Nurses resuscitate passenger on plane leaving for San Jose

By Sara Wykes

Sophia Loo and Angela Bingham barely made their connecting flight to San Jose. The cardiac care nurses at Stanford Hospital were on their way back from a December health-care conference in Orlando, Fla.

As they settled into their seats, Loo heard a woman a few rows ahead of her saying, "Sir, sir, are you OK?" and then, "I think this man needs help. Can someone help him?"

Loo saw a male passenger who appeared to be in real trouble. He was pale, unresponsive, sweating and breathing in a way that Loo recognized immediately. Called agonal respiration, it is accompanied by a snorting sound and comes in gasps. Loo knew the breathing pattern because it's often a sign of imminent cardiac arrest.

Bingham, seated a few rows back from Loo, had noticed the commotion and was on her way to help, too, when she heard Loo call out, "Angela, get up here!" Other passengers had left their seats, blocking the aisle and forcing Bingham to crawl over empty seats to get to the passenger.

Bingham and Loo had resuscitated many cardiac patients during their careers with Stanford Health Care, which is part of Stanford Medicine. "That's expected as part of the job," Loo said. "But in the hospital we have the proper equipment."

Springing into action

Both nurses knew that they had to start CPR immediately. "But we couldn't do CPR while he was in the seat," Loo said, so she recruited three passengers to maneuver the man into the aisle. He was in his late 60s, Loo estimated, and weighed about 180 pounds. In the narrow aisle, there wasn't much room.

"It was surreal," Bingham said. "We just went into nursing mode," Loo said, "but the stress was beyond anything I've ever known as a nurse. We were so focused on what we were doing; we knew the gravity of his condition."

Lacking a ventilating device to help deliver air through the passenger's nose and mouth — and because he occasionally gasped and opened his eyes, which would have interfered with rescue breaths — the nurses focused on chest compressions, conducted at a rate of 100 times per minute.

Flight attendants brought them an automated external defibrillator, which the Federal Aviation Administration requires all commercial

Researchers say they resolved century-old argument about brain

By Amy Adams

What started a few years ago as a brain-imaging study turned into a scientific mystery that eventually ended in the basement of the Lane Medical Library, within the pages of a book first published in 1881 and last checked out in 1912.

That journey, described in a paper published online Nov. 17 in the Proceedings of the National Academy of Sciences, revealed the long and contentious history of an otherwise innocuous tract of nerve fibers of the visual system, running from just below the ear. It also revealed the many ways scientific knowledge has been gained and lost over the centuries, and in some cases written out of history through a combination of scientific in-fighting or poor record-keeping.

The journey began when Jason Yeatman, co-lead author of the paper, was carrying out his brain-imaging studies to better understand how kids learn to read. Yeatman, then a graduate student in the lab of Brian Wandell, PhD, professor of psychology, noticed that all the brain images in his study contained a structure

Researchers isolate type of stem cell that gives rise to bones, cartilage in mice

By Christopher Vaughan

Researchers at the School of Medicine have discovered the stem cell in mice that gives rise to bone, cartilage and a key part of bone marrow called the stroma.

In addition, the researchers have charted the chemical signals that can create skeletal stem cells and steer their development into each of these specific tissues. The discovery sets the stage for a wide range of potential therapies for skeletal disorders such as bone fractures, brittle bones, osteosarcoma or damaged cartilage.

A paper describing the findings was published Jan. 15 in Cell. Lead authorship is shared by former Stanford postdoctoral scholars Peter Brodin, MD, PhD, and Vladimir Jojic, PhD.

Environment drives human immune response, study finds

By Bruce Goldman

A study of twins conducted by School of Medicine investigators shows that our environment, more than our heredity, plays the starring role in determining the state of our immune system, the body's primary defense against disease. This is especially true as we age, the study indicates.

Much has been made of the role genes play in human health. Stunning advances in gene-sequencing technologies, in concert with their plummeting costs, have turned many scientists' attention to minute variations in the genome — the entire toolboxes of genes carried in virtually every cell in the body — in the hope of predicting people's future health. Such studies have revealed a genetic contribution to health outcomes. But, with some notable exceptions, very few individual genetic variants contribute much to particular health conditions.

"The idea in some circles has been that if you sequence someone's genome, you can tell what diseases they're going to have 50 years later," said Mark Davis, PhD, professor of microbiology and director of Stanford's Institute for Immunity, Transplantation and Infection. "But while genomic variation clearly plays a key role in some diseases, he said, the immune system has to be tremendously adaptable in order to cope with unpredictable episodes of infection, injury and tumor formation.

"The immune system has to think on its feet," said Davis, senior author of the new study, which was published Jan. 15 in Cell. Lead authorship is shared by former Stanford postdoctoral scholars Peter Brodin, MD, PhD, and Vladimir Jojic, PhD.

Read more by visiting the Stanford News Service website.
By Amy Adams

A panel of Stanford University scientists spoke Jan. 25 at the World Economic Forum in Davos, Switzerland, about their interdisciplinary approach to tackling major brain diseases like stroke, neurodegenerative disorders and mental illness.

The panelists were all members of research teams created through the Stanford Neurosciences Institute’s Big Ideas in Neuroscience initiative. The panel discussion was moderated by Phil Campbell, editor-in-chief of Nature. In addition to their own research, the scientists discussed the pressing need to bring diverse ideas and expertise together to solve health challenges that are becoming an increasing economic and emotional burden as our society ages.

“We are really lucky here at Stanford that we can leverage the work of engineers and basic scientists, and we have expertise in moving discoveries into the clinic,” said Marion Buckwalter, MD, PhD, assistant professor of neurosurgery, and lead author of the study.

Panelist Amit Etkin, MD, PhD, professor of neurology, co-leads the Stanford Brain Rejuvenation Project, which focuses on brain maintenance and regeneration and the role of the immune system in these processes.

