

Young bioengineers inspired by VA training

Some young scientists can point to a pivotal experience that inspired their career—a fascinating lecture, a successful experiment, an academic award.

Shruti Pai's magic moment came when she broke a piece of lab equipment.

Pai, a graduate biomechanical engineering student at the University of Washington, spends most of her week at VA's Center of Excellence for Limb Loss Prevention and Prosthetic Engineering, where she is studying how to prevent foot ulcers in people with diabetes. She and about a dozen others are currently part of the center's ongoing training program for graduate and medical students.

One day, Pai was working with a load cell—a sensitive piece of equipment for measuring force—when she entered a wrong value and broke the device. She had been worried about her overall progress and now feared being ousted from the program.

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Graduate student Shruti Pai's research focuses on preventing diabetes-related amputations.



With images of her coronary arteries on the monitors above, a patient prepares for surgery to bypass blockages and thereby improve blood flow to the heart.

Heart bypass trial finds better results with older 'on-pump' method

The topic has been hotly debated: Is it safer and more effective to do bypass surgery with or without a heart-lung pump that allows doctors to stop the heart while they operate?

A clinical trial at 18 VA medical centers found that while both methods are generally safe and effective, the more traditional "on-pump" method yields better outcomes after one year. The findings appeared in the Nov. 5 *New England Journal of Medicine*.

"There was good survival in both groups at one year, but the conventional method proved safer and somewhat more effective than the newer off-pump method," said study co-leader Frederick Grover, MD, a cardiothoracic surgeon with VA and the University of Colorado.

After a year, patients in the on-pump group fared better on a composite measure that included death, nonfatal heart attacks, and repeat cardiac procedures. Their vein grafts were also more likely to remain open. The study included follow-up angiograms performed by cardiologists who were "blinded" as to which type of bypass the patients had undergone.

In particular, Grover pointed to the fact that both groups scored equally well a year after surgery on neuropsychology tests. Some experts have believed the on-pump

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Managing antipsychotics' metabolic side effects

More than 8 in 10 VA patients with schizophrenia or other psychotic disorders are prescribed a class of drugs known as second-generation antipsychotics. The drugs are considered an improvement over earlier medications that often caused muscle stiffness, spasms and other troubling side effects. But the newer drugs come with side effects of their own—weight gain, diabetes, high cholesterol.

A 2007 VA report and other research suggested VA doctors could do a better job of tracking and managing the side effects of second-generation antipsychotics. In response, VA's Office of Mental Health Services set up a workgroup to enact a wide-ranging set of recommendations.

A new study based at the Central Arkansas Veterans Healthcare System will add to those efforts. "We anticipate that national implementation of these recommendations will improve care overall, but the improvement is likely to be less pronounced at a substantial number of facilities that are 'stressed,'" explains study leader Richard Owen, MD, director of VA's



Ounce of prevention—Drs. Richard Owen (right) and Jeffrey Smith (center), along with their team, aim to help VA doctors better prevent and manage antipsychotic side effects such as weight gain.

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103 S. Gay Street, Rm. 517
Baltimore, MD 21202
(410) 962-1800, ext. 223
research.publications@va.gov

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Center for Mental Healthcare and Outcomes Research. "These are facilities with fewer resources and more difficulty undertaking quality-improvement efforts."

Owen's team will test a targeted quality-improvement intervention at those sites. Clinicians and leadership at each facility will be kept abreast of the latest research evidence; develop their own plan to monitor and better manage side effects, with help from the researchers; and be given access to quality improvement tools such as VA-Department of Defense clinical practice guidelines and supporting materials; educational pocket-sized cards for clinicians with reminders about dosing and side

effects; clinical reminders in patients' individual electronic medical records; and computer-generated lists for providers that identify all of their patients who are due for side-effect monitoring

Owen says one overarching goal will be enhancing coordination between primary care and mental health clinics.

