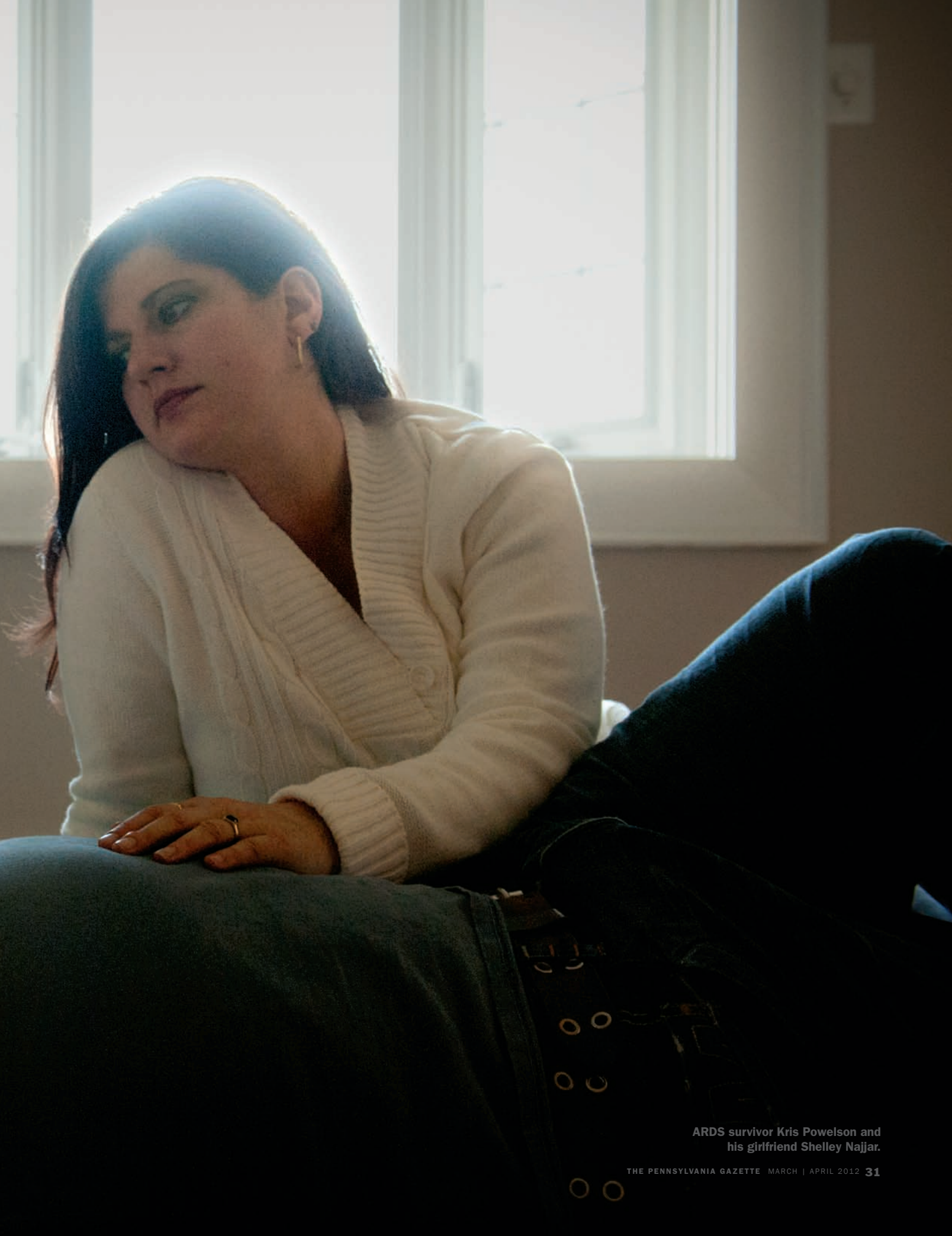
# *Insidious* ARDS

Few people outside the medical world have heard of Acute Respiratory Distress Syndrome, even though it kills more Americans than breast cancer and often leaves survivors in various stages of disability. Some Penn-related physicians and researchers are working hard to blunt its impact. **BY SAMUEL HUGHES**

PHOTOGRAPHY BY CANDACE DICARLO



ARDS survivor Kris Powelson and his girlfriend Shelley Najjar.

BY the time Kris Powelson arrived at HUP's medical intensive-care unit, he was teetering on the thin edge of life.

A week before, that statement would have seemed preposterous. Just 33 years old and in seemingly robust health, he had—shortly after having his wisdom teeth removed, of all things—found himself wheezing and out of breath. He felt pretty sick, but even when his urine started turning brown, his oral surgeon said it was nothing to worry about—just a normal reaction to the Naproxen he had been taking for pain.

When Powelson's take-charge girlfriend, Shelley Najjar, told a CVS pharmacist about that last symptom, his response was: *Get him an emergency appointment with his primary doctor at once.* She did. There they did a quick pulse-oximeter test. Powelson's blood-oxygen level was barely 60 percent. (Normal is 95 to 100 percent.) His doctor sent him by ambulance to the nearby Pottstown Memorial Medical Center.

