

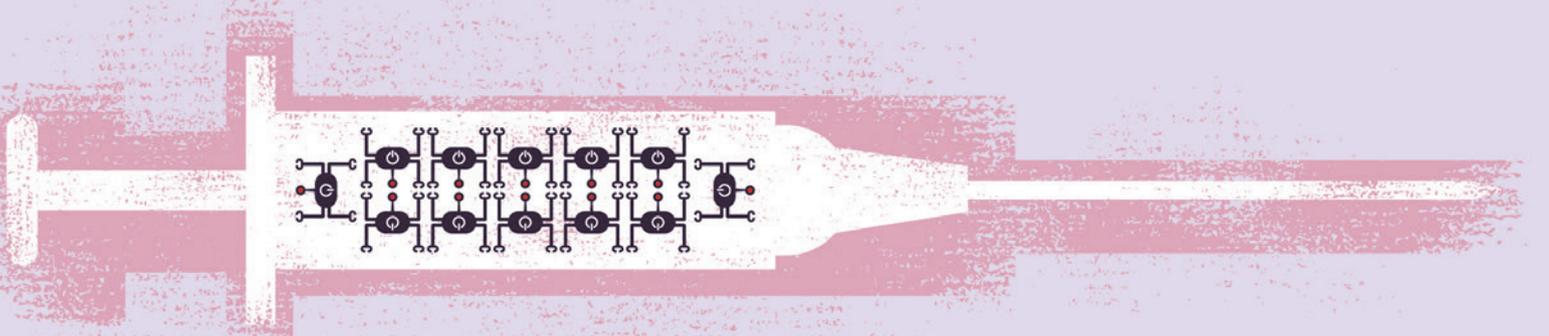
yale medicine



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In the months since our last issue of *Yale Medicine* appeared, we've seen a visit from our nation's Surgeon General (who also happens to be a recent alumnus); teenagers with diabetes climbing rock walls thanks to an artificial pancreas developed by School of Medicine faculty; hackathons that seek novel solutions to health care problems; and a new joint M.D./Ph.D. program with the University of Puerto Rico.

Exciting news also comes from beyond the corner of Cedar Street and Congress Avenue. A member of the Class of 2004 has been working

with indigenous people in the Amazon rainforest to compile an encyclopedia of medicinal plants used by shamans. Another alumnus from the Class of 1949, still active at the age of 93, is seeking ways to help doctors in training cope with the personal and professional stressors of a life in medicine. A member of the Class of 1990 has taken a contrarian view of e-cigarettes—despite their dangers, he believes, they can still help people quit smoking. On a lighter note, a lunchtime painting class offers participants a brief respite from the office, lab, or clinic.

Chronicles of all these activities and more are inside the pages of our Winter issue of *Yale Medicine*. As ever, we strive to let you know not only what's happening on the medical school campus, but also what our alumni, faculty, and students are accomplishing in New Haven and the world. And because there's always more news than we can fit inside the pages of the magazine, we encourage you to visit us online for more events and discoveries from the School of Medicine.

John Curtis
Editor, *Yale Medicine*

SECOND OPINION BY SIDNEY HARRIS



"SINCE MY TREATMENT OF THE SIDE EFFECT CAUSED BY YOUR TREATMENT OF THE SIDE EFFECT CAUSED BY FRED'S TREATMENT OF THE ORIGINAL COMPLAINT IS CLEARED UP, LET'S SEND HIM HOME."

Send letters and news items to

Yale Medicine, 1 Church Street, Suite 300, New Haven, CT 06510 or email yym@yale.edu. Please limit letters to 350 words and include a telephone number. Submissions may be edited for length.

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Abbreviations used in *Yale Medicine* include HS to denote the final year of residency for house staff, FW for the final year of a fellowship, and YNH for Yale-New Haven Hospital.

Yale SCHOOL OF MEDICINE

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The machinery of medicine: how technology influences medical research and clinical care

SINCE NEOLITHIC HUMANS fashioned the first scalpel out of stone, new machines and methods have changed the way we practice medicine and learn about the human body. Physicians moved on from those early scalpels to stethoscopes, X-rays, and MRIs, the better to understand the workings of the human body. With these new understandings has come translational research that transfers findings from the lab into new, more effective treatments and medicines. Dean Robert J. Alpern, M.D., Ensign Professor of Medicine, discussed basic science and advances in clinical care; technology and patient care; and the role of serendipity in research with *Yale Medicine*.

What have been some of the key inventions or discoveries that have advanced clinical care and medical research? In the past 50 to 100 years, there have been so many advances that it's hard to rank any one above the other. Obviously, some come to mind—the discovery of the structure of DNA, recombinant DNA, electron microscopy, knockout technology. The new gene editing technology, CRISPR, is really going to transform research. It's important to point out that the major advances in health care have been based on basic scientific findings. DNA technology and the structure of DNA were basic science findings that now drive clinical genetics. The understanding of how cells grow has transformed cancer care. Basic understandings of the immune system have led to immunotherapy for cancer.

How do physicians integrate new technologies into medicine while maintaining the doctor-patient relationship? Technology is always good for improving what physicians can do, but you run the risk that doctors won't hone their clinical skills as well as they could because they know that the technology will end up defining the diagnosis. There needs to be a combination of the two. I don't see technology replacing the need for outstanding clinicians. Technology should enhance clinical skills, not replace them.

How important is serendipity in scientific discovery? There are stories of serendipity, but the best investigators always appear to have good luck. The best investigators are asking the right questions, the important questions. It's a matter of staying knowledgeable about all of the technologies, including those from other fields, and thinking about how to apply them to your field. When you ask the right question and use the right technology, serendipity falls upon you.



Our collective will, says the Surgeon General, can give “every man, woman, and child a fair shot at good health”



After his talk in Harkness Auditorium, Surgeon General Vivek Murthy posed for a selfie with Neil Pathak, a first-year medical student, and Rachel Solnick, a resident in emergency medicine.

WHEN VIVEK H. MURTHY, M.D. '03, M.B.A. '03, returned to Yale in September, it was his first visit to his alma mater in the navy blue uniform of the U.S. Surgeon General. As he walked through the campus during his two days at Yale, he encountered constant reminders of the five years he spent in New Haven as a student—the shade tree on Hillhouse Avenue where he studied and wrote in his journal; the lecture hall where a classmate was so intent on taking notes that he never noticed when the professor called on him; and the former teachers who are now his colleagues.

During a talk in Harkness Auditorium, one of four he gave in New Haven, Murthy fielded a question from Cary Gross, M.D., professor of medicine, who said, “Welcome back. You’ve made us all proud.”

Murthy turned to the audience and said, “Dr. Cary Gross was, in fact, my thesis advisor.” And to Gross, “I just had a flashback to sitting in your office.”

The exchange was a reminder that Murthy is just 12 years out of med school and one of the youngest surgeons general in recent history. And that his ties

to the School of Medicine are both recent and strong. “It really feels like coming home,” he said. “I spent five years here, exploring new ideas, meeting new people.”

He came at the invitation of Howard P. Forman, M.D., M.B.A., a mentor since Murthy’s student days. “He agreed immediately,” said Forman, professor of radiology and medical imaging, of

economics, of management, and of public health, and director of the M.D./M.B.A. Program. “It was just a matter of finding the time.”

In Murthy’s talks at Yale and at Gateway Community College, he advanced his vision of a healthy nation—one that relies on partnerships and collaborations that may seem like strange bedfellows. Take shopping malls. For many of us, they symbolize consumerism and crass consumption. Others see them as a convenient place to shop or hang out, a place where you can buy everything from handbags to sleeping bags, enjoy a meal, and take in a movie.

Murthy sees a partner.

Such a seemingly offbeat collaboration is central to Murthy’s vision of a healthy America, one that he outlined in his multiple appearances in September. He stopped first at the School of Epidemiology and Public Health on September 16, followed by a talk that afternoon at the School of Management. The next day he joined a panel (which included city and state health officials) at Gateway Community College to discuss antismoking efforts. That afternoon he spoke at the School of Medicine in the same Harkness Auditorium where, as Forman noted, he’d donned his first white coat.

It was at the School of Management that Murthy discussed the partnership he’s seeking with owners and operators of shopping malls. His vision starts with his belief that all things in life—from taking a walk in your

neighborhood to nurturing your dreams and passions—stem from good health. “Health is the common thread that weaves through everything that we do,” he said.

“If we don’t have health, we don’t have anything else.”

If all things flow from health, then it behooves all of society—not just doctors and nurses and public health experts—to take an active role in keeping people healthy. All of us have a part to play, whether we know it or not. Murthy recognizes that health is a complex issue that must take into account more than blood pressure readings and our body mass index. Good health also means access to healthful food, the ability to exercise, and freedom from poverty—in other words, addressing the inequities and disparities in our society.

But Murthy remains undaunted. “We are used to thinking that complex problems require complex solutions,” he said. “That is not always the case.”

In all his presentations, he broke down large problems into manageable pieces and suggested solutions that usually involve some sort of collaboration. As Surgeon General, Murthy seeks to harness the power of eclectic partnerships among apparently disparate sectors of society—like the Indiana community in which police, educators, and public health leaders work together to tackle an epidemic of opiate abuse. “We can’t prosecute our way out of the problem,” Murthy said of drug abuse. “It is not a

moral failing. It is something that requires treatment.” Other examples of the times when “we get it right” include a program in Virginia that introduces students to fresh vegetables, and another that doubles the value of food stamps at farmers’ markets, making fresh produce more accessible.

One of Murthy’s favorite solutions is walking, part of “restoring a culture of physical activity.” Just 22 minutes of walking a day, he said, greatly reduces the risk of heart disease or diabetes.

“Walking is one of the most powerful things we can do as a society to roll back the wave of chronic disease we are facing,” he said. That’s why he’s been partnering with mall owners to implement walking programs. “When it’s incredibly hot or incredibly cold, where better to walk than in a mall? You can do it with other people. It’s a social event.”

A healthy society, he believes, can be achieved through “collective will,” the force that led a band of colonists to take on the British Empire; a nation to take on racial discrimination; and medicine and science to take on the HIV epidemic. With collective will, he said, we can improve health for all. At the medical school, he called on the future physicians to join him by seeing themselves in a new role as leaders in their communities who bring together resources and experts. “That shift from



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Med students add Medical French to their arsenal of skills.

Medicine in the wild: students learn how to treat ailments in the outdoors.

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being individual providers of care to being leaders who can communicate and convene—that is a cultural shift, an important one, and one that I’m hopeful we can achieve,” he said.

“What kind of country do we want to build with our collective will?” he continued. “I see a country where every man, woman, and child has a fair shot at good health. Never, ever believe that this challenge is bigger than our collective will. ... Together we can translate this vision into reality.”

—John Curtis



An encyclopedia of medicine from the Amazon

When a member of the Amazon Matsés tribe develops the tell-tale sore of the parasitic disease leishmaniasis, the tribal shaman knows what to prescribe: heated scrapings from the outer bark of a particular vine. For untold generations, this indigenous group on the Peru–Brazil border has counted on the forest’s vast array of medicinal plants and animals to treat its maladies and enhance survival practices like hunting.

But the tribe’s self-sufficient healing tradition and the forest it depends on are under threat. Recent sustained contact with the outside world has rapidly led to cultural erosion, discrimination, and resource grabs by outsiders, hurting the



tribe’s self-sufficiency and its relationship to the land. Worse, the elderly shamans who know the rainforest’s secrets are dying, and their knowledge is becoming lost even as the tribe depends on them for health care. And because of shame learned from missionaries who viewed traditional healing as “witchcraft,” until recently no younger Matsés were training to become shamans.

They are now. Thanks in part to Acaté Amazon Conservation, a nonprofit co-founded by Christopher N. Herndon, M.D. ’04, the tribe has captured and preserved its elders’ knowledge and inspired its youth by writing an encyclopedia, one intended for use in training the next generation of tribal healers. The encyclopedia—which Herndon believes is the first ethnobotanical inventory of an Amazonian tribe to be written by the indigenous people themselves—describes hundreds of plants in 500 pages of text,

Christopher Herndon learns about medicinal plants on a rainforest trail from Cesar Necqua, a shaman from the Matsés village of Esitrón in the Peruvian Amazon.

Herndon played a role in producing an encyclopedia of such plants, and Esitrón is the village where an apprentice program was piloted to pass on this knowledge.

photographs, and illustrations. Filled with pride and optimism in the wake of the project, several young Matsés have now stepped up to apprentice to shamans, Herndon reported.

“With the medicinal plant knowledge disappearing fast among most indigenous groups and no one to write it down, the true losers in the end are tragically the indigenous stakeholders themselves,” Herndon said. “The methodology developed by the Matsés and Acaté can be a template for other indigenous cultures to safeguard their ancestral knowledge.”

That methodology was entirely homegrown. To compile the encyclopedia, five elderly shamans paired off with younger tribe members literate in the Matsés language. Over two years, the elders divulged all they knew about pharmaceutical organisms, diagnoses, and treatments, while the youths took notes and photographs.

Last May, tribe members met to compile the information into a single document. Though Acaté provided support, including a laptop and help with formatting, the project was entirely led and undertaken by the Matsés.

Significantly, the tome is in the Matsés language—whose written version was developed by missionaries in order to translate the Bible—but it won't be translated.

That's a measure to protect this traditional body of knowledge from commercial exploitation, a practice some call biopiracy and one the Matsés are all too familiar with. The rainforest's pharmaceutical gifts are legion, including the antimalarial drug quinine, the muscle relaxant curare, and the stimulant cocaine, among others. Westerners eager to explore them further don't always take tribal interests into account. In the early 2000s, without permission from or sharing with the tribe, a Seattle company and others patented versions of several peptides from the Acaté frog (*Phyllomedusa bicolor*)—whose skin secretions the Matsés use to alter consciousness, heighten senses, and confer feelings of strength and courage—for use as painkillers. Another substance in the public domain used by the Matsés and neighboring tribes is *bécchête*, a type of milkwood whose secretions applied to the eyes are reported to help hunters better distinguish textures. Seeds from this plant are

now sold on the Internet by non-Matsés. Herndon said he can't disclose Matsés remedies due to Acaté's agreement with the tribe.

Ethnobiology and ethnomedicine have long emphasized the importance of cataloging traditional plant uses, said Yale anthropology professor Claudia Valeggia, Ph.D., who studies the health of Latin American indigenous groups. What makes the encyclopedia unique, she said, is that its monolingual nature will keep it within the community. "This is an invaluable survival kit, not only literally—it can save lives and alleviate a lot of suffering—but also metaphorically as an important aspect of the Matsés culture."

Herndon, a reproductive endocrinologist in Berkeley, Calif., has worked with indigenous South American tribes since he was in medical school, initially through a Downs Fellowship in the summer of his first year at Yale. For his medical student thesis, which was awarded the Ferris Prize on his graduation in 2004, he studied the Tiriyo people of Suriname, a small country on the northeastern coast of South America, and wrote about their knowledge of anatomy and disease as well as plants. This knowledge remains vitally important. Though Western medicine can be helpful in the Amazon, remote health stations are often understocked, personnel poorly trained, and treatment options expensive, impractical, or able to cause dangerous side effects.

