



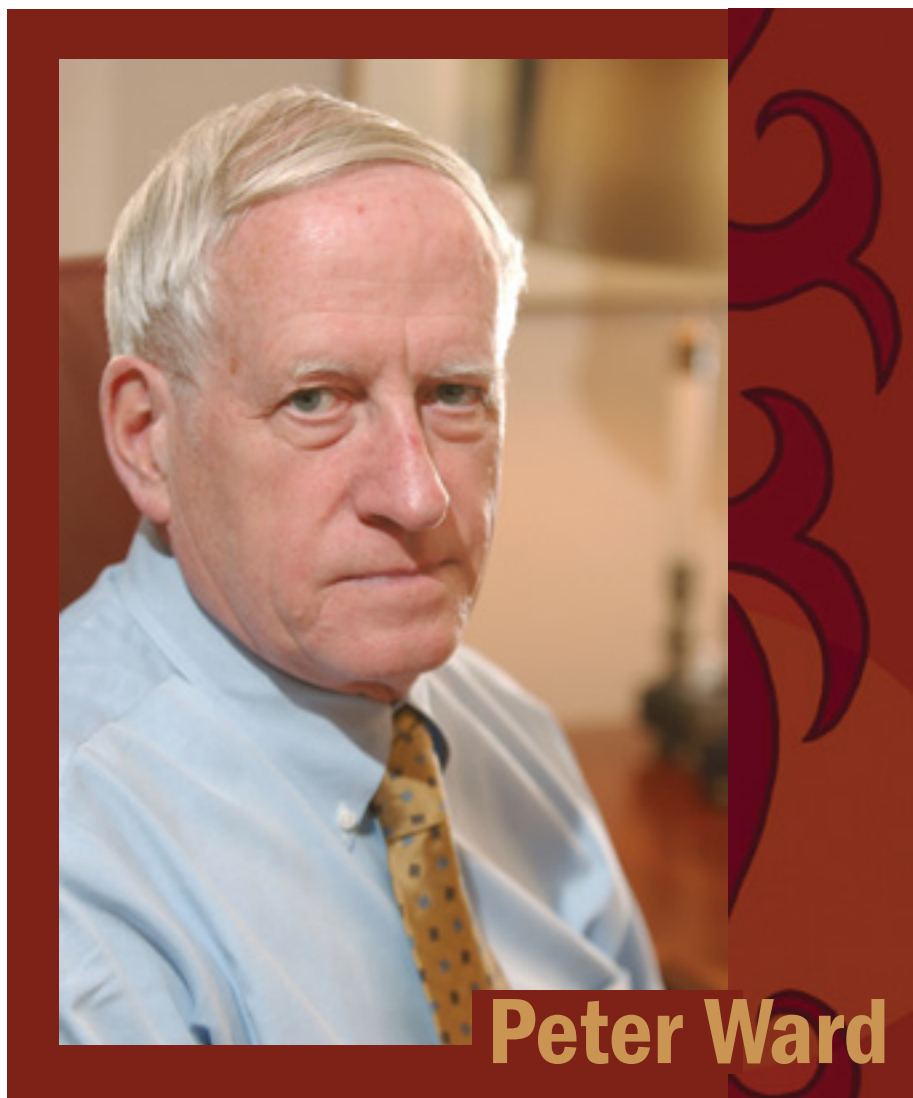
“When immune systems go awry, virtually without exception the problem begins with the triggering of a strong inflammatory response,” Ward says. “All autoimmune diseases — such as rheumatoid arthritis, psoriasis, lupus or multiple sclerosis — are diseases in which the inflammatory response is unregulated, excessive and out of control. So understanding the inflammatory system from A to Z will have huge applications in any number of diseases or clinical situations.”

Over six feet tall with the posture and presence of a military officer, Ward is a distinguished looking gentleman who always wears a dress shirt and tie under his freshly pressed white lab coat. Not one for rash statements or hyperbole, Ward is as precise and methodical when talking about his research as he is doing the work itself.

Peter Ward’s fascination with inflammation began more than 45 years ago while he was a student at the U-M Medical School. During a two-year research fellowship at California’s Scripps Institute, then five years of service in the U.S. Medical Corps and nearly 10 years as head of pathology for the University of Connecticut Health Center, Ward concentrated on learning how acute inflammation affects the lung.

Ward says he focused on inflammation in the lung because so little was known about what caused it or how to treat it effectively. While at the University of Connecticut in the 1970s, Ward made many important contributions to the field, including developing animal models with injuries that trigger an inflammatory response. Many of these models are still used in research by scientists today. In addition, Ward published hundreds of papers describing how substances produced by immune cells called macrophages and neutrophils contribute to lung damage during an inflammatory attack.