Etkin noted that many children with very-low-birth-weight babies born in the state during 2010 and 2011, 20 percent were not referred to the state’s high-risk infant follow-up program, according to a new study by researchers at the School of Medicine. Babies who weigh less than 3.3 pounds at birth, nearly all of whom are born prematurely, are at risk for a variety of neurologic and developmental problems in childhood. In California, all very-birth-weight who received care in California Children’s Services-approved neonatal intensive care unit qualify for a state-supported, follow-up program that provides diagnostic assessments and services until they turn 3. However, if they cannot succeed in that first step of getting these babies referred to follow-up, “we’re at a critical disconnect for what we can offer them as they grow and develop,” said Susan Hintz, MD, professor of neonatal and developmental medicine and lead author of the study.

The study found that larger neonatal intensive care units were more likely to make referrals, whereas larger infants, as well as infants of African-American or Hispanic descent, were less likely to be referred. The study’s other co-author is Juliann Saquib, PhD, assistant professor of neurology.

Panelist Paul Costello, chief communications officer for the Brain Rejuvenation Project, described her own ongoing research exploring how circuits are altered by existing treatment under development that could enable possible therapies discovered in animals to be translated more effectively to humans. She also described her ongoing research into the role the immune system plays in stroke recovery.

In addition to the panel discussion, Wyss-Coray and Etkin spoke with NPR science correspondent Joe Palca, who moderated a series of on-stage conversations about the human brain at the Davos forum.

Amy Adams is the director of interdisciplinary life sciences communications for Stanford University.

Screening people for diseases does not necessarily help save lives, study finds

By Becky Bach

It seems like it should work: If everyone were tested for a disease, lives would be saved, right? These conditions would be spotted quickly, treated, and voilà: The deadly illness would be vanquished. As it turns out, this isn’t necessarily the case, according to a new study by researchers at the School of Medicine.

“Screening for diseases that can lead to death typically does not prolong life substantially,” said John Ioannidis, MD, DSc, professor of medicine, obstetrics and gynecology, and Cancer Prevention at Stanford and senior author of the study. “A few screening tests may even cause some deaths by the disinterest being screened, but even then it is difficult to document an improvement in overall survival.”

The lead author of the study, published online Jan. 15 in the International Journal of Epidemiology, is Nazmun Saquib, PhD, a former postdoctoral scholar at Stanford.

Ioannidis and his team examined the results of screening for 19 diseases to determine whether screening helped prevent death. The researchers looked at evidence from randomized, controlled trials and from meta-analyses combining the results of the trials. Patients were asymptomatic when tested.

The researchers found that screening decreased mortality in a few circumstances: ultrasound for abdominal aortic aneurysm in men, mammography for breast cancer, and fecal occult blood test and flexible sigmoidoscopy for colorectal cancer. But no other tests reduced the number of deaths caused by the 19 diseases. Why? The test might not be able to detect accurately enough early stages of a disease, or these might not be lifesaving treatments available, the study said.

Ioannidis acknowledged that screening might ward off other ill effects of disease, aside from death. But in general, few screening tests among the many new ones being proposed are subjected to a randomized, controlled trial before they are introduced.

“This is unfortunate,” said Ioannidis, also director of the Stanford Prevention Research Center. “All screening tests should be evaluated with rigorous, randomized, controlled trials. I see no alternative to prove that they are worth being adopted in large populations. This study followed another recently published paper in which Ioannidis and colleagues argue that screening all baby boomers for hepatitis C isn’t necessarily beneficial.

The study’s other co-author is Juliann Saquib, PhD, a former postdoctoral scholar at Stanford. The study was supported in part by grants from the National Heart, Lung and Blood Institute.

Many of state’s smallest babies not referred for follow-up care

By Erin Digitale

The tiniest babies need special follow-up care when they go home from the hospital after birth. But, of the thousands of very-low-weight babies born in California during 2010 and 2011, 20 percent were not referred to the state’s high-risk infant follow-up program, according to a new study by researchers at the School of Medicine. Babies who weigh less than 3.3 pounds at birth, nearly all of whom are born prematurely, are at risk for a variety of neurologic and developmental problems in childhood. In California, all very-birth-weight babies who received care in California Children’s Services-approved neonatal intensive care unit qualify for a state-supported, follow-up program that provides diagnostic assessments and services until they turn 3.

But in California, as in many states, babies are often not referred to the state’s high-risk infant follow-up program. In California, all very-birth-weight babies who received care in California Children’s Services-approved neonatal intensive care unit qualify for a state-supported, follow-up program that provides diagnostic assessments and services until they turn 3.

The study noted that large neonatal intensive care units were more likely to make referrals, whereas larger infants, as well as infants of African-American or Hispanic descent, were less likely to be referred. The study found that larger neonatal intensive care units were more likely to make referrals, whereas larger infants, as well as infants of African-American or Hispanic descent, were less likely to be referred.

The study was supported in part by grants from the National Heart, Lung and Blood Institute.
By Kris Newby

Michael Ackermann, PhD, knows how to make you cry. But this is a good thing for the more than 20 million Americans who suffer from a painful condition in which the lacrimal glands don’t create enough tears to lubricate the surface of the eye.

To help these patients, Ackermann, PhD, a former spine-fusion surgeon, and his new company, and his former company are testing two tiny devices that promote tear production by delivering micro-electro-physical pulses to the lacrimal glands. One model is inserted into the mucous membrane in the nasal cavity, and the other is inserted under the skin below the eyebrow. Tear delivery rates can be adjusted manually with a wireless controller.

Stanford Biodesign is a training program in medical-technology innovation and development. Each year, it admits 12 applicants with backgrounds in medicine, engineering and business. These Biodesign fellows work to address unmet medical needs through the development of new technologies and devices.

Ackermann, 32, who has a boyish grin and buzz-cut hair, joined the program in 2010 after earning a PhD in biomedical engineering and a master’s in business administration from Case Western Reserve University and working on chronic-pain and movement-disorder devices at Boston Scientific and On-Call Biomedical. He said he enjoyed the corporate work but realized he wasn’t a big-company person.