Herndon met the Matsés in 2011 after completing his fellowship in reproductive endocrinology at the University of California, San Francisco. In 2012 he co-founded Acaté with William Park, an agroforester who helps the formerly seminomadic Matsés develop sustainable farming techniques to adapt to their now-more-permanent settlements.

Their health system too may soon become more sustainable. One of the young shamanic apprentices is also the local government health promoter, a vanguard of the Matsés' next plan: to develop an integrated Western and tribal health system that offers the best of both worlds.

—Jenny Blair



Yale and University of Puerto Rico collaborate on M.D./Ph.D. studies

When Daniel A. Colón-Ramos, Ph.D., arrived from Puerto Rico to begin his Harvard undergraduate career in 1994, things didn't exactly go as planned. Moving to the campus early for a summer program, he took a taxi from Logan Airport into Cambridge. But once in his dorm room, he set down his bags and lay on the bed feeling dizzy—and by the time his roommate arrived, Colón-Ramos recalled, "I told him, 'I'm dying. You have to take me to the hospital.'"



ONLINE EXCLUSIVES

Harnessing the power of online video to promote health.

Full circle: a New Haven high school student returns to Yale in the Class of 2019.

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Dignitaries from Yale and the University of Puerto Rico, including Peter Salovey and UPR President Uroyoán Walker, met last summer to discuss a new program that would allow medical students from Puerto Rico to complete Ph.D. studies in New Haven.

No one could figure out what was wrong. The hospital physicians suspected meningitis, but results of a spinal tap were negative. Eventually, said Colón-Ramos, now an associate professor of cell biology and neuroscience at the School of Medicine, they tracked down his family doctor: “It took my doctor from Puerto Rico calling the hospital to tell them these were all the symptoms of dengue fever. I was coming in with a tropical disease. They had no idea.”

This gap in medical knowledge was part of his inspiration for spearheading the new M.D./Ph.D. collaboration between the School of Medicine and the University of Puerto Rico (UPR). A global context, Colón-Ramos believes, is necessary for today’s health care. In this new program, students from the M.D. program at UPR can apply to Yale’s Combined Program in the Biological and Biomedical Sciences and will be assigned

mentors while studying for their doctorates in New Haven. UPR students compete for spots along with Yale’s regular applicant pool; the universities are looking for two or three students per class to enroll in the program.

After their first year in medical school at UPR, successful applicants will spend a summer at Yale completing an eight-week lab rotation to familiarize themselves with the campus. They’ll return to Puerto Rico for two years of training, after which the students will conduct their Ph.D. research at Yale and then return to UPR for the final year of medical school. The first round of applications tagged for the program was due in December 2015. The process is open to students currently enrolled in their first year of medical school at UPR, as well as new students applying simultaneously to UPR and Yale for their M.D./Ph.D. degrees.

Training and mentoring at Yale will prepare the UPR students to create a new connected community on their return. “In Puerto Rico, we don’t have many physician-scientists,” said Marcia Cruz-Correa, M.D., Ph.D., director of the Office of Research for the UPR School of Medicine. “There are other programs that are trying to fill that void, but the gap is huge. The opportunity to grow is dramatic.” Cruz-Correa hopes that the program will bring together medical professionals trained to think

differently who will remain to serve Puerto Rico.

Dignitaries from UPR visited Yale last July to celebrate the new agreement. For members of the delegation, the trip was their first time to New Haven. They met with Yale President Peter Salovey after a whirlwind day of meetings and tours, finalizing the program, and brainstorming more ways to take advantage of the new connections. “It’s a historical moment, but it’s just the beginning,” said Cruz-Correa.

The agreement is a first point of contact that could open up new opportunities for Yale’s medical community. It may serve as a springboard for future interactions, perhaps encouraging students to gain medical experience in the tropics as well as connect more deeply with the New Haven community. “There are many changes going on, definitely in the United States, but also worldwide—think about Cuba,” said Colón-Ramos. “Patients in Puerto Rico are similar to a whole continent that lies south of the United States. And really, not that different from communities five minutes down the road.”

“We’re all very excited and looking forward to the rewards that the students will bring after they finish,” said Uroyoán Walker, Ph.D., president of UPR. He added, “We’re training our next generation. And when I say ours, I mean the world’s.”

—Karen Zusi



round up

a collection of recent scientific findings

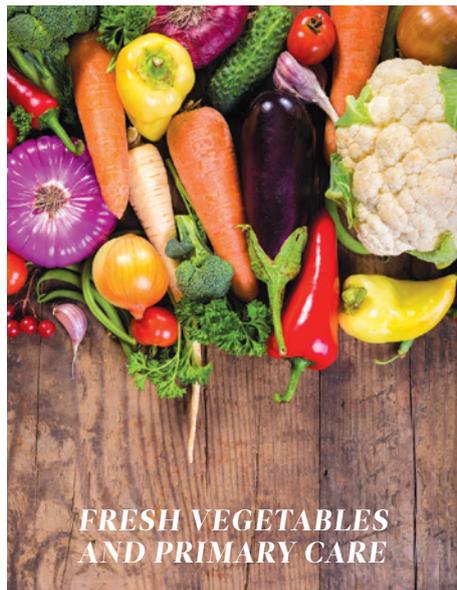


GREEN LAWNS AND FROGS' SEX

Neatly manicured suburban lawns and gardens are playing havoc with the frogs' endocrine systems, according to a Yale study published in the *Proceedings of the National Academy of Sciences*.

In 2012, researchers at the School of Forestry & Environmental Studies counted frogs at 21 ponds in southwestern Connecticut and found almost twice the proportion of females being born as in forested ponds. "The fact that we saw such clear evidence was astonishing," said lead author and doctoral student Max Lambert. Previous studies had found such effects from agricultural pesticides and wastewater effluent, but this is the first to find them in the suburbs as well.

Because some common plants naturally produce phytoestrogens, Lambert said, just maintaining a lawn may be a source of contamination. And other species—wood frogs, gray tree frogs, salamanders, birds, and turtles—may be affected as well.



FRESH VEGETABLES AND PRIMARY CARE

It's time to add gardening to the arsenal of clinical skills. A nutrition workshop that was developed as part of a new Community Engagement Curriculum had 25 internal medicine residents preparing simple, nutritious dishes with vegetables harvested on a farm at Yale's West Campus. The goal is for the residents to use what they learned to communicate more effectively with their patients about healthful food choices.

"We want our residents to be able to offer practical advice about local food systems and healthy eating habits, and to enhance their abilities to integrate preventative health in their regular communications with patients," said chief resident Sanjeet Baidwan, M.D., who is leading the new curriculum with Tracy Rabin, M.D., HS '10; Julie R. Rosenbaum, M.D. '96, FW '02; and Justin Freiberg of Yale's West Campus.

The workshop is part of a Community Engagement Curriculum that the Yale Primary Care Internal Medicine Residency has undertaken, which includes communication skills, cultural awareness, home visits, and advocacy.



AFTER A HEART ATTACK, A DISPARITY IN OUTCOMES

A study that analyzed data on more than 132,000 white heart attack patients and almost 9,000 black patients—and used zip codes to assess income levels—found that the survival rate 17 years later was 7.4 percent for white patients, but only 5.7 percent for black patients.

White patients across all ages in low-income areas lived about 5.6 years after a heart attack, longer than the average 5.4 years for black patients. In high-income communities, however, the gap widened—white patients had a life expectancy of 7 years, compared to 6.3 years for black patients, according to the study published in *Circulation*, the journal of the American Heart Association.

The study, said lead author Emily Bucholz, M.P.H. '09, M.D. '15, Ph.D. '15, suggests that improving socioeconomic standing may improve outcomes for black and white patients globally, but is unlikely to eliminate racial disparities in health.

A DRUG FOR WOMEN TESTED MOSTLY IN MEN

Some scientists see a major flaw in a recent study of the effects of alcohol consumption on a drug intended only for women.

The study of interactions between alcohol and Addyi, the first drug to treat female sexual dysfunction, enrolled 23 men—and two women.

"There is no valid reason to ignore the well-established biological and behavioral differences between men and women when conducting

biomedical research," said Carolyn M. Mazure, Ph.D., director of Women's Health Research at Yale. "Yet it continues to happen."

Sprout Pharmaceuticals, which markets Addyi, said in a statement that the study was designed with FDA guidance. "More men than women agreed to enroll in this kind of study," the statement said, adding that Sprout plans to conduct additional studies on the effects of alcohol in women.



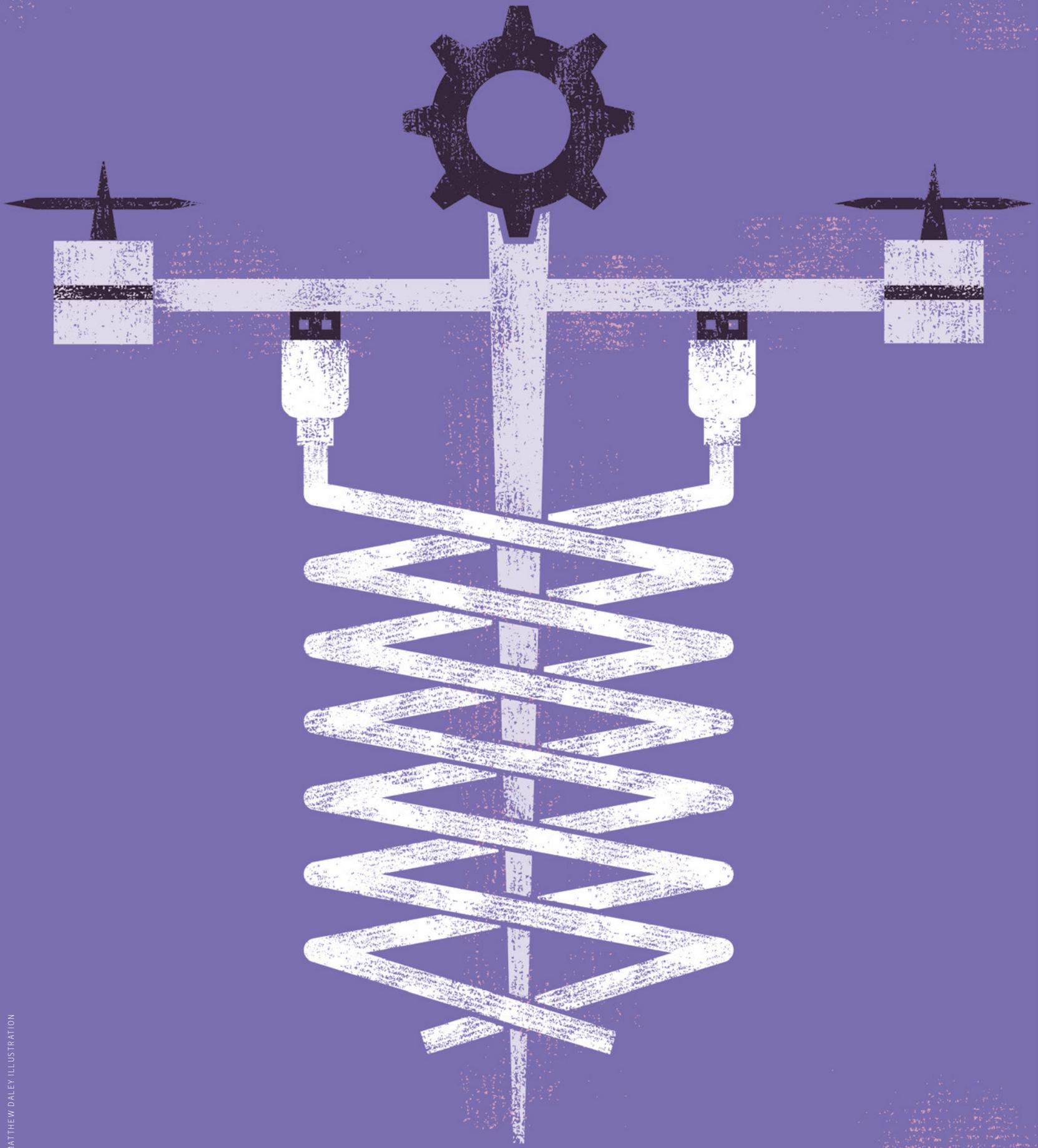
The Machinery of Medicine

OVER THE LAST FEW YEARS, as electronic medical records have become the norm in hospitals, clinics, and doctors' offices, clinicians have tried to come to terms with the computer. Is this machine demanding their attention at the expense of the patient? How does a doctor engage her patient while typing data into a template? The tools of medicine—from the stones that Neolithic humans honed into scalpels to the earliest stethoscopes that emerged in the 19th century to today's sophisticated imaging devices—have changed the way physicians interact with their patients. And those tools are changing biomedical research as well.

At Yale and around the world such new technologies as 3D printing or biomedical engineering have advanced medical research. But scientists still rely on hunches, instinct, and serendipity as well as these tools. When an experiment in biomedical engineering yielded unplanned results, the scientists didn't scrap their findings—they looked for a way to use what they'd found and *voilà*, a new approach to sun-screen. Another team tried to synthesize a compound found in a red sponge from the Caribbean to make a medicine to block HIV infection. It took eight or nine tries, and with each failed effort, they reevaluated and adjusted until they got it right. Physicians at Yale spent almost 10 years developing an artificial pancreas that would control insulin delivery for people with diabetes. Last summer they tried it out on a group of teenagers in New Haven, with dramatic results.

In this issue of *Yale Medicine* we take a broad view of the machinery of medicine to explore the ways in which physicians, scientists, and engineers work to advance both their understanding of the human body and how they apply that knowledge to clinical care.