In 1980, Ward returned to the U-M to become professor and chair of the Medical School’s Department of Pathology, serving also as interim dean from 1983 to 1985. Since then, he has continued his focus on inflammation in the lung, especially the importance of messenger molecules called cytokines and chemokines, and the complement system — a group of about 25 related proteins that patrol the bloodstream ready to assist or “complement” the immune response.



**Peter Ward**

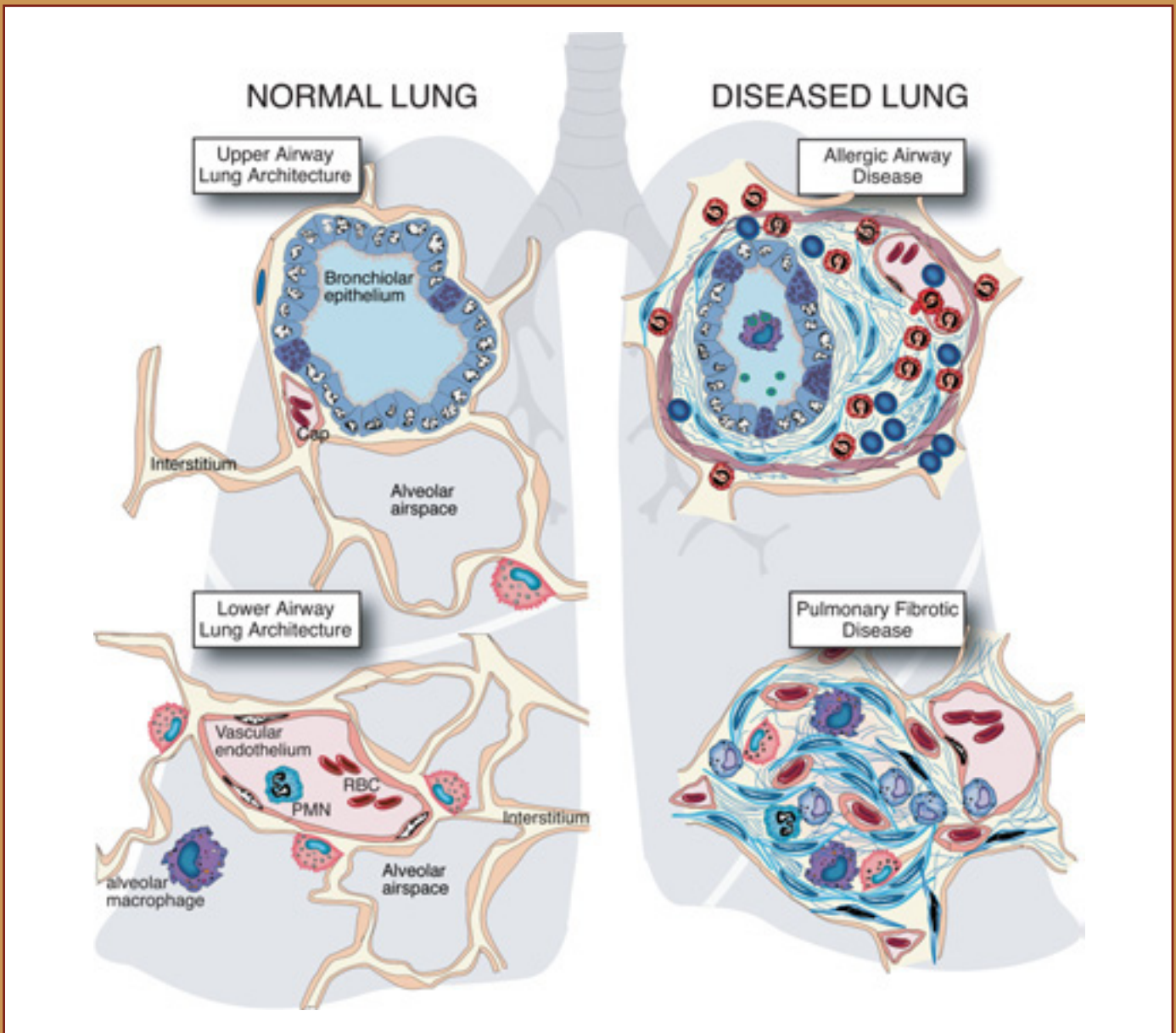
### **Mediating the inflammatory frenzy**

The inflammatory response has one all-important goal: respond immediately to detect and destroy infection or toxic material in damaged tissue before it can spread to other areas of the body. In its zeal to protect the body, it will destroy as much tissue as necessary to accomplish this goal. Left unchecked, a hyperactive inflammatory response can even react to the traumatic effects of accidents, burns or surgery on the body and start attacking healthy tissue.