After a chest X-ray, the ER staff put Powelson on a BiPAP mask, which blows oxygen into the face with gale-wind force. He was admitted to the ICU. That night he was sedated into a coma and hooked up to a mechanical ventilator, with a breathing tube down his throat. The ICU physician pulled Najjar aside and showed her an updated X-ray: One lung was only 20 percent clear. The other was completely white, filled with fluid. They weren't sure why. The next day a physician specializing in infectious diseases told her that a urine test indicated Legionnaire's disease, a dangerous but treatable infectious disease that causes high fever and pneumonia. (Powelson probably contracted it because he had been on an immune-suppressant drug for ankylosing spondylitis, a connective-tissue disorder.) But they still didn't know why his lungs were in such horrific shape. Najjar knew that he needed to be transferred immediately, to a place where they could deal with a condition whose outlook, she had just been told, "was not favorable at all."

And so that night, in an induced coma, he was Medevaced to HUP, where he was admitted to the medical ICU. The resident on duty, Joanna Hart (now a pulmonary and critical-care fellow) comforted Najjar by telling her that her boyfriend was "in the best possible place." But Hart could not promise a favorable outcome. She had never seen a patient that sick survive.

Powelson's condition had morphed into something much more deadly: Acute Respiratory Distress Syndrome (ARDS), which kills more than one-third of the 150,000-plus Americans who come down with it each year, and leaves many more in various stages of disability.

The next 16 days were a wild ride through the underworld for the unconscious Powelson, whose lungs were drowning in fluid—barely functioning, even with a ventilator pumping in the maximum amount of oxygen. (In a healthy person, the P/F ratio—the amount of oxygen in the arterial blood divided by a fraction of the oxygen being given to the patient—is between 500 and 600. Below 300 is considered an acute lung injury, or ALI. Below 200 is full-blown ARDS. Powelson's P/F ratio was less than 60.) He also had severe sepsis, which is characterized by an infection plus multiple-organ dysfunction. Given the dangerously low oxygen level, Hart notes, there was a very real possibility of brain damage.

It was an even wilder ride for the heroic Najjar, who would spend the next 86 nights sleeping in hospital recliners, including 16 while Powelson was unconscious.

"It was just relentless," she says. "For many days they said it was minute-to-minute. Basically, all of his vital organs failed. He wasn't even making his own urine anymore, so they took the catheter out because they didn't even need one. They put him on the CRT machine, a 24-hour dialysis to clean his blood out. Then that machine would get clots in it, and that alarm would go off, and they'd have to get a new one to come in."

At one point his fever spiked to 106.3 degrees, and at four o'clock one morning he started bleeding internally.

"All of a sudden he just started dropping off," says Najjar. "It was like out of a movie, except in the movies they always throw the family member out and shut the curtains. I was jammed up against the wall, and I couldn't even tell you how many doctors and nurses flew in there. They rolled the crash cart in, and right when they were getting ready to paddle [defibrillate] him, they're like, 'Wait! Wait! He's OK!' His heart bounced back."

Somehow, from that point of no return, Powelson's body began the long climb back. The ICU team slowly cut back his meds. And finally, after nearly 400 hours in a coma, the ventilator was removed. Eventually, he opened his eyes.

"Wow," he said weakly.

**ARDS occupies a curious place among life's insidious threats.** Not just because of its very high mortality rate, though that is sobering enough. (It kills upwards of 50,000 people in the United States each year, more than breast cancer.) Thirty years ago, the mortality rate from ARDS was more than 60 percent, so progress has been made. But still:

It's insidious because there are so many pathways that can lead to its onset, because it strikes with appalling speed, and because it is so damnably difficult to treat. Furthermore, it's "an equal-opportunity disease," says Jason Christie, associate professor of medicine and epidemiology, and section chief of medical critical care at HUP. "Doesn't matter the gender or ethnicity. It affects everybody, everywhere."

The *New England Journal of Medicine* has warned that ARDS and its understudy, ALI, represent a "serious public-health issue," especially given the "looming expansion of the elderly population."

And yet, outside of the medical world, it seems that the only people who have heard of it are those who have lost, or almost lost, someone to it.

"ARDS is clearly reported in the scientific literature," says Barry Fuchs, associate professor of medicine, director of the medical ICU, and medical director of respiratory care services at HUP. "But it's definitely underappreciated by and underreported to the lay public."

Part of the problem, Fuchs adds, is that "unlike cancer and heart disease, the public and the politicians don't hear [enough] about the heart-wrenching stories to really have an impact." Adding to

its stealth is the fact that "ARDS is a syndrome, not a specific diagnosis. It's caused by so many things. You could get it from a blood transfusion, an infection, aspiration—it's an ICU thing that people get sick from and die of. This is nebulous to patients and families."

"You have to have something bad happen to you" to come down with ARDS, says Christie. "And that's hard because people don't walk down the street and get it, or they don't get it for three months and are sitting thinking about how they can battle it. They get it really quickly, and then they live or die."

Take a deep breath. Then take a moment to savor that simple act. We breathe from the time we're first slapped on the butt in the delivery room, tens of thousands of times a day, every day. Until we don't.

Without oxygen, the cells in our bodies can't function. When we inhale air, oxygen is brought into the alveoli, the air sacs in our lungs, where it is transported to the surrounding blood vessels; the oxygenated blood is then delivered to our bodies' cells. The alveoli are also responsible for the magical exchange in which carbon dioxide is exhaled as a waste gas.

