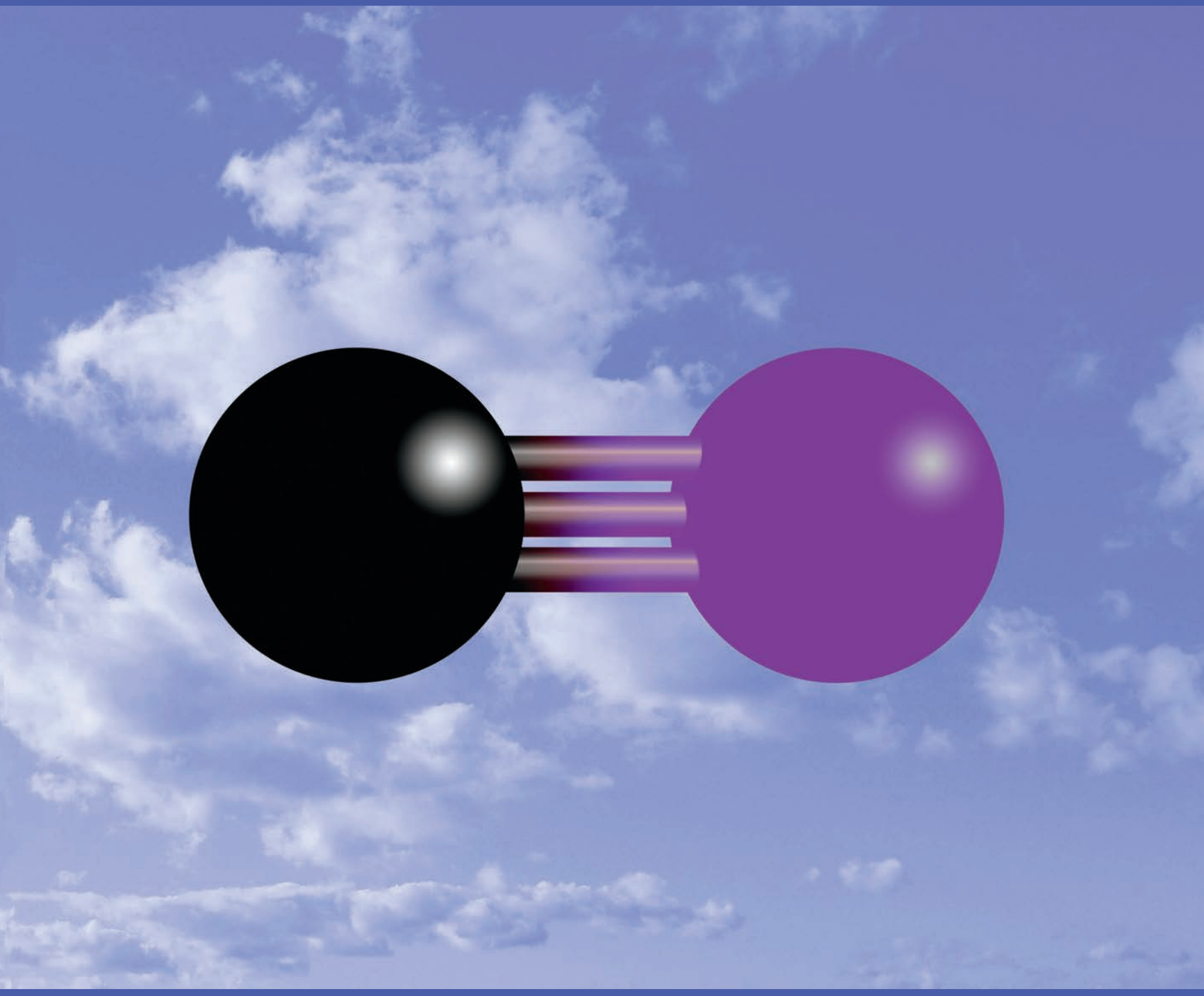
Explorations and revelations taking place in the medical school



Normally, carbon monoxide (shown here) has a half-life of 320 minutes. An engineered form of neuroglobin brings the half-life down to 35 seconds.

ANTIDOTE ANECDOTE

POTENTIAL NEW THERAPY FOR CARBON MONOXIDE POISONING

BY ALLA KATSNELSON

ILLUSTRATION BY STACY INNERST

Mark Gladwin was at his family's Oregon summer house almost four years ago when a visiting colleague posed a vexing question. "Just out of the blue, he asked me if there was an antidote to carbon monoxide poisoning," recalls Gladwin, a critical care physician and chair of medicine at the University of Pittsburgh.

