Cahill Professor of Biochemistry Emeritus at Stanford and winner of the 1980 Nobel Prize in Chemistry, was raring to take a position in the school's famous Department of Biochemistry. He soon realized, though, he had accepted a post in the Department of Clinical Biochemistry, a much smaller and less noteworthy program at the school, now known as Case Western Reserve. What happened next? Find out in this excerpt from the newly published *A Biography of Paul Berg* by Errol Friedberg (World Scientific Publishing Co., 2014).

WHEN BERG first entered the premises that were to be his workplace for the foreseeable future he witnessed the harsh reality that his dream of working on metabolic studies using radiotracer technology may well become the nightmare of finding himself in the wrong department. • By the time he realized his grave error there was precious little Berg could do about the situation — few alternatives existed at that late stage of the game. Besides, Millie had already obtained a nursing position at one of the Western Reserve University hospitals. Even more dispiriting, soon after his arrival in the laboratory Berg learned that [the department's chairman, Victor] Myers had assigned him the mundane task of measuring cholesterol levels in a cohort of postmortem human hearts to determine if there was any correlation with the cause of death. His brief career as a graduate student seemed poised to take a further nosedive when, about a month later, the aging Myers passed away, and the two remaining faculty members in the defunct department adopted Berg — reluctantly or otherwise! • As things turned out, Berg was far more fortunate than he might otherwise have been. Jack Leonards (who was immediately appointed interim chair of the department) and his colleague, Leonard Skeggs, were collaboratively working on the development of an artificial kidney for renal dialysis. Though this was a far cry from the metabolic labeling experiments being pursued in [biochemistry department chairman] Harland Wood's laboratory just a floor away, Berg rationalized that work with the artificial kidney was nonetheless cutting-edge research in clinical chemistry. So without a word of complaint (at least to anyone within earshot) he rolled up his sleeves and got to work.

The notion of renal dialysis is credited to Dutch physician and engineer Wilhelm Kolff, who, having witnessed the demise of a 22-year-old man from renal failure, was inspired to invent the first functional kidney dialysis machine. Kolff fashioned a device from cellophane tubing wrapped around a cylinder that rested in a bath of cleansing fluid. Blood was tapped from an artery and, after being cleared of urea and other toxic metabolites, was returned to the venous circulation. Skeggs, who had impressive engineering skills in his own right, was convinced that with Leonards' help he could improve on Kolff's efforts.

Remarkably sanguine about a situation that might have prompted serious concern (perhaps even frank panic) in less determined individuals, Berg diligently set about his assigned duties, beginning with learning how to nephrectomize dogs. While assiduously reading the relevant literature, he noted that several putative but as yet unidentified urinary proteins were alleged to have been imbued with remarkable physiological assets. One was claimed to have anticoagulant properties, another to protect against gastric ulcers, and a third putative urinary protein had been suggested to reduce blood pressure. Their extremely low concentration coupled with the enormous salt content of urine had thus far discouraged the purification of these proteins for detailed study.

PAUL BERG IN 1952 ON GRADUATION DAY AT WESTERN RESERVE UNIVERSITY IN CLEVELAND, WHERE HE GOT HIS DOCTORAL DEGREE. AT HIS SIDES ARE PROFESSORS HARLAND WOOD (LEFT) AND WARWICK SAKAMI.

Here we witness the first of many instances in which Berg squarely faced a challenge in the laboratory — and contrived an innovative solution. The enterprising idea came to him that he might be able to exploit the dialyzer to reduce the amount of salt in the urine he routinely collected in huge jugs placed in the local men's rooms, and then concentrate the dialyzed fluids by low temperature distillation to a manageable volume that he could test for biological activity. Berg located an old freezer with an intact and functional condenser and single-handedly fashioned a distillation apparatus with which he was able to effectively distill off much of the liquid and collect reasonably concentrated samples of urine to test for biological activity. "It was really a Rube Goldberg type of operation," he laughingly recalled. "But in the end I was able to detect the anticoagulant factor, as well as an activity that suppressed ulcer formation in rats" — an impressively innovative start for a total novice in a research laboratory.

In the midst of these experiments Berg took graduate-level courses for credit in the "real" biochemistry department, including one that once again required oral presentation of relevant papers from the current literature. He elected to present a seminar on transmethylation, a biologically important chemical reaction in which a preformed methyl group is transferred intact from one compound to another, then a topic of considerable interest and controversy in biochemical circles.

Conventional dogma held that mammals were unable to synthesize methyl groups of methionine and choline de novo. They had to be supplied in the diet. But Berg uncovered hints in the literature that if one supplemented the diet of experimental animals with folic acid and vitamin B12, one could do away with the methionine requirement. Indeed, Warwick Sakami, a Japanese-born professor in the Department of Biochemistry well-versed in the use of radiolabeled substrates, had detected radioactive methyl groups in methionine and choline in the livers of rats previously injected with radioactive serine and later with radioactive formic acid.

Berg delivered a polished and thoroughly researched seminar that greatly impressed the assembled faculty. Buoyed by the enthusiastic reception to his presentation, Berg approached Sakami to express his interest in determining how 1-carbon compounds are converted to methyl groups in choline and methionine. Sakami was in turn becoming increasingly impressed with Berg's keen intellect, his enthusiasm for biomedical research and his