To measure improvement, the researchers will track the rates at which care teams check patients' weight, body mass index, blood glucose levels and cholesterol levels, and the extent to which patients who are obese or who have diabetes or high cholesterol receive interventions consistent with VA guidelines. —

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method is riskier for cognitive health. According to first author A. Laurie Shroyer, PhD, the findings of the large, multisite VA study contradict findings from earlier studies that showed “some advantages of [coronary bypass] surgery using the off-pump procedure, including quicker recovery and less impact on cognitive function. This study indicated a consistent trend toward better outcomes in patients who had undergone the conventional on-pump technique.”

Study included more than 2,000 veterans with blocked arteries

The 2,203 veterans in the study all had clogged or narrowed coronary arteries, resulting in less blood flow to the heart. This can cause chest pain—angina—and increase the risk of heart attack. In bypass surgery, also called coronary artery bypass grafting, doctors take a healthy piece of vein from elsewhere in the body and sew it in place as a “detour” between the heart and a point in the problem artery below the blockage. As long as the graft remains open—“patent,” in medical terms—and doesn’t close down over time, the heart enjoys a renewed flow of blood and oxygen.

For more than 30 years, most bypass procedures have been done with the use of a cardiopulmonary bypass pump, or heart-lung machine. During an on-pump procedure, the heart is stopped with medication and the machine takes over blood circulation. This allows doctors to work on a still heart.

An alternative, “off-pump” method that has gained some popularity in the past decade is also known as “beating heart” surgery. The heart keeps beating during the procedure and no heart-lung machine is used. Doctors use special devices to stabilize only the small section of the heart where they are stitching in the graft.

Controversy has existed as to which method is safer and more effective. Some studies suggested that using the pump could weaken heart function after surgery, harm the lungs and kidneys, result in more blood use during surgery and longer hospital stays, and bring on problems with memory and thinking. Many experts came to see the off-pump method as enabling a quick recovery, with lower healthcare costs and less risk of cognitive decline.

Recent studies, though, have raised concerns about the newer procedure as well: Is it too technically difficult? Are surgeons sometimes unable to complete multiple grafts on a patient? Are

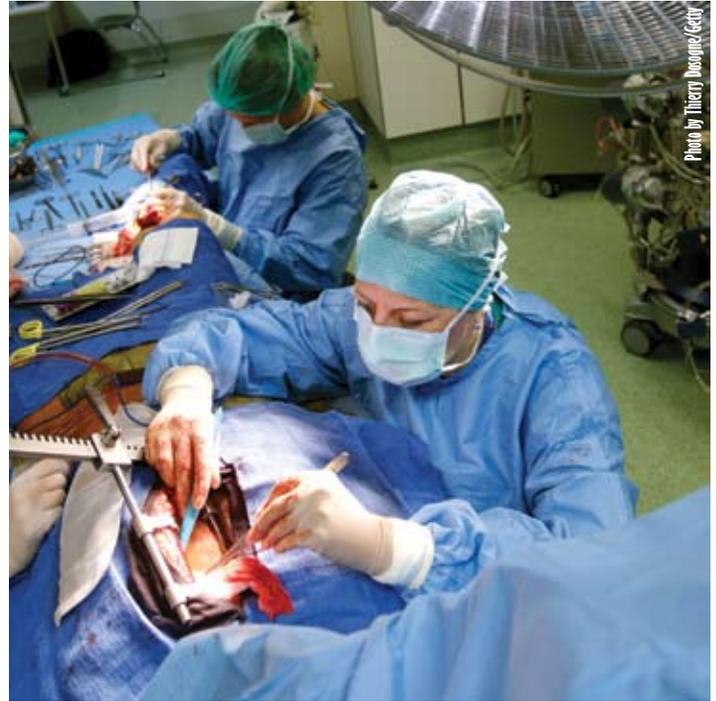


Photo by Thierry Mooney/Getty

Cardiac comeback—In cardiac bypass surgery, doctors remove healthy veins from elsewhere in the body and sew them in place between the heart and blocked arteries to reroute the flow of blood to the heart.

the grafts more likely to fail? And as a result, are patients more prone to heart attacks or repeat procedures?