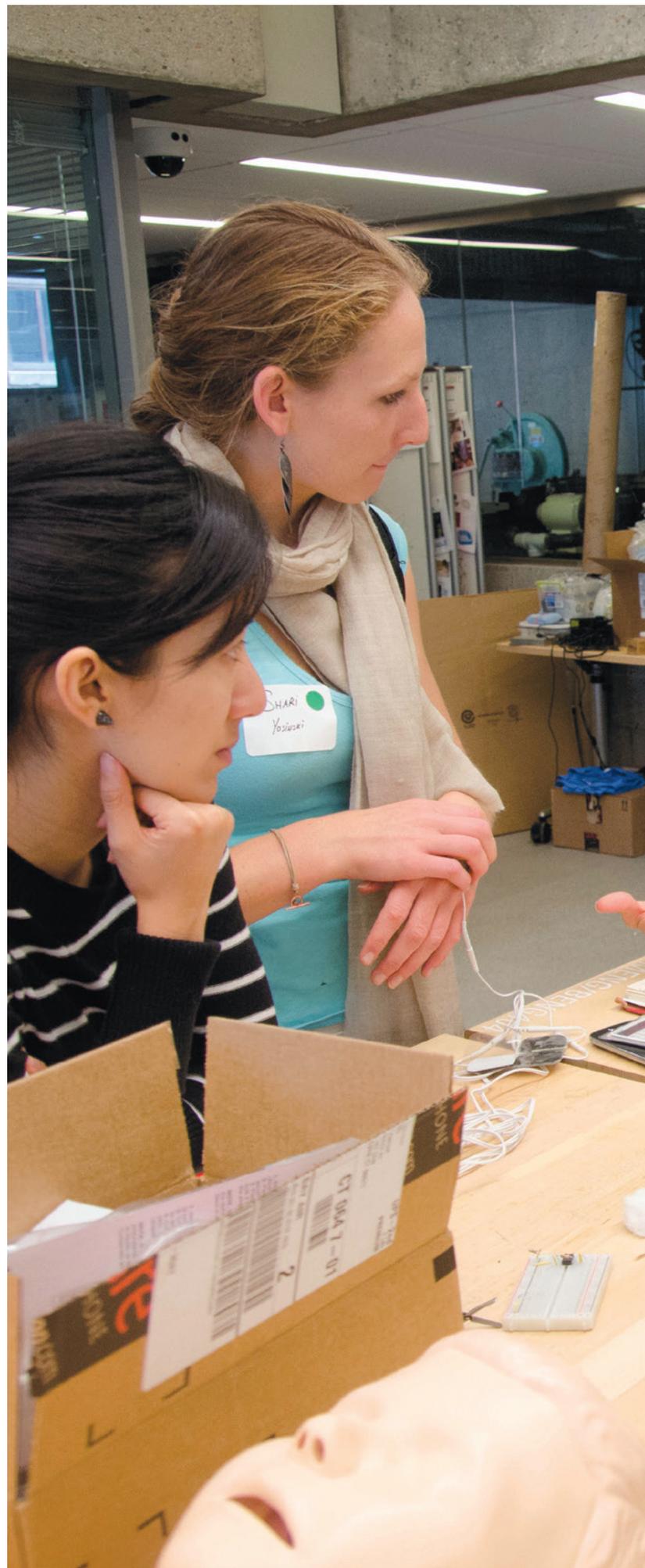
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From raw idea to finished product

Hackathons are great for sparking creativity, but turning a concept into a marketable product takes time.

By Christopher Hoffmann
Photographs by John Curtis and William Sacco





At a hackathon in the fall of 2014, a team that included (from left) public health student Sharon Wu, biomedical engineering student Shari Yosinski, School of Medicine research associate Eydis Lima, and biomedical engineering students Tobi Akindoju and Francis Mburu proposed a dermal patch for dosing and tracking a patient's treatment during a clinical trial. The team is still pursuing the project, which is now focused on developing a patch to detect infectious agents. "Many of the challenges involve time," says Lima, "... being a student and trying to be an entrepreneur and finding time to think outside the box and move the project forward."

Over the course of a frenetic weekend in March, five unlikely colleagues—an undergrad, a nursing student, a doctoral candidate, an employee at a marketing startup, and a hospital resident—came together to design a device to help asthma sufferers. Inspired by a keynote speech at a hackathon, the initial group formed over a shared interest in asthma dosing. Rounding out their team at lunch, they then spent the rest of the weekend working like mad to complete their device.

The group labored until 10:30 Saturday night, returning at about 7:30 or 8 the next morning to develop a prototype. At one point, they sent the resident scurrying to the hospital for an incentive spirometer, a simple instrument that measures inhalation.

The “INcentiHALER,” as they named their device, was an easy fix to a widespread and vexing problem: the failure of many asthma sufferers to use their inhalers properly. Patients commonly fail to breathe in at the correct rate or length of time, compromising the medicine’s effectiveness. The team’s solution—simple, cheap, and elegant—was an instrument that enables users to monitor their inhalation rate.

“We focused on how design can cue a user to have proper technique,” said team member Angela Hasler, the nursing student.

“Sometimes, innovation can just be a better-designed piece of plastic housing,” added team member Justin Koufopoulos, the marketing startup employee. “We actually hacked together two medical devices.”

Their device garnered the grand prize at Yale’s second biomedical hackathon in March, sponsored by the Yale Center for Biomedical and Interventional Technology (CBIT) and the Center for Outcomes Research and Evaluation (CORE). The five-member team walked away with the \$500 first prize, and they appeared to be on their way.

Six months later, the “INcentiHALER” team is still working on their project, despite some bumps in the road. The top prize in a follow-up competition that would have provided \$3,000 in seed money—to build a prototype and apply for a patent—went to another contestant, team member Catherine Jameson said. Summer arrived, and the team members scattered, and other commitments also got in the way. Jameson, for example, is entering her senior year as an engineering major at Yale College.

But the group isn’t giving up. Since classes resumed in September, the team has met twice, Jameson said. Their plan is to construct a better prototype, do market research, and then approach drug companies.

“We’re trying to see if it’s viable and what we need to do to make it viable,” she said. “We are fully committed to doing everything to make it happen because we’ve gotten such positive feedback, and it would improve the patient experience.”

INcentiHALER’s experience is not uncommon for hackathon participants, said Jean Zheng, Ph.D. ’13, CBIT’s engineering director. Hackathons may promote innovation at warp speed, but turning those innovations into viable products usually takes several years, she said.

And that’s just fine, said Zheng and Chris Loose, Ph.D., CBIT’s executive director. Hackathons are about building excitement and energy as well as creating viable products.

“These [hackathons] are really educational at heart, and they can lead to some great things, and have led to some great things,” Loose said, adding that they’re just one part of CBIT’s strategy to jumpstart biomedical innovation and entrepreneurship at Yale.

“The purpose of the first hackathons was to create a culture of biomedical innovation,” Zheng said. “It was raising awareness, creating excitement.”

And even though hackathons appear to focus on applying cutting-edge technology, that’s not always the case. Grand prizewinner INcentiHALER, for example, was about engineering, not algorithms, team member Koufopoulos pointed out. “There are many places where just better design is needed,” he said. “This is not always apparent at a hackathon—where that might mean ‘code’ to most people. Nearly all of our competitors were software projects.”

Hackathons, which originated in the computer industry and later spread to medicine, seek to speed up innovation. Motivated, creative, and accomplished people come together for a short period, typically a weekend. They are given a challenge, and then they identify specific problems derived from that challenge and pitch solutions. At the close of the hackathon, judges give out awards in a variety of categories.

The goal of CBIT, founded in 2014, is to get the Yale community—everyone from medical students and residents to engineering undergraduates and Ph.D. candidates—amped up about creating cutting-edge medical devices and computer applications. As part of its strategy, the center teamed with MIT Hacking Medicine, InnovateHealth Yale, CORE, and other sponsors to hold the first-ever Yale medical hackathons, one in October 2014 and the other in March 2015.

Organizers invited diverse groups, including residents, doctors, nurses, doctoral candidates, and undergraduates as



During the 2014 Hackathon, Yale College student Austin Muñoz (center) and teammates (from left to right, Matt Reagor, Amy Wong, and Dan Freed) devised a juvenile diabetes kit with a kid-friendly testing meter. Present to help them were Kyle Jensen, Ph.D., associate dean and the Shanna and Eric Bass Director of Entrepreneurial Programs at the Yale School of Management, and his 5-year-old daughter Charlotte, who has type 1 diabetes. Wong, CBIT executive director Chris Loose, and Muñoz watched as Charlotte demonstrated how to administer insulin. Muñoz and a friend at the School of Architecture continued the project, but put it on hold after they were unable to build a medical-quality prototype. “There’s more to hackathons than simply building a new app or product in a weekend,” Muñoz says. “The relationships formed and the skills learned are the true reward. Failure on one idea should never discourage someone from continuing to solve tough problems.”





Nursing student Angela Hasler, Yale College student Catherine Jameson, Justin Koufopoulos of Percolate, and a doctoral student in biomedical engineering, Linda Fong, won top prize for Best Patient Experience at a hackathon in March. The team redesigned an asthma inhaler that would let patients know whether they're using it correctly. The team that devised the "INcentiHALER" is still working on the project. Their plan is to build a better prototype, do market research, and approach drug companies. "We're trying to see if it's viable and what we need to do to make it viable," says Jameson.

well as public health, medical, engineering, forestry, law, art, and business students. Both events were successes, Zheng and Loose said, producing a plethora of potential innovations.

But once the "hack" is over, the real work begins, they said. Persistence, time, and cold hard cash are needed to succeed. Post-hackathon, teams must build strategies to further develop their ideas, Loose said. Especially important is determining a product's market viability, he said.

"Defining the market means both how many patients are in need, and how big is the final market," Loose said. "It also means identifying the stakeholders that need to be addressed. The hackathon helps start that journey."

The emphasis on entrepreneurship and market viability is what sets hackathons apart, said Linda Fong, an INcentiHALER team member and a doctoral student in biomedical engineering. "Hackathons are unique in that they urge you not to focus simply on the invention, but to also build a viable business strategy around it," she said. "Focusing on the inhaler actuator was our business opportunity—most companies only care about the drug, not the delivery."

Of the 30 teams that took part in the two hackathons, about five have continued their journeys, said Loose, a figure

he is happy with. Some have ended up working with the Yale Entrepreneurial Institute as well as his center to flesh out their ideas, he said. "I think it's going extremely well."

Another team still working on its idea called itself "Keep an Eye on It." Its mobile application, developed in the March hackathon, would allow users to take photos of skin conditions, creating image libraries that physicians could examine and monitor, said team member Kristen D'Angelo, M.B.A. '15. The app would analyze the images and provide a social network for patients, she said. The team is focused now on market research and recruiting iOS and Android coders to advance a prototype, she said.

D'Angelo was effusive in her praise of the hackathon, saying she was "blown away" by the experience. "I didn't picture myself standing up to propose a problem, but it was just such a welcoming environment," she said. "The hackathon really stimulates a level of energy that lets ideas surface and grow." */yale medicine*

Christopher Hoffman is a freelance writer in North Haven, Conn.

If you have a lemon, make lemonade

When an experiment in his lab took an unexpected turn, W. Mark Saltzman, Ph.D., saw a serendipitous opportunity, even if the Goizueta Foundation Professor of Biomedical Engineering and professor of cellular and molecular physiology and of chemical engineering wasn't sure where it would lead. One of his postdocs had been looking at nanoparticles that would circulate through the blood to target tumors for drug delivery. Instead, he found that the particles stuck to proteins and tissues.

"That is not what we wanted them to do," Saltzman says. Still, his team thought they might find a use for these sticky nanoparticles. The postdoc, Yang Deng, Ph.D., tested them on skin samples, and found they still stuck fast.

When Asiri Ediriwickrema, M.D. '14, then a medical student working in Saltzman's lab, got a look at these bioadhesive nanoparticles (BNPs), he saw clinical possibilities. His first thought was sunscreen.

Saltzman's team found a way to encase an organic sunscreen agent called padimate O inside the sticky nanoparticles. Padimate O, the active ingredient in many commercial sunscreens, soaks up the sun's UV rays, but also soaks into the skin. Nanoparticles, on the other hand, are too large to pass through hair follicles and pores, and they remain on the skin's surface even when it's wet.

Such a sunscreen could answer the concerns of those who fear that UV-absorbing chemicals have harmful side effects. The next step was to find an expert on photodamage of the skin to see whether the team's nonabsorbent sunscreen would work. The team knew just the person: Michael Girardi, M.D., professor of dermatology. His lab specializes in the early events of skin cancer development, and in examining the molecular markers of direct and indirect damage from UV exposure. "Yale is a small community," Saltzman says. "People know what others are doing and you can quickly get to the person you need."

Saltzman and his team reached out to Girardi, and "there was instant chemistry," Girardi says. "And a recognition that together we could accomplish so much more than individually."

The two labs joined forces to test the sunscreen on mouse skin and pigskin models. "We were floored with its performance," Girardi says. Not only did the

sunscreen adhere to skin for up to a full day and absorb UV rays, but it did not penetrate the skin. What's more, the sunscreen, which used less than 5 percent of the active agent as commercial sunscreen, proved equally effective.

All of this means that the team is on the way to building a longer-lasting and less toxic sunscreen. Chemicals in commercial sunscreen can cause allergies, and have been found in urine and breast milk. While such concerns as hormonal side effects have yet to be proven, "a lot of people feel that if they could avoid having these chemicals get inside the body, they would choose to," Girardi says. "This technology would give them that choice."

The team's findings were recently published in the journal *Nature Materials*, with Deng and Ediriwickrema as co-first authors. Planning has begun for a clinical trial, and the team has received a pilot grant to explore the new technology further. They'll be testing its effectiveness with other sunblock agents and addressing additional safety concerns.

Beyond that, Girardi and Saltzman see even greater potential for the sticky nanoparticle: they are looking at how it might be used to treat other skin conditions. "We have come up with more than 100 other possible ways to use it," says Girardi.

—Jeanna Canapari



Keeping the “Goldilocks” organ cool

Since the first human heart transplant nearly 50 years ago, the standard of care for transporting donor organs has changed little. A heart, kidney, or liver is harvested, cleaned, placed in a cooler on ice, and shipped off via ambulance or jet plane. There are fancier transport containers, but they can be prohibitively expensive or too unwieldy to travel long distances. For a particular organ—the intestine—a cooler simply won't work. These intricate tubes demand more sophistication than a plastic bag on ice can offer. The intestine's complex lining, or epithelium, “allows salts, fluids, and nutrients to go in and out on a regular but very regulated basis,” said John P. Geibel, D.Sc., M.D., vice chair and director of surgical research and professor of surgery (gastrointestinal) and of cellular and molecular physiology. “You don't want to have secretory diarrhea, and you don't want constipation. It's the Goldilocks organ—[the environment] has to be just right.”

Besides the need for a delicately balanced environment, the intestine, teeming with bacteria, presents its own challenge. If the bacteria are not properly controlled, then parts of the intestine can fill with toxins and kill off healthy cells, putting the patient at further risk of infection. The problem with the standard ice transport method, said Geibel, is “that nobody is perfusing the tissue.” The intestine needs to be bathed in a constantly circulating liquid.

Geibel did not have to sit on his idea for long. In 2013, Joseph Zinter, Ph.D., associate research scientist and lecturer in the School of Engineering & Applied Science, invited Geibel to give a presentation to his students in a medical device design class. Geibel presented his idea for an Intestinal Preservation Unit (IPU), for which he had no prototype. A team of students signed up to “take the back-of-the-napkin drawing to a fully functional prototype,” Geibel said.

While intestinal transplants are not as common as those of the heart, lung, or kidney, slight improvements in transplantation procedures could mean significant gains. Patients who cannot absorb nutrients due to a damaged or missing small intestine often face one option: getting nutrition through an IV or catheter.