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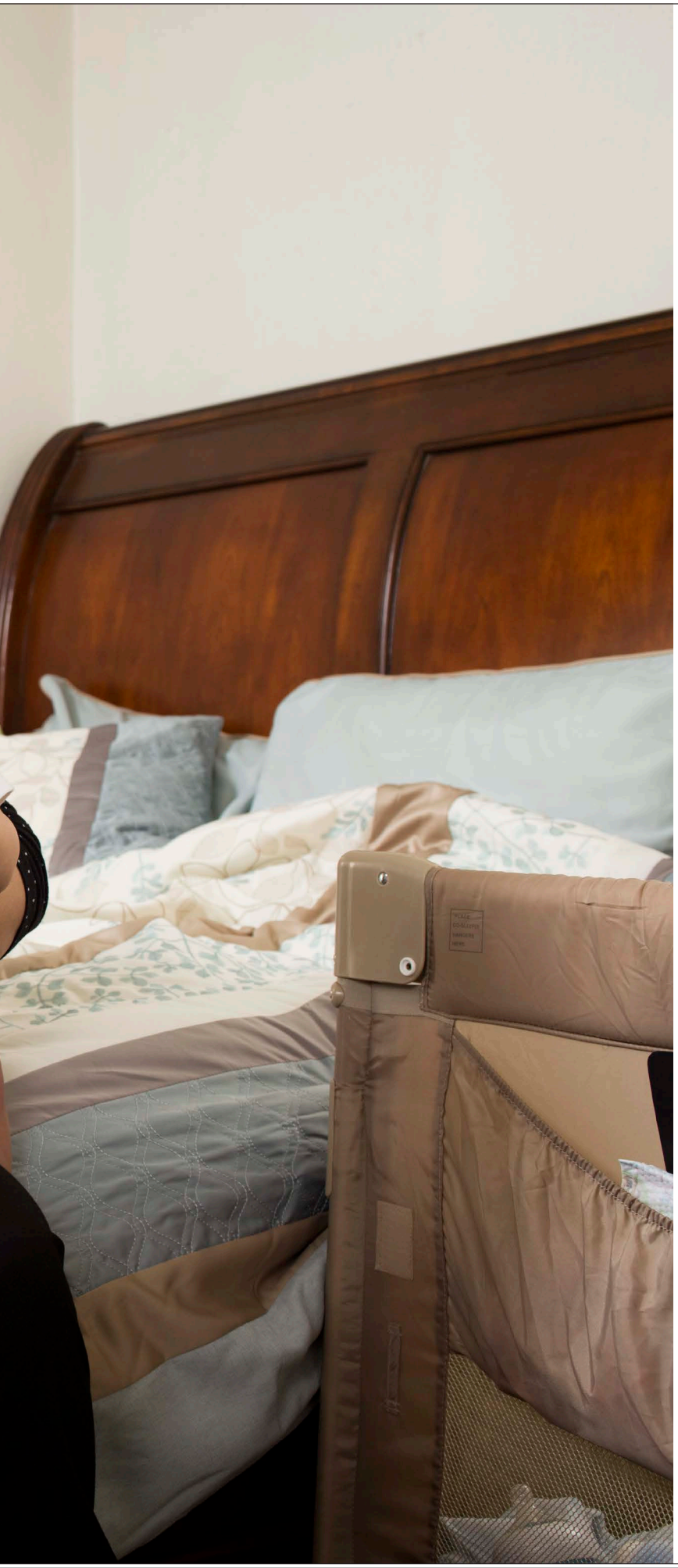
'IT WAS REALLY A RUBE GOLDBERG TYPE OPERATION. BUT IN THE END I WAS ABLE TO DETECT THE ANTICOAGULANT FACTOR ....'

PHOTOGRAPH COURTESY OF PAUL BERG



SIDE BY SIDE BY SIDE

SAVING THE LUEVANOS TRIPLETS

WHEN LILY ESTRADA was six weeks pregnant, she and her husband found out she was carrying triplets. • "We were just shocked," Estrada recalls. The Salinas, Calif., couple, who had three teenagers at home, had been excited about the idea of a new baby. Triplets, though? "My husband almost fainted," Estrada says. • But the bigger shock was yet to come. As the pregnancy progressed, Estrada's doctors discovered that her triplets, identical boys, shared a single placenta with a serious defect. During pregnancy, the blood-vessel-rich placenta connects fetuses to their mother and serves as an essential conduit for nutrients and waste disposal. But this placenta was slowly killing Estrada's three boys. • "It was very bad," says Yair Blumenfeld, MD, assistant professor of obstetrics and gynecology at the Stanford School of Medicine, who led a team of maternal-fetal medicine experts that cared for Estrada. "Her trajectory meant there was a very high chance she would lose all three babies." • Early on, the team explained the gravity of the situation to Estrada, who was 35 at the time of the diagnosis in the fall of 2013 and who works

By Erin Digitale

PHOTOGRAPH BY GREGG SEGAL

LILY ESTRADA AND HER TRIPLETS, PEDRO, WILLIAM AND AYDEN, SURVIVED A COMPLICATED BIRTH.

in patient registration at Natividad Medical Center in Salinas, and her husband, Guillermo Luevanos, then 36 and an agricultural worker in the Salinas Valley. Estrada's placenta had several blood vessels connecting the three babies directly to each other, and blood was shared unequally through these connections, a condition called twin-to-twin transfusion syndrome. Researchers don't know why the disease develops in some cases but not others, though they are trying to figure it out.

Not only was Estrada's entire pregnancy at risk, at the time no one at Stanford could perform the surgery that might alleviate the problem. But the team could offer something new: Lucile Packard Children's Hospital Stanford had just entered into a clinical and scientific collaboration on fetal treatment with Texas Children's Hospital and Baylor College of Medicine, in Houston, which did offer the surgery she needed. Estrada could become their first shared patient.

The collaboration is part of a widespread effort to refine fetal surgery. Excitement about these unusual surgeries rose in the 1980s and '90s as surgeons attempted to fix many different congenital defects during pregnancy, but the buzz fizzled when the risks became apparent. Cutting into a pregnant uterus often triggers preterm labor, putting not one but two patients — mom and baby — at risk of complications that can easily outweigh benefits of the surgery. Today, surgeons have narrowed the range of conditions for fetal surgery to those with the best chance of averting death or long-term disability for the future baby, and they are developing new tools and techniques to improve safety for both patients.

One big shift: For most diagnoses, surgeons now favor laparoscopic procedures that use tiny incisions and instruments instead of the large, risky, open incisions through the uterus that were once used to access the fetus.

