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Deep Breadth

By Jennifer Nachbur

From research on the effects of asbestos to vaping, Vermont Lung Center members continue a leading-edge tradition.

Charles Irvin, Ph.D., and Anne Dixon, M.A., BM BCH

It's easy to take breathing for granted;

for most of us, it happens whether we're paying attention or not. But if you're like Vermonter Bruce Towne, one of the hundreds of millions of people worldwide with a serious lung disease, walking and breathing "become an ordeal fairly quickly."

Healthy lungs work in concert with the trachea, diaphragm, and nasal passages, allowing us to inhale and exhale between 15 to 25 times per minute. Like a bellows that fuels a fire, the lungs expand, drawing oxygen into the body and bloodstream, and compress, expelling waste in the form of carbon dioxide. When something genetic, or in the environment, causes lung injury, the ability to breathe—and one's quality of life—is compromised.

For centuries, lung diseases have threatened human health and motivated scientists and clinicians to determine causes and find solutions. At first, all shortness of breath was considered asthma—a term coined by Greek physician Hippocrates. The condition, along with other lung diseases, became more well-defined over the centuries, and better understood over the past nearly half-century since the Vermont Lung Center at the University of Vermont was founded.

The Age of Asbestos and Silicosis

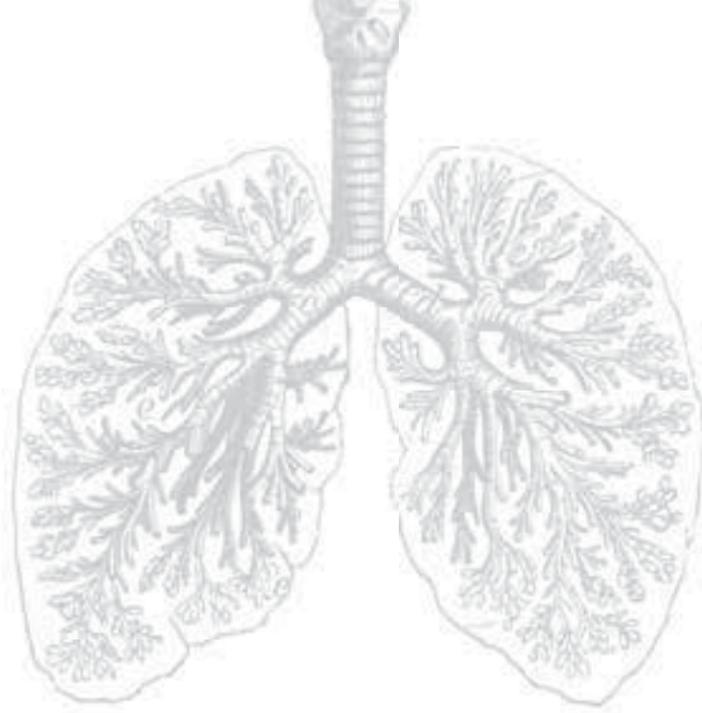
In the early 1970s, decades before the tragedy of 9/11 and the appearance of "World Trade Center cough," a few groundbreaking studies by a small interdisciplinary group of Lung Center-affiliated researchers were putting UVM on the map in the field of environmental impacts on lung function.

In an effort to better understand the causes of interstitial lung disease—fibrosis or scarring in the lungs—UVM's first Lung Center director, the late Gareth Green, M.D., applied for and received the first-ever National Institutes of Health (NIH) National Heart, Lung and Blood Institute Specialized Center of Research (SCOR) grant. Among the populations the group studied were granite workers in Barre, Vt.

"He was a real leader in lung defense immunity and got the SCOR grant for pulmonary fibrosis when we didn't even really know what that was," says current Vermont Lung Center Director and Professor of Medicine Anne Dixon, M.A., BM BCh.

Green's bold move led UVM to become "a world leader in silica and asbestos-induced pulmonary disease," according to Robert Low, Ph.D., professor emeritus of molecular physiology and biophysics, who took on leadership of the SCOR grant after Green left the university in 1978. The award also ignited the careers of faculty like Professor Emeritus of Medicine Gerald Davis, M.D., and University Distinguished Professor of Pathology and Laboratory Medicine Brooke Mossman, Ph.D. A clinician, Davis spearheaded research involving granite workers using a novel tool called bronchoalveolar lavage to diagnose lung disease; Mossman published the first paper on asbestos exposure and lung injury and went on to become an internationally recognized expert on mesothelioma, an asbestos-related cancer.