“I thought the Biodesign Program was a good opportunity to try out entrepreneurship in a safe, academic environment,” he said.

Solving problems with fresh eyes

At the start of the program, Ackermann was assigned to a four-person team tasked with looking for medical needs in eye clinics. His team members included Victor McCray, MD, a board-certified surgeon; Brandon Felkins, a graduate student in mechanical engineering at California Polytechnic State University; San Luis Obispo; and Garrett Smith, a PhD candidate in bioengineering at UC-San Diego.

They began by observing all facets of a busy ophthalmology practice, shadowing the eye specialists, and interviewing patients. At the end of two months, they had documented more than 300 clinical needs.

Early in this process, Ackermann recognized dry eye as a promising area. “Every third person visiting the clinic seemed to be suffering from dry eye, which ranged from something that was a nuisance to a genuine, sight-threatening disease,” he said. “It was a huge medical need with no optimal treatments.”

With every blink, healthy eyes are lubricated by a mixture of oils, water, proteins and mucus. This fluid helps protect and moisturize the eye. Each year, the thin film that it creates is necessary for clear vision. Dry eyes become vulnerable to painful abra- sions of the eye surface, which can distort vision.

Dry eye can be trig- gered by a number of fac- tors, including gland defects, medication side effects and hormonal changes. The thin film that is produced can be disrupted by pregnancy or menopause. It is also associated with some immune-system disorders.

“There are very poor treatment op- tions for my dry-eye patients,” said Mark Blumenkranz, MD, professor and chair of ophthalmology at Stanford, who was a mentor for the fellows on this project.

The two most common dry-eye treat- ments are lubricating eyedrops and cy- coporesis, a topical emulsion, but both have drawbacks. Some patients do not respond, and others develop a number of side effects.

“Aiming for a market blind spot

Once the fellows focused on dry eye, they began to spot a number of trends and potential market opportunities. At first, I thought their solution was quirky,” Blumenkranz said. “But nobody was thinking about the neurological basis of dry eye. I recognized that it had the potential to be a breakthrough product.”

Building the business

During the past two years, the team worked to develop prototype devices, and now they are in the process of picking a single technology to take forward.

“Today, Ackermann runs his 20-per- cent company from a corner office with a panoramic view of the San Francisco Bay. When asked about the challenges of launching a company, Ackermann points to a large padlock with a key in it that sits on the crown of this head: “This wasn’t here before I started. It’s incredibly hard managing a company where the money only flows out. I won’t consider it a success until the products are on the market, treating patients and profitable.”

And when this happens, there proba- bly won’t be a dry eye in the house.

Early support for this project came from Biodesign, which is part of the uni- versity’s interdisciplinary Bio-X institute; and Spectrum, the Stanford Center for Clinical and Translational Research and Education.

Infants

The researchers ranked hospitals by their volume of very-low-birth-weight patients, finding that among the hospitals with the highest volume, an average of 85 percent of the high-risk infants were referred to follow-up care, while only 65 percent of the hospitals with the lowest volume, an average of 65 percent were referred. There was a wide range of referral rates for infants with a quarter- to a half-size head.

During the analysis process, California Children’s Services was able to provide feedback to specific hos- pitals, allowing them to see how they ranked and what they could do to improve. Hinz noted. It is also possible that some babies during the study period did receive high- risk referrals but were never referred by the hospital to follow-up care, which could explain the gap.

“The new system is good data that was collected relatively early in the state’s revamped program for high-risk infant follow-up.” Hinz said. “We’ve already made substantial improvements in site-specific online tools and resources available to hospitals for nearly real-time feedback, and referral rates now appear to be higher.”

California is ahead of other states in hav- ing a comprehensive, statewide program to help high-risk infants, Hinz noted. “The expectation that 90 percent of infants born at risk will be referred is enormously innovative in this country,” she said.

More work needed

However, the data indicates that there’s still work to be done. Nearly one-quarter of the state’s largest CCS-approved neon-atal intensive care units already have referral rates below very-low-birth-weight infants of 95 percent, Hinz noted. “We don’t have enough evidence to tell us what the success rates are,” she said. “This is an opportunity for us to learn where there may be disparities in resources among units across the state, launch quality-improvement initiatives, and look toward building more comprehensive, com- munity-based early intervention programs to improve outcomes for children and families.”

Other Stanford co-authors of the study are Jeffrey Gould, MD, professor of pedi- atrics; data analyst Mihoko Bennett, PhD; project manager Erika Gray; California Perinatal Quality Care Collaborative exec- utive director Barbara Murphy, MSN, who also is executive director of the medical school; and Henry Lee, MD, assis- tant professor of pediatrics. Hinz, Gould and others are part of the California Peri- natal Quality Care Collaborative.

Stanford’s Department of Pediatrics also supported this work. ©

Kris Newby is the communications man- ager for the Stanford Center for Clinical and Translational Research and Education.

Michael Ackermann

This wireless device is designed to stimulate natural tear production in patients with dry eye.

For efficacy and safety in animals. In October 2012, after proof-of-con- cept testing, Byers and Ackermann as- sembled a group of health-care venture capitalists — KPCB, Versant Ventures and New Enterprise Associates — and convinced them to invest $7.6 million into the startup. With this funding, they plan to launch their first prototype de- vice and launch clinical trials in Australia, New Zealand and Mexico.

“The first time I saw our device actu- ally working in a real patient, it was out of this world,” Ackermann said.

“In May 2014, Oculeve investors con- tributed an additional $6.6 million to the company. That money will hopefully carry the company through the expen- sive, time-consuming process of getting a medical device through its European and Canadian round of regulatory approvals, Ackermann said. U.S. regulatory autho- rities are in progress, and patients interested in participating in future clinical trials can visit http://www.clinicaltrials.gov (and search for “Oculeve”).

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Blumenkranz sits on the board of Oc- ulev, inc.