No studies to date have been conclusive, but the new VA trial results should greatly inform the debate. Grover said he thinks the results may influence cardiology referrals and cardiac surgery practice, but he stresses that individual patient differences still need to be taken into account. Patients with certain risk profiles and patterns of coronary damage, he said, may still be strong candidates for the off-pump method, notwithstanding the general results seen in the trial. —

More about the trial

- The study included 2,203 veterans: 99 percent men, 84 percent white, average age 63. Two-thirds had blockages in at least three arteries. A third were smokers at the time of enrollment in the study.
- VA doctors who performed off-pump surgeries in the study—the more technically demanding of the two methods—had done an average of 120 such procedures.
- The study ran from 2002 to 2008. It was funded by VA’s Cooperative Studies Program and coordinated by CSP’s Perry Point, Md., center.

Nonprofits give critical boost to VA research

Kerstin Lynam oversees a staff of 250 and a budget of \$30 million. Her days can be hectic, but her vision is simple: “We want every veteran to receive the finest research-based care.”

Lynam is CEO of the Veterans Medical Research Foundation, which supports research at the VA San Diego Health Care System. The foundation offers a wide range of services, from administering grants and hiring staff to renovating labs and buying equipment.

“Essentially, we get to know our researchers and their needs and will do whatever is necessary to assist them administratively,” says Lynam.

The San Diego nonprofit is the second largest of 82 such organizations nationwide. The largest is about 500 miles up the California coast, in San Francisco. Authorized by Congress in 1988, the nonprofits have become a powerful engine for VA research nationwide. In fiscal 2008, they took in and paid out close to \$250 million in support of more than 4,000 studies.

“Everything the nonprofits do is designed to support the research and education programs at their facility,” says Barbara West, executive director of the National Association of Veterans’ Research and Education Foundations. “The studies they administer are all VA studies—their research focus is 100-percent VA.”

One example of a grant being administered by the San Diego nonprofit is a \$1.8-million award from the National Institutes of Health to HIV-AIDS researcher Doug Richman, MD, of VA and the University of California, San Diego. His team will study enzymes that enable the virus to stay latent and evade treatment. “It’s a highly innovative area of research, focusing on cure rather than chronic suppression,” says Richman. His lab can be more productive, he says, thanks to support from the VMRF.

“Because the VMRF is based right here at the San Diego VA, they tend to be

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Seed money from Seattle VA-affiliated foundation leads to PTSD breakthrough

The men would sleep only four or five hours a night. The bad dreams came with devastating regularity.

The Vietnam veterans being seen by psychiatrist Murray Raskind, MD, at the Puget Sound (Wash.) VA in the late 1990s needed a treatment for their ongoing trauma nightmares. Nothing seemed to work. Many had turned to alcohol over the years—anything to help them fall asleep.

Raskind had a theory: If he could make their brains less responsive to norepinephrine, a hormone related to adrenaline, that would ease the nightmares. Scouring the literature, he learned of a particular class of hypertension drugs that worked by blocking norepinephrine. Only one, prazosin, could cross the blood-brain barrier. That drug became his focus.

“I simply started using prazosin clinically with veterans who had treatment-resistant PTSD trauma nightmares and sleep disruption,” recalls Raskind. “It worked dramatically well, where nothing else had been helpful.”

Raskind knew the idea had promise. “We thought we had something interesting, but we had to prove it in a well-controlled study.”

Pilot funding would soon come from the Seattle Institute for Biomedical and Clinical Research, one of the 82 nonprofits that foster VA research nationwide.