The answer was no. Each year, some 50,000 Americans find themselves in the emergency department after inhaling the noxious gas. Gladwin recalled a recent incident in which a man and his 17-year-old son had been brought into the emergency department, unconscious, after working with power tools and a generator in their home when the power had gone out. Neither survived.

As he puzzled through possibilities after his colleague's departure, inspiration struck. Gladwin's team had been working on a genetically engineered version of a molecule called neuroglobin, a form of hemoglobin naturally produced in the brain. They had hoped to put the molecule to work ferrying oxygen to brain tissue starved of it after a stroke but encountered a snag: The altered neuroglobin, called H64Q, bound oxygen too tightly.

That clinging property, Gladwin realized, could be a boon in this alternative context: If the molecule also bound carbon monoxide, it might be able to mop up the poison from the blood and deliver it to the kidneys for excretion.

To his delight, the strategy worked. "The concept of the therapy is quite simple," he says. "It binds carbon monoxide with almost irreversibly high affinity." Normally, carbon monoxide's half-life—the amount of time needed for it to clear the body—is 320 minutes. In hyperbaric oxygen therapy, the standard treatment for carbon monoxide poisoning, the half-life is 20 minutes. Meanwhile, animal studies show that the gas's half-life in the presence of H64Q is just 35 seconds. Mice would normally die a little over 4 minutes after exposure to lethal doses of carbon monoxide. In the studies, H64Q worked universally, saving the animals' lives. "When we give our antidote at the end, we really pull them back from the edge," says Gladwin, who is Pitt's Jack D. Myers Professor.

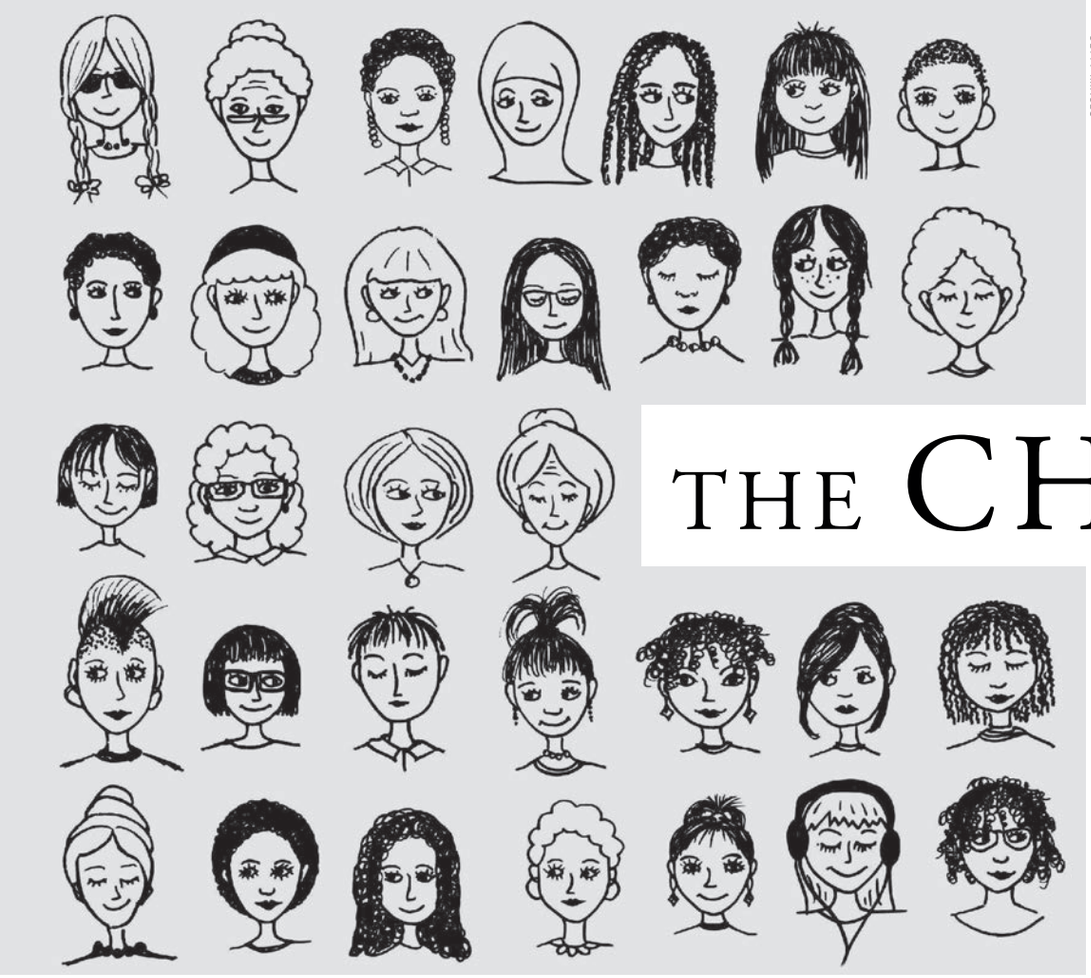
Each year, some 50,000 Americans find themselves in the emergency department after inhaling the noxious gas.