"Over time, people realized aggressive interventions may improve neonatal survival but have very high risk to the mom and the integrity of the uterus," Blumenfeld says, adding that early techniques left mothers at risk of bleeding and uterine rupture as well as premature delivery.

"Our two teams, at Stanford and Texas, have a very similar perspective on the future of fetal intervention: It is as minimally invasive as possible," says maternal-fetal medicine expert Yasser El-Sayed, MD, professor and director of Maternal-Fetal Medicine and Obstetrics at Stanford University, and obstetrician-in-chief at Lucile Packard Children's Hospital Stanford.

'THE BABY PUMPING BLOOD HAS TO WORK VERY HARD AND CAN GET VERY SICK, AND THE RECIPIENT BABY, WHO IS GETTING A LOT OF EXTRA FLUID, CAN GO INTO HEART FAILURE.'

BEFORE SURGERY

ESTRADA WAS 17 WEEKS pregnant when it became clear that something was wrong. On a routine ultrasound, her doctor in Salinas saw too much amniotic fluid. Estrada had some fluid removed, but the problem recurred, prompting her referral to Stanford.

The Stanford team soon realized Estrada's pregnancy was a perfect storm of rarity. Triplets who share a single placenta occur in one to two births per 100,000, and just a small fraction of these have twin-to-twin transfusion.

"With a shared placenta, there are always going to be some vascular connections between the babies," Blumenfeld says. Although most of the blood from each baby's umbilical cord travels deep into the placenta to exchange nutrients and wastes with mom's circulation, some blood flows into surface blood vessels that connect the babies directly to each other. In 10-15 percent of shared placentas, these connections lead to the unequal blood flow that characterizes twin-to-twin transfusion. (The condition is so named because most cases affect identical-twin pregnancies, which are much more common than triplets.)

Shared placentas with abundant artery-to-artery connections between fetuses seem not to develop problems, researchers have noted, whereas those with predominantly artery-to-vein and vein-to-vein connections are primed for uneven blood flow.

"The baby pumping blood has to work very hard and can get very sick, and the recipient baby, who is getting a lot of extra fluid, can go into heart failure," Blumenfeld says. In the 1980s, before surgical treatment was developed, the medical literature reported 95 percent mortality of fetuses like Estrada's that were affected by a severe fluid imbalance before 24 weeks of pregnancy. Surgery on the placenta has improved survival substantially, but many fetuses still die before birth. And the high mortality is especially sad because, in most cases, the fetuses are otherwise normal.

In Estrada's case, one fetus was donating blood through the placenta to the second, who

was passing it through other shared blood vessels to the third, and sickest, fetus. Although they shared a placenta, each brother had his own amniotic sac, the "bag of waters" in which a fetus develops. Amniotic fluid, the cushioning liquid in the womb, was accumulating in the third fetus's amniotic sac as his kidneys produced extra urine to lighten the fluid load from the excess blood, while the fluid in the sacs of the donor fetuses dwindled away to almost nothing.

Extra fluid was changing the structure and function of the recipient's heart, putting him at risk for heart failure before birth. Not only was his health in danger; if he died in utero, his brothers could suffer permanent neurological injury. (No one is sure why this happens — perhaps a sudden change in blood pressure or rush of cytokines at the time of the death is responsible — but experts agree that the brain injury to surviving fetuses seems to occur instantaneously.)

MAKING A DECISION

The Stanford team gave Estrada and Luevanos several options: End the whole pregnancy, do nothing and face the hazards of the condition, terminate one fetus's life in the hopes of improving the chances of the other two, or have Estrada travel to Texas for surgical treatment that uses a laser to seal off problematic blood vessels in the placenta.

The medical team faced a delicate balance of trying to convey the potential benefits and risks of each option without raising falsely high hopes. They also wanted to give the couple enough information to make an informed decision but enough room to feel like they were in the driver's seat, even if the options were potentially heartbreaking.

"It's a very difficult situation for a family to be in," says neonatologist Susan Hintz, MD, medical director of Fetal and Pregnancy Health Services at Lucile Packard Children's Hospital Stanford and one of the leaders of the Stanford-Texas Children's Collaboration. "We do not want to be paternalistic about conveying the options, especially in a very challenging and rare case such as this one. We're working with a family to understand what their goals are, and we want to be honest about our estimates of the risks and the limits of what we can predict with certainty about the outcomes."

No one was sure how well the surgery might work for Estrada's triplets because so few triplets are treated for twin-to-twin transfusion.

"We were saddened and sort of confused," Estrada says, recalling the first reactions that she and her husband had to the news. "It was: We could wait and see what happened, but the likelihood was that we were going to have no baby, or we could terminate one and see what happened with the other two, or take the risk, go to Houston, have the surgery and hope it worked for all three. But they didn't guarantee anything."

One piece of background that helped inform the couple's decision was the fact that when the surgery worked, research had shown it helped moms stay pregnant about four weeks longer, allowing their babies more time to develop before birth. (Because the uterus gets so crowded, twins and other multiples are almost always born early, but a less premature delivery makes a huge difference for the babies' health.) Sealing the connecting blood vessels also seemed to protect surviving fetuses in the event that one died. "We're separating, or attempting to separate, their fates," Blumenfeld says.

After a lot of counseling and discussion with the Stanford team, "we decided to go for it and do surgery," Estrada says.

Once they had made the choice, they had no second thoughts. "My husband was a little bit stronger," Estrada recalls. "He just wanted me to go for it, and see what happened."

Interacting with Estrada and her family had left Blumenfeld, like the rest of the Stanford team, anxious to do the best he could for her.

"She's an absolute gem to take care of," he says.

IN THE OPERATING ROOM

Estrada's flight to Houston, when she was 21 weeks pregnant, was difficult in itself. She was traveling alone; Luevanos had to stay home with their older children, while Blumenfeld, who was coming to observe and help manage the patient, was following on a later flight. The accumulated amniotic fluid added challenges at every step. "It was scary," Estrada recalls. She was very uncomfortable sitting still, had trouble drawing a deep breath and had enough difficulty walking that she needed a wheelchair to navigate the airports. When the four-hour flight to Houston took off, her uterus swelled even more, putting her whole belly under extreme pressure. "It was a mission just to get from one place to another," she says.