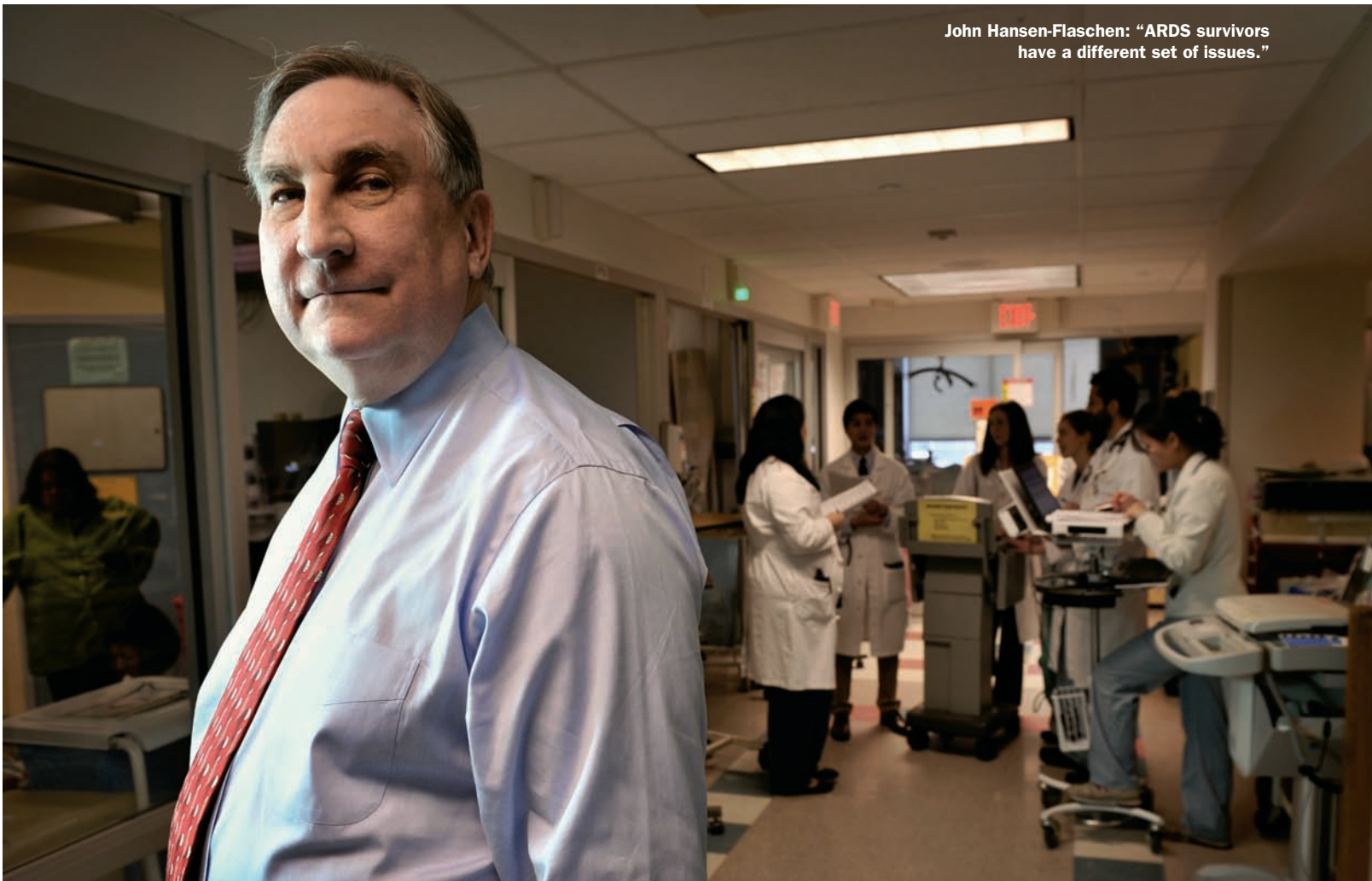
A lot of things can cause the intense inflammation of lung tissue that characterizes ARDS. Among the most common are sepsis, pneumonia, trauma, aspiration, pancreatitis. But the end result is that the alveoli lose their ability to exchange oxygen and carbon dioxide with the blood, owing to a collapse of the air sacs and leakage of fluid (edema) into them. As the lungs try to heal the damage, scar tissue is formed, adding to the problem.

"In ARDS, basically your lungs leak like a sieve," says Anthony Dal Nogare, a physician specializing in pulmonology and critical-care medicine at Rocky Mountain Heart and Lung in Kalispell, Montana. (Note: He's been patiently explaining things to this writer on and off since our elementary-school days.) "The function of lungs is to exchange gas. And for that to happen you have to have a very thin membrane between the blood—where the oxygen and carbon dioxide go in and out of—and the alveoli, where the air comes down. So in a normal lung, there's just a few micrometers separating those two."

With ARDS, "that barrier gets broken down, and the capillaries become permeable, and fluid just leaks out of the blood space and into the alveolar space," he adds. "So now you've replaced that beautiful, fine, thin structure with just a bunch of fluid and cells, and you can't exchange gas anymore."