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The relationships forged between the Departments of Medicine, Physiology, Pathology, and Engineering during that time still remain today, says Dixon, and are critical to the Lung Center's success as "a forum for investigators from multiple departments to come together to collaborate on the science of pulmonary disease," says E. L. Amidon Chair and Professor of Medicine Polly Parsons, M.D.

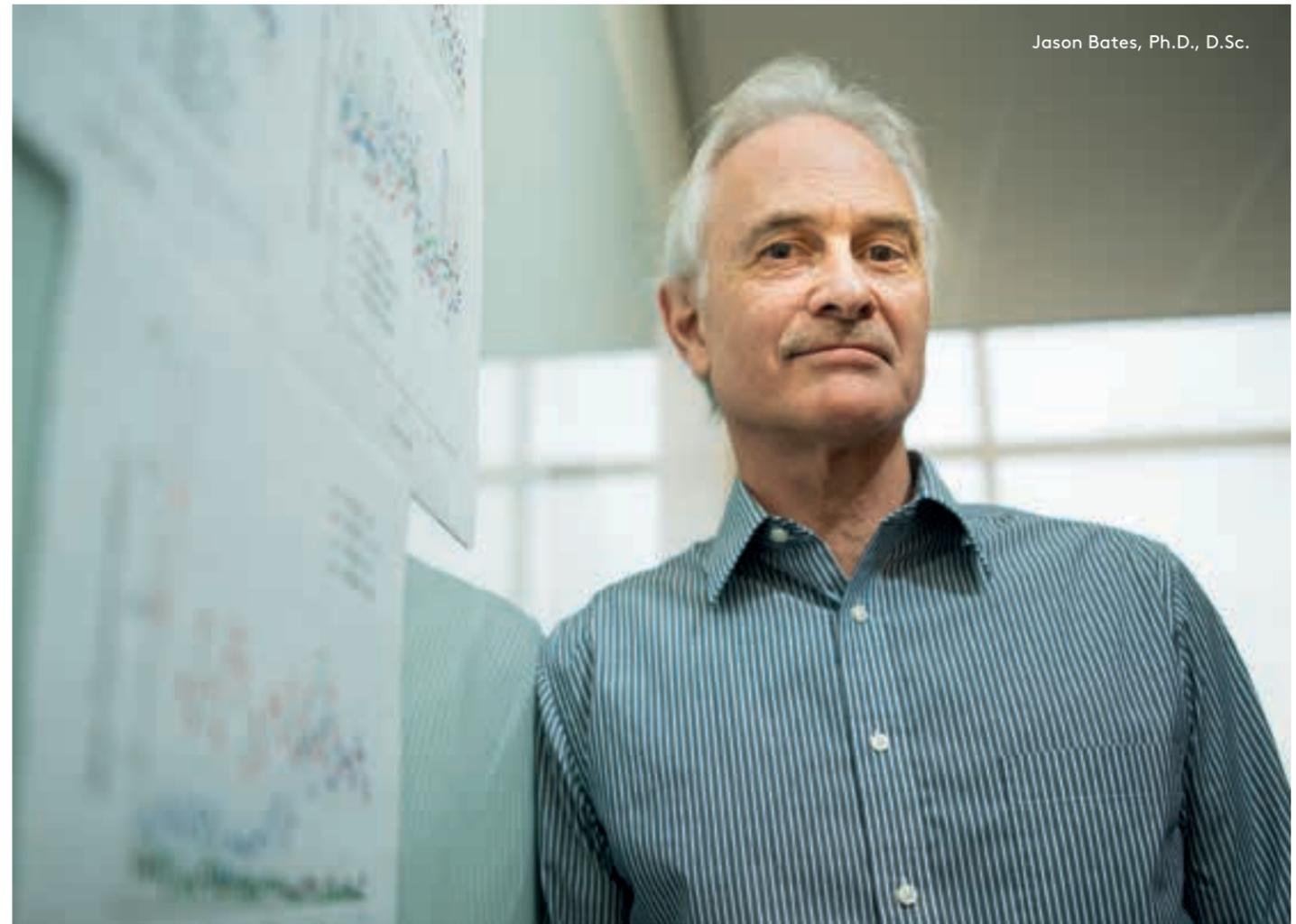
Chartering an ACRC and UVM's First COBRE

Despite a lull in the 1990s, the Center entered a revitalization phase in 1998 when UVM's Division of Pulmonary and Critical Care Medicine hired several "key recruits who really formed an incredibly

important nucleus," says Dixon. The first was David Kaminsky, M.D., an expert in pulmonary physiology and pulmonary function testing who'd just completed a fellowship at the University of Colorado who Davis—then chief of pulmonary—hired. Soon after, biomedical engineer and lung mechanics expert Jason Bates, Ph.D., D.Sc., came on board, followed by a new director for the Lung Center: Charles Irvin, Ph.D., an expert in the mechanisms of airway dysfunction in asthma.