When she arrived at Texas Children's on the evening of Dec. 14, 2013, she began spotting — just a little vaginal bleeding, but it was still worrisome. Although the bleeding had stopped by the next morning, echocardiograms showed the babies were in distress, and the operation was moved up a day. Blumenfeld came directly from the airport to Texas

Children's, arriving at 3:30 p.m. on Dec. 15, just as Estrada was being wheeled into surgery.

Estrada's surgeon, Michael Belfort, MD, PhD, obstetrician- and gynecologist–in-chief at Texas Children's Hospital, had two goals: to remove excess amniotic fluid and, more important, to seal every abnormal blood vessel connecting the babies that he could find. He aimed to avoid shutting down any vessels that were not involved in the transfusion syndrome so that each baby would get the maximum benefit of his piece of the placenta.

But although Belfort would try to seal off every problematic blood vessel, in a uterus crowded with three babies, he knew he might have difficulty finding them all. And it would take about a week of monitoring the babies' fluid levels to see if the procedure had helped.

"We do the best we can," says Belfort, chair of Baylor's Department of Obstetrics and Gynecology, who has performed more than 200 surgeries for twin-to-twin transfusion since he learned the procedure in 2007. Even with his years of experience, though, Estrada's was only the second case of triplets he had treated. "If we're able to identify all of the abnormal blood vessels, we are definitely able to help. If we can't identify them all, we maybe get partial resolution."

In the operating room, Belfort made a 10-millimeter incision and inserted the surgical tool, which contained both a tiny camera and a laser, into the amniotic sac of the triplet who was receiving blood flow from his brothers. The view on the monitor in the operating room — a round window into the babies' prenatal world — showed a jumble of pale limbs, glimpses of umbilical cord, a flash of a tiny ear, and, near the top of the field of view, the network of blood vessels on the surface of the placenta. The recording of the surgery illuminates a prenatal world most people never see. It's entrancing, a little scary and hauntingly beautiful. Watching it, one can't avoid imagining the hopes of everyone in the operating room: that the surgery would work, that the babies would keep growing, that they would be born safely, that Estrada and Luevanos would get to hold their three infant sons and kiss them and tell them everything was going to be OK.

To begin, Belfort looked for the fetuses who were pumping blood onward, known as "donors." He could identify them by the fact that they were in nearly empty amniotic sacs and appeared trapped behind the very full amniotic sac of the triplet receiving the most fluid.

Once he had identified the donors, Belfort began visually tracing blood vessels that ran laterally across the surface of their placenta to the recipient. Each vessel got a zap of green laser light to seal it. He aimed the laser at the point where the vessels met between two fetuses, or at a spot as close to that as he could reach that allowed him to shut down the connection. In total, he sealed seven blood vessels, a typical number for this type of surgery, then made some shallow passes with the laser to catch other small blood vessels on the placenta's surface that he might have missed. He also removed about a liter of amniotic fluid from the recipient's amniotic sac. The entire procedure took about an hour.

BETTER TOOLS

BLUMENFELD'S TRIP TO TEXAS to observe Estrada's procedure was the first step in building the surgical skills of the Stanford team, a key aspect of the Stanford-Texas collaboration. Since then, both Blumenfeld and Stanford pediatric general surgeon Karl Sylvester, MD, obtained Texas medical licenses to enable them to get hands-on training in Houston, and Lucile Packard Children's Hospital Stanford ordered new surgical equipment for fetal interventions. The team conducted their first surgery for twin-to-twin transfusion syndrome at the hospital in January.

"In fetal surgery, the surgeons need better hands and better eyes," says Christopher Contag, PhD, a Stanford professor of pediatrics and of microbiology and immunology who builds medical-imaging and visualization tools for surgeries. With the shift to minimally invasive techniques for fetal procedures, surgeons are limited by the cameras and laparoscopic instruments already on the market. Better "hands" would be a big help in one common fetal surgery: repairing spina bifida, a congenital defect in which portions of the spinal cord are exposed to the exterior of the body. Ideally, surgeons would like to have dextrous laparoscopic tools to hold the needle they use to repair spina bifida. But now, their tools have so little articulation that they're forced to make stitches by passing the

'IF WE'RE ABLE TO IDENTIFY ALL OF THE ABNORMAL BLOOD VESSELS, WE ARE DEFINITELY ABLE TO HELP. IF WE CAN'T IDENTIFY THEM ALL, WE MAYBE GET PARTIAL RESOLUTION.'

needle back and forth between two surgeons.

For twin-to-twin transfusion surgery, the "hand"— the laser used to seal blood vessels — is already extremely effective. But surgeons want better eyes: "Doctors need to see the blood vessels, and need to have them stand out against background," Contag says.

Right now, the light source used to look for problematic placental blood vessels is ordinary white light. Under that illumination, it's tricky to pick out the blood vessels and impossible to check whether a cauterized vessel has been sealed.

But blood's intrinsic spectral properties will probably make it possible to solve these problems. For finding blood vessels, "we can illuminate the tissue at one wavelength and collect light at another," Contag says. "It makes the blood vessels jump out at you." (His team has already incorporated this technique into tools they've developed for gastrointestinal endoscopy.) To check the seal on cauterized vessels, surgeons could use photoacoustics to listen for blood flow: You shine laser light at the blood vessels, which absorb some energy, heat, expand and reflect back patterns of ultrasound waves that can be heard with ultrasound transducers and transformed into 3D images. "You can very clearly see if you were successful," Contag says.

HAPPY BIRTHDAY

After the surgery, Estrada stayed a week in Houston for monitoring. Since surgical tools that verify cauterization of blood vessels are still in the future, the best way to confirm the success of the surgery was to watch what happened to the babies. "The proof is in the pudding," Texas Children's Belfort says.