A real tear-jerker: team creates device to alleviate dry eye

Infants

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Stanford’s Department of Pediatrics also supported this work. ©

Kris Newby is the communications man- ager for the Stanford Center for Clinical and Translational Research and Education.
On March 2, 2009, something snatched inside Paul Michael Nelson. In the middle of the night, his parents found the 7-year-old boy stabbing the door of the family's Berkeley, Calif., kitchen with a knife, trying to get on a computer that was off-limits after his bedtime. When they stopped him, he flopped around on the floor on his knees, barking like a dog. He tore at blankets with his teeth and snorted in gibberish.

It was Paul Michael’s first episode of psychosis. “It was like he was demon-possessed,” said Mary Nelson.

The Nelsons rushed to their local emergency room, where staff didn’t seem to believe their account of the incident. “We have to take him into custody,” the officer on duty told them. Paul Michael must have been in a temper tantrum. The staff wrote a referral to a psychi atrist and sent him home. The next day, the Nelsons took him to the emergency room again. She was told he had an antipsychotic, but changed her mind after reading his blood work.

“She said, ‘Oh, my God, he’s got low platelets; I can’t prescribe this,’ and she shuffled us out,” said Paul Nelson, the boy’s father. Paul Nelson’s levels of platelets, the blood cells that form clot to stop bleeding, were far below normal, but the Nelsons were not sure why the psychiatrist thought this justified avoiding antipsychotics. After the family left the psychiatrist’s office, Paul saw his sister, Amanda. “I held him tight,” she said, for the doctor, becoming overwhelmed. “He’s very scared; he knows something’s wrong. When she shut the door, he just started screaming and crying.” When the family got home that day, Paul Michael exploded into another psychotic fury.

Sucked into the whirlpool of Paul Michael’s compulsive behavior, neither the Nelsons nor the doctors who took on Paul Michael’s case realized that the little boy’s abnormal blood work held an important clue. Paul Michael was seen several times at a psychi atric hospital for several years before retiring to return to school, so he could easily see these scenes from the officers’ perspective. There were times he found himself consoling the officers because they had been there so distant from the intensity of the outburst and said it must have been just the little boy’s abnormal blood work held an important clue.

When the immune system gets derailed from its usual infection-fighting role and attacks the brain, it can cause a condition known as PANS, or pediatric autoimmune neuropsychiatric syndrome. This rare disorder is often thought to be associated with strep infection and is the name for this list of devastating symptoms — orographic disturbances. For instance, a patient may first notice a sense of normalcy to the life of Paul Michael’s older sister, Amanda.

Meanwhile, Paul and Mary began a search for answers, starting with Paul Michael’s general pediatrician and the psychiatrists, social workers and counselors they found through their health insurance provider and the psychiatric hospital where they worked. They visited several times a week, while also trying to return to school, so he could easily see these scenes from the officers’ perspective. There were times he found himself consoling the officers because they had been there so distant from the intensity of the outburst and said it must have been just the little boy’s abnormal blood work held an important clue.

By Erin Digitale

A discovery that changed minds

The 2007 discovery of a molecular explanation for some cases of autoimmune encephalitis — a specific form of brain inflammation caused by an immune at tack — has made a big difference in convincing phy siicians to look for autoimmune underpinnings when patients suddenly seem to go off the deep end.

In this disease, known as anti-NMDA receptor en cephalopathy, an autoimmune response against a specific component of cell systems attacks a receptor for a single neurotransmitter, N-methyl-D-aspartate, producing psychiatric and neu rological disturbances. This autoimmune reaction can reverse all of this. The book Brain on Fire, Susannah Cahalan’s 2012 best-seller describing her bout with the condition, became a best-seller.

A discovery that changed minds

Case illuminates immune system, psychiatric disorder link

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Meanwhile, Frankovich struggled for months to convince even the Nelsons of the connection between their son’s immune and psychiatric problems. "They were so distrusted by his psychiatric nurse that it was hard for them to have insight into what was going on," she said. For a long time, Paul and Mary dissected their own behaviors to try to figure out how they might have sparked episodes of Paul Michael’s rage.

“We were looking for triggers, but there was no trigger," Paul said. When the illness was at its worst, it was impossible to avoid setting the boy off. “If it wasn’t going to happen at 9 a.m. when the phone rang, it would be at 9:15 when the car wanted to go out," Paul said. The Nelsons eventually discarded the concept of triggers. "Now, when he’s getting edgy, we call it ‘storm season,’" Mary said.

“This illness has leveled our pride and our expectations,” Paul said. "There has been a lot of grief for both of us, his sister and for him, too." Mary said. “But it’s lucky he had the clear autoimmune blood disorder, because it allowed us to use immune-modulation therapy," Frankovich said. "Had he just come in with behavioral deterioration, he would still be in a mental hospital.”

**Hunting for answers — and treatments**

Because it’s unclear whether PANS is actually one disease or many, Frankovich and Chang are conducting research to clarify the jumbled picture presented by all 114 children they’ve seen to date at Stanford’s PANS clinic. In one study, they’re looking for genetic markers that appear more often in PANS patients, the first step toward figuring out whether certain genes increase a child’s vulnerability to the disease.

They’re also using brain imaging to ask how PANS could change two brain regions. One of these, the basal ganglia, plays important roles in fine-motor control and in fine-tuning mood and anxiety. It is also a region where the blood-brain barrier tends to break down, providing a possible entry for antibodies, which researchers suspect may attack the brain.

Figuring out whether PANS patients make antibodies against their own brains is perhaps the most important key to the disease’s mysteries. The research bears similarities to the discovery of anti-NMDA receptor encephalitis, and the path to that breakthrough may provide a road map of sorts for PANS researchers.

There are hints that PANS may also be associated with misplaced antibodies. Madeleine Cunningham, PhD, professor of microbiology and immunology at the Oklahoma University Health Sciences Center, has developed a possible PANS diagnostic panel that tests for one brain enzyme and four antibodies against different brain proteins. Clinical studies at several sites around the world are attempting to independently validate the panel.