Like everything else in the human immune system, the inflammatory response is controlled by an incredibly complicated communications network made up of multiple cells, cascading signal pathways and feedback loops. It starts when scavenger cells called neutrophils arrive at the site of injury or infection. They surround and engulf tox-

ins, microbes or damaged tissue and broadcast biochemical “SOS” signals calling for reinforcements. Complement proteins join the fray triggering the production of powerful, pro-inflammatory molecules and tissue-destroying enzymes. This intensifies the response and causes inflammation to spread to surrounding tissue. Once activated, the feeding frenzy will continue until the immune system sends an all-clear signal to indicate that the crisis is over.

One of the most important discoveries made by Ward and other scientists over the last 20 years has been the identification of a network of natural anti-inflammatory mediators, produced by the immune system to offset activity of pro-inflammatory agents. This network of “chill out” signals keeps inflammation focused on the area of local infection or injury, and prevents a runaway response that can spread through the body. ➤



In the normal lung (left), very thin walls in the upper and lower airways allow the normal exchange of gases between blood vessels and the airspace. The diseased lung (right) shows pathological changes. Upper airway diseases, like asthma, produce an influx of inflammatory cells, increased fibrosis and constriction of the bronchiolar airways. In lower airway diseases, such as interstitial pulmonary fibrosis, fibroblasts and mononuclear inflammatory cells lead to collagen deposits and a thickening of the lung walls.

“When you trigger an inflammatory response, two types of mediators are produced,” Ward explains. “Some are strong pro-inflammatory mediators, while others tend to suppress or balance the inflammatory process. Most of our work has involved acute inflammatory responses in the lung, but we don’t believe pathways of inflammation in the lung are unique. So learning more about these natural anti-inflammatory agents should provide information that can be applied to many situations where you hope to suppress the inflammatory response.”

Out-of-control inflammation has different effects on different types of tissue. In the respiratory system, these effects can be disabling, as is often the case with asthma; or lethal, as in chronic obstructive pulmonary disease. COPD, which includes emphysema and chronic bronchitis, is caused by an inflammatory reaction which modifies the upper airways and makes it difficult to breathe.



## THE INFLAMMATORY SYSTEM IS SO COMPLEX THAT PETER WARD BELIEVES IT COULD TAKE A DECADE OR MORE OF INTENSIVE RESEARCH BEFORE SCIENTISTS UNDERSTAND EXACTLY HOW IT WORKS.

According to a 2001 study conducted by the National Heart, Lung and Blood Institute, more than 12 million Americans ages 25 and older have been diagnosed with COPD and as many as 24 million show signs of impaired lung function. It is the fourth leading cause of death in the United States.

“Patients with COPD typically have a slow, progressive loss of pulmonary function over a period of many years,” Ward says. “It’s been linked to smoking and industrial air pollution. COPD is difficult to treat because, for reasons we don’t understand, patients don’t respond to the anti-inflammatory effects of steroid drugs like cortisol. Non-steroidal anti-inflammatory drugs treat symptoms, but do little to stop the progressive tissue destruction.”

Then there’s idiopathic pulmonary fibrosis — another group of progressive lung diseases, in which inflammation slowly destroys air sacs in the lung and replaces

them with scar tissue. Both the cause and a cure for pulmonary fibrosis are unknown, and 40,000 people die from its effects every year.

According to Stewart C. Wang, M.D., Ph.D., an associate professor of surgery in the Medical School who treats critically ill patients in the U-M Trauma/Burn Center, the lung also is particularly vulnerable to collateral damage from the immune system’s attempts to fight infection elsewhere in the body.

“The lung is such a vital organ, and it must function at high capacity at all times. As you get sicker, your body has to work harder, which means the lung has to work harder to provide more oxygen,” Wang explains. “Also, because all blood passes through the lung, it’s exposed continually to inflammatory signals carried in blood from other parts of the body. This makes the lung especially prone to damage from sepsis, which can lead to acute lung failure.”

### The enigma of sepsis

Sepsis is the most dramatic example of what can happen to the human body when it is attacked by an out-of-control inflammatory response. In the United States this year, more than 600,000 Americans will experience the deadly combination of symptoms — high fever, elevated white blood cell count, rapid heartbeat, falling blood pressure and confusion — that physicians call sepsis. Even with the best possible intensive care, mortality from the most severe forms of sepsis can be as high as 40 percent. Sepsis kills more people each year than breast cancer and prostate cancer combined.