The fetus that had appeared least affected by fluid imbalance before the surgery developed worrying swelling in his skin and umbilical cord in the first day after the procedure. At first, the doctors weren't sure if he would get better or worse.

Waiting to find out what would happen was taxing for Estrada. Separation from her family and worry about her triplets left her feeling lonely and depressed.

But good news was coming. "Within days, we saw improvement," Belfort says. The worrying swelling abated, and ultrasound scans showed all three fetuses had reassuringly normal-sized bladders, a sign that their bodies were not fighting the fluid imbalance that affected them before surgery.

With less amniotic fluid, the trip home was much easier for Estrada. After returning to California, she stayed in an apartment near the Stanford campus with her husband; the medical team wanted her close to the hospital for delivery. Triplet pregnancies last an average of 32 weeks, eight weeks short of the 40-week gestation period that is normal for single babies. To reduce the effects of prematurity, the doctors wanted to get Estrada as close to that goal as possible, but weren't sure how long her pregnancy would last. "Every day we get now is a gold mine," Blumenfeld said at the time.

On Jan. 30, 2014, when Estrada was 28 weeks pregnant, she went into labor. Her due date was still 12 weeks away, but the babies had a strong chance of surviving the effects of prematurity. At the hospital, Blumenfeld determined that one fetus — the baby who had been receiving fluid before surgery — had a falling heart rate, so an emergency C-section was performed.

Baby Pedro was born first, weighing 2 lbs. 9 oz. Then came his brother William, at 2 lbs. 6 oz., and finally little Ayden, the recipient of the fluid, at 1 lb. 9 oz.

"I was emotional," Estrada says. She couldn't see the new arrivals in the delivery room, but she heard their three first cries. Later, when she was wheeled on a gurney to meet them in the neonatal intensive care unit, "I was scared for them because they were so tiny," she recalls.

Although the babies all had complications of their premature arrival, under the ministrations of the neonatology team they gradually matured and gained strength. Ayden, the baby who had been most severely affected by twin-to-twin transfusion, also had the most difficulty after birth, but was ultimately able to go home to Salinas in April, just a week after his brothers. He still gets checkups with Stanford Children's Health specialists every six months to monitor potential complications of premature birth, including possible problems with his lungs and his vision, but his doctors are encouraged by his progress.

Today, though Estrada and Luevanos feel the exhaustion one would expect of parents of young triplets, they're also delighted to be watching all three of their little ones grow. Pedro and William are crawling, playing peek-a-boo and trying to walk; and Ayden, though a bit behind his brothers developmentally, is rolling everywhere and picks things up off the floor. "They're really happy babies," Estrada says. "They're doing well."

The Stanford team, meanwhile, is looking forward to being able to help other patients with twin-to-twin transfusion. "This is one of the greater success stories of fetal intervention: It's minimally invasive, the alternative of no treatment is horrific, and the surgery gives you a chance of taking home two babies if you have twins or three babies if you have triplets," Blumenfeld says. "Before, there wasn't this opportunity." SM

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CONTINUED FROM PAGE 11

mice score better on memory tests. When Heller switches the timing of the daily PTZ dose, though, giving the drug at night instead of during the day, suddenly its effects completely disappear.

"This is becoming more and more appreciated in medicine," says Heller. "The body is not the same at all hours of the day, and some drugs should be given at particular times to be most effective."

The brain, it turns out, goes through daily cycles of learning and memory storage, coinciding with when a mouse (or a person) sleeps. So at different times of day, PTZ interacts differently with the brain.

When Heller made the observation that his Down syndrome treatment wasn't as effective at night, when mice are active, as it was during the day, when mice are asleep, he began trying to make a link between circadian rhythms and sleep cycles and learning and memory. The crux of his research rests on the basic idea that the brain has two opposing functions: turning on neurons so they can communicate, and — at other times — blocking neurons from communicating. While people are sleeping, Heller has shown, this mandatory quiet time in the brain is especially vital. When the circadian rhythms of hamsters are obliterated, the animals no longer remember things from day to day.

"You'd think that inhibiting brain activity would always be contrary to our ability to learn and remember," Heller says. "But while a person or animal is sleeping, memories from their daily experience are being translated into long-term memories, and as these memories are being moved from one part of the brain to another, they're vulnerable to being altered." During that process, he says, it's important for most of the brain to not have any new activity, which could change the memory. PTZ, though, helps ensure that the activity ban isn't too harsh; some areas of the brain need to function to store the memory. Having shown that PTZ treatment before sleep can lead to memory improvements in mice with Down syndrome and in hamsters lacking circadian rhythms, Heller is investigating whether the drug can treat other neurological conditions as well.

To further understand the role of this daily activity cycle in the brain, Heller's group has studied what happens when memories are, incorrectly, reactivated during sleep. He trained mice to associate a particular smell with a shock. Then, during the day while the mice were sleeping, he piped the odor back into some of their cages. The mice who had re-experienced the smell had a much stronger fear response to the smell the next day. And, on the flip side, when the scientists blocked the whole brain from making new connections during the night, the mice didn't remember the smell at all the next day.

RESETTING THE BODY'S CLOCK

In collaboration with Jamie Zeitzer, PhD, associate professor of psychiatry and behavioral sciences at the medical school and at the Veterans Affairs Palo Alto Health Care System, Heller has also been studying more basic questions about circadian rhythms in people — and how to change these rhythms. The easiest way to alter the circadian clock, scientists know, is by exposing someone to light during their normal sleeping hours. This more quickly shifts the body's clock than exposure to darkness during the waking hours.

"Typically, researchers thought someone had to be exposed to at least half an hour of constant light to shift the clock," says Heller.

But if you're on a plane with the lights out, working nights or arrive in a new time zone after the sun has set, it might not be possible to get this half-hour of light to get your clock on the right schedule. So Heller and Zeitzer started investigating whether shorter bursts of light could do the trick. In both human and mouse studies, they've now shown that 2 millisecond flashes of light every 30 seconds for an hour during the night — while it doesn't interrupt sleep — can make people wake up earlier in the morning, shifting their circadian clock by almost an hour. The finding could lead to the development of new devices to help people avoid jet lag or adjust to a new shift at work.