Despite crystal-clear results in animal studies, Gladwin foresees some hurdles in bringing H64Q to the clinic. First, he and his colleagues are currently producing the tweaked protein by inserting the DNA coding for it into the genome of the bacterium *Escherichia coli*. Poisoned patients will probably require 50–100 grams of H64Q. "One major issue is, can we make enough of it?" he says. The lab is working with a company that believes it can.

Another challenge is safety. "We know that if we give it to a mouse that has carbon monoxide poisoning, it's safe," Gladwin says. "What we don't know yet is, what if we give it to someone who doesn't have carbon monoxide on board?" The molecule's hungry binding site could cause trouble by reacting with another substance in the body, such as nitric oxide. "It could be toxic, particularly in the kidneys," he says. That makes it risky to test the treatment in healthy volunteers, a necessary step for gaining approval from the Food and Drug Administration. It also raises concerns for situations when the antidote might be given by mistake to people who appear to be suffering from carbon monoxide poisoning but are misdiagnosed.

Gladwin and his colleagues are actively testing H64Q, and they are also developing backup versions of the molecule that might not have these drawbacks. But even if neither the original nor the knockoffs pan out, he believes that their efforts have forged a clear way forward.

"We've introduced a new paradigm—that you can design a high-affinity carbon monoxide scavenger," Gladwin says. "So while we hope our molecule will be the molecule that becomes the antidote, we are also satisfied that we've shown proof of principle—that this approach can work." ■



GETTY IMAGES

SHIFTING WOMEN'S HEALTH IN THE RIGHT DIRECTION

BY ELAINE VITONE

THE CHANGE

TYPOGRAPHY: ELENA GIALAMAS CERRI

Pitt/UPMC scientists recruited premenopausal women across the city for a multi-institutional study in 1996. They were asking a lot: an extra doctor's visit once a year, forever. Yet about 400 from Pittsburgh volunteered, and at last count, 90 percent were still in. "They have been wonderful," says Karen Matthews, Distinguished Professor of Psychiatry and principal investigator for the Pittsburgh arm of the study. "It's quite a testament to their commitment to helping to figure out what is going on during these transitional years."

Though most women now live at least a third of their lives after menopause, its long-term effects on women's health are just beginning to come into focus, thanks in large part to the study, known as SWAN, or Study of Women's Health Across the Nation. SWAN was funded in part by the National Institute on Aging (NIA). The study, which recruited more than 3,000 women in seven sites, has yielded more than 400 papers to date, including several recent findings from Pitt investigators.

Matthews has long been intrigued by changes she's observed in women's cholesterol levels around the time of the final menstrual period. In January, she published in *Stroke* a paper outlining her findings that the extent of these changes can be used to predict the extent of plaque buildup in coronary arteries about six years later. Interestingly, the women's lipid levels were still well below what would trigger a physician to prescribe a drug or recommend a behavioral change, per current guidelines. This paper suggests that doctors should be aware of not just the absolute cholesterol levels, but also a sizeable uptick therein.

Among Matthews' collaborators is Graduate School of Public Health colleague Samar El Khoudary, the first author on a paper published this January in the *Journal of the American Heart Association*. The study found that high levels of pericardial fat—a type of fat surrounding the heart—may signal a higher risk of heart disease in women who are postmenopausal. This risk is most pronounced at lower levels of estrogen, supporting a potential role of the hormone in explaining this association.

Last fall, Rebecca Thurston, a PhD professor of psychiatry, clinical and translational science, epidemiology, and psychology, published in *Menopause* a SWAN study showing that hot flashes and night sweats are not just a fleeting nuisance, lasting around three to five years, as everyone has always assumed. They last upwards of a decade on average. And hot flashes can point to serious health problems for some women. As detailed in *Stroke* in January, SWAN data revealed four distinct trajectories in menopausal women's cardiovascular health, each with its own outcome pattern. Women with early onset menopausal symptoms were especially at risk, she found. And the unfortunate "super flashers," who have these symptoms for some 15 years, are also at heightened risk for cardiovascular disease.