“The key is to detect sepsis early, before the infection gets out of control,” says Wang. “We need to figure out ways to treat the complications of sepsis to reduce the mortality rate. That’s what is so promising about the work Dr. Ward is doing. His research is giving us potential

future therapies to prevent the damage that occurs from infection, especially during sepsis.”

Even though it’s a major killer, doctors know little about what triggers sepsis and even less about how to treat it successfully. Patients at highest risk are those recovering from traumatic injuries or surgery, and those with serious infections or chronic diseases. Unless it’s caught early, sepsis can kill a formerly healthy adult in just a few days.

“Essentially, it’s a waiting game,” says Ward. “There is no diagnostic test and only one drug approved for treatment of patients with severe sepsis. All we can do is give broad-spectrum antibiotics with traditional supportive therapy, and hope it doesn’t progress to the stage where organs start to shut down. If you’re still alive after 28 days, you’ll probably be OK.”

Four years ago, Ward expanded his research on the inflammatory response

to include what he calls “the enigma of sepsis.” Since then, he has discovered that the complement system in laboratory rats with sepsis is hyperactive, and the rats have abnormally high amounts of a pro-inflammatory protein called C5a in their bloodstream. When the animals are given drugs to block C5a’s effects, their survival rates improve substantially.

“C5a is an intriguing protein,” Ward says. “It’s vital to the immune system’s ability to fight infection in tissue, but if it starts cascading out of control and enters the bloodstream, it’s an indication that bad things are going to happen.”

In recent research, Ward and his team discovered that, once C5a is in the bloodstream, it blocks all the receptors on circulating neutrophils — preventing them from attacking invading bacteria and effectively paralyzing the immune response.



**Stewart Wang**

“We hope to find a way to block the activity of C5a in animals with sepsis,” Ward says. “If we are successful, it could be an effective therapeutic intervention in humans. We also are investigating how to measure the C5a receptor content of neutrophils. This could be the basis of an early diagnostic test for sepsis to help physicians identify patients who need immediate aggressive treatment.”

### **The pharmaceutical approach**

Considering the number of people affected by inflammatory diseases, it's surprising that few new pharmaceutical drugs have been developed to treat these medical conditions. The mainstays of treatment are still corticosteroids, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen. Aspirin's anti-inflammatory properties were discovered in the early 1900s. Steroids, the first class of drugs with

generalized anti-inflammatory effects, were developed in the 1950s.

In the 1990s, several new anti-inflammatory drugs called COX-2 inhibitors, which are sold under trade names like Celebrex, Bextra and Vioxx, were approved by the Food and Drug Administration. They were hailed as miracle drugs for the treatment of chronic inflammatory diseases, because they don't irritate the stomach lining, like aspirin or other NSAIDs often do.

“NSAIDs are effective at treating symptoms, but we've learned they don't have much ability to suppress the inflammatory response. The disease continues to progress,” says Ward. “Steroids are very effective, but they have serious side effects. And long-term use of COX-2 inhibitors is now associated with a higher risk of strokes and heart attacks.”

Recently, pharmaceutical companies introduced a new type of anti-inflamma-

tory drug, which works by preventing the biological function of tumor necrosis factor (TNF) — an important pro-inflammatory molecule. When TNF binds to immune cells, it triggers the inflammatory response. Ward says these drugs reduce symptoms and can be effective, especially in rheumatoid arthritis, but their cost per patient ranges from \$12,000 to \$20,000 each year.

“So here we are, 50 years after the anti-inflammatory effects of steroids were discovered, and there's still no new powerful, reasonably priced drug that can be used across the board for these inflammatory diseases,” Ward says. “It's a real dilemma. There are serious questions about where the pharmaceutical industry will go from here in relation to anti-inflammatory drugs.”

According to Ward, the pharmaceutical industry has traditionally developed drugs that interfere with the immune system's pro-inflammatory pathway by binding to a cell receptor or blocking the actions of specific proteins or signaling molecules. He suggests it may be time for a different approach.

“We need to explore novel strategies using nature's own inflammatory regulatory apparatus,” Ward says. “This means concentrating on finding mediators with anti-inflammatory effects.”

The trick to Ward's approach is figuring out how to turn on genes that control production of these anti-inflammatory molecules. Right now, he has hopes for a protein called Stat3. Stat3 has a strong anti-inflammatory effect, and scientists in Ward's lab have shown that it reduces tissue damage in rats with acute lung injuries.

**U**ltimately, Ward believes the answer to controlling inflammation's dark side will be found in basic scientific research conducted jointly by scientists from academic and corporate research laboratories. The inflammatory system is so complex that Ward believes it could take a decade or more of intensive research before scientists understand exactly how it works.

“It's just like investing in the stock market,” he says. “You can't look for short-term returns. It's a long-term investment.” 