When he met the engineering students, Geibel presented them with an extremely lightweight cooler and challenged them to fill in the missing pieces: a reliable battery and motor, a system of tubes to keep liquids moving throughout the intestine, and a temperature gauge and other tools for monitoring the status of the organ. It would be necessary to perfuse both the main blood supply, called the mesentery, and the lumen of

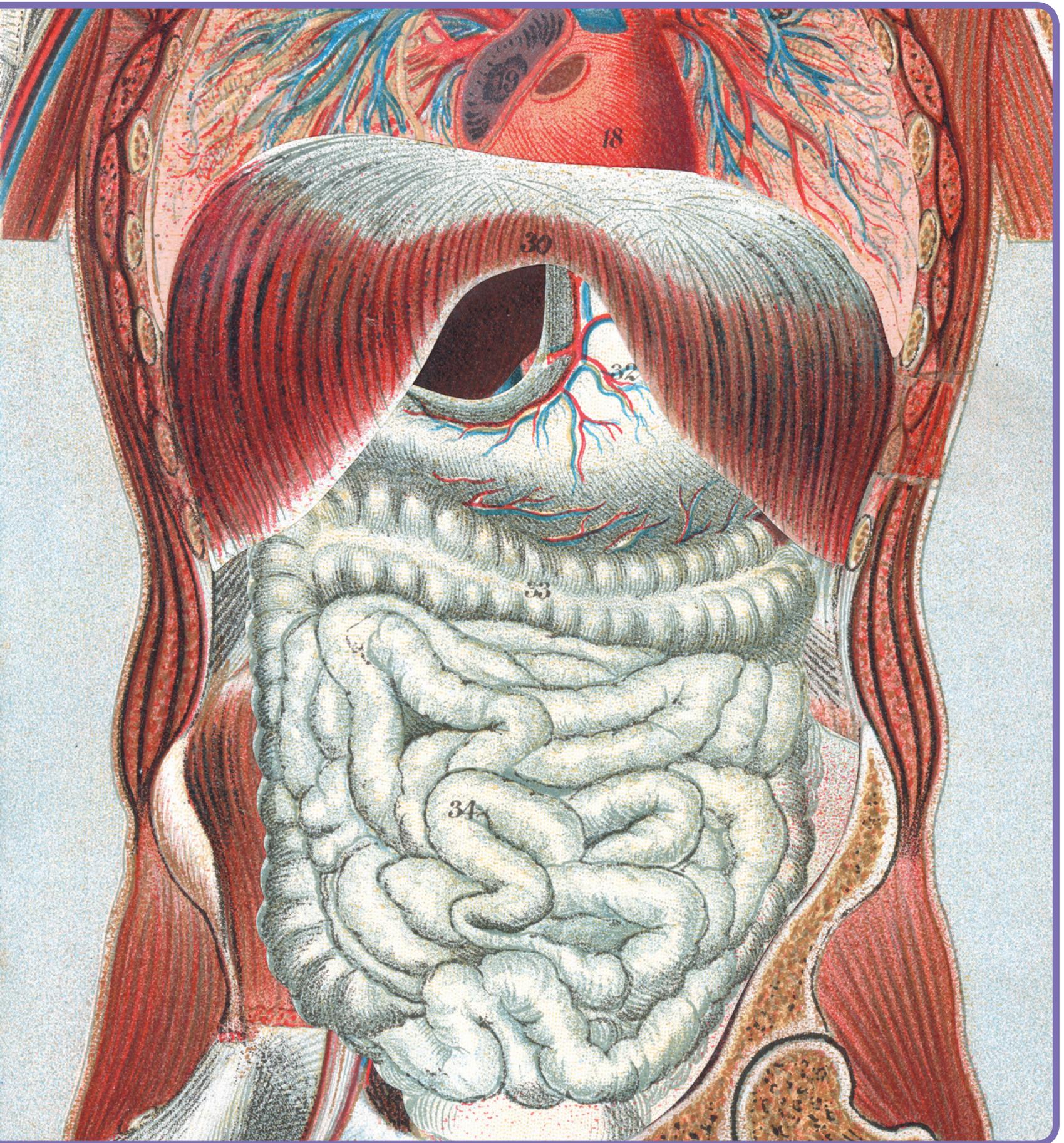
the intestine. Within weeks, the engineering team presented a prototype, which contained a large battery and oversized top to fit the gauges and screens. “It was still kind of kludgy, but it was an engineering first, so we were very happy with it,” Geibel said. After the students graduated, Geibel kept momentum going by consulting with fellow transplant surgeons on the design. Soon, Geibel teamed up on another project with Jesse Rich and Jen Graze, students at the School of Management. In September 2014, the team established Revai, the company behind the medical device. By this time, Geibel and his team had tested swine organ explants in a “version 3.0” of the transport device, and all the animals looked healthy when examined in the histopathology lab after the transport.

To improve the design, Geibel and his team used a 3D printer to create a cooler top that could hold the batteries, tubing, and measuring devices, and would fit over the cooler. But the team stopped short of reinventing the wheel for a preservation solution. They used a commercially available hypothermic solution rather than trying to keep the liquids at body temperature. (The field is engaged in a fiery debate about whether hyperthermic, or body-temperature, transplants should be the standard of care rather than ice, Geibel said.) For sanitary and safety reasons, the interior of the IPU, as well as the tubing and connectors, are completely disposable. The Food and Drug Administration (FDA) requires this feature for all organ transport devices.

Transporting the intestinal organ can usually occur only within a narrow window of two to four hours. But the Revai team has kept an intestinal organ alive and functioning for eight hours, Geibel said. “We want to get our box so that it can keep things alive and keep things viable for longer periods of time,” he said.

So far, the group has reenacted an organ transplant in a veterinary operating room. Working with medical residents and fellows, Geibel and the Revai group watched while an animal intestine was harvested, placed in sterile towels, and taken to the “back table,” or what surgeons refer to as the organ transplant area. The intestine was then kept in the Revai cooler for eight hours. The team has also tested the transport of five donated human intestines. Without FDA approval yet, the transplants could not be used for implantation in a real-life patient. The next step, Geibel said, will be partnering with a high-traffic intestinal transplant center to conduct a clinical trial. “I think the number of transplants would go up dramatically if patients knew they had a device that gave them a very high [transplant] success rate,” Geibel said.

—Kathleen Raven



The artificial pancreas

Ten years in its development, the artificial pancreas is the marriage of a sensor that monitors glucose levels and a pump that sends insulin into the bloodstream as needed. This device could revolutionize how patients manage their diabetes.

By Jill Max

Photographs by Robert A. Lisak





Rachel Hicks scrambled up the wall at a New Haven climbing gym last spring. Hicks has type 1 diabetes and was participating in a test run of an artificial pancreas that helps her monitor her blood glucose readings. The device, which transmits the readings to a smartphone device, doesn't interfere with normal activities.

Last May, 15-year-old Jacob Conte was scaling a rock wall at City Climb Gym in New Haven. Hand over hand, grabbing onto holds protruding from the wall, he made his way up the artificial cliff. Underneath his clothing—indeed, under the skin on his abdomen—he wore a small sensor that transmitted his blood glucose level readings every five minutes to a smartphone device in his backpack. Conte has type 1 diabetes and requires regular infusions of insulin. The smartphone told an insulin pump affixed to his belt when and how much insulin to deliver. The pump—smaller than a smartphone—injects insulin under the skin of the abdomen through a short thin tube.

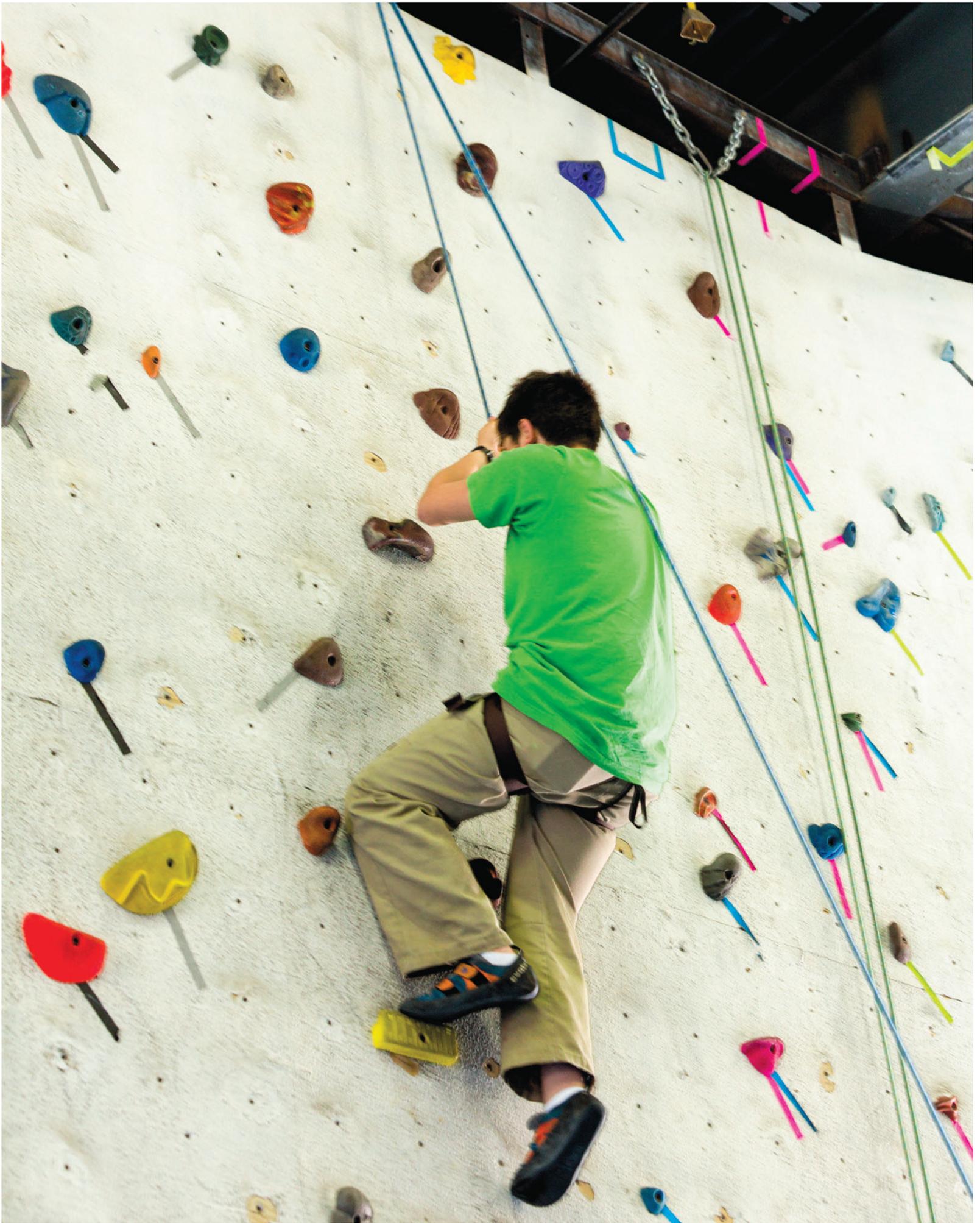
Maintaining his blood sugar control requires constant vigilance and dozens of decisions each day. When Conte plays football or snowboards, he has to avoid a drop in blood sugar that could make him dizzy or pass out. Before eating, he tests his blood sugar and takes insulin, but if food is delayed, the insulin might kick in too soon, causing his blood sugar to drop. Nighttime—when more than half of hypoglycemic (low blood sugar) emergencies occur—is especially perilous. If he wakes up with symptoms of hypoglycemia, he tests his blood sugar and eats a snack. “It’s kind of a burden,” he said. “Everything in my life revolves around it.”

Handling his diabetes is about to change. The climbing session was part of a four-day clinical trial in which Conte and four other teenagers with type 1 diabetes took those sensors and pumps—which when combined with a dosing algorithm are known as an “artificial pancreas”—for a test run. Rather than a bio-medically engineered organ made of tissue, the artificial pancreas is a system of devices and software that transmits his blood glucose level readings to the device that controls insulin delivery. Wearing the sensor and pump doesn’t interfere with Conte’s normal activities—including climbing the rock wall, playing football, or sleeping—and the devices are worn under his clothing, so nobody knows they’re there. Yale researchers have been studying the artificial pancreas for the last decade, but this spring was the first time it was tested in pediatric patients outside the hospital—here and at Stanford University and the Barbara Davis Center for Childhood Diabetes in Denver.



ABOVE The artificial pancreas is a system of devices and software that transmit blood glucose level readings to a device that controls insulin delivery. Ten years in the making, it was developed by physicians and researchers at the School of Medicine.

OPPOSITE Anthony Alvarez also participated in the four-day clinical trial last spring. The artificial pancreas works with an insulin pump to adjust delivery every five minutes in response to glucose levels.



CLOSING THE LOOP

Most of the 35 million people around the world who have type 1 diabetes inject themselves with insulin several times a day or use an insulin pump. The pump, which is programmed to deliver tiny doses of insulin, has advanced diabetes treatment. It sometimes works with a continuous glucose monitor (CGM) that has a sensor like the one Conte wore. Both devices are approved by the Food and Drug Administration (FDA) but work independently of each other. The artificial pancreas closes the loop between the two (it's sometimes referred to as a closed-loop system) by allowing the pump to adjust insulin delivery every five minutes in response to the body's glucose levels. "The ability of the system to self-adjust automatically while patients go about their daily lives would really be transformative in the lives of people with diabetes," said Stuart Weinzimer, M.D., professor of pediatrics at the School of Medicine. Weinzimer and his colleagues have been working on an artificial pancreas for the last 10 years, with support from the Yale Center for Clinical Investigation. The device tested last spring, developed by Medtronic, is being tested at 10 centers (of which Yale is one) in a phase III clinical trial that is expected to lead to FDA approval in 2017.

The path to the artificial pancreas began in the late 1970s, when researchers found better ways to monitor and control blood glucose levels. With the advent in 1977 of the hemoglobin A1C test, known simply as A1C, doctors could analyze blood sugar control over a period of two to three months, providing a longer view than isolated blood glucose readings taken during clinic visits. The insulin pump—first tested in a clinical trial at Yale in 1979—more closely resembled the way the pancreas produces insulin by delivering small doses throughout the day with larger doses at meals. By the early 1980s, home blood glucose monitoring had replaced urine testing, and synthetic human insulin began to replace animal insulin. But diabetes remained difficult to manage. "In those days, when we started to be able to measure more accurately how well controlled our patients were, most of the numbers would have been viewed today as totally unacceptable," said Robert Sherwin, M.D., the C.N.H. Long Professor of Medicine, who was on the team that first tested the insulin pump. The pump, which gave patients better glycemic control, gained traction in the

early 1990s when the landmark Diabetes Control and Complications Trial showed that controlling blood sugar levels reduced such diabetes-related complications as blindness, kidney failure, and neuropathy. The next step was to replace a finger stick every few hours with a sensor that would measure glucose continuously. "As long as insulin delivery was not linked to changes in blood sugar, no regimen would be perfect," said William Tamborlane, M.D., professor of pediatrics (endocrinology), another member of the Yale insulin pump team.

Sherwin tried to interest medical device companies in developing a sensor, but they weren't ready to make a financial commitment. Eventually Tamborlane, who was also keen to develop a sensor, began working with Medtronic to test a CGM device that received FDA approval in 1999. In 2002, he recruited Weinzimer to Yale to look at the possibility of combining the sensor with a pump to develop an artificial pancreas.

