THE QUESTION I OWN —
Leo Otterbein, PhD

Most people equate carbon monoxide (CO) with deadly danger, largely from reading about CO poisoning in the news. But Leo Otterbein, PhD, a basic scientist in the Division of Transplantation, has an entirely different perspective on CO — a perspective based on years of pioneering research.

In fact, he lauds its virtues. “At low, non-toxic concentrations, CO has potent protective effects in many clinically relevant models of disease including lung injury, hemorrhagic and septic shock, vascular disease, and cancer,” says Otterbein.

Otterbein and his collaborators have even shown that CO improves the outcomes of kidney transplants in animals, which led to the first clinical trial in humans, and may also be beneficial for patients undergoing partial liver resection.

Administered by various delivery methods, many of which Otterbein developed in collaboration with engineers and medicinal chemists, CO is now being evaluated in clinical trials of patients with a wide range of conditions, from sickle cell anemia and pulmonary disease to gastrointestinal disorders.

As a result of Otterbein’s longtime investigations of CO, which began when he was a graduate student at Johns Hopkins University, it is now broadly accepted that the much-maligned gas has important biologic effects and, at the right levels, provides benefits that are still being revealed. “The question I own,” says Otterbein, “is how does this simple molecule impart such powerful physiological effects in the body?”

Launching a new field
CO is one of three products generated from the actions of a basic metabolic enzyme called heme-oxygenase-1 (HO-1), which has long been characterized as a protective gene in various cell types and tissues in the body.

When Otterbein began working on his doctorate in physiology at Johns Hopkins, everyone chalked up the protective effects attributed to HO-1 to the end product bilirubin, the most potent antioxidant in the body (and another focus of Otterbein’s research).

Ignoring most of his advisors, who thought it would result in a dead end, Otterbein set out to discover whether CO might also offer beneficial effects. CO had been studied for decades as a poison, but Otterbein was convinced it could be repurposed to provide benefit.

“At the time, no one would have guessed that CO, which everyone considered toxic, might also be protective,” says Otterbein, who worked as a scientist in biotech for five years before receiving his PhD. As a result of his perseverance, Otterbein is credited with launching an entirely new field of investigation that is being pursued by basic and clinical researchers worldwide.

A critical experiment
In one critical experiment conducted while he was at Johns Hopkins, Otterbein administered very low levels of CO to rats that were destined to die within a few days from extensive lung inflammation and injury. “Based on the anti-inflammatory effects I’d seen in cells, my hypothesis was that CO would similarly benefit the animals,” explains Otterbein.

He was correct. But even Otterbein was surprised by the results. “After four days, all the rats who breathed the CO were still alive, while those who hadn’t were dead.” Further experiments over many years administering CO in models of shock, vascular disease, acute liver injury, and organ transplantation resulted in equally compelling evidence of the gas’s beneficial effects.

After receiving his PhD, Otterbein continued his research at Yale University under the mentorship of Augustine Choi, MD. During that period, he began a collaboration with renowned BIDMC transplant surgeon-scientist Fritz Bach, MD.

Bach knew about Otterbein’s work and became interested in the potential of CO to prevent organ