Circumstantial evidence also suggests antibodies contribute to PANS, Cunningham notes, because plasmapheresis, a technique in which a patient’s plasma is replaced with the plasma of a healthy individual, has successfully treated some PANS patients.

“Plasmapheresis removes antibodies and the person gets better," Cunningham said. An immune-suppressing treatment, intravenous immunoglobulin, or IVIG, may also help. IVIG, a blood product consisting of IG antibodies from healthy donors, is infused into the patient to tamp down inflammation. Scientists aren’t entirely sure how it works, but the NIEHS is now conducting a phase-3 clinical trial of IVIG versus placebo to see if it’s an effective PANS treatment, part of her larger effort to standardize PANS therapy.

Without a universally accepted PANS treatment, Stanford’s doctors currently approach PANS patients one symptom at a time. Depending on the patient’s presentation and what the clinical workup reveals, treatments possibly employed include immune-modulating drugs if autoimmune markers or signs of inflammatory disease are present, or antibiotics for repeated sinus or throat infections. They occasionally use limited trials of high-dose steroids to help suss out whether inflammation is behind the symptoms, an approach that’s also used for some forms of encephalitis. Chang often addresses psychiatric symptoms with lithium, which has a long history as a therapy for bipolar disorder, but may be generally protective for the brain. “We’re trying to support these children’s brains and lives as best we can,” he said.

**A family looks forward**

Today, Paul Michael is 13, and his condition is much better. Mary estimates he is “90 percent back.” After 15 months living at Edgewood, he moved home and spent another two years mostly as a day patient at the facility, with some shorter hospital stays when things temporarily became worse.

He transitioned in the fall of 2013 to a special-needs classroom in a public school near his family’s home. He attends mainstream classes for three subjects, something the Nelsons could never have imagined during the worst days of his illness. Frankovich’s attempts at weaning him from immunosuppression medication resulted in simultaneous flares of his blood disorder and his psychiatric symptoms, so he is now on a longer term protocol similar to that used to treat diseases like lupus.

And it’s been more than a year since his last serious outburst of rage.

In other diseases where the immune system can hurt the brain, such as lupus, controlling the autoimmune attack takes up to five years. So Frankovich is not disheartened by the gradual nature of Paul Michael’s improvement. It also takes time for the bombarded brain to recover from immune attack, she points out. “It’s the same as in brain trauma; even after we get the inflammatory response under control, it still takes time for the brain to heal,” Frankovich said, adding that she thinks it is likely that Paul Michael will ultimately be able to complete school, hold a job and live independently.

Paul and Mary are grateful for how far their son has come.

Paul Michael loves to make art and has excellent visual-spatial reasoning skills. In her office, Mary proudly displays several examples of this ability, among them a perfectly proportioned, 2-inch, orange-and-white guinea pig crafted out of looped-together rubber bands. Paul Michael planned and made the three-dimensional critter on a Rainbow Loom, a tool most kids use for much simpler projects, such as making bracelets. The family has begun talking with him about careers that might put his spatial ability to use, such as engineering or art.

Of late, they’ve been granting Paul Michael more independence as well. “He walked to the store alone yesterday,” Paul said during a conversation in July 2014. “That’s freedom a teenager needs, he can do it, and he’s happy with himself. It’s a real good development.”

But Paul and Mary never feel like they can let their guard down. The disease could recur. The immune-suppressing medications Paul Michael takes have potentially serious side effects, including increased risk for infectious diseases and some cancers. And they worry about what happens if he stops the medications.

“He can be extremely volatile,” Mary said. “But when he’s not, he’s this perfectly wonderful, creative, artistic, loving guy.”

Seeing the struggles that patients like Paul Michael endure has convinced Frankovich she’ll be treating PANS patients for a long time, in spite of all the obstacles.

"Some days, I think ‘Why are we doing this?’ It’s so frustrating and hard,” she said. “Other days, I see a kid we clearly made better. I’ve seen families crying, saying, ‘I haven’t had my kid in a year, and now I have my kid back’.” We cannot give up on this. There are so many of these cases out there.”

A more in-depth version of this story appears in the fall 2014 issue of Stanford Medicine magazine.
Skeletal
continued from page 1
Stanford Institute for Stem Cell Biology and Regenerative Medicine
An intensive search
The researchers started by focusing on groups of cells that divide rapidly at the ends of mouse bones, and then showed that these cells make bone from all parts of the bone: the bone itself, cartilage and the stroma — the spongy tissue at the center of bones that helps hematopoietic — blood — and the immune cells. Through extensive effort, they then identified a single type of cell that could, by itself, form all these elements of the skeleton.

The scientists then went much further into the developmental tree of skeletal stem cells to track exactly how they changed into intermediate progenitor cells and eventually each type of skeletal tissue.

"Mapping the tree led to an in-depth understanding of all the genetic switches that have to be flipped in order to give rise to more specific progenitors and eventually highly specialized cells," said postdoctoral scholar David Lo, MD, graduate student James Chen and research assistant Elly Eun Young Seo.

With that information, the researchers were able to find factors that, when properly activated, could turn the right gene on or off at the right time, would steer the development of skeletal stem cells into cartilage, bone or stromal tissue.

"If this is translated into humans, we then have a way to isolate skeletal stem cells by age and from wear and tear or aging, repair bones that have non-healing fractures and renew the bone marrow niche in those who have had it damaged in one anore, or older," said Irving Weissman, MD, professor of pathology and of developmental biology, and a senior investigator at the Stanford Institute for Stem Cell Biology and Regenerative Medicine, Weissman, the other senior author who also holds the Virginia and Daniel K. Ludwig Professorship in Clinical Investigation in Cancer Research.

Reprogramming fat cells
In addition to learning how to create bone from skeletal stem cells, the researchers found out how to create skeletal stem cells from fat. The ability to reprogram mature fat cells directly into skeletal stem cells through the application of specific signals "was really interesting and quite unexpected," Longerak said.