ARDS has really only been on the medical radar since the 1960s, when ICUs—and ICU-related illnesses—became a regular part of Western hospitals. (It's sometimes referred to as Adult Respiratory Distress Syndrome, to distinguish it from the version that afflicts infants.) In the early days the syndrome was known as Shock Lung, or White Lung (from the near-total whiteness of the lungs when viewed on X-rays), or Da Nang Lung (from the site of the Vietnam hospital where so many young soldiers succumbed to it after they had seemingly survived their battle wounds).

"People have traced it back to World War I, when forensic physicians doing autopsies on soldiers killed on the battlefield would find their lungs filled with fluid,"



**John Hansen-Flaschen: "ARDS survivors have a different set of issues."**

says John Hansen-Flaschen, a Penn professor of medicine and chief of the pulmonary, allergy, and critical-care division at HUP, and a prominent figure in the field. "They called it Drowned Lung, and it was recognized also in World War II as a post-mortem finding in soldiers who were severely injured but didn't die right away."

Why some people develop ARDS and some don't is still a mystery; it's like some terrible Borgesian lottery, where the winning ticket may get you a viper. This susceptibility is the part of the dark puzzle that Penn researchers are trying to solve.

"One of the most striking features of acute lung injury and ARDS is that it's very hard to predict which patients will get it," says Nuala Meyer, an assistant professor of medicine whose research focuses on identifying genetic and molecular risk factors for acute lung injury and organ dysfunction during critical illness (see sidebar below). "I've seen very sick septic patients who never required more than 30 or 40 percent Fi02, which is an amount of oxygen from the ventilator. And yet I've seen other people with what seems like a controllable infection that still seems to flood their lungs.

"I think some patients are predisposed to flood their lungs," she adds. "And some of the genetic variants we're looking at may have been evolutionarily selected to help you respond to injury or inflammation in ancient times, when the biggest threat to life was infection or trauma."

There's a similar variation on the treatment-response side, she points out. "Some people go from being impossible to oxygenate for an hour or two, to coming down to 50 percent within a day or two, whereas others just stay at 100 percent and require high amounts of PEEP [positive end-expiratory pressure]—another ventilator maneuver we can use for oxygenation. There's a lot of heterogeneity, both in who's susceptible to it and in how patients respond to our therapy."

For the families and loved ones of patients, "dealing with that uncertainty is tough," says Paul Lanken, professor of medicine and former director of the medical ICU and Intermediate Medical Care Unit at HUP. "Thirty percent mortality—who is that 30 percent? When they first come in, I can't tell."

**I became interested, if that's the word, in ARDS this past summer,** when my tap-dancing, grandchild-adoring mother-in-law went into a New Haven hospital for minor surgery on her small intestine. At 79, she knew well that there is no such thing as minor surgery, and this one turned out to be more involved than her surgeon had anticipated. But afterwards she was alert and joking with her family, and the doctors expected her to be released in a day or two. That was June 1. By June 3, she was starting to act "a little loopy," in the words of my wife, Pat. With her blood-oxygen levels slipping, she was put on an oxygen mask, then, after quickly being moved to the ICU, a BiPAP mask.

## Evolution, Inflammation, and ARDS

"Stop and think about the fundamental question," Jason Christie is saying. "A hundred people get pneumonia, or major trauma—hit by a car or something—or a severe bloodstream infection. About 30 to 40 of them get ARDS. The others don't. Why? Why do they have susceptibility for a given insult?"

That question is at the heart of Penn's research efforts in the field. But—apart from certain known behavioral risk factors such as chronic alcohol abuse—it's a damnably difficult one to answer.

"It's difficult because it's a very complicated set of events that lead to the Shock Lung picture, where your lung fills up with fluid and inflammatory cells and makes it so you can't breathe without a ventilator," says Christie, whose many titles include senior scholar in the Center for Clinical Epidemiology and Biostatistics and director of clinical research in the pulmonary division. "So we spend a lot of time thinking about *Why?*"

Part of that question involves "whether there's an inter-individual genetic variation to this," since over the centuries, our ability to survive events such as bleeding, severe infection, and plagues may have "conferred a survival advantage in the setting of those environmental insults."

But in recent years, medicine has evolved a lot faster than our bodies. "Now, when faced with a severe insult—such as trauma that people wouldn't have survived 50 years ago, severe pneumonias that people wouldn't have survived a hundred years ago when we didn't even have oxygen to give to them, other bloodstream infections that would have claimed people's lives—now that we're good at treating some of those, why then do some of these people go and have this severe Shock Lung?"

The biological causes of acute lung injury (ALI) and ARDS "are not perfectly understood," Christie notes. "There's one theory that you have an over-exuberant inflammatory response, either on the basis of your own immune system or on the basis of how you respond to some of the pressures such as clotting, which can cause inflammation, or fibrin deposition—how your blood vessels handle acute inflammation—which may have been selected for based on how you would heal a cut."

The tragic irony is that for some people, a strong, evolutionarily honed immune response to infections "may tip over to an over-exuberant inflammatory response that might actually end up causing the disease," says Christie. The numerous "checks and balances in the modulation of the immune system" were developed in a different era. "I mean, there's no evolutionary pressure on surviving an intensive care unit, right? Because we've only had them for 30 or 40 years. There's no evolutionary pressure on surviving severe major trauma, because [in the past] you just died! Now that we can handle the early phases of the critical illness, these organ failures that occur are good targets for thinking about how we can approach susceptibility to them."