"You could build these timed light pulses into glasses or travel alarm clocks or the cabins of airplanes to prevent jet lag," says Heller. By exposing someone to a series of flashes during a flight, for instance, Heller thinks he could shift their clock enough to at least ease the transition to a new time zone, although the flashes of light wouldn't help you sleep in if you're traveling in the other direction.

For world travelers, preventing jet lag might be the ultimate biological clock hack. But even if you don't jet around the globe on a regular basis, the ways scientists are learning to take advantage of your body's cycles could help you recover faster from an illness, sleep more effectively, adjust to a new schedule or get better at learning new things. And as researchers continue to learn more about how cycles drive the rhythm of life, they'll surely realize new ways to use this information. **SM**

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The researchers identified seven intertwined "pillars of aging" for targeted research, including adaptation to stress, stem cells and regeneration, metabolism, macromolecular damage, inflammation, epigenetics (the process by which cells control when and where genes are expressed based on chemical signposts on their DNA) and a concept called proteostasis, which describes the intricate dance in which proteins are made, transported and degraded within a cell.

So far Brunet and her killifish-loving colleagues have focused on several genes involved in these pathways, including the gene for telomerase. They've homed in on genes known to play roles in epigenetics and nutrient sensing, paying particular attention to a cascade of signals initiated by insulin and the insulinlike growth factor receptor that modulates the hormone's effect on cells. (Mutation in the receptor molecule extends by two to three times the life span of laboratory roundworms, and mutations in insulin or the receptor have a similar effect in fruit flies and laboratory mice.) In fact, many genes associated with aging are involved in some way with common metabolic processes.

In addition to playing a role in normal aging, there's fascinating evidence that organisms have evolved to manipulate these processes to their advantage. In 2013, Brunet showed that male roundworms, for example, actively secrete pheromones to shorten the life span of the egg layers after eggs are produced. It appears that the male worms have devised a calculated plan to off the baby makers to keep them from consuming valuable resources or mating with a competitor.

"In worms, once the male has mated and eggs are produced, the mother can be discarded," Brunet says. "The *C. elegans* mother is not needed to care for the baby worms. Why should it be allowed to stay around and eat? Also, if she dies, no other male can get to her and thus introduce his genes into the gene pool."

Will we one day be able to so casually (but perhaps with more compassion?) tweak our own life spans with simple medications? And what would be the ethical and societal implications of such an intervention? Will access be limited to a privileged few with the know-how to ask and the means to pay? Or will such treatments come to be regarded as the standard of care, covered by health insurance and dispensed as casually as vaccines and vitamins?

Bioethicist Christopher Scott, PhD, specializes in such thought-provoking questions. "Longevity research could be considered the newest iteration of 'enhancing life' technologies," says Scott, "connected deeply to what some call a moral imperative to portray aging as the ultimate enemy of humanity. But highly consequential decisions (funding research, creating new companies, establishing new scientific disciplines), technological inventions and social changes are being pursued on the tacit assumption that such decisions, inventions and changes will lead to a healthier, longer life and the promise of a better future. In ethics, I think these assumptions are largely unexplored and unacknowledged."

"We're going at this because it seems the right thing to do," says Rando. "But we're not sure what we're going to end up with. What kind of health span will we achieve? Is extending life span worthwhile if we can't control the development of diseases like Alzheimer's, which is extremely prevalent in the very old?" Conversely, if we begin to live much longer, perhaps humans will begin to develop entirely new diseases that are as unheard of now as cancer was in the Stone Age.

Scott also wonders whether the longevity research attracting attention today will manage to escape the commercialism and over-promises that beset similar research on aging conducted in the previous two decades. Those findings spawned a multibillion-dollar industry peddling largely useless nutraceuticals and pseudomedicine to legions of baby boomers eager to tack on at least a few more years to their lives.

"I'm fascinated by how quickly longevity research has taken off," says Scott. "One question is whether the promise of healthy life spans will outrun the reality of the science. It will be interesting to see whether longevity research will somehow duck the ethical and social issues that plagued aging research, or whether a supercharged repeat is in store."

Swimming in their tanks, the killifish are oblivious to the hype. But like humans, killifish age visibly. They lose muscle mass, their shimmering colors dim and their backbones begin to hunch. They move more slowly, conserving energy. Internally, they develop cancerous tumors of the liver and kidney and even cataracts in their eyes. Eventually they just stop swimming.

Death may come more quickly for the killifish than for any other vertebrate. Odds are that the darting, silvery individual that paused to give me the fish-eye in early October has already passed on. But he, and others like him, have already achieved a kind of immortality — living on as tiny data points and annotations in the laboratory notebooks of researchers like Brunet, Rando and Artandi, who are keeping their eyes on the real prize: unlocking the mysteries of longevity and health. **SM**

— Contact Krista Conger at krista@stanford.edu

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But Gardner has made a quick assessment of the mother, who, while visibly upset, seems to be keeping her emotions in check. He has noted her attire, including her black suede sneakers, is suitable for running in the event of a crash landing. Most important, she will be there to comfort the little girl when she arrives in a strange place.

Gardner takes a seat in the back of the aircraft, helping monitor Aeshna, who is now anchored in a head brace and whose eyes are fluttering in and out of sleep. Griffis massages the little girl's throat and face to keep her stimulated. At times, the child is staring into space, and Griffis waves her hands over Aeshna's eyes to elicit a blinking response and ensure she is still breathing. Gardner checks the girl's eyes with a flashlight to see that her pupils are constricting — a sign of normal brain stem function. And he injects her with an anti-nausea drug to help prevent vomiting.

The little girl seems so still and her responses so limited that the nurses worry she could quickly deteriorate.

"I'm thinking, OK, if she codes [goes into cardiac arrest], what is the nearest hospital where I can take her?" Griffis says later.