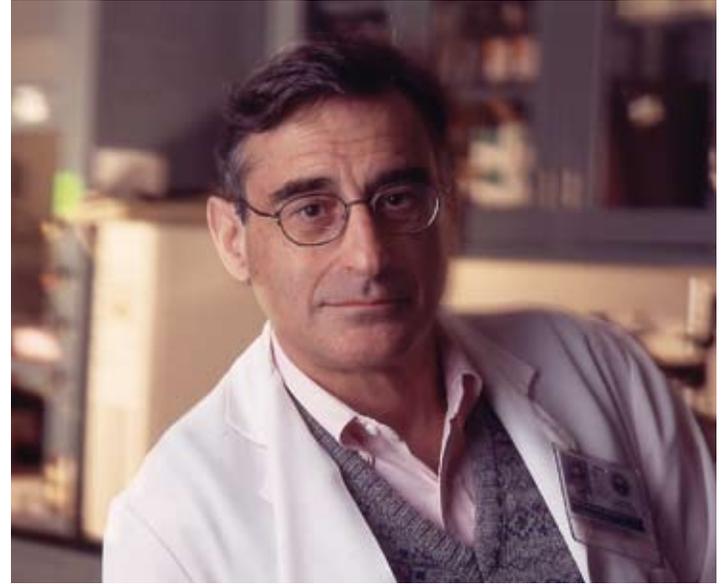


Nightmare remedy—VA’s Dr. Murray Raskind has pioneered the use of an inexpensive generic drug called prazosin to treat trauma nightmares and other symptoms of posttraumatic stress disorder.

Eileen Lennon, executive director of SIBCR, recalls: “We provided seed money, unrestricted dollars. It was only a small amount until Dr. Raskind was able to get outside funding.” Says Raskind: “It was important in getting the ball rolling. Based on the results of the placebo-controlled pilot study, we were able to apply through SIBCR for larger grants and to perform larger and more definitive trials.”

Today, thanks to a series of studies supported by VA, the Department of Defense, and the National Institute of Mental Health, prazosin is part of clinical treatment guidelines for PTSD and traumatic brain injury. The

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Productive partnership—The Veterans Medical Research Foundation, led by Kerstin Lynam, left, provides grant administration and other services to support San Diego VA investigators such as Doug Richman, MD, right, who studies HIV-AIDS. The VMRF is one of 82 such organizations nationwide.

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flexible and able to fulfill individual one-time requests,” says the scientist. “Research is a highly variable endeavor, and having a service provider who is willing and able to individualize services to support my lab is just terrific.”

Lynam agrees that support tailored to individual researchers is a big part of what makes the VA-nonprofit partnership work so well. “We’re able to provide individualized and flexible grant management because we are much smaller than most other research foundations and other organizations conducting research. We will ‘case manage’ a project through the compliance process from start to finish when necessary. We also often come to the aid of our researchers when there is a time crunch to meet a proposal submission deadline.”

She adds that “because we are a VA foundation, we know and understand VA processes well. We work particularly closely with the VA Research Service and their staff.”

Local VA research offices administer funding that comes directly from VA’s Office of Research and Development. But VA researchers also receive funding from many other sources—other government agencies, nonprofit groups, private drug and biotech companies. These grants are administered by the researchers’ academic institutions or the VA nonprofit foundations.

In fiscal 2008, more than half the money received by the VA nonprofits—59 percent—was research funding from federal agencies other than VA, such as the National Institutes of Health and the Department of Defense. The rest came from private-sector companies and organizations.

About half the money is used to pay nurses, technicians and other study personnel. Travel is another big expense, says West. The nonprofits help foot the bill

Authorized by Congress in 1988, the nonprofits have become a powerful engine for VA research.

so VA researchers can attend conferences and meet with collaborators.

Up till now, the VA nonprofits haven’t done much in the way of fundraising to augment their revenue. That may be changing, though. There are at least three foundations that are now actively seeking donations, including Lynam’s group and two others in California. Among other steps, says Lynam, the VMRF is retooling its website “to be interesting to potential donors. Our donation program is not disease-based, but centered on the veterans we are proud to serve. We believe this is a compelling reason to give in our military-friendly region in and around San Diego.”

Even without proactive fundraising, says Barbara West, most nonprofits manage to bring in enough revenue—over and above the direct costs of studies—to invest generously in the research infrastructure at their site.

“They will support a lot of recruitment packages for new clinician-investigators. They will renovate a lab or building. They’ll

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The way you walk—At VA's Center of Excellence for Limb Loss Prevention and Prosthetic Engineering, Dr. Michael Hahn, above, walks on a split-belt treadmill with electrodes capturing the electrical activity of his leg muscles. Hahn is working with a graduate student to study ankle function under different walking conditions. Below, graduate student Patrick Aubin tests the performance of a robotic gait simulator using a plastic model of the foot. The foot is fitted with reflective markers. As it "walks" on the robotic simulator, video cameras track the markers and provide data about bone motion.