For Nuala Meyer, an assistant professor of medicine whose research focuses on identifying genetic and molecular risk factors for ALI/ARDS and organ dysfunction, the balance between "pro-inflammation and anti-inflammatories" is one of the critical unsolved puzzles. "On the one hand, [ARDS] looks like an over-

The next day she was sedated into a paralyzed state and put on a mechanical ventilator. According to my wife's detailed notes, ARDS was not mentioned until June 13, 10 days after she arrived in the ICU. The next day, the pulmonologist who had finally been summoned told the family that "unless she comes up with some new problems, I'd expect her to make a full recovery."

She died five days later.

It was only then that I realized that ARDS was the same syndrome that had killed a wonderful, healthy 11-year-old boy in my neighborhood, an event for which words like *tragedy* are pathetically inadequate. This had gotten personal.

The day after her mother's death, my distraught wife was searching on the Internet for answers when she came across a notice on the ARDS Support Center's website (ards.org), noting that Penn and HUP had been designated by the NIH as one of six Specialized Centers of Research in ARDS. After describing the nature of Penn's research, the notice thanked the ARDS Support Center for letting the Penn team share its findings with "the larger community of people who know first-hand the devastation of this terrible disease." The author was John Hansen-Flaschen.

Pat, still in Connecticut, sent me an email: "Do you know this guy by any chance?"

As it turned out, I did. He had done a photo essay for the *Gazette* some years ago ["Learning to See Lancaster Avenue," Jan|Feb 2003], and I remembered him as a good guy whose interest in medicine went well beyond the clinical and deeply into the humanistic aspects. I sent him an email, asking if he'd be willing to talk with Pat about her recent unhappy experience with ARDS. A few days later I heard back from him: Yes, he would. The next evening, after offering his sympathies, he got right down to business.

"Tell me exactly what happened," he began. And so she did.

He listened intently, "totally focused on what I was saying," Pat recalls. "I didn't think he'd want to hear every last detail, but it became apparent that he did, stopping me to ask a number of questions along the way about the specifics of when different events occurred." After she finished, he asked her if anything was still bothering her about the experience.

"I told him how I had been obsessing about certain things," she says. "He said that the [loved ones] of ARDS victims sometimes have PTSD-like symptoms—which I totally believe. You go over the same things again and again in your head."

It was something of a relief when he told her that "once my mom was at 100 percent oxygenation and paralysis, the best possible outcome was a very prolonged illness, with a high expectation that she would never be herself again. I knew she would not have wanted to live that way. Up till that moment I had thought that if my mom had been able to turn the corner and survive, she would have been fine.

exuberant inflammatory response, and maybe those pro-inflammatory molecules are what break down your lungs' vascular barrier, and that's why you leak," says Meyer. "On the other hand, you actually need functional immune cells, monocytes and T cells, to get better. So it may be that if you're immunosuppressed, and sepsis can incite a type of immunosuppression, maybe that's suppressing your body's ability to heal from ARDS.

"So we certainly haven't quite figured out the timing and the balance of pro- and anti-inflammatory molecules in ARDS. Maybe some patients, their problem is that they have too much pro-inflammatory, and others it may be that they don't have the type of immune cells that resolve inflammation."

Much of Meyer's research involves looking at "both the genetics and the proteins in tandem."

"Can we identify proteins, either in the blood or in the lung-lavage fluid, that might help distinguish between people with a good prognosis or a poor prognosis, or can we learn something about why that individual developed ALI based on the pattern of proteins that we see?" she asks. "If I find what seems to be a genetic risk factor, I can look at the protein product of that gene and try to determine if there's something different about the protein for the people carrying the genetic variant or the polymorphism. And by doing that, maybe we're going to identify a subgroup of people whose ARDS is somehow related to this protein."

One intriguing finding concerns a protein called angiopoietin-2, "which seems to contribute to making the vessels leaky," Meyer adds. What happens, she posits, is that the "barrier at the endothelial side and the epithelial side—the cell that lines the air sacs in the lungs—breaks down and lets fluid leave the blood vessel and enter the air space. So maybe there's a subgroup of patients whose ARDS somehow is related to irregular handling of this protein, for lack of a better term. We're trying to figure out if there's something different about the protein they secrete. Is it in a higher amount? Is it a slightly different isoform of the protein? And, if so, does that different isoform have a stronger effect disrupting the endothelium?"

Other researchers around the country are looking at "molecular markers, biomarkers in general, to see if we can see things in the blood, the plasma of patients that might mark somebody as being a high risk to develop ARDS," Meyer adds. If one of these markers were discovered in the emergency room, "maybe you'd be more likely to admit [a patient] to the ICU or to take the ventilator from over-stretching the patient's lungs."

While one goal of much of this research is to identify drug therapies, "those therapies may not apply to the whole population of ARDS patients but [just] to the patients who have a molecular subtype." The other goal is thus to develop a personalized therapy that follows the contours of an individual's risk profile. Patients often have "different molecular reasons for flooding their lungs," she adds, and "we're going to need to be testing therapy only in the patients whom you might predict it will have an effect on in order to show a benefit."