4:26 p.m. Just 47 minutes after the call to Stanford, the helicopter glides back over the bay, the Dumbarton Bridge visible through a haze in the distance. The aircraft approaches Palo Alto, passes over the Stanford Stadium, then begins to vibrate heavily as it prepares to meet the helipad.

The back door of the aircraft is opened, and hospital security officials swiftly offload the gurney into an elevator and down to the first floor. A greeting committee of some 15 doctors, nurses and technicians is waiting in the hall just outside the emergency department to welcome the little girl and wheel her into the trauma room.

4:47 p.m. The clinicians cut through her red T-shirt and remove the head brace to reveal the little girl's slender frame and her shock of black hair. They gently poke and prod her to see if her limbs are working and ask simple questions to gauge her mental status. "Who is this?" asks emergency physician Phil Harter, MD, pointing to her mother. "Is it your daddy? Is it your uncle? Is it your mom? The girl just nods, then yells one of the few words she will utter during the ordeal: "Mama!"

Harter, an associate professor of surgery, orders a CT scan, which will help determine the extent of her injury, and Aeshna is rolled into the big machine next door.

An hour later, results in hand, he issues the diagnosis: Aeshna has a skull fracture and a concussion. She needs to be watched closely for possible bleeding, but no surgery is called for now. She has suffered significant head trauma, and it will take time to heal. He briefs the parents, as the girl's father has arrived from his job in San Francisco. "Right now, we don't think she's at risk for bleeding, but that's why we're watching her," he says. "There is no intervention other than to watch and see that she improves. And that takes time."

Hammer, who takes over her care in the pediatric intensive care unit at Packard, says there is a depression of a few millimeters in her skull — not enough to put pressure on the brain. But the fracture occurred close to a major artery, a spot where clinicians sometimes see disastrous bleeding, he says. So she is lucky the fracture wasn't too deep.

The concussion also knocked around her brain inside the skull, jarring the nerves. So she is very sleepy and "out of it" and is prone to vomiting. In the intensive care unit, she is awakened every hour during the night for "neuro checks" — a test in which nurses ask her to grab a hand or answer a question and check her eye movements and see if the pupils are normal. Her scores aren't perfect, but they are OK. A CT scan the next day again shows no signs of bleeding.

"She was extremely lucky," Hammer says. "To have this thing fall off the wall and cause a skull fracture and no worse injury, that's good news…. It's amazing how lucky some people are, given the circumstances."

Though Aeshna hasn't returned to normal, Hammer sees she has supportive parents and he feels comfortable enough to let her go home later that day. She leaves the hospital at 5:17 p.m.

The flight nurses are relieved: "It could have gone differently," Gardner says. "She could have had a crushed head, blood everywhere. I've done CPR on patients on the helipad."

Because the nurses operate independently, they feel ultimately responsible for the outcome. "It's emotionally taxing," Gardner says. "If that kid didn't have a good outcome, we go home with that. You feel it's all on you."

Four days after the incident, Alameda County officials shut down the preschool because of multiple code violations. The loaded, 2-by-4-foot cabinet had shorn away from the wall because it had not been properly secured: It was attached only to sheet rock, not to studs in the wall, says Diane Hendry, a division chief in the Fremont Fire Department.

Back at home, Aeshna is slowly recovering in a process that could take months. She has to limit her activities so her brain does not become fatigued.

That means no story books, no exciting games, limited TV watching and certainly no somersaults or headstands, as any further injury to the brain could cause long-term problems, such as cognitive difficulties or memory loss. That is a tough prescription.

"She has resumed activities and wants to do all things, but it's hard to keep her tied down to bed," her mother says. As a result of the accident, the family went to India for a few weeks to stay with relatives, who helped provide support and care, she says. She says she is optimistic about Aeshna's prognosis, but she is nonetheless shaken by the experience.

"It looks like it's going well, but you have this insecurity in the back of your mind until she has a full recovery," Bhatt says. Like the accident itself, it's all a matter of time. **SM**

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Q & A

A conversation with Abraham Verghese

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patient who had the misfortune to contract HIV from the blood products he got for hemophilia. I got to know him well. Toward the end of his life he remained incredibly stoic and brave, dealing with one HIV-related crisis after another. When I asked him how he coped, he shared with me that as a young boy he often would wake up in the middle of the night and feel a joint swelling up and know that he was starting to bleed in that joint. He knew what lay ahead for him and his parents if he were to wake them — that they would have to go to the hospital and get a Factor 8 infusion. He also knew his parents were working two jobs, driving an old car, mostly because of all his medical needs. He knew how they needed their sleep. So instead of disturbing them and despite his pain, he would wait a few hours till dawn so they could get a full night's sleep. Next to his bed was a little record player and he would play the hymn *Joy Comes in the Morning*.

You know, sometimes I think our illusion in medicine is that we fix things forever. We don't make people immortal. If we're lucky we get to minimize the impact of disease, sometimes reverse it. To me, it's all about hope. It's the desire to hang in there, to just keep it going. There's a saintliness I saw in so many of my patients. There's a certain attitude and powerful lessons for the rest of us. What a privilege. **SM**

This interview was condensed and edited by Paul Costello.

FEATURE

Nobel beginnings

CONTINUED FROM PAGE 31

impressive knowledge of the topic at hand. Aware that the independent youngster had inadvertently landed in the essentially defunct Department of Clinical Biochemistry, Sakami asked Berg if he was interested in transferring to the Biochemistry Department proper as a graduate student, where he might undertake some of the experiments suggested in his seminar. Sakami sang the graduate student's praises to department chairman Harland Wood, who enthusiastically reinforced Sakami's overtures. Berg was beside himself with joy. When, in later years he published an account of these events for the prestigious Feodor Lynen Lecture delivered in 1977, Berg expressed his appreciation for the opportunity to launch his scientific career in the "real" Department of Biochemistry at Western Reserve.