A STUDY LAUNCHES A PROJECT

While their experience with the pump gave Yale researchers a head start, other centers were also interested in developing an artificial pancreas. In 2006, researchers at the University of California, Los Angeles, published the first study that combined sensor data with an algorithm to adjust insulin infusion automatically. However, there was an inherent delay in insulin delivery: while insulin-producing cells in the pancreas read glucose levels every few minutes and secrete insulin directly into the bloodstream, the probe and the pump work via the fluid surrounding tissue, so there is a delay in both reading blood sugar levels and delivering insulin into the bloodstream. Still, the study, which showed that the system could work in adults, piqued the interest of the Juvenile Diabetes Research Foundation (JDRF), which then launched the Artificial Pancreas Project. The project had two arms: a large clinical trial of CGMs co-chaired by Tamborlane, which showed that the devices improved blood glucose control; and another, involving Yale and four other academic sites, to develop an artificial pancreas system.

Type 1 diabetes is typically diagnosed in children, so the next step was to study a closed-loop system in pediatric patients. In 2008, Weinzimer published the results of a study involving 17 children who used an

Joanne Conte, mother of Jacob, 15, says that with his participation in the clinical trial, “He’s making history.”

artificial pancreas in the hospital. A closed-loop system, the study showed, keeps blood sugar stable overnight but can’t deliver insulin fast enough at mealtime. The solution was a manually administered extra dose at meals, a concept that is incorporated in the Medtronic device currently being tested.

Weinzimer presented the findings of the pediatric study at the national JDRF conference. “People were crying,” he said. The artificial pancreas offered hope to parents who stay up at night worrying about hypoglycemia, which can lead to unconsciousness and even death.

Compared to today’s artificial pancreas systems—several are in development, but Medtronic’s is furthest along—the early systems were cumbersome. The sensors were much larger, and a radio transmitter had to be taped to the body and connected to a receiver plugged into a laptop. Today, the components are compact and the systems use wireless technology to transmit sensor readings.

A NEED TO WORK TOGETHER

Research is often a collaborative effort, and nowhere is this teamwork more evident than in the development of the artificial pancreas. “At first, we all did our own thing,” said Weinzimer. “Now we’re realizing that in order to demonstrate the safety and efficacy of these devices on a large scale, we need to work together.” Researchers at the University of Virginia; Boston University; the University of California, Santa Barbara; the University of Cambridge; Schneider Children’s Medical Center of Israel, and elsewhere are testing devices and designing sophisticated algorithms to fine-tune different systems. Yale researchers have often been at the forefront of these efforts. Weinzimer showed that the artificial pancreas effectively controls nighttime hypoglycemia, while Jennifer Sherr, M.D., assistant professor of pediatrics (endocrinology), is looking for ways to increase the system’s effectiveness at mealtimes. Says Francine Kaufman, M.D., Medtronic’s chief medical officer and vice president for global medical, clinical, and health affairs, “We rely on an institution like Yale with the capability of their investigators, which is immense, to be a push-and-pull with us.”

The artificial pancreas is based on two devices that already existed, yet at times, progress has been frustratingly slow. Resolving safety issues—such as



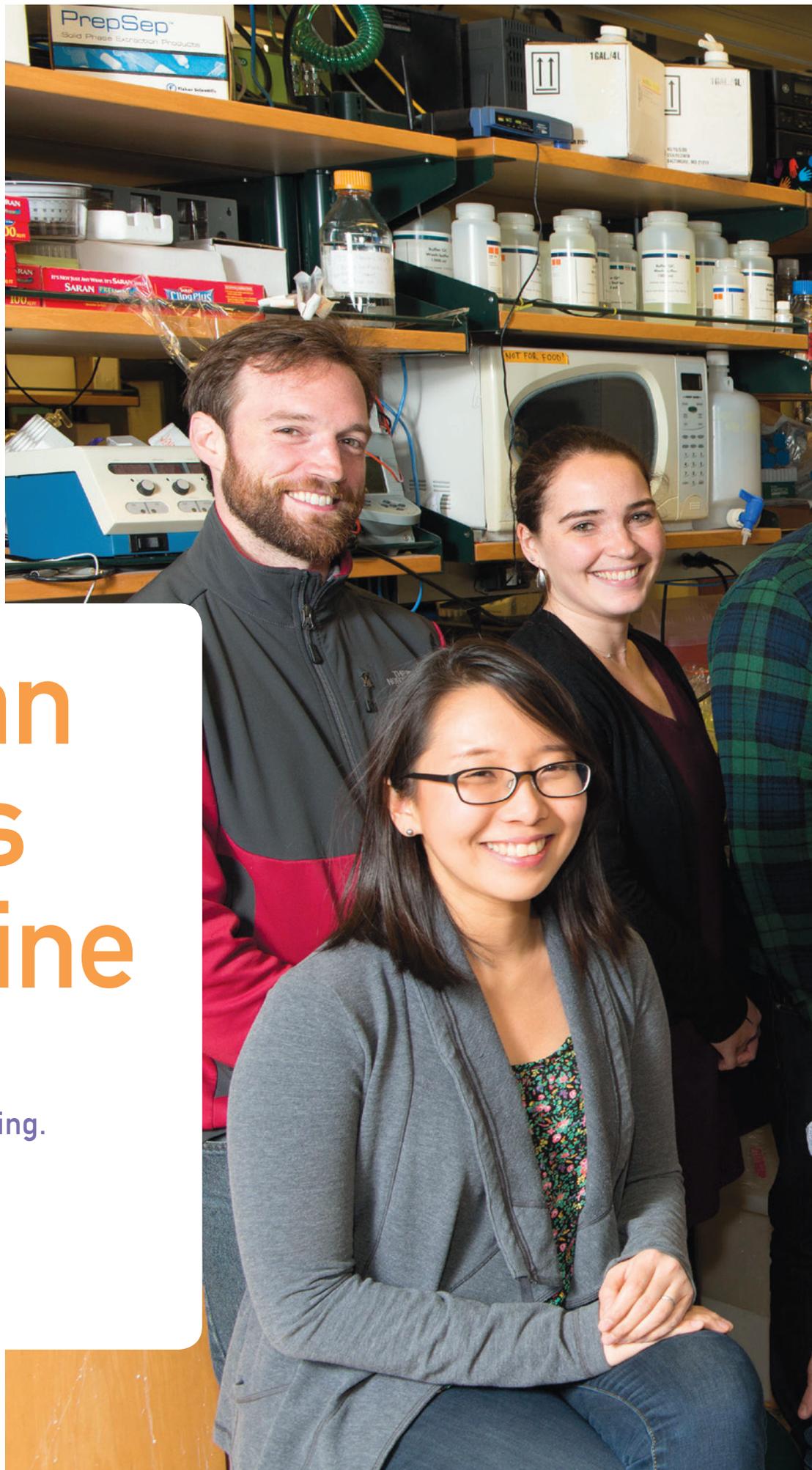
delivering too much or too little insulin—was a major hurdle. Now increasingly tech-savvy patients are increasing the pressure to bring a system to the market. In fact, the ability to tap into sensor data remotely began with a group of diabetes patients and family members who developed a software program to hack into sensor data via a smartphone or computer.

There is also a pressing need to improve diabetes treatment despite the advances over the last 25 years. The recommended target hemoglobin A1C level is less than 7 percent for adults, and less than 7.5 percent for those under 19, according to the American Diabetes Association. Yet a recent study by the T1D Exchange, a network of more than 70 clinics dedicated to type 1 diabetes treatment and research, showed that the average adult A1C is 8.4 percent, with adolescents averaging 9 percent.

In clinical trials, the artificial pancreas helps patients manage their blood sugar better with less effort. “He had the best control while he was on this closed-loop system than he’s had in the past nine months,” said Nicole Liedke, whose 15-year-old son was part of last spring’s clinical trial.

When the first iteration of the artificial pancreas hits the market, the device won’t be totally automatic. Patients will still have to instruct the pump to provide a dose of insulin before meals to maintain optimal blood sugar control, and the sensor has to be recalibrated twice a day. But for patients like Jacob Conte, letting go of the reins a bit, especially at night, will be life-changing. His mother, Joanne, who also has diabetes, was with him during the clinical trial. “He’s making history,” she said, as tears welled up in her eyes. “For him and for our family, this was an unexpected opportunity of a lifetime.” */yale medicine*

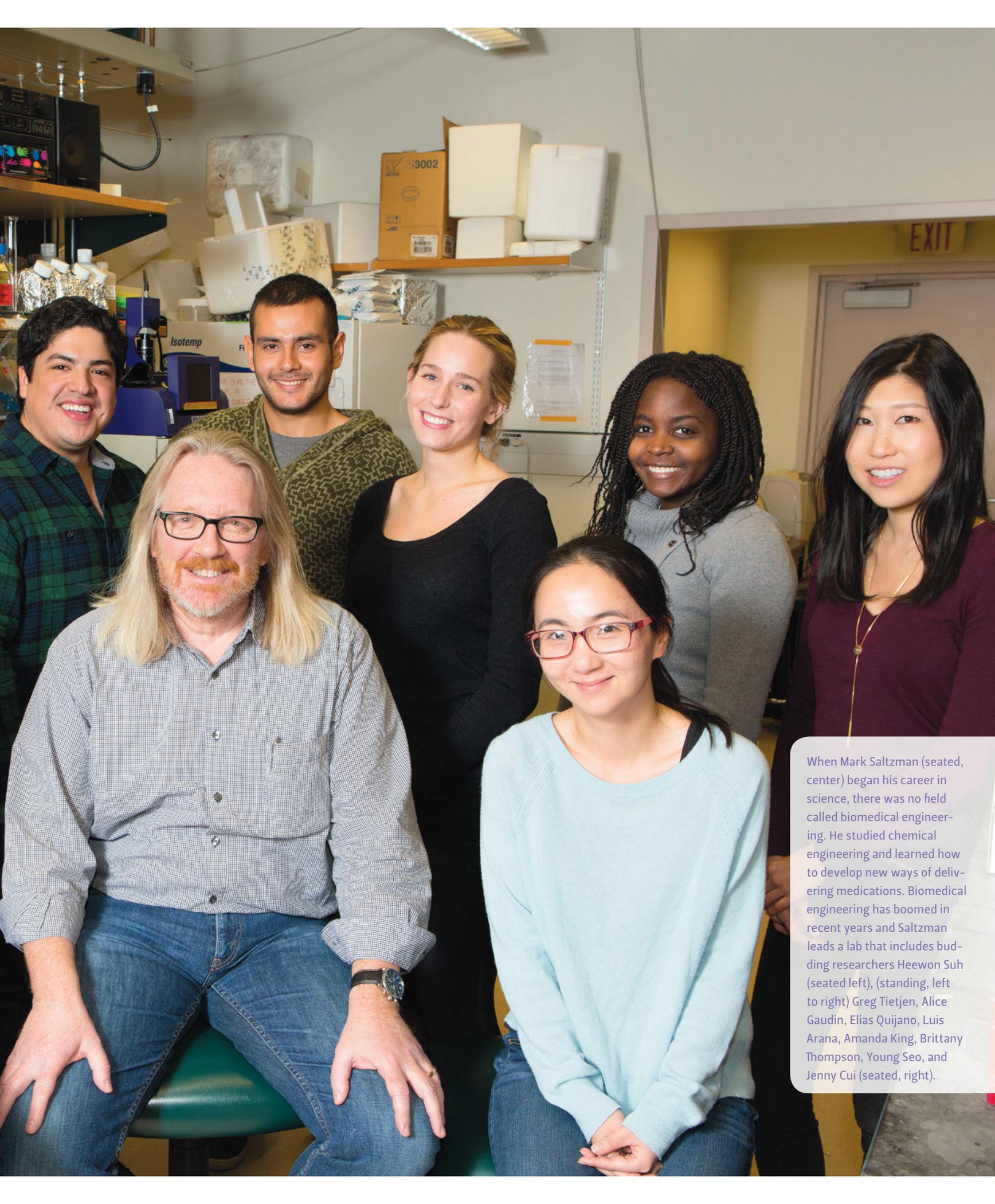
—Jill Max is a freelance writer in Trumbull, Conn.



Human body as machine

How Yale launched
the Department of
Biomedical Engineering.

By Christopher Hoffmann
Photographs by Harold Shapiro



When Mark Saltzman (seated, center) began his career in science, there was no field called biomedical engineering. He studied chemical engineering and learned how to develop new ways of delivering medications. Biomedical engineering has boomed in recent years and Saltzman leads a lab that includes budding researchers Heewon Suh (seated left), (standing, left to right) Greg Tietjen, Alice Gaudin, Elias Quijano, Luis Arana, Amanda King, Brittany Thompson, Young Seo, and Jenny Cui (seated, right).

To understand biomedical engineering, says Jon S. Morrow, Ph.D., M.D. '76, HS '77, FW '80, chair and Raymond Yesner Professor of Pathology, one must start in the 1970s. The tools of the time confined research to such narrow areas as a single protein or gene. "We called it the streetlight phenomenon," he said. "You could only study what you could see or measure, and it was very limited." That began to change in the mid-1980s and into the 1990s. Advances in computers, computation, imaging, biology, and the completion of the mapping of the human genome in 2003 enabled a far deeper understanding of biological processes. Suddenly, scientists could view and measure much more. "You've got these massively parallel technologies that allowed you to see the whole landscape of processes in large scale," Morrow said. "Instead of a streetlight, you had a floodlight."

This deeper understanding elicited an "aha" moment—the human body looked more and more like a hugely complex machine. Researchers started applying engineering principles to biology and clinical treatment. "People began to realize that a biological system is just a complicated device, and that the engineering and computer science side of things has solutions," Morrow said.

By the late 1990s, biology and engineering had merged into a new and exciting discipline with the promise of everything from artificial limbs and organs to individualized drug therapies, from medical devices to cures for genetic diseases.

Universities around the nation were creating departments in this innovative area, which held enormous promise for advancing medical practice and biomedical research. How would Yale respond?

Yale already had a head start. The medical school had become a leader in imaging technology—a key component of the new discipline. And there was interest among faculty and students in pursuing this field. The building blocks were there; the question was how to assemble them.

"Not only did we have experts, not only was it coming together at Yale, but it truly tapped into the needs of the students who wanted to pursue this," said David A. Kessler, M.D., J.D., then dean of the School of Medicine, and now professor of pediatrics at the University of California, San Francisco.

Yale was ready to jump into biomedical engineering, but key questions arose: How should Yale incorporate this new field within its existing areas of study and research? Should it create a new department or a stand-alone institute? If the university inaugurated a department, should it be part of the medical school or the Faculty of Arts and Sciences?

Kessler and the provost at the time, Alison F. Richard, Ph.D., appointed nine senior faculty members from the medical school and the graduate school to form a panel to explore the possibilities.