"We have an active and productive program in molecular epidemiology, genetics, or ARDS risk-factors prevention," says Paul Lanken. "The ultimate goal is this personalized, molecular medicine. And it's really taking everything to the next step. And that's what a place like Penn should do—do the basic science, and then do the translational, and then do the clinical. We have it all here, potentially. And we're part of an international group trying to move things forward."*–S.H.*

"Talking to John Hansen-Flaschen made me realize that my mom's experience was far from unique," Pat concluded. "He told me that line-by-line of my narrative, my mom's was a 'textbook case of ARDS.'" Including the fact that ultimately, we may never know exactly what happened to bring it on.

Though there are no drugs to treat ARDS on the immediate horizon, the fact that the medical world has been able to cut the mortality rate roughly in half shows that its lethal nature can be somewhat contained, if not halted.

In the two and a half decades that Barry Fuchs has been practicing medicine, there have been "lots of ideas of potential therapeutic bullets that were going to make a difference in the lives of these patients who have ARDS," he says. "But in reality all that has really fallen by the wayside. And at present the most remarkable advance in this field during the 20-25 years of my practice is just to change how we ventilate these patients. The new, life-saving ventilator practice is simply to turn down one of the dials to reduce the size of the breath that we give."

Physicians refer to that as the "tidal volume," and the gist of it is that less is often more. As much as oxygen is needed, too much of it can cause serious damage when forced into sick lungs. Back in the era when "generous tidal volumes" and often "multiple chest tubes" were used, says Fuchs, the ventilator used to be "associated with a much higher mortality than we see now."

"I think of the ventilator as a medieval torture instrument," says Hayim Daniel Brodie C'91, assistant professor of clinical medicine and co-director of the Center for Acute Respiratory Failure at New York Presbyterian-Columbia University Medical Center. Not that Brodie is denying the vital role of ventilators in patients with ALI and ARDS. "It's like what Churchill said about democracy: It's the worst form of government except all the others. The ventilator is the worst thing we can do to the lungs, except that we have no other choices. If somebody has respiratory failure, it's life-saving—but it's also doing all sorts of bad things." Brodie is a cautious proponent of a device called ECMO, which stands for extracorporeal membrane oxygenator and acts as a kind of external lung (see sidebar below). But it can only be used in certain circumstances.

It took roughly a quarter of a century, from the late 1960s to the early '90s, for the medical world to conclude that putting people on ventilators at maximum tidal volume "was actually perpetuating the injury and sort of accelerating it," notes Paul Lanken. The introduction of CAT scans made it clear that "what looked like the whiteout in the plain X-ray actually showed heterogeneity of those densities—so that there are some

## The Class of ECMO

**Jay Shiland W'91 was already a very sick man** when he arrived at New York Presbyterian-Cornell Hospital two years ago with a soaring fever, plummeting blood-oxygen levels, and pneumonia in both lungs. Within two days he was put on a ventilator, and over the next week and a half his pneumonia morphed into severe ARDS. To say that his outlook was grim is putting it gently.

**Jay Shiland, left, with Dan Brodie.**

At that point, the medical team at NY Presbyterian-Cornell "reached out to their counterparts at the Columbia campus of NY Presbyterian, and asked if Jay was a candidate for their ECMO program," says Elizabeth Maringer, Shiland's wife. ECMO is the acronym for extracorporeal membrane oxygenation, a device that circulates the patient's blood through an external machine that oxygenates it, removes the carbon dioxide, and returns it to the body, bypassing the lungs entirely. By doing so, it allows doctors to reduce the amount of mechanical ventilation, "thereby giving Jay a chance to stabilize and his lungs time to heal."

It was hardly an open-and-shut case, and in fact seldom is. The use of ECMO "carries many risks, and very few institutions have the ability to keep someone on ECMO for days and weeks," says Maringer. "Even at Columbia, it has only been used for a very small number of adult ARDS patients, with only a 60 percent survival rate."

Shiland had already been rejected for ECMO earlier that week; having been on a ventilator for 10 days already, three days longer than Columbia's guidelines recommend, he was deemed too sick. But thanks to the persistent chief of Cornell's medical ICU, the Columbia ECMO team reevaluated Shiland and had him in surgery for ECMO that evening.

Among the Columbia ECMO team leaders was Hayim Daniel Brodie C'91, assistant professor of clinical medicine and co-director of New York Presbyterian-Columbia's Center for Acute Respiratory Failure (www.nyp.org/ecmo), which he and Matthew Bacchetta, a thoracic surgeon, recently founded.

"By the time I saw Jay, he had been critically ill for quite a while," recalls Brodie. "He was going downhill so fast, and in such a bad direction, and got so much worse once he went on [the ventilator], that it is likely he would not have survived. All of our patients who go on ECMO are really sick, but he was *really* fading."

For all the risks and high-maintenance staffing, ECMO can be a life-saver, says Brodie, who describes himself as both an "evangelist and a skeptic" on the subject and recently published an article on the use of ECMO for adults in *The New England Journal of Medicine*. Realizing that "there weren't too many options," he agreed that Shiland should be a candidate for the treatment.