Now, with a $3.7 million grant from NIA, Thurston's team is connecting menopausal symptoms and cardiovascular health to sleep disturbances, mood, and changes in the cerebral vasculature and other markers of brain aging. This comes after a series of papers from her group linking loneliness, anxiety, depression, and history of physical and sexual abuse in childhood to cardiovascular events down the road.

Thurston—a member of the board of trustees for the North American Menopause Society and recipient of the International Menopause Society's Henry Burger Prize—is a psychologist at the Midlife Health Center at Magee-Womens Hospital of UPMC, one of the few clinics in the country devoted exclusively to the menopause transition. "We try to take this mind-body approach," she says of her MD colleagues Amy Imro, Director Mary Elizabeth Peterson, Kathy Scruggs, and Judith Volkar, each of whom is trained and credentialed in menopause management. At the center, clinical practice is directly informed by the university's robust menopause research efforts.

SWAN participants often tell Matthews they hope for a change for the better in women's health, having grown up at a time when even less was known about menopause, and their mothers wouldn't talk about it. Says Matthews, "A number of them will say that they're doing this [study] so that there can be more information for their daughters." ■

SHARPEN YOUR FACULTIES

SUPPORT FOR NEW PROFESSORS

BY JENNIE DORRIS

Iain Scott, an assistant professor of medicine at the University of Pittsburgh, pauses while appetizers are shared around a table at Soba, a restaurant in Shadyside.

"Did you always think you were going to end up in a position of leadership, or did you fall into it?" he asks, addressing Mark Gladwin, chair of the Department of Medicine, who is sitting at the head of the table. (See p. 8 for a story about his recent work.)

Assistant professors Nathaniel Weathington and Cynthia St. Hilaire nod with interest.

Gladwin laughs and describes the anxiety he used to experience making presentations during his first leadership role as chief resident at Oregon Health and Science University.

"Over time, as confidence grows, it gets easier. You do have to like leadership. You fill vacuums. You fix things," Gladwin says.

Setting up the informal get together was actually an "assignment" for the University of Pittsburgh School of Medicine's Career Mentoring Program (CaMP), which creates contemplative space for junior faculty. The assistant profs were charged with meeting their department chairs to ask burning questions, like: How do they delegate? What happens when they have to discipline a team member? And how do they balance their personal and professional lives?

Ora Weisz, associate dean for faculty development at Pitt med and assistant vice chancellor for faculty excellence in the health sciences, notes that no one even uttered the word "mentor" when she was a junior faculty member. So four years ago, Weisz started CaMP with professors Ann Thompson, vice dean; Jennifer Woodward, associate provost; and Doris Rubio, director of the Data Center at the Center for Research on Health Care. (The organizing committee has since added Gabriella Gosman, vice chair for education for obstetrics, gynecology, and reproductive sciences, and Lori Shutter, vice chair of education for critical care medicine.) CaMP is for faculty members in their second year.

The long-term, in-house approach has received praise from outside consultants, who note that faculty from other universities often have to travel to off-site conferences to learn similar skills. They end up not developing relationships allowing for casual, open conversations that can help smooth their transitions.

Most scientists didn't learn how to run a lab while they were grad students or fellows. But once they are hired as faculty, in addition to pursuing research, teaching, and perhaps seeing patients, they are expected to write grants, balance budgets, and manage employees.

Gladwin compares it to suddenly becoming a small-business owner. "You have venture capital in your program, and you have to be self-sustainable," he says. The series helps junior faculty prepare themselves for these challenges.

It's a juggling act, says Weisz: "It takes about three years to figure out how you should be spending your time. When I was working on my lecture, I felt like I should be in the lab. When I was in the lab, I felt like I should be writing a grant."

Regular meetings also help the new faculty members bond outside of work. At the beginning of the night at Soba, Weathington, who arrived on his bike, was teased by Scott and St. Hilaire for pedaling in the November cold.

Weathington said the CaMP program helped him meet others while doing what can be an isolating job. As he took off his bike helmet, he gestured to Scott and said that without these monthly meetings he would have talked with him only "once or twice in the hall" in the two and a half years they've worked together.

St. Hilaire agreed, noting she can feel detached from colleagues as she works on the top floor of the Biomedical Science Tower, which houses six principal investigators and their labs. "In lab science it's very easy to silo yourself," Weathington says.

With the series, organizers have strived to create a sense of community and involvement, which can be particularly important for the retention of women and faculty from underrepresented groups.

And, Weisz notes, "breaking down barriers is really critical to maintaining innovation in research. Those people who can cross boundaries can make the new sparks that lead research forward." ■