After nine months of study, the committee issued its report in August 1999, recommending the formation of a biomedical engineering department within the Faculty of Arts and Sciences and tied to the medical school. The committee rejected the stand-alone model favored by some institutions. "They become insular," said Morrow, who served as one of the committee's two co-chairs along with Bruce McClennan, M.D., professor emeritus and biomedical imaging. "They talk to themselves. You never learn anything by talking to someone who does the same thing you do."

The new department would have its own faculty; and faculty from the medical school and elsewhere at Yale would hold secondary appointments in biomedical engineering. "That was a very important piece, allowing faculty the freedom to participate across schools and disciplines, and across graduate and professional and undergraduate boundaries," Kessler said.

The university, including then-President Richard C. Levin, endorsed the committee's recommendations. "Everyone got behind it," Kessler said. "It was across Yale. Nobody owned it and yet everybody owned it."

WE DON'T WANT TO BE AN AVERAGE PROGRAM

Yale's new Department of Biomedical Engineering opened its doors in 2003 within the School of Engineering and Applied Science. The university lured W. Mark Saltzman, Ph.D., the Goizueta Foundation Professor of Chemical and Biomedical Engineering, and Cellular & Molecular Physiology, from Cornell University to serve as chair. When Saltzman graduated from Iowa State in 1981, biomedical engineering was not yet an established field, so he earned his undergraduate degree in chemical engineering. A pioneer



In 1999, pathologist Jon Morrow co-chaired a committee to determine whether Yale should create a department dedicated to biomedical engineering. Advances in computers, computation, imaging, biology, and the completion of the mapping of the human genome in 2003, says Morrow, enabled a far deeper understanding of biological processes and helped create the field.



Elias Quijano got hooked on biomedical engineering while a student at Yale College. Now a first-year student in the M.D./Ph.D. program, he's working in Saltzman's lab on new ways to deliver HIV medications.

in drug delivery and tissue engineering systems, Saltzman relished the chance to build a department from scratch.

“I liked the idea of starting something new at a place where I was pretty confident it would be successful,” said Saltzman, whose team devises novel methods for the controlled delivery of drugs, proteins, and genes.

Saltzman’s initial goals were to hire outstanding faculty and build a curriculum. He hired slowly, knowing that each new person would have a significant effect on the overall department culture. Given that the department would never be very large—today it has about 15 members—Saltzman gave a lot of thought to its focus. “We picked areas that we wanted to excel in,” he said.

Saltzman settled on four: imaging, an area in which Yale was already a leader; biomolecular engineering, Saltzman’s specialty, applying engineering to biological systems; biomechanics, understanding how the body works from a mechanical engineering perspective; and systems biology, studying biological systems as a network of components that interact with one another.

A dozen years later, the department is thriving, Saltzman said. It has developed largely as its founders envisioned—multidisciplinary, collegial, integrated with the medical school, and committed to undergraduate education. The department confers about 40 undergraduate and 10 graduate degrees a year, with an average of 50 doctoral students at some stage of their studies at any given time. “We don’t want to be an average program,” said Saltzman, who ended his 12-year tenure as chair on July 1. “We want to be an outstanding program. Even though we are a young department, I think we are judged as among the best programs in the country. This happened fast for us because of the strength of Yale.”

The program has produced numerous startups and endless innovation. Saltzman cites the work of Rong Fan, Ph.D., associate professor of biomedical engineering. Fan uses nanotechnology to “talk to cells”—employing tiny sensors to take dozens of measurements of an individual cell. Saltzman also mentions Laura E. Niklason, M.D., Ph.D., professor of anesthesiology and biomedical engineering, who joined the biomedical engineering faculty a decade

ago. She credits Yale with allowing her to pursue what some might consider her “outlandish” research in lung regeneration. “Yale’s culture is pretty good at embracing new ideas,” Niklason said.

Saltzman adds that biomedical engineering isn’t just high-tech. A whole other aspect involves engineering a complex device, such as a ventilator for newborn babies, into something so simple and foolproof it can operate in a third-world hospital without reliable access to electricity—a project now underway in the department under the guidance of Anjelica Gonzalez, Ph.D., the Donna Dubinsky Associate Professor of Biomedical Engineering. Gonzalez teaches a course—called Biotechnology for the Developing World—that introduces students to engineering design for low-resource environments in global health.

A PASSION FOR BIOMEDICAL ENGINEERING

In many ways, Elias Quijano embodies the way in which Kessler, Morrow, Saltzman, and others envisioned the program. The son of immigrants from Ecuador and Colombia who never attended college, Quijano arrived at Yale College in 2008 with no interest in science. Needing to fulfill a requirement, he took Saltzman’s course, “Frontiers of Biomedical Engineering.” “In Dr. Saltzman’s class, I developed a passion for biomedical engineering and decided to study it,” Quijano said. “It allowed me to appreciate the contributions that an individual can make to medicine.”

After graduating in 2012, Quijano worked on gene therapies for cystic fibrosis in Saltzman’s lab. Now he is a first-year student in Yale’s M.D./Ph.D. program. “I don’t know exactly where that’s going to take me,” Quijano said, “but I’m confident that my engineering education will provide me with the skills to bridge the gap between the lab and the clinic, between research and medicine.” */yale medicine*

Christopher Hoffman is a frequent contributor to Yale Medicine.

New artery? We can print that

Mark Michalski, M.D., HS '15, on call late one night in 2013, was browsing through *Wired* when he came across an article about 3D printing. It is, as the name suggests, a technology for printing—not ink on a sheet of paper but structures made of diverse materials in three dimensions. Then a radiology resident at Yale-New Haven Hospital, Michalski spent many working hours examining cross-sectional images of the human body and body parts. These images, taken from computed tomography (CT) and magnetic resonance imaging (MRI) scans, depict the body as if it were cut up into many thin slices; taken together, they represent three-dimensional structures. Most of the time, surgeons scroll through these images to create mental pictures of the anatomy that they will meet in 3D only in the operating room. 3D printing, Michalski realized, offered a new possibility: custom-printed 3D models, which surgeons could handle and experiment with, of the structures that they would later cut, stitch, and screw together.

"I thought to myself, 'Well, I have a lot of the raw materials here; I wonder if I can just start printing things,'" recalls Michalski. "Of course, it wasn't that simple."

Since then, Michalski and other radiologists at Yale have used 3D printing to make models in both plastic and plaster of knees, feet, pelvises, shoulder blades—"just about anything bony," says Michalski. Physicians use these models to teach young doctors, plan surgeries, and communicate with patients. In the department of surgical research, doctors are using Bio3D printers, which print live cells, to make not models but the organs themselves, starting with blood vessels. 3D-printed organs, doctors hope, could eventually be used in organ transplants.

Invented in the 1980s, 3D printers build up objects layer by layer. The printer draws out one layer of "ink" (which can be plastic, metal, plaster powder, wood composite, even chocolate); the platform moves downward, and the printer adds another layer atop the first. Successive strata form a three-dimensional object in the same way that a surgeon may use multiple cross-sectional images to envision a 3D form. The printer follows a digital template; and luckily for doctors, software can turn radiological data from MRI and CT scans into these very guides.

In 2013, the raw materials that Michalski had at his disposal included not just troves of radiological scans but also 3D printers in the Yale Center for Engineering Innovation and Design (CEID). The CEID has five 3D printers, three

of which are available to any Yale student or faculty member. These open-access printers, produced by the New York City-based company MakerBot, extrude melted plastic through a heated tip that moves around the platform, creating a design in the same the way a baker writes with frosting on a cake.

In mid-2013, Michalski started printing anatomical objects on the MakerBot printers; his first print was a blue plastic model of the chambers of a child's heart. It was not long before Michalski began to collaborate with the CEID's assistant director, Joseph Zinter, Ph.D., M.H.S. '11, to 3D-print models that could help surgeons. In June 2013, for example, they printed a model of the tumor-invaded tibia of a patient scheduled for surgery at Yale. "We brought the model to the orthopaedic surgeon and said, 'This is the case you have on Thursday,'" recalls Zinter. The model helped the surgeon plan an operative approach that would avoid cutting the patient's patellar tendon, says Zinter.

Based on the success of Michalski's work at the CEID, the Department of Diagnostic Radiology acquired its own 3D printers in 2014. Radiology uses powder printers, a different type of 3D printer from those at the CEID. The powder printer lays down a bed of powdered plaster and the printer tip dispenses glue, causing the powder to stick together where the tip writes. By the end of the print job, the object is essentially buried in plaster dust, which supports the structure as it is being printed; the unused powder is then vacuumed away. (Since mid-2015, Michalski has worked full time for a medical device company, the Butterfly Network, of which he is president. As a research affiliate in the hospital's diagnostic radiology department, though, he maintains his ties to Yale and still does the occasional 3D print.)

Elliott Brown, M.D., HS '12, FW '13, who has led radiology's 3D-printing program since Michalski left Yale, explained how 3D printing helps physicians with their cases. Some things are easy to understand from looking at a radiological image, says Brown, but in tricky cases, "a 3D model is very helpful, because you get depth perception and you get proprioception, meaning you can understand the shape of an object by its feel." Since it's possible to drill into plaster, the models also allow orthopaedic surgeons, who may need to screw a patient's bones back together, to test various surgical approaches.

Beyond models, researchers want to print living organs for patients awaiting organ transplants. In the ideal case, these could be printed from cultured cells taken from the

recipient, eliminating both the wait for a donor organ and the risk of immune system rejection.

This past summer, Yale's department of surgical research joined the effort to 3D-print organs when they acquired a Bio3D printer through a partnership with the bio-printing company Organovo. John Geibel, D.Sc., M.D., M.S., vice chair of surgery, director of surgical research, professor of surgery and of cellular and molecular physiology, and his colleagues began by printing blood vessels using mixtures of rat smooth muscle, fibroblasts, and endothelial cells. In a laboratory hood, the bioprinter lays down the "bio ink," strips of cells resembling ground meat, supported by

strips of a water-based gel. The result: a cylinder of cells around a gel interior, which later can be removed to become the lumen of the blood vessel. The next benchmark, says Geibel, is to implant 3D-printed vessels into rats.

Eventually, Geibel would like to print a liver. During his career, Geibel hopes to create a 3D-printed "assist liver" that could be transplanted into patients and help them survive while they await a donor's liver. "If we get that far," says Geibel, "it's not impossible to think that we could eventually create a complete replacement organ."

—Ashley P. Taylor



A year ago Mark Michalski was finishing up his residency. Now he's heading a startup with millions of dollars in financing and dozens of employees.

ROBERT LISAK

A photograph of medical tools including a blue stethoscope, blue gloves, and a syringe, resting on a wooden surface. The stethoscope is positioned in the upper left, the gloves are in the middle left, and the syringe is in the lower left. The wooden surface is composed of horizontal planks with a natural wood grain.

The tools of medicine

From the first stone blades of the Neolithic age to electronic health records, medical advances have altered the relationship between doctors and patients. And sometimes the technology has overwhelmed the human touch.

By Jenny Blair, M.D. '04
Pamela Moore Photo



There's more than one way to secure an airway. Emergency medicine residents and paramedics learn early about the tools at our disposal to ensure that air gets into a patient's lungs. In my residency, we called these tools airway toys, especially when we tried them out at conferences. The right toy could save a life, and there were always newfangled ones coming along.

So it goes throughout medicine today, with its explosion of new medical devices and the increasingly ubiquitous computer. Biologically, our bodies are largely structured as they were in the Neolithic age, when practitioners used stone blades to carve holes in the skulls of patients—who often survived the procedure. But our instruments are now infinitely more complex, our era the most tech-saturated in history. Many of us owe our lives to the tools of medicine—including those that have brought unforeseen consequences.

Diagnostic devices, for example, have quietly and profoundly changed the doctor-patient relationship. Such devices haven't been around long, and the first ones were comparatively simple. René Laennec's 1816

stethoscope was a wooden tube; it impressed many, not least those who were shy about laying an ear on the chests of buxom women, but some physicians continued to rely on the old technique and on feeling the patient's pulse. In 1868, Carl Wunderlich published a landmark work on monitoring body temperature—a proposal that did not go over well with some of his German colleagues steeped in a philosophical rather than observational approach to medicine. Hermann von Helmholtz used his ophthalmoscope to observe the retina in 1850, wowing colleagues the following year at the Great Exposition in London; in 1868, John Aylwin Bevan wrote to *The Lancet* that he had “discovered” a candle-powered esophagoscope, with which “morbid growths, &c., can be clearly seen.” In the meantime, laboratory medicine was beginning to flower, thanks in part to the mid-19th-century adoption of the medical microscope and advancements in histology over the latter half of that century. Scipione Riva-Rocci gave the world the sphygmomanometer for measuring blood pressure in 1896, and



In the mid-19th century, Hermann von Helmholtz invented the ophthalmoscope, which allowed physicians to observe the retina.

Willem Einthoven introduced the electrocardiograph—it weighed 600 pounds and required five assistants to operate it—in 1902. Wilhelm Roentgen’s X-rays debuted in 1895, and dominated medical imaging until the 1950s, 60s, and 70s saw the first ultrasounds, CT scans, and MRIs.

IS DIAGNOSIS A ZERO-SUM GAME?

Today, among practitioners trained in modern imaging and lab tests, practicing without them can seem almost unthinkable. In 2005, doctors in the United States ordered an estimated 1 billion needle punctures of veins for blood sampling, and by 2007 they were ordering 80 million CTs a year.

Such wizardry can make diagnosis seem like a zero-sum game. Why cultivate the difficult orally transmitted art of physical diagnosis when it’s so much quicker and more accurate to order a study? In the process, costs go up, along with such unintended consequences as radiation-induced cancers from too many CT scans. Or the patient can find himself parceled, body part by body part, system by system, amongst specialists. Or “incidentalomas” pop up, unexpected findings that may not truly warrant treatment, but that can cause anxiety and even harm from further testing. There is also a loss of resiliency, something any tech-saturated physician discovers if she tries practicing in a developing country and realizes she’s forgotten the difference between S₃ and S₄ heart sounds. Back at home, we may be just a power outage or hurricane away from discovering how much our effectiveness depends on these technologies.

In fact, older physicians like Irwin Braverman, M.D. ’55, HS ’56, professor emeritus of dermatology, are concerned by what they see as a loss of physical diagnosis acumen among today’s house staff and attendings—a phenomenon historians of technology call deskilling. When Braverman trained, the most admired senior physicians were highly observant and sharply deductive. With X-rays their main confirmation tool, they had to be. “Physicians were using all their senses plus whatever images they had to pull things together. They were actually pretty good at it,” Braverman says. Today, by contrast, he says, “the doctors’ cognitive skills keep declining because they rely

so much on technology.” (Ironically, at least one group of technologies—simulators—can be used to train students in old-fashioned physical diagnosis skills.)

THE SKILLS HUMANS BRING TO THE TASK

At worst, too much specialty testing can lead to a potentially fatal valuing of abstraction over examination, a sort of cognitive abandonment of the patient. Thomas P. Duffy, M.D., professor emeritus of medicine, recalls a patient with fever, back pain, and neurological findings whose physical exam suggested an epidural abscess—an emergency that requires immediate treatment. Yet that treatment was delayed by the providers’ wish to schedule an MRI to confirm the diagnosis. Somehow, the diagnosis seemed not to exist until a machine said it did.