And so, on April 10, 2010, Shiland was put on a specially adapted portable ECMO machine and transferred—in an ambulance led by a police escort—the seven miles from NY Presbyterian-Cornell to its Columbia counterpart. By then he was hanging on by a thread.

spots that were closed off and some spots that were open." As a result, "the standard tidal volume didn't go to a whole lung; it went to a small fraction of the lung, way over-inflated those alveoli, and damaged them. And those damaged alveoli released cytokines, which are biologically active molecules that go in the bloodstream and cause people to go into multi-organ system failure."

The patient then goes into "what looks like septic shock," Lanken adds. But unlike sepsis, "most of the time we can't grow any organisms from their blood or find any source of infection."

In the late 1990s an NIH-funded study compared the results of high tidal volume versus low tidal volume among 861 patients at sites across the country. The results were "highly significant," notes Lanken (who was the principal investigator for the Philadelphia part): the mortality rate for low tidal volume was 22 percent lower than in patients receiving high tidal volume. "That was basically the first time in our country that we showed something made a difference."

Another variation on the theme has been used in recent years: oscillators, which are essentially high-frequency ventilators.

"Imagine a big woofer hooked up to a ventilator, and you're woofing away," says Lanken, referring to the bass driver in a stereo speaker. "That's what it is. Goes from 3.5 to 11 cycles per second. It defies conventional physiology because the woofed movement of the air is less than the dead space. It's a new way of breathing for people. But it does produce the equivalent of extremely low tidal volumes. So the stretch of those lungs that are still open to air exchange is going to be the least."

Oscillators have been used in nurseries for some 20 years, and have been approved for use in adults with ARDS for at least 10 years, Lanken notes. But the NIH, with its limited funds, has yet to approve any studies on its efficacy.

"It's taken the Canadian government and a group of investigators in Canada to actually fund and coordinate this trial," he says. "The ARDS Network went on to a Phase II trial that I wasn't part of. But I am part of this oscillate clinical trial, and there's 400 patients enrolled ... So in two years we'll see whether that is the same, better, or worse."

While the small hospital that treated my mother-in-law did its best and appears to have done the right things, the fact that it took them nearly two weeks to realize that they were dealing with ARDS does suggest that the critical window for diagnosing it is often missed.

Back in the mid-1990s, when Barry Fuchs first began supervising the ICU, he found that physicians often "failed to recognize when their patients had the syndrome of ARDS."

"He was described to me more than once as just about the sickest patient in the hospital," says Maringer. "Beyond the concern about his lungs, Jay also spiked high fevers, had clotting issues, and faced the risk of additional infection due to his prolonged ICU stay and ECMO." But finally, after 10 "very, very long days, the doctors determined that his lungs were sufficiently functional to withstand the ventilator alone, and he was taken off ECMO on April 20th."

Following several more long weeks in the ICU, he was taken off the ventilator. When he finally came to, he says, he was "even more drug-addled" than most ARDS survivors (on account of the large amount of sedatives given to ECMO users). And finally, in the second week of May, his two young sons were allowed to see him. It was then that the enormity of what he had been through really hit him.

Amazingly, by the following September, he was able to return to work.

"Today, you'd have no idea that I was sick, except that I have a lot of holes in my body," says Shiland, who has become something of an ECMO evangelist himself. While it's "more invasive than a ventilator," he allows, "ECMO allows people to not just survive but survive really well."

There are still a lot of ECMO-skeptics out there. But there have also been a lot of improvements over the years, in both technology and technique.

True, ECMO is expensive even by ICU standards, and can only be used in the tiny number of medical centers (including Penn's) that have the trained personnel to administer it, but Shiland says that it's "not a loss leader" at places like NY Presbyterian-Columbia. "They actually make money on this thing now," he says. "It's something that is both clinically advantageous and economically advantageous for a hospital to pursue." Given that he's a senior managing director of MTS Health Partners—a healthcare merchant bank that provides "strategic advisory and capital raising services as well as private equity capital to companies in the global healthcare industry"—Shiland's observations on the economics of ECMO carry more weight than those of most patients. (Four of MTS's six partners, incidentally, have Penn degrees.)

As he recuperated at NYP-Columbia, Shiland gradually became aware of Brodie's frequent presence in his room.

"I was wondering, 'Why is this guy hanging out with me?'" Shiland recalls. "Turns out he was the guy who approved me for ECMO. Now he's hanging out with me, wants to chat. For two and a half weeks he was in there almost every day. He's just a great guy, and we became friendly on that basis."

Some six months later, when Shiland and Maringer were having dinner with Brodie, he "asked if I knew somebody," says Shiland. "He made the connection that I went to Penn. Then he asked me, 'What class were you in?'" It was then that they realized that Shiland's life had been saved by a classmate. The rest of the dinner was spent emailing mutual friends and telling the tale of that remarkable convergence of time, space, and life.

The grateful couple promptly started the Shiland-Maringer Fund for the Advancement of Adult ECMO at NY Presbyterian-Columbia. (To contribute, contact Allison Yessin at alb9020@nyp.org.) "They've been amazing supporters of the program," says Brodie.