It raises fascinating possibilities for future therapies, he added. "Right now, if you have lost a significant portion of your leg or jaw bones, you have to borrow from Peter to pay Paul in that you have to cut another bone like the fibula into the shape you need, move it over there and fix it." Longerak, who is also the Deane P. and Louise Mitchell Professor in the School of Medicine, "But if your existing bone is not available or not sufficient, using this research you might be able to use some of your own fat into a biomimetic tissue that will grow into the bone you want in a muscle or fat pocket, and then move that new bone to where it’s needed.

Other therapies might be deployed in one surgical session, Chan said. "The number of skeletal stem cells increases dramatically with age, so bone fractures or dental implants don’t heal very well in the elderly because new bone doesn’t grow easily," he said. "But perhaps you will be able to take fat from the patient’s body during surgery, combine it with these reprogramming factors right there in the operating room and immediately transform skeletal stem cells back into the patient.

Now that the researchers have success reprogrammed the mapped skeletal stem cell system in mice, they are confident that they will be able to do the same in humans. “In this research we have a Rosetta stone that should help find the human skeletal cells and decode the chemical language they use to steer their development,” Chan said. "The pathways in humans should be very similar and share many of the major genes used in the mouse skeletal system.”

Other Stanford co-authors of the paper are postdoctoral scholars in medicine; Kelly Yan, MD, PhD, instructor of medicine; former instructor drive Shabol, PhD, research associate Jun Seita; postdoctoral scholars Adrian McArde, Rahul Sinha, Wan-Jin Lu, Koehemera Senarath-Yapa, Julianne Wedner, undergraduate students Rosalyn Upton, Graham Walmsley and Andrew Lee; and research assistants Justine Vincent-Tong, Alex Taylor Wearda, Owen Marcise and Mishi Tran.

This work was supported by the National Institutes of Health, the Vir- ginia and D.K. Ludwig Fund for Cancer Research, the Thomas and Stacy Siebel Foundation, the Prostate Cancer Foundation, the California Institute for Regenerative Medicine, the Oak Foun- dation, the Hager Laboratory for Pedi- atric Regenerative Medicine, the Guptas/ Olivier Research Fund, the Stinehart- Reed Fund, the Stanford Medical Sci- entist Training Program, the Stanford University Transplant and Tissue Engi- neering Center of Excellence, the Plas- tic Surgery Foundation/Plastic Surgery Research Council, the American Society of Maxillofacial Surgeons, the Burroughs Wellcome Fund, and the Anonymous Donor Skeletal Stem Cell Research Fund.

Christopher Vaughan is the communica- tions manager for the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

Brain
continued from page 1
that he couldn’t find in any texts. Had he discovered a new brain pathway?

Driven by curiosity
Kevin Weiner, PhD, a postdoctoral scholar and the paper’s other lead author, had been working with Yeat- man on the imaging studies. Weiner, who is in the lab of Kalani Grill-Spector, PhD, associate professor of psychology and psychiatry, said he had long been interested in science history, and this mystery piqued his interest.

"Jason and I decided for our own curiosity to un- derstand what happened to this pathway," Weiner said.

A few things could have led to brain structures be- ing discovered and forgotten. In the late 1800s and early 1900s, Weiner had learned, the roughly 30,000 names of brain structures in various languages were consolidated into a list of 4,500 as part of an effort to create a universal nomenclature. "In trying to make it easier to remember names, some got written out of history," Weiner said.

"In this specification wasn’t the reason for the region’s disappearance from the literature. The region was the source of controversy between its discoverers and Werner’s predecessors," said Theodor Meynert, a German-Austrian neuroanato- mist and psychiatrist.

Meynert was believed that all of the brain’s association pathways ran from front to back — hori- zontally. But the pathway in question, which Wer- nicke had called the vertical occipital fasciculus, ran vertically. Although Yeatman had found refer- ences to the VOF under a variety of different names in texts published for about 30 years after Wernicke’s original 1870s report, he had been unable to identify any previous references to it became contentious before largely disappearing from the literature entirely over the next few decades.

Into the archives
Although the VOF disappeared, Wernicke’s publi- cation of its discovery still existed in the archives of the School of Medicine’s Lane Library, where Yeatman and Weiner eventually tracked it down.

That was a really cool experience that most people don’t have any more, when you have to check your be- longings at the door because the book you are about to look at is worth thousands of dollars per page," Weiner said. "You are literally smelling 100-year-old ink as you find the images you have been searching for.”

Yeatman said the journey gave him an education in early neuroscience research. "There are a lot of gems in the literature that have been overlooked ever since," he said. "This project made me appreciate the detail and precision of these classic pieces of work.”

Reproducible science
Both Yeatman and Wandell said this work also highlights the value of modern techniques for repro- ducing results. No longer a field can simply disregard findings that don’t fit a prevailing idea. "Now we can record our methodologies and software algorithms to be distributed with our papers, allowing any researcher in the world to reproduce our results," Yeatman said. And indeed, the researchers concluded that the VOF exists and is functionally important.

"The library material was hard to find and required someone with passion for the effort," said Wandell, the paper’s senior author and the Isaac and Madeline Stein Family Professor. "Modern tools should help with sharing, transparency and reproducibility of research, and hopefully what we learned won’t be forgotten.”

The idea of sharing data to speed scientific prog- ress is a cause Wandell has championed at the Center for Cognitive and Neurobiological Imaging, which he directs, and that he has been promoting in his work helping the Stanford Neurosciences Institute plan the computing strategy for its new facility.

With shared data and labs worldwide attempting to reproduce published results, the teams said it is less likely that modern neuroscience findings today will be lost due to differences of opinion over a discovery’s relevance.

Other Stanford co-authors of the paper are postdoctoral scholars Ariel Rokem, PhD, and Avi Mezer, PhD, and former research associate Franco Pestilli, PhD.

The brain imaging that resulted in the rediscovery of the earlier work was funded by the National Cancer Foundation and the National Institutes of Health.

Amy Adams is the director of interdisciplinary life sci- ences communications at Stanford.