Yet these tests can uncover crucial information that no physical exam ever could. The question, says historian Joanna Radin, Ph.D., is how to combine knowledge from scan results and the expertise of an experienced physician, rather than reflexively valuing one kind of knowledge over the other.

“There are many, many examples of the ways in which technology has been introduced in a way that doesn’t honor the skill and the richness of knowledge that humans bring to a task,” says Radin, assistant professor in the history of medicine, of anthropology, and of history. “Which isn’t to say that we should reject technology—but it’s worth considering what ways we want to deploy technology.”

WHEN OLD PRACTICES FALL BY THE WAYSIDE

In the 1980s, amid bitter controversy, laparoscopy transformed surgery. Inspired by gynecologists who were employing the technique for tubal ligations in the late 1970s, some pioneering surgeons tried it a few years later for gallbladder removal and were vilified by their colleagues. What was then the standard open surgical technique for gallbladder removal had remained essentially unchanged since the 1940s. Ultimately, though, laparoscopic cholecystectomy became the gold standard for uncomplicated gallbladder disease, driven by patient demand and studies finding advantages like less postoperative pain and shorter hospital stays.

Those attending surgeons who did make the switch had to learn laparoscopy on the job; one study in Germany found that this catching up meant temporarily depriving trainees of available cases.

There's another problem, one that runs parallel to what physicians like Braverman are noting: these days, so many routine cholecystectomies are done via laparoscopy that younger surgeons seldom use the open technique any longer. If complications force them to "convert" to the once-routine open procedure, the surgeons' inexperience could lead to patient harm. In 2012, a group of Harvard surgeons wrote that for that very reason, open cholecystectomy is no longer the safe alternative it once was. Last year, this situation led a team of London historians to reenact 1980s-era open cholecystectomies in a period operating suite with the aid of retired surgeons and nurses, in the hope of preserving knowledge of the older technique.

TECHNOLOGY IS NEITHER GOOD NOR BAD—NOR NEUTRAL

A koan-like axiom of the history of technology proposed by historian Melvin Kranzberg, Radin adds, holds that technology is neither good nor bad—nor is it neutral. Its value is all in how you roll it out.

There might be no more heated debate about that idea today than the one that is taking place over electronic health records (EHRs). As practitioners and hospitals across the country scramble to switch from paper records to meet federal benchmarks, some commentators are pointing out unintended consequences. The promise of convenient record-sharing and streamlined billing, not to mention access to clinical data for studies, has been offset by design flaws (like defaulting to the wrong measurement units); high cost; and the alienating, time-consuming task of data entry. It's a less than ideal doctor-patient encounter, after all, if the doctor is chiefly communicating with a computer monitor.

Yet EHRs, Radin says, can offer an opportunity "to bring the technology more in alignment with what makes a physician an excellent physician." For instance, a system may automatically rate physicians for speed, forcing them to hurry through history-taking. What if, Radin asks, those same programs rated the physicians for the number of adjectives they chose

to describe the patient, guiding them to record a more richly descriptive history?

Lisa Rosenbaum, M.D., made a similar point in an October 22, 2015 *New England Journal of Medicine* perspective piece.

"We measure many things that have no value to patients, while much of what patients do value, including our attention, remains unmeasurable," Rosenbaum wrote. "The technology will support and improve medical care only if it evolves in ways that help, rather than hinder, us in synthesizing, analyzing, thinking critically, and telling the stories of our patients."

Better alignment of technology in this way requires not only conversations between users and designers, but also paying attention to what's being lost, Radin says. "Technology is always about changing human relationships," she says. In the humble stethoscope, there is precedent for such thoughtful design. In its modern form, says Duffy, the stethoscope's tubing isn't the optimum length for good acoustics: if it were, it would be shorter. Rather, it represents a compromise between good acoustics and the need to honor the patient's personal space. The modern stethoscope can create an intimate yet respectful encounter, one that preserves the solemnity and grandeur of professional mastery.

During auscultation, Duffy says, "No matter what I hear, the patient is fascinated and always asks me, 'What did you hear, doctor?' ... This is the beginning of a wonderful trust, because of the hovering, listening, [and] attention. It's quiet, and it has a magic all its own. We shouldn't give that up." *yale medicine*

Jenny Blair, M.D. '04, is a frequent contributor to Yale Medicine.

A hunch leads to an anti-HIV compound

What if there were a natural compound that could prevent HIV infection without damaging living cells? Batzelladine B is such a compound. It was discovered in the late 1990s in the red sponge from the Caribbean. But the process of synthesis, or recreating it in the lab, proved complex and lengthy. Seth Herzon, Ph.D., professor of chemistry and pharmacology, whose lab focuses on natural product synthesis, recently discovered a new and efficient route for synthesizing batzelladine that makes it more readily available for HIV-related research. With the shorter synthesis comes the ability to modify the structures of batzelladine more easily and make improved derivatives with better properties.

Batzelladine's advantage is that it blocks the HIV protein GP120 as it tries to bind with CD4 receptors on the membranes of immune system T cells. Once the protein binds, the virus then injects its genomic information into the cell where it replicates, bursting the T cell and spreading infection. Batzelladine binds to the T cell's CD4 receptors and prevents the HIV protein from fusing to the cell membrane.

Herzon's team, which included postdoctoral associate Brendan Parr, Ph.D., and graduate student Christos Economou, hoped to find a faster way of synthesizing batzelladine. One hurdle was that batzelladine contains nitrogen, an element with conflicting attributes. It helps compounds interact with biological systems, but it can also be unpredictable—requiring extra steps to temper its reactivity. So the team used stable ringed compounds called pyrroles as the molecular starting point. "Making this connection allowed us to develop a very short route that used about half of the steps other people have needed to create similar structures," Herzon explained.

Throughout the process Parr and Economou worked through each reaction and then met with Herzon to brainstorm changes. "We began with what we thought would happen and then ran the reaction. But as is common in synthesis, what we thought would happen usually didn't occur," said Herzon. "First, we had to understand what had happened. Then, we tried to adjust how we were thinking about the structure in order to think of new reactions that might do what we wanted them to do." For example, batzelladine consists of two fragments. While the first fragment was created quickly, it took eight or nine approaches to the second fragment before finding one that worked.

Just as no plan of battle survives the first shot, experiments require some artistic capacity and intuition. "It takes a bit of faith, and willingness to go on your hunches," he

said. For example, they had a hunch that they could control nitrogen's unpredictable nature until the last step in the plan. This allowed them to consolidate 10 discrete chemical reactions into a single step. "We didn't initially plan this," Herzon said. "But as the synthesis evolved we recognized that [multiple reactions] were possible and we were able to go for it."

Once the synthetic plan was solidified, it was important to ensure that each step and reaction yielded the maximum amount of the chemical building block for the next step in the process. Though time-consuming, this phase resulted in a synthesis that requires only 15 steps and provides a good quantity of batzelladine.

The project took about 18 months; batzelladine can now be synthesized in about two weeks. This September, an interdisciplinary team, headed by Karen Anderson, Ph.D., professor of pharmacology and of molecular biophysics and biochemistry, began conducting further HIV research on batzelladine.

—Katherine L. Kraines



Seth Herzon discovered a compound found in red sponge that could prevent HIV infection without damaging living cells.

Greek drama's lessons for veterans

A classics professor helps veterans of war find their voice through literature.

By Karen Zusi

It's the fifth century BCE, and Athens is in turmoil. Civil war, plague, and revolts against the Persian Empire have left the countryside in tatters. By the end of the century, half the population is dead and the city has emptied its treasury battling Sparta in the Peloponnesian War—but for

the artistic Athenians, even in troubled times, theaters remain open and festivals are celebrated every year to honor the gods. “Why on earth does this stuff continue? It was regarded as so important, and so central to public life, that it was the last thing that they were going to stop doing,” said

Peter Meineck, Ph.D., clinical professor of classics at New York University, during his lecture in August at summer Psychiatry Resident Grand Rounds, “Combat Trauma and the Ancient Greeks: Does Ancient Greek Literature Reflect a Society Dealing with the Stresses of War and Can It Be Used to Help the Veteran Community Today?”

In the midst of conflict and disease, Athenians found solace in their theaters. Sophocles, Euripides, and Aeschylus wrote the plays we remember today as highlights of Greek tragedy: *Antigone*, *Oedipus Rex*, *Medea*, *Ajax*, to name a few, in addition to Homer's *Odyssey* and *Iliad*. These playwrights told legends of Greek heroes—heroes dealing with insanity, depression, anger, and

homecomings tainted by the traumas they had experienced in mythical wars.

Plays were performed in large open-air spaces by actors hiding their faces behind masks. Meineck posits that the whole affair was a visceral, cathartic experience not found in today's entertainment industry, where audiences are expected to keep their emotional reactions private. The ancient theaters

[The sea battle near Salamis was a decisive victory of the Greco-Persian War in 480 BCE, when Greek city-states united under Themistocles defeated King Xerxes of the Persian Empire. The 19th-century German painter Wilhelm von Kaulbach depicted the battle that took place between the Greek mainland and the island of Salamis.](#)



also served as a place of healing; they were often situated next to hospitals and healing centers. “It was their form of mass cultural therapy,” Meineck said.

Given the history of ancient Greece, these dramas would have been written, performed, and viewed by combat veterans—and now, Meineck works to connect modern-day veterans with the classics. “Even if they don’t know anything about the Greeks, they get it,” he said. “[The plays] speak to combat veterans, and I think they make it okay for combat veterans to speak for themselves, if they want. They know that these are culturally valued artifacts—so if these culturally valued artifacts seem to talk about their experiences, it actually creates an environment where it’s okay for them to talk.”

For the last eight years, Meineck has directed an organization called YouStories, which brings veterans to the stage to perform Greek tragedies and connect with civilian audiences in a nuanced way. The program isn’t offered by trained therapists, but Meineck often hears that performing together has helped veterans process their experiences. The program also gives younger men and women returning to the United States from Iraq or Afghanistan an

opportunity to connect with those who may have served in Vietnam or Korea. Such informal mentorship wasn’t part of his original vision, but Meineck said it’s helped create a deeper sense of community. “I try to be really honest about what we’re trying to do, which is really just create a conversation,” he added.

Meineck, a native of Great Britain, served in the Royal Marine Reserve himself as a teenager during the Cold War, though he never saw combat. But he has met countless combat veterans who understand Greek tragedies on a level different from that granted by years of academic study. Some have found personal moments of catharsis in reading the ancient works: “One Vietnam veteran really broke down and said, ‘I thought I had dealt with this. After 40 years, I thought it had been dealt with,’” recalled Meineck. “And it was very shocking to him that it hadn’t been.” Their experiences allow veteran-actors to bring a new depth to the plays, offering an intensity and wisdom that even the best civilian actors might otherwise be missing. “You pick up the vibe of these men and women,” said Meineck. “They have told me that they’re getting to speak through this drama—and it’s really quite indescribable, but it’s remarkable.”

As long as humans have waged war, they have suffered from the psychological trauma of the battlefield. In World War I this trauma was known as “shell shock.” By the time of World War II it was called combat stress reaction or battle fatigue. Throughout history artists have depicted the horrors of the battlefield in paintings, plays, novels, songs, and film.

RIGHT During the Civil War, reactions to the battlefield were known as “soldier’s heart.” In 1862, two photographers hired by Matthew Brady produced the first images, taken after the Battle of Antietam, to show dead bodies on the battlefield. The “Bloody Lane” was a sunken road so crowded with dead bodies that it slowed the Union advance.

BELOW The Imperial and Royal War Press Bureau of the Austro-Hungarian Army, produced thousands of photos from the front lines, including this one of a medical aid station.



RIGHT The term “posttraumatic stress disorder” came into use in the late 1970s to describe the trauma of veterans of the Vietnam War. U.S. Army helicopters covered a South Vietnamese infantry advance with machine gun fire in March 1965, as they moved to attack a Viet Cong camp northwest of Saigon.





Alum sees place for e-cigarettes in smoking cessation

IN THE FIELD OF TOBACCO CONTROL, Michael B. Siegel, M.D. '90, is a lone wolf. The Boston University public health professor stands at odds with most of his public health colleagues on one matter: e-cigarettes.

“Why so many public health groups are trying to block them is beyond me,” said Siegel. “Cigarettes are highly toxic and kill 400,000 people a year, while e-cigarettes are not particularly harmful and they’re helping many people quit.”

During his medical internship at Berkshire Medical Center in Pittsfield, Mass., Siegel saw that most people are admitted to the hospital for preventable reasons: smoking, alcohol, drugs, poor diet, and lack of exercise. “We can counsel every patient who walks in the door about smoking,” he said, “but wouldn’t it be more effective to have mass public health campaigns that reduce smoking? You’ll have a much larger impact on the public’s health.”

That’s what led him to a fellowship in the Centers for Disease Control and Prevention’s Office on Smoking and Health after residency. “That

experience convinced me that I wanted to pursue an academic career in public health.” But smoking cessation had been Siegel’s passion since he was an undergraduate at Brown. There he lobbied to make Rhode Island the 13th state to ban smoking in the workplace. During medical school, he lobbied for tobacco control laws in Connecticut.

Siegel believes that e-cigarettes can make the big public health impact he’s been waiting for. Users inhale vaporized liquid nicotine from the battery-operated devices that sometimes resemble cigarettes. Nothing burns. There is no tobacco, no smoke, only vapor. Hon Lik, a Chinese pharmacist and former heavy smoker, invented e-cigarettes as a smoking cessation device in 2003 after his father died of lung cancer. Since the products came to the United States in 2007, the FDA has regulated them as tobacco products. A misnomer, Siegel laments, that undermines the good the products could do.

“More than 90 percent of smokers who try to quit fail. E-cigarettes work for them because they simulate actual smoking behavior—the hand motion, the throat hit, the holding of the cigarette, even some of the social aspects. You can [vape] with others in a group,” Siegel said.

But the devices are not FDA-approved for smoking cessation, so ads can’t say that vaping is safer than smoking or that e-cigarettes help smokers quit.

“You have a product that could help the public, and you’re not allowed to tell them what it does,” Siegel said. “No one is arguing that e-cigarettes shouldn’t be regulated. The question is, How?”

To sell their wares, e-cigarette makers resort to the same advertising themes that tobacco companies use—sex, freedom, and independence. This, said Siegel, tells smokers who might

A full-page photograph of Michael Siegel, a man with short grey hair and glasses, smiling at the camera. He is wearing a light purple long-sleeved button-down shirt, a striped tie with purple, blue, and white diagonal stripes, and khaki trousers. He stands on a city sidewalk with his hands in his pockets. In the background, there are brick buildings, a street with traffic, and a black lamppost with two white globe lights. The sky is a clear, pale blue.

Michael Siegel's thinking on e-cigarettes runs counter to prevailing views in the public health community. He believes that they are safer than cigarettes and can help people quit smoking.



ONLINE EXCLUSIVES

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Looking to her clerkship years, a med student learns about New Haven

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otherwise try e-cigarettes that these devices are just more of the same.