Center director Bruce Sangeorzan, MD, an orthopedic surgeon and researcher, says the training program aims to "teach a little about how research is done, inspire a few young people to consider careers in research, and apply scientific principles to clinical problems."

Unlike some students in the program, Pai usually doesn't interact directly with VA patients or research volunteers. But her work, nonetheless, may eventually help improve many veterans' lives.

Doctoral project focuses on diabetic amputations

About one in five VA patients has diabetes. Some 15 percent of those with diabetes overall will develop a foot ulcer during their lifetime. These open sores, usually on the bottom of the foot, tend to become infected and do not heal well. They are often the first step in a downward spiral leading to amputation. At least three-quarters of non-traumatic amputations in VA involve patients with diabetes.

Pai studies the mechanical properties of tissue samples from diabetic and healthy feet. She wants to learn how the tissues

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Instead, she received a priceless lesson that fueled her passion for research. "I called my advisor immediately, ready to take some heat," she candidly recounts. "Instead, his first reaction was relief that I had not physically hurt myself, and his second was to 'welcome me to the club.' He related a similar incident that happened

when he broke a load cell and had to call his boss!"

Pai says she learned that "if you don't break something first, you may never know how to fix it. I have since been able to make more rapid progress. I stopped fearing not knowing the answers to things and recognize that I am bound to make mistakes. That's the nature of experiments."

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respond differently to pressure. One goal is to develop new shoe orthoses that do a better job of distributing the stress in the soles of diabetic feet. This could prevent ulcers and amputations.

Pai's involvement in the program goes beyond working in the lab. She says her mentor, William Ledoux, PhD, has her helping with grant-writing, attending key conferences, and meeting other researchers in the field. She adds that she admires his "work ethic and ability to maintain a healthy balance between work and [other areas of] life while still being ahead of the game in research."

Those qualities are also important to Patrick Aubin, another student in the program. He says Ledoux and his other VA advisor, Glenn Klute, PhD, taught him how to "set high goals and work hard while still having a good balance between work and other areas of life."

Passion for robotics

Aubin is interested in the "intersection of medicine and robotics." He is helping to develop a robot that simulates walking. Hooked up to either a prosthetic or cadaveric foot, the "robotic gait simulator" recreates the motion and forces that occur between a person's foot and the ground during walking. This way, the researchers can study the mechanics of walking more extensively than they could with a human volunteer.

"We can use more invasive foot and ankle sensors and instrumentation than ethically permitted in a live volunteer," notes Aubin. He says this can also help researchers understand the causes of some foot conditions and the effects of surgery.

Aubin has been part of the center's training program since 2004 and plans to stay till he completes his PhD early next year. He says a highlight of his training was



Photo by Jim Bryant

Sole science—Using custom calipers she helped design, biomechanical engineering student Shrutu Pai performs initial measurements on tissue from the soles of diabetic and non-diabetic feet.

when a veteran with a below-the-knee amputation visited the center in 2006. He and the group used a system of video cameras and reflective body markers to record data on the veteran's foot and leg mechanics as he walked on a treadmill. "We can now recreate the same exact walking motion and force with the robotic gait simulator," says Aubin. The technology could aid the design of prosthetic feet.

Aubin says part of what drew him to the VA center's training program was the camaraderie and mix of disciplines he found there. "This is a great multidisciplinary center. We have electrical engineers, mechanical engineers, bioengineers, orthopedic surgeons, prosthetists, and exercise and movement scientists all working together on common goals."

After nearly six years with the program, Aubin has a clear vision for his future. "I plan to pursue a career in robotics research," he says, modestly downplaying his professional accomplishments thus far. One key lesson he'll take with him from the VA program, he says, is that "it's important to follow your passions."

Photon therapy for diabetes nerve pain

A study at the VA Northern California Health Care System found that "photon stimulation"—a therapy that applies light to the skin to promote healing—led to some improvements for patients with diabetic peripheral neuropathy. The findings appeared online Nov. 6 in the *Journal of Pain and Symptom Management*.