Inside Stanford Medicine

January 20, 2016

Christopher Vaughan

Sara Wykes is a writer for the Stanford Health Care communications office.

Nurses
continued from page 1
aircraft to carry, giving Loo and Bingham their first chance for an objective reading of the passenger’s heart activity.

This type of defibrillator uses two adhesive-backed leads, which are placed on the skin of the chest to evaluate heart rhythm and deliver at appropriate shock. The de- vice showed that the man’s heart was in a life-threatening rhythm and advised a shock. “I told the flight attendant to press the button to deliver the shock. We called out ‘Eyes open’ and the shock did deliver,” Bingham said.

Eyes open
Protocol dictates that the shock be followed by three minutes of CPR. When they did a second read of the defi- brillator, it instructed, “No shock.” That advice, Bingham said, happens when there is no heart activity at all. But the two nurses continued to perform CPR. Once, the man opened his eyes, Bingham said, “so we knew something was happening, that we were getting through.”

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The Stanford team then applied sophisticated laboratory methods to the blood samples to measure more than 200 distinct immune-system components and activities. The researchers immediately sent them to Stanford’s Human Immune Monitoring Center, which houses the latest immune-sleuthing technology under a single roof.

**The power of environment**

Examine differences in the levels and activity states of these components within pairs of monozygotic and dizygotic twins. The Stanford scientists found that in three-quarters of the measurements, nonheritable influences—such as previous microbial or toxic exposures, stresses, and environmental conditions—trumped genetic ones when it came to accounting for differences within a pair of twins. This environmental dominance was seen in identical twins (age 60 and up) and younger twins (age 20).

Davis and his associates also observed considerable environmental influence over the quantities of antibiotic producers in members of twin pairs who had been vaccinated for influenza in a separate Stanford investigation directed by study co-author Cornelia Dekker, MD, professor of pediatric infectious disease and medical director of the Stanford-Lucile Packard Children’s Hospital Vaccine Program. While many previous studies had suggested a powerful role for vaccine responsiveness, Davis noted that those studies typically were performed in very young children who followed a known environmental exposure that appears to reshape the immune system over time.

In a striking example of the immune system’s plasticity, the Stanford scientists found that exposure to a single, chronic, viral infection could have a massive effect on the immune systems of the pair. Among the 10 people in the developing world are chronic carriers of chronic, viral infection could have a massive effect on the immune systems of the pair. Among the 10 people in the developing world are chronic carriers of the virus, and most are not aware that they are infected. This virus, which is called cytomegalovirus, can cause serious health problems in people who are immunocompromised but otherwise generally benign. In 16 of the 27 monozygotic twin pairs participating in the study, one member of the pair had been exposed to cytomegalovirus but the other had not. For nearly 60 percent of all the features Davis’ group measured, cytomegalovirus presence in one twin and absence in another made a big difference.

“Nonheritable influences, particularly microbes, seem to play a huge role in driving immune variation,” said Davis. “As I look for the first 20 or so years of your life, when your immune system is maturing, this amazing system appears able to adapt to wildly different environmental conditions. The human immune system continually adapts to its encounters with hostile pathogens, friendly gut microbes, nutritional components, and much more, overshadowing the influences of most heritable factors.”

Other Stanford co-authors of the study are Atul Butte, MD, PhD, associate professor of pediatrics (systems medicine and genetics); and Holden Maecker, PhD, associate professor of microbiology and immunology and director of Stanford’s Human Immune Monitoring Center; former postdoctoral scholar Shai Shen-Orr, PhD; research associate David Furman, PhD; software specialist Sanchita Bhattacharya; and MD/PhD student Cesar Lopez-Angel.

The study was funded by the National Institutes of Health, SRI, the Howard Hughes Medical Institute, the Wannier-Gren Foundation and the Sweden-America Foundation.

Stanford’s Department of Microbiology and Immunology also supported the work.

**Grants for projects using Human Immune Monitoring Center**

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Stanford’s Department of Microbiology and Immunology also supported the work.

Four projects get seed grants aimed to jump-start Ebola research

Responding to an urgent need to combat the Ebola epidemic in West Africa, the Stanford Institute for Innovation in Global Health has awarded seed grants to four multidisciplinary teams of investigators who are designing, developing and engineering vaccines and other tools to combat the disease and mapping the epidemic to help prevent further outbreaks.

Michele Barry, MD, professor of medicine, for “Evaluating Mycobacterium Tuberculosis Transcriptional Responses as a Treatment Option”.

Niaz Banaei, MD, associate professor of pathology, for “Defining Human Lung Alveolar Macrophage Subsets and Dissecting Their Cellular and Molecular Interactions with Mycobacterium Tuberculosis”.

Lynette Cegelski, PhD, assistant professor of chemistry, for “Translating Mechanical Properties of Host-Pathogen Interface into New Strategies to Target Urinary Tract Infections”.

Everett Meyer, MD, PhD, assistant professor of medicine, for “Clincal Monitoring of HLA-allele Mismatch Alloreactivity Using T-Cell Repertoire Populations and Single Cell Sequencing”.

Julie Parsonnet, MD, professor of medicine, for “Prospective Validation of Tolerogenic Invariant Natural Killer T Cells for Promotion of Solid Organ Transplant Tolerance and Prevention of GvHD”.

Timo Sweeney, PhD, a student in the immunology and biomedical informatics, with Purvesh Khatri, PhD, assistant professor of medicine, for “Prospective Validation of an Artificial Intelligence System for Sterile Sepsis in Pediatric ICU Patients at Admission”.

Fuqing Cen, PhD, a student in the biology and computer science, with Robert Neumann, MD, PhD, associate professor of medicine, for “Tolerogenic Invariant Natural Killer T Cells for Promotion of Solid Organ Transplant Tolerance and Prevention of GvHD”.

Mike Osterholm, MD, MPH, a professor in the medicine, for “Systematics, Evolution and Ecology of Yersinia pestis in the context of the current and future global risk of plague”.