Labeling e-cigarettes as tobacco products, Siegel worries, amounts to a missed opportunity for smokers. “The best thing is to quit smoking completely, but very few people are able to do that.” For the rest, Siegel argues, e-cigarettes are far less harmful than tobacco cigarettes. “You’re no longer inhaling tens of thousands of chemicals from tobacco smoke, including more than 60 known human carcinogens.”

Siegel doesn’t argue that the products are completely harmless. Nicotine alone may pose heart risks. It’s about harm reduction for those who would otherwise smoke for life, he said. A 2015 review published in *BMC Medicine* cites emerging evidence that smokers who switch to e-cigarettes show improvement in airway function and respiratory symptoms. A recent study in the *International Journal of Environmental Research and Public Health* showed similar outcomes in smokers with asthma who switched to vaping.

“There is a deeply entrenched ideology in tobacco control that, one, anything that looks like smoking could not possibly be endorsed, and two, any addiction is terrible,” Siegel said.

This makes would-be vapers think, “Why bother?” Siegel adds.

Perhaps the only issue on which Siegel and his colleagues see eye to eye is kids.

E-cigarette opponents argue that the products should be banned or tightly regulated so that kids don’t take them up. “I’m sure they will ban the sale of these products to minors, and to me, that’s a no-brainer. It makes sense.”

But that’s where Siegel’s and his peers’ common ground ends. E-cigarette opponents argue that vaping breeds nicotine addiction and is a gateway to smoking. “The majority of youth who use e-cigarettes are already smokers. There are some who are non-smokers who are just experimenting with these products.”

Siegel’s adversaries want to keep e-cigarettes from kids by hiding them from view completely. Siegel said just quit telling kids e-cigarettes are sexy and tell them what they really are.

“You don’t see kids using nicotine patches and nicotine gum. That’s because they know that these are for smoking cessation. And that’s not a cool thing.”

—Sonya Collins



Helping doctors help themselves

Rows upon rows of manila file folders sit like soldiers on the credenza behind the desk of DeWitt “Bud” C. Baldwin Jr., M.D. ’49, where they have a bird’s-eye view of Chicago’s urban landscape and Lake Michigan. Their contents fuel the research that the

93-year-old Baldwin conducts as a scholar in residence at the Accreditation Council for Graduate Medical Education (ACGME). Every day and often on weekends too, he reads, thinks, and writes in his 24th-floor office, often about job burnout. Not for his personal well-being, but for the growing number of trainees pushed to the brink by their chosen profession.

Ironically, doctors—who are drawn to helping others—suffer high rates of depression, substance abuse, divorce, and suicide. Some 40 percent of medical residents report feelings of depression. As many as a dozen take their own lives every year, said Baldwin.

“Medicine today has become too complex for the still-rigid way we train physicians, leading to an intense, nonsupportive learning environment,” said Baldwin, who joined the American Medical Association in the mid-1980s to head the Office of Education Research. There he launched pioneering studies that revealed disturbing findings: Medical students and residents routinely endured a great deal of mental and physical abuse. “Years ago I said, ‘It’s not just the hours [residents work] but what goes on in those hours that matter.’”

Hired by the ACGME in 2002, Baldwin focuses on better understanding the resident experience. His research helps to develop strategies and guidelines that allow young physicians to heal themselves

or at least let others help them. To that end, Baldwin encourages trainees to speak up via a variety of methods, including anonymous surveys to measure satisfaction and define the best learning methods.

“Bud has provided a venue for the voice of residents,” said Nick Yaghmour, M.P.P., a research analyst at the ACGME who assists with Baldwin’s studies. “He has brought the importance of physician communication and self-care into the discussion.”

A noted champion of humanism in medical education, Baldwin has long advocated reforming medical school curricula. For him, such soft sciences as sociology and psychology are as important to shaping future physicians as the hard sciences of biology and chemistry. He promoted the once-radical notion that budding practitioners must learn to appreciate that many factors influence health, from socioeconomic status and cultural differences to gender and race. A maverick throughout his more than 60-year career, Baldwin practiced what he preached at four traditional and two new medical schools he helped to establish in Connecticut and Nevada. One of the founders of the Association for the Behavioral Sciences and Medical Education, he received the organization’s lifetime achievement award in 2007.

This physician educator didn’t stop at enhancing the

development of well-rounded compassionate doctors. He also introduced the concept of inter-professional teamwork: teaching physicians and other health providers to care for patients with a collaborative team approach, for which he has received two honorary doctorates. “I learned to think health instead of disease,” said Baldwin, who applied this model at the University of Washington in Seattle in the 1950s. “When it comes to disease, doctors are the experts. When it comes to health, doctors don’t know much. It’s the nurses, social workers, nutritionists, dentists, and occupational therapists who help make people healthy.” His tenure in the Northwest also proved personally satisfying, as he met his wife, Michele. A French native, she was studying in the United States on a Fulbright scholarship. The couple has two daughters and four grandchildren.

Baldwin credits much of his passion for education to his parents, who believed in experiential, small-group, and problem-based learning. They were educational missionaries in Burma (now Myanmar), where Baldwin lived until age 10. When they returned to the United States in 1933, he said, “They came back with the belief that ‘We have as much to learn as we have to teach’ and were promptly fired by their mission board.”

While Baldwin’s ideas for educational reform for physicians may have started decades

ago, they remain relevant to graduate medical education. In early 2016, the ACGME will bestow the first DeWitt C. Baldwin Jr. award to an academic institution that demonstrates a humanistic culture and fosters a respectful and supportive environment for medical education.

“Bud has taken the temperature of the soul of American residents in ways no one else has,” said Timothy P. Brigham, M.Div., Ph.D., chief of staff and senior vice president for education at the ACGME. “He has touched the lives of literally thousands of physicians and, by extension, thousands of patients who have benefited from the impact of his work.”

—Cheryl SooHoo



At 93, Bud Baldwin is still hard at work, researching the experience of residency and looking for ways to help young doctors in training deal with depression, substance abuse, divorce, and suicide. “It’s not just the hours that residents work, but what goes into those hours that matters.”

Why Nicole Sitkin adds a plus sign to LGBTQI+

WHEN SECOND-YEAR MEDICAL STUDENT Nicole Sitkin speaks, her words flow quickly, her sentences packed with information, just as her professional life brims with accomplishments. In June 2013, the University of California, Davis, awarded Sitkin the University Medal, given to the top graduating senior who excels in academics, community service, and promise of future scholarship. In September 2014, Sitkin was appointed to the Learning Environment Sub-Committee of the Association of American Medical Colleges (AAMC) Advisory Committee on Sexual Orientation, Gender Identity, and Sex Development.

She has co-authored nine peer-reviewed research articles and recently won a \$5,000 medical student leadership award from Women In Medicine (WIM), a national organization that provides medical education and networking opportunities for lesbian, gay, bisexual, transgender, and queer (LGBTQ) female physicians. In November 2015, she earned a Best Poster Presentation award in Public Health at the American Medical

Association interim meeting. Sitkin was subsequently elected to the board of WIM. “Nix has brought energy and clarity to LGBTQ issues, especially as they affect the education, practice, and professional experience of medical students and physicians. She has a voice in national discussions,” said Forrester A. Lee, M.D. ’79, HS ’83, associate dean for multicultural affairs and professor of medicine (cardiology). Sitkin recently sat down with *Yale Medicine* to talk about her work on LGBTQ issues.

How are you involved with LGBTQ issues at the School of Medicine?

Last year I was president of the student group, OutPatient, previously the Gay Straight Medical Student Alliance. One of our first orders of business was to change the name, since it wasn’t inclusive of the wonderful diversity of identities and experiences of LGBTQI+ folks. The “I” stands for intersex, an identity term sometimes used by people who biologically don’t fall into the male-female sex binary. The plus sign is meant to include whatever identities or experiences people may have. Additionally, last year I approached Dean Schwartz [Michael L. Schwartz, Ph.D., associate professor of neuroscience and associate dean for curriculum] with a presentation on LGBTQI health disparities, physicians’ power to perpetuate or mitigate those disparities, and the first LGBTQI physician training guidelines, issued by the AAMC in 2014. That conversation blossomed into an ongoing collaborative effort between faculty, staff, and students to incorporate new and enhance existing LGBTQI health content in the curriculum.

What might a sample of medical education on LGBTQ health look like?

Our idea is to provide training like a spiral staircase.

{ To nominate a subject for Q&A, contact
Yale Medicine, 1 Church Street, Suite 300, New Haven, CT 06510 or email yymm@yale.edu

You start at the bottom with the facts. For example, what do the terms LGBTQ, intersex, and cisgender mean? How does sex differ from gender, which differs from sexual orientation? As students progress, they acquire communication tools, such as by practicing inclusive interviewing with standardized patients. During clerkships, students then have the opportunity to reflect on real patient care experiences and to hone and implement their knowledge and communication skills.

In your experience, do peers feel comfortable being “out” on medical school campuses? There has been limited institutional support for sexual and gender minority individuals at medical schools historically. Fortunately, the culture of medical education is shifting in parallel with society generally, to greater respect and recognition of the lives and identities of LGBTQI folks. That being said, everyone’s experience is different. Some folks may never want to be “out” in a professional context, while it may be very important to others to have their identity recognized. Institutional culture and visible support systems also deeply

affect whether students feel comfortable and safe being out. I know students who are uncertain about whether they can be out in their professional lives. For people who are figuring it out or are coming out, it’s so important to be able to connect. I’m out, I have a partner I’m crazy and open about, and I still benefit so much from interacting with supportive allies and LGBTQ role models and mentors at the School of Medicine. At Yale, we are bringing together faculty, staff, and other resources to provide more visible, accessible support for students.

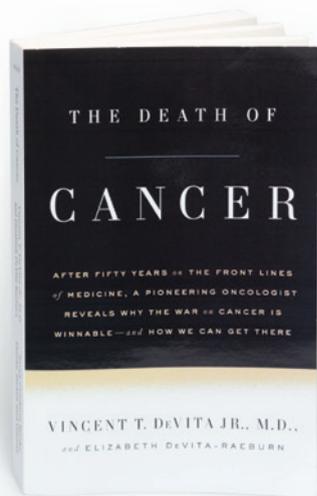
What is your partner, Mariko Zelin, doing now?

Mariko is a gifted research scientist. She’s currently doing research at a start-up company while completing a master’s of science in biotechnology at Northwestern University. She’ll be graduating in December and moving to New Haven. She’s excited to explore the opportunities in the biopharmaceutical industry out here.

What can people do to support the LGBTQI+ community? One of the ideas I’ve talked about with Dean Angoff [Nancy R. Angoff, M.P.H. ’81, M.D. ’90, HS ’93, associate professor of medicine (general medicine) and associate

dean for student affairs] and Dean Lee is what we can do to institutionalize LGBTQI programming in terms of formal curriculum, support services, and educational opportunities for the whole health campus. We are actively seeking to bring together people, LGBTQI and allies, and to identify resources to support this work. We welcome the involvement of any Yale community members interested in LGBTQI health.





Winning the war on cancer

By Cathy Shufro

Vincent T. DeVita Jr., M.D., HS '66, had “zero interest in cancer” when he began a fellowship at the National Cancer Institute (NCI) in 1963. But he decided that even cancer research sounded better than “getting shot at in Vietnam.”

The Death of Cancer follows DeVita's transformation from a reluctant researcher to a leader in a struggle that he says we're winning. DeVita communicates that same optimism in the hefty subtitle of the book that he wrote with his daughter, science writer Elizabeth DeVita-Raeburn, M.P.H.: *After Fifty Years on*

the Front Lines of Medicine, a Pioneering Oncologist Reveals Why the War on Cancer Is Winnable—and How We Can Get There.

They wrote the book, says DeVita, because, “The people who have put over \$100 billion into the war on cancer have the right to know what was done with it.”

It's a story that DeVita, now 80, has witnessed at NCI and on Capitol Hill, at Memorial Sloan Kettering Cancer Center in New York, and at Yale Cancer Center, which he directed for a decade. At NCI, part of the National Institutes of Health (NIH), he climbed the ranks to serve as director from 1980 to 1988.

His daughter was there, too: “People talk about Army brats, and there was such a thing at NIH. I grew up around all the oncologists,” said DeVita-Raeburn. “I thought all men carried beepers.”

Her mantra was to make the book “relentlessly useful.” It warns that when a doctor is willing to reduce a chemotherapy dose to minimize horrible side effects, or schedules treatments based on convenience rather than the life cycles of cancer cells, that doctor might be knocking out a patient's best chance of survival. It advises readers that no name-brand cancer center, including Yale's, can offer optimal treatment for every type of cancer; different institutions do better with different cancers. It provides recommendations, with the caveat that they'll soon be outdated.

The book begins by describing how DeVita thought through which prostate cancer treatments to suggest to a family friend. It closes with the story of DeVita himself, who suffered “the double curse of being a doctor who gets a disease from his own field.” The book explains how he charted his own cancer treatment. (He says he's doing fine.)

The Death of Cancer illustrates how greed, turf wars, and myopia have often obscured the central goal of

patient survival. Nonetheless, argues DeVita, “The war on cancer is being won, though the general tenor in the press is that it's not.” That may be because reporters focus on short-term setbacks, not the big picture, says DeVita-Raeburn.

Overall cancer mortality has dropped by 25 percent since the 1990s. Due to three paradigm shifts, beginning in the 1960s with the recognition that combination chemotherapies worked better than single drugs, DeVita and colleagues designed a four-drug treatment that for the first time cured patients with advanced Hodgkin's disease, for which he won a prestigious Lasker Award in 1972. At a time when most tumors were treated with surgeries and radiation, the treatment proved that chemotherapy could vanquish cells that escape tumors to enter the bloodstream or organs. The second shift was the advent of targeted therapies, which can turn cancer into a chronic rather than a fatal disease. The third shift derives from new approaches that use a patient's own immune system to quell cancer.

“The best is yet to come,” said DeVita. “I think you're going to see some really startling stuff in the next five or 10 years.”

{ Send notices of new books to
Yale Medicine, 1 Church Street, Suite 300, New Haven, CT 06510 or emailymm@yale.edu

Not by the numbers

LUNCHTIME PAINTING BECOMES A BREAK FROM THE OFFICE. Ni La and Roshni Srivastava, researchers in cardiovascular medicine, were among about 30 Yale workers, ranging from postdocs at the School of Medicine to IT techs to administrative assistants, who spent a lunch break painting in August. Being Well at Yale sponsors the painting class as a way to ease the stress of the workplace.

“We’re looking for a creative way to encourage employees to step away from the office for a little bit, recharge, and reset,” said Lisa Kimmel, manager of Being Well at Yale. Art Plus Studio on Chapel Street hosts the once-a-month painting sessions. Rachel Rasfeld, an instructor at the studio, guided the painters through the process. “It’s like art therapy. We do a painting together, but the point is to relax,” Rasfeld said.

—John Curtis

{ To view a video on the lunchtime art class, visit yalemedicine.yale.edu/art