"It's amazing that Jay and Dr. Brodie were in the same class at Penn, and there is no question that he—and many other doctors at New York Presbyterian Cornell/Columbia—saved Jay's life," Maringer concluded. "You just never know what a classmate might end up doing for you." *–S.H.*

One of the problems was the "prevailing notion that ARDS meant that your chest X-ray had to be completely white, with the whole X-ray involved," Fuchs explains. "And that's not the case." Another had to do with calculating the P/F ratio, a practice that is "cumbersome" and often not done routinely. As a result, patients were not being treated appropriately.

"Even in a center like my own that had participated in the NIH trial [that confirmed the efficacy of lower tidal volumes for ARDS patients]—and we were believers!—to see that roughly 70 percent of the patients were not getting this therapy was shocking," says Fuchs. "Which is why I sort of devoted my career to trying to improve the implementation of practices that are well established and evidence-based into routine ICU care."

About eight years ago, with the help of several dedicated IT people, Fuchs began working on an automated system that he hoped would diagnose ARDS and ALI among patients at HUP. It's now informally referred to as the "ALI Sniffer."

When they tested its accuracy, says Fuchs, "we found that it was highly accurate and very, very sensitive—it picked up more people with ARDS than an experienced NIH research coordinator who was responsible for screening patients for ARDS in our clinical trials."

The Sniffer, which HUP started using in the fall of 2010, automatically sends text pages to the phones of attending physicians and residents. "It reminds them that the patient meets criteria for ARDS and recommends the use of a low-stretch protocol—lung-protective ventilation—that's in our order-entry system," Fuchs explains, "so you just click a button and it automatically does the calculation for the appropriate-size tidal volume. We tried to make it as easy as possible to implement this intervention.

"I'm still working on this, because ARDS is just such an important problem to diagnose," Fuchs adds. "Lots and lots of people have ARDS in our ICU. You can lose a very, very young person from this complication."

Shelley Najjar still tears up a little when she talks about the medical team, led by Paul Lanken, that treated her boyfriend at HUP's MICU. "I cried when we left the ICU to go to the rehab, because I didn't know what I was going to do without them."

It wasn't just the technical skills and knowledge they brought to Powelson's desperate situation. It was the way the team of doctors interacted with *her*.

"They educated you so much," she says. "We participated in the rounds in the morning and afternoon. I was at every round and listened to what they said. They would let me ask questions. They explained everything. And they were honest. I really trusted them.

"I can't explain how they're different than other doctors that we come in contact with. But there's something different and special about them."

That interaction is the result of a concerted effort, preceded by years of thought and planning.

"We need to actively earn the trust and the confidence of the families," says Hansen-Flaschen, who has been working for decades to do just that. "We can't take it for granted and say, 'I'm a doctor, so therefore bow at my knees and accept everything I say.'

"Families play a critical role in intensive care in that they authorize the treatment, and they authorize the withdrawing of it," he adds. "They sign consent to put a new line in, or to do some surgical procedure, and there isn't any backing out of intensive care into palliative care without their engagement and concurrence. So for more than 10 years I've been inviting families and encouraging them to join us in our daily work rounds. They hear the whole technical conversation. We'll ask them questions, and then they're invited to ask questions and make comments and share observations into the rounds—playing the exact same role of other members of the team."

"It's pretty exciting to be in a place where it's not just the technology," says Paul Lanken. "It's carefully understanding the patient and managing, like a really good team would do, with nursing care, respiratory care, physical therapy, pharmacy—things like that."

That approach meant a lot to Najjar.

"It was huge for me," she says. "I learned so much. They should do that at all hospitals, and I don't know that they do. But in the ICU setting, it's so important."

**One of the first things that Powelson said** when he regained consciousness was a woozy-sounding question: "How's my fantasy football team doing?" He then recited the names of all the players on his team.

Lanken and the others were amazed. Given how long he had been unconscious, and how precarious his blood-oxygen situation had been, Powelson could have suffered serious brain damage. Besides, all those paralyzing drugs and painkillers don't just disappear from the body overnight.

But Powelson wasn't exactly home free. He had lost 40 pounds, and literally was too weak to move a finger or keep his head up. He needed a "coughalator" to help him cough. After he was released from the ICU he would spend nearly two months in an inpatient rehab center, battling everything from mental confusion to bedsores that looked like they had been caused by hand-grenade implants. Today, a year and half later, he looks quite healthy. But he's still not well enough to go back to his job operating heavy machinery for a masonry firm.

"Survivors have a different set of issues," says Hansen-Flaschen, who notes that most of the posts on the ARDS Support Center's website by patients and family members are about the problems of survivors. "Their muscles feel weak all over. They have some hearing loss, difficulty staying on track with a complex set of thoughts like doing your taxes. Flashback memories that sound like post-traumatic stress syndrome. And then this funny emotional lability, where they break into inappropriate laughter or tears."

Which is why the questions that Penn researchers are exploring include: How does that type of long-term impairment develop during a critical injury? Is it a feature of the inherent underlying disease—say, sepsis with kidney and lung injury? Or is it something that occurs during treatment? Stay tuned for answers.

"I have one goal with this thing, and it's to go back to work," says Powelson. "I just want to be back outside, back with the guys I was working with. You know, like life as usual."

And yet: as he and Najjar sit together on the couch in their new home in Phoenixville, looking forward to the rest of their lives, they know, better than anyone, just how lucky he is to be breathing at all.◆