The study included 121 patients. About half received four light treatments. The others were given placebo in the form of sham treatments. No overall differences in pain intensity or relief were found between the groups. However, those who received the real treatment reported improved sensation in their feet and less tingling and cramping, as well as improved mental health and social functioning.

Lead author Arthur Swislocki, MD, says his team is now considering a longer study of the therapy.

**Inside: Large VA study finds better results
with ‘on-pump’ bypass surgery**

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provide bridge funding to tide over investigators if there’s a gap in their funding, or seed funding for an investigator who’s got a new idea and just wants to collect some preliminary data. The nonprofit might be able to provide \$10,000 or \$15,000 to support them that way. They also buy a lot of equipment and donate it or otherwise make it available to the VA.”

She is quick to point out, though, that her group NAVREF—the national umbrella organization for all the VA nonprofits—still has the crucial job of advocating for adequate annual funding from Congress to support VA research. That money—expected to be \$580 million for fiscal 2010—is still the mainstay of VA research, even with the sharp growth of the nonprofits’ contribution in the past two decades. From the NAVREF website: “As successful as these [nonprofit] corporations have become in enhancing the VA research program, the funds they administer can never replace a robust federal VA research appropriation.”

To learn more about the VA-affiliated nonprofit research and education foundations, visit www.navref.org.

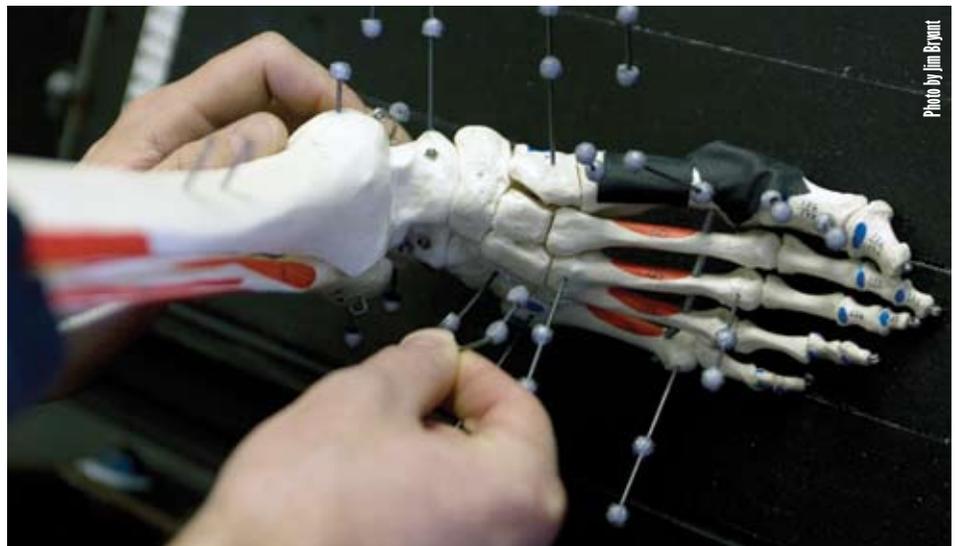


Photo by Jim Bryant

Boning up on biomechanics—At VA’s Center of Excellence for Limb Loss Prevention and Prosthetic Engineering, a graduate student places reflective markers on a model of the foot. Video cameras will track bone motion as the foot “walks” on a robotic simulator. See more on page 6.

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drug, an inexpensive generic, is still being studied, says Raskind, to arrive at a “sharper definition of the range of symptoms that respond to it.” Given in small doses throughout the day, prazosin may also help daytime PTSD symptoms, notes Raskind.

Raskind points out that a current trial of prazosin in 200 active-duty troops with PTSD at Walter Reed Army Medical Center and Madigan Army Medical Center is “the first placebo-controlled trial of a medication for a mental health disorder ever done in the active-duty military population.”

He told the success story of his partnership with SIBCR at this year’s annual meeting of VA nonprofits. SIBCR executive director Lennon was among those listening. “Everyone was thrilled,” she says. “It was an inspiring reminder of why we do what we do.” ➔