Irvin, several of his UVM colleagues, and a small local chapter of the American Lung Association (ALA) took on the daring task of bringing an Asthma (now Airways) Clinical Research Center (ACRC) to Vermont in 1999. The following year, he secured a Center of Biomedical Research Excellence (COBRE) award, which provided 15 years of funding from the National Institutes of Health's (NIH) National Institute of General Medical Sciences and gave the Vermont Lung Center an international leadership reputation in basic and clinical respiratory and critical care disease research.

UVM's charter membership in the ACRC network played a pivotal role in moving asthma research to the forefront, and reinforced the Lung Center's position as a leader in the field. The network saw early



success with its first major clinical trial, which demonstrated the safety of the flu vaccine for children and adults with asthma. The study, which was published in the *New England Journal of Medicine*, led the Centers for Disease Control and Prevention to change their flu shot recommendations to include everyone six months of age and older.

Since then, the ACRC network has completed 16 studies and the medical world's understanding of asthma and lung diseases has evolved. "We've learned about the importance of some comorbidities—westernized lifestyle, nutrition, and obesity—and the effects that has on asthma, which has really transformed the epidemiology of asthma," Dixon says.

In 2016, the ACRC changed the network's name from "Asthma" to "Airways" to incorporate clinical research on COPD—chronic pulmonary obstructive disease—a condition closely linked to cigarette smoking that is now the fourth leading cause of death worldwide. Dixon and Kaminsky are leading several clinical trials relating to COPD. Surprisingly, "Vermont's ACRC is still the only ACRC site in New England," says Irvin.

The COBRE grant—the first ever received at UVM—helped establish state-of-the-art laboratories and jump-start the careers of now-senior faculty members like Dixon, Kaminsky, Matthew Poynter, Ph.D., and Yvonne Janssen Heining, Ph.D. Bates considers the milestone "the seminal event that really launched the entire lung research enterprise."

The structure of the grant encouraged clinical and basic scientists to work together, and that became the trademark

culture of the Vermont Lung Center. "The research environment established by the COBRE grant was critical in the research I conducted and led to my patent applications involving novel ways to assess lung function in both animal models and in patients with acute lung injury," Bates says.

Bates' expertise lay in the area of lung function assessment and for the COBRE, he oversaw the mouse phenotyping core facility, which houses a micro-CT scanner and several Flexivent computer-controlled mouse mechanical ventilators, which he developed at McGill University before coming to UVM.

"The Flexivent was subsequently commercialized by Scirec, a Montreal company, leading to a now widely-used device that is quite expensive," says Bates. "The COBRE funds allowed us to setup a phenotyping core based around these devices."

Bringing Breakthrough Cystic Fibrosis Treatments to Patients

In 2019, UVM Medical Center's Adult Cystic Fibrosis Program, led by Charlotte Teneback, M.D., associate professor of medicine, was named a Cystic Fibrosis Foundation-accredited Care Center and received a Cystic Fibrosis Therapeutic Development Center Award. The Pediatric Cystic Fibrosis Program at UVM Children's Hospital, led by Thomas Lahiri, M.D., professor of pediatrics, received a Quality Care Award from the Cystic Fibrosis Foundation (CFF). The award recognizes CFF-accredited care centers that have continuously demonstrated a commitment to improving the quality of care they provide to people with cystic fibrosis.



“The CF Foundation partnered with pharmaceutical companies to form this [Cystic Fibrosis Therapeutic Development Center] network,” which investigated drugs to treat the molecular deficit in CF,” explains Dixon. “Those drugs have come to fruition and have transformed how CF looks. The CF team, who are members of the Vermont Lung Center, does an incredible job recruiting patients and involving patients.”

A Culture of Collaboration

Gwen Skloot, M.D., Ph.D., a professor of medicine at Mount Sinai National Jewish Health Respiratory Institute and chair of the Assembly on Respiratory Structure and Function for the American Thoracic Society, is a longstanding research collaborator with many Vermont Lung Center members, including Dixon, Bates and Kaminsky. She considers these UVM researchers her “go-to people” in the U.S. for research expertise in the field of pulmonary physiology.

“In addition to understanding physiology, Dr. Bates, with his engineering background, has applied mathematical complexities and boiled it down to something simple that anyone can understand,” she says.