Rasmea Bajwa, MD, a postdoctoral scholar in bone and marrow transplantation, with Robert Neumann, MD, PhD, associate professor of medicine, for “Tolerogenic Invariant Natural Killer T Cells for Promotion of Solid Organ Transplant Tolerance and Prevention of GvHD”.

Michele Barry

Grants made for projects using Human Immune Monitoring Center
Alpha Omega Alpha association elects new members

Christopher Almond, MD, was appointed assistant professor of pediatrics, effective Aug. 1. He focuses on improving the outcomes for children with end-stage heart failure. He regularly leads investigations of ventricular assist devices. He also directs the Cardiac Anticoagulation Service at Lucile Packard Children’s Hospital Stanford.

Niaz Banaei, MD, was promoted to associate professor of pathology and of medicine, effective Dec. 1. He is the medical director of the Clinical Microbiology Laboratory at Stanford Medicine. He also directs the pathology fellowship in global health diagnostics. His research interests include the development and assessment of infectious disease diagnostics, enhancement of diagnostic results for *Clostridium difficile* and the characterization of the determinants of tuberculous virulence.

Victor Carrion, MD, professor and associate chair of psychiatry and behavioral sciences, has been elected chair of California’s Mental Health Services Oversight and Accountability Commission. He directs the Stanford Early Life Stress and Pediatric Anxiety Program. He investigates the effects of stress on developmental physiology and brain development and function, and is working to develop new therapies for children who experience trauma. He is also a co-founder of the Center for Youth Wellness in San Francisco.

Danton Char, MD, was appointed assistant professor of anesthesiology, perioperative and pain medicine, effective Dec. 1. His clinical work focuses on providing perioperative care to children with cardiac disease. His research focuses on ethical issues that arise in pediatric cardiac anesthesia.

Heike Daldrup-Link, MD, PhD, associate professor of radiology, was elected a member of the American Society for Clinical Investigation. She is a practicing pediatric radiologist. Her research focuses on using cell biology, nanomedicine and medical imaging to develop cellular imaging technologies for cancer and stem cell tracking. Several of these imaging applications are being used to help patients.

Francisco Gimenez, a graduate student, was the lead author of “A novel method to assess incompleteness of mammography report content,” which won first place in the student paper competition at the 2014 American Medical Informatics Association Symposium. The paper also won the competition’s Martin Epstein Award, a recognition reserved for a first-place paper judged to be “truly extraordinary,” according to the association. Gimenez is a member of the lab of Daniel Rubin, assistant professor of radiology and of biomedical informatics research, who is the paper’s senior author.

Claudine Laurent-Levinson, MD, PhD, was appointed associate professor of psychiatry and behavioral sciences, effective May 1. She is a child psychiatrist who specializes in learning disabilities and their psychiatric comorbidities, including language disorders; nonverbal learning disabilities, such as dyspraxia; and early onset schizophrenia.

Mary Leonard, MD, was appointed professor of pediatrics and of medicine, effective July 1. She investigates the effect of childhood chronic diseases, such as kidney or heart disease, on bone and muscle development. She is developing methods to promote bone development and treat the skeletal complications of these diseases.

Cara Liebert, MD, a surgical education fellow, received a 2014 Outstanding Resident Teaching Award from the Association for Surgical Education. She develops and teaches surgical curricula for medical students and residents and has worked with interprofessional simulation-based training, flipped classroom curricula and medical-student mistreatment. She is a degree candidate in the Masters of Health Professions Education Program at the University of Illinois-Chicago and will return to her clinical residency training at Stanford in the summer.

Emmanuel Mignot, MD, PhD, was awarded a Lifetime Achievement Award from the National Sleep Foundation. An event will be held March 6 at Stanford in his honor. He is the Craig Reynolds Professor in Sleep Medicine, and directs the Stanford Center for Sleep Sciences and Medicine. He discovered that narcolepsy is caused by an immune-mediated destruction of neurons in the hypothalamus. He is also interested in Web-based assessments of sleep disorders, genome-wide association research, computer-based processing of polysomnography and outcomes research.

Robert West, MD, PhD, FACS, associate professor of neurosurgery, was elected to a two-year term as member-at-large on the executive committee for the Congress of Neurological Surgeons. He is vice chair of operations and development in the Department of Neurosurgery. He specializes in spine disorders and focuses on patient outcomes and decreasing the risk of operative complications.

Die-in staged to protest killings

Students, faculty and researchers at the medical school participated in a “die-in” on Jan. 15 to protest police killings of unarmed black men. Clad in “Black Lives Matter” T-shirts, demonstrators lay down on the school’s Discovery Walk while listening to Martin Luther King Jr.’s “I Have a dream” speech. The demonstration was organized by the Biomedical Association for the Interest of Minority Students.

Staff and residents:

- Dr. John Ratliff, MD, FACS, assistant professor of neurosurgery, was elected as chair of the Department of Neurological Surgery.

- Dr. Lloyd Minor, MD, the Carl and Elizabeth Naumann Professor for the Dean of the School of Medicine and professor of otolaryngology-head and neck surgery.

- Dr. Charles Prober, MD, professor of pediatrics and of microbiology and immunology, and senior associate dean of medical education.

- Dr. Terrell Stevenson, MD, clinical instructor of pediatrics.

- Dr. Robert West, MD, PhD, professor of pathology and of medicine, effective July 1.

- Dr. Michael Federman, MD, associate professor of medicine, effective July 1.

- Dr. Dawn Christensen, MD, associate professor of medicine, effective July 1.

- Dr. Ryanne Brown, MD, MBA, resident in anesthesiology, effective July 1.

- Dr. Robert Harrington, MD, the Arthur L. Bloomfield Professor in Medicine and chair of the Department of Medicine.

- Dr. Gloria Lewis, MD, MPH, resident in pediatrics.

- Dr. Cara Liebert, MD, resident in surgery.

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- Dr. Gloria Lewis, MD, MPH, resident in pediatrics.

- Dr. Cara Liebert, MD, resident in general surgery and a surgical education fellow.