"Although I only moved from one floor to the next, the change altered my life: I was brought into contact with people who loved and lived for biochemistry and thereby created an environment where the spark could be nurtured in others. Enzymology, intermediary metabolism and the trials of learning how to do a meaningful experiment occupied my waking hours." **SM**

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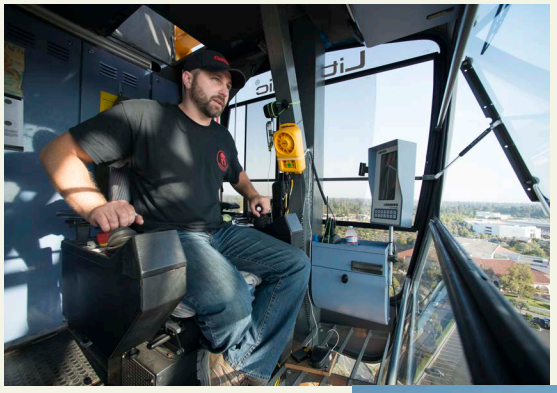
WHAT'S GOING ON UP THERE?

A HIGH-RISE CRANE OPERATOR ON 'FLYING IRON'

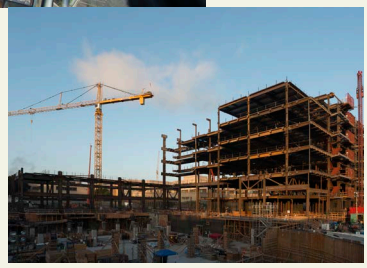
Each workday, A.J. Barker makes a 15-minute climb up 200 feet of steel to the cabin of an enormous yellow tower crane — one of two at the Lucile Packard Children's Hospital Stanford expansion work site. • He then spends the next eight or nine hours "flying iron," moving steel girders and beams throughout the construction site and helping assemble the framework of the new center for pediatric and obstetric care. • Sitting almost 16 stories in the air, Barker uses two joysticks to maneuver the crane's 267-foot working arm, or jib, into position, lowering a hook or coupling into place, coordinating the connection and then moving the object to the desired location — all while keeping an eye on the activity on the ground, other cranes, the direction of the wind, even the arrivals and departures of the hospital's Life Flight helicopter. • "I have the coolest office view, and it changes all the time," says Barker, who is working with a subcontractor to DPR Construction, the firm that is overseeing the 521,000-square-foot addition that's part of the Stanford University Medical Center Renewal Project.



Crane operator A.J. Barker moves beams at the Lucile Packard Children's Hospital expansion work site. When complete, the superstructure will consist of 7,900 tons of steel.

Barker is a second-generation crane operator who learned the ropes by shadowing his father at work. By the time he was 10 he had soaked up the basics. Now, with 13 years of professional experience, Barker is so attuned to the nuances of his equipment that he can maneuver the crane to pick up a five-gallon bucket, adjust its lid and place it on a table. A computer console displays the weight he is carrying, the trolley location, the degree of swing on the hook and the wind speed, though Barker says he uses the computer only for additional reference, focusing his attention more on the crane and load.

"It's like driving a car," he says. "Most of it is about feel. It's a matter of making a connection to the movements of the machine."



He remains in constant communication with those on the ground through two-way radios, while a direct phone line to the other crane operator prevents any overlaps of loads between the two jibs. Though the jibs are different heights and lengths, the cranes' loads could infringe on the other's perimeter without perfect coordination.

"When the job starts, you can see everything. But once the building goes up you lose visibility, and there are a lot of blind spots," says the 36-year-old father of three. "You have to rely on the guys on the ground to keep everything safe and up to speed."

The signalmen tell him how heavy a load to expect and where to move the trolley along the jib before he can lower his hooks. While placing gingerbread — smaller I-beams that reinforce the steel framework of the building — Barker responds to a series of nonstop radio instructions:

"Move it up a dog."

"Left easy. Down easy."

"Swing left. Up easy."

"OK, we're working. Down."

"There's no room for error," says Barker, "when you are flying iron and sending a load weighing thousands of pounds over to guys who are standing five stories high on beams that are 8 inches wide. You have to pay attention at all times." — RUTH SCHECHTER

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Pilot study

EXPERIENCED AVIATORS MAKE BETTER DECISIONS WHILE USING LESS BRAINPOWER

Landing an airplane is one of the hardest piloting techniques to master, and the stats show it: 36 percent of all airplane accidents and 25 percent of fatalities occur during the final approach and landing. Research led by Maheen Adamson, PhD, a Stanford clinical associate professor of psychiatry and behavioral sciences, reveals that expert aviators make safer decisions during this phase than less-experienced pilots because their brains behave more efficiently. • The scientists rigged an fMRI scanner so that 20 pilots — 12 moderately experienced pilots and eight experienced pilots — could operate a flight simulator while the scanner imaged their brain activity. Their task: landing at a virtual San Francisco International Airport.

They were instructed to begin their descent based only on their instrument readings, as is typical in most real-life flights. Once they reached 200 feet, the screen displayed the runway, either clearly or obscured by varying degrees of fog.

The pilots then needed to look from the instruments to the runway and back to make a snap decision about whether it was safe to land. Expert pilots made the correct decision 80 percent of the time, whereas those with less experience did so only 64 percent of the time. Interestingly, the fMRI scans revealed that the expert pilots scored higher while displaying only half as much brain activity.

Landing a plane involves constantly scanning instruments as well as the view out the window, says Adamson, and reduced neural activity in expert pilots indicates that they are able to complete the task at hand with fewer brain resources. The scientists traced the skill to the caudate nucleus, an area of the brain involved in regulating gaze as the eyes quickly shift their focus to different fixed objects. Adamson suspects that the brain's ability to streamline multiple visual inputs is the result of experience.

This work opens the door to pairing fMRI and flight simulators — something that NASA is already doing in limited trials — to test pilots' mental engagement during various flight maneuvers, or to guide pilots into behaviors that mimic the more efficient brain activity of more-expert pilots. "If we are able to train pilots to process instruments' and other visual cues more efficiently," Adamson says, "you could reduce the likelihood of accidents during landing." — BJORN CAREY