“Dr. Kaminsky has taken a lead role in establishing guidelines for various aspects of pulmonary function testing—he is a leader in the field. Dr. Dixon is a leader in understanding obese asthma.”

“Their work on the pulmonary pathophysiology of obesity and asthma has really made great strides in understanding the late-onset non-allergic obese asthma phenotype,” says Skloot, citing the multiple studies that demonstrated this phenotype may be characterized by increased collapsibility of the peripheral airways.

A key part of the Lung Center culture is its emphasis on training the next generation of researchers. In 2004, Irvin, with support from Parsons, was awarded a T32 training grant from the NIH’s National Heart, Lung and Blood Institute to fund the training and work of predoctoral students pursuing their Ph.D. or M.D. degrees and postdoctoral fellows seeking advanced research experience after earning an M.D. or Ph.D. The NIH training grant has just been renewed for a fourth cycle of funding.

“We’ve had some postdocs that have gone and done incredible things,” says Irvin. He points to Darcy Wagner, Ph.D., as an example. Wagner worked with Professor of Medicine Daniel Weiss, M.D., Ph.D., doing lung regeneration research. She now leads studies as a faculty member at Sweden’s Lund University and co-chairs the biennial international “Stem Cells, Cell Therapies, and Bioengineering in Lung Biology and Diseases” symposium at UVM.

New Frontiers

While some lung diseases of the past have improved over the last century, new diseases are on the rise, including the latest issue of acute lung injury related to e-cigarettes and vaping.

At left, clockwise: Prema Menon, M.D., Ph.D., Yvonne Janssen Heininger, Ph.D., Darcy Wagner, Ph.D. (left) and Daniel Weiss, M.D., Ph.D. and David Kaminsky, M.D.

Over the past several years, Menon has brought a number of pulmonary fibrosis clinical trials to UVM, two of which became FDA approved treatments. This, in the end, is the key promise of the lung center, bringing new hope to patients.

The VLC will be part of the American Lung Association’s new NIH Adult Cohort for Lung Disease. The objective of the six-year grant is to recruit 200 adults between the ages of 25-35 to perform a baseline of lung health, with the objective of identifying the determinants of ideal lung health and trying to detect early signs of abnormal lung health before it develops.

“I think the Lung Health cohort is going to be a great opportunity to fully understand the impact that nutrition and obesity have on lung health,” says Dixon, whose team will be recruiting patients in fall 2020. “We hope to eventually follow these people over time, but it’s just being formed,” she says, adding that “this is going to be an incredible part of what we do.”

In addition, she says, “Pulmonary fibrosis is going to be an important part of our future, with clinicians like Prema Menon, M.D., Ph.D., and basic scientists like Yvonne Janssen-Heininger, Ph.D., and Jos van der Velden, Ph.D., collaborating,” says Dixon.

Though decades have passed since Vermont Lung Center members’ research on the mechanism of pulmonary fibrosis—a disease which

causes a thickening and stiffening of lung tissue that complicates normal breathing—the condition persists, affecting more than 200,000 people in the U.S. and causing 40,000 deaths annually. About 50 percent of patients with pulmonary fibrosis die of the disease within three to five years. But there is good news, thanks to groundbreaking discoveries by an interdisciplinary collaboration among several Lung Center members. Janssen-Heininger and colleagues, including Associate Professor of Pathology and Laboratory Medicine Vikas Anathy, Ph.D., discovered and patented the use of glutaredoxin (GLRX)—an oxidant-controlling enzyme that shows promise as a treatment for patients with lung fibrosis

and other diseases, which has been shown to reverse fibrosis in mouse models. In 2019, the generous donation of lung tissue from recently-passed pulmonary fibrosis patients of Prema Menon, M.D., Ph.D., assistant professor of medicine and director of the Interstitial Lung Disease Clinic at the UVM Medical Center, allowed members of the team to do research with human tissue. Now, researchers like Jos van der Velden, Ph.D., assistant professor of pathology and laboratory medicine, are using that tissue to create mini lungs to test the potential of GLRX to repair damaged proteins in the lungs of pulmonary fibrosis patients.

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The new pulmonary fibrosis treatments have given hope to one of Menon’s patients, Bruce Towne, from Colchester, Vt., who credits his participation in the trials and recent treatment regimens with keeping him alive years beyond his diagnosis.

“It took me probably six months to come to terms that I was going to die from this disease,” Towne said, when interviewed for a WCAX-TV report in 2019. Now, he says, his future has expanded. “[I’m] feeling like I’d like another 15 years. I’m greedy now.” VM