



## FEATURE STORY

# The Internal Flame

BY KAREN PATTERSON

*Chronic inflammation causes cancer. Find out how and what's being done about it.*

While cancer is often characterized as invasive, many tumors get their start with the help of a different kind of biological invader, one that slipped quietly into the body years earlier.

Like a clever saboteur, that early interloper—a bacterium such as *Helicobacter pylori* in the stomach, a virus like hepatitis B or C in the liver, or even a parasite in the bile duct—can keep the body's own defenses off balance, aiding and abetting the tumor yet to come.

Such invaders, which may persist for decades undetected, cause a chronic inflammatory state in infected tissues, a situation in which the immune system is constantly primed for battle. Chemicals and processes normally geared to wage short-term war on an acute infection or traumatic injury are instead engaged for the long haul, creating an environment that is fertile ground for tumors to form—and then to thrive.

“Cancers will do whatever they can to survive and prosper,” says cancer biologist Raymond DuBois, MD, PhD, of M.D. Anderson Cancer Center in Houston. “One of the ways they’ve been able to do that is to usurp some of the body’s immune mechanisms.”

The inflammation-cancer connection has become a hot topic—hot enough that in 2004 the National Cancer Institute convened a “think tank” panel to make recommendations for future research.

“One of our tasks was to identify gaps in knowledge, and we identified a lot,” says participant Richard Peek Jr., MD, of the Vanderbilt-Ingram Cancer Center at Vanderbilt University in Nashville, Tennessee. “It’s a very complicated picture.”

Inflammation induced by infection is thought to contribute to between 10 and 20 percent of cancers worldwide, Peek says. “There are specific examples where it’s clearly proven that a viral agent or a bacterium that induces inflammation significantly raises the risk for cancer,” he says.

[View Chart : Making the Connection](#)

View Chart : Making the Connection

But there are other causes of chronic inflammation related to cancer as well, notes Robert Weinberg, PhD, director of the Ludwig Center for Molecular Oncology at the Massachusetts Institute of Technology in Cambridge. Many such causes are not well-understood, he says. For instance, tiny areas of inflammation can exist in the breast before a tumor develops—and an uncommon type of breast cancer known as inflammatory breast cancer has long puzzled physicians. Chronic irritants like cigarette smoke may promote lung cancer in part through an inflammatory process.

Meanwhile, inflammation's role in some cancers of the colon is well-established. Patients with inflammatory bowel disease, such as ulcerative colitis or Crohn's disease, have a marked increase in cancer risk. Inflammation has also been implicated in bladder cancer, and there's some evidence it may play a role in prostate cancer as well.

In all, there may be many more sources of cancer-related inflammation than scientists—or patients—are currently attuned to. "It's not as if we humans are actively aware that these local areas of inflammation exist in many sites in our bodies," Weinberg says. "They may exist for decades without our knowledge." Indeed, many people may be unaware they have chronic inflammation since the conditions to blame can cause varied, or even little or no symptoms.

Retired bricklayer Lou D'Andrea, 70, of New Rochelle, New York, says he didn't have much chance to consider his risk of liver cancer after he learned in 2006 that he had chronic hepatitis C. Before he could even get the hepatitis treated, an early-stage tumor was detected. But the tumor wasn't on his liver. It was where his stomach meets his esophagus—gastroesophageal junction cancer.

---

Indeed, many people may be unaware they have chronic inflammation since the conditions to blame can cause varied, or even little or no symptoms.

---

Because of various health factors, he was not a candidate for surgery. So the stage 2 tumor was treated with chemotherapy and radiation.

Meanwhile, D'Andrea's body never cleared the hepatitis C—he was deemed unable to tolerate the treatment—and he remained at high risk for liver cancer. In 2008, a CT scan found a small cancer on his liver—a new primary tumor—most likely a result of the chronic inflammation from the hepatitis, says Manish A. Shah, MD, D'Andrea's physician at Memorial Sloan-Kettering Cancer Center in New York City. That tumor was treated with radiofrequency ablation.

### Cooling the Flame

For many years, research into the origins of cancer focused on the notion of one cell unilaterally going awry and spawning a malignancy. More recently, scientists have grasped that a multiplicity of factors in the vicinity of a cell—its so-called microenvironment—can help the process along.

"The question is, what happens to a normal cell en route to becoming a cancer

cell?” says Weinberg. “It may find itself in inflamed tissue, where the -biochemical conditions of inflammation encourage it to proliferate and acquire more and more genetic changes, incrementally leading it to develop into a malignant cell.”

### View Illustration : When the Defense Never Rests

View Illustration : When the Defense Never Rests

Such tumor-friendly microenvironments—which not only can help a cancer get started but also grow—can vary substantially from site to site. “People in the research labs are looking at what inflammatory mediators are present, which immune cells are infiltrating the cancer—is there something specific about liver versus bladder versus prostate where we can use some sort of immune therapy along with the standard [cancer] therapy?” says DuBois, provost and executive vice president for academic affairs at M.D. Anderson. “We’re pretty much in a discovery phase.”

Among the many inflammation-related players in tumor microenvironments are a class of signaling molecules known as proinflammatory cytokines, with names such as interleukin-1 beta (IL-1 beta), IL-6, and TNF-alpha. These chemicals can activate processes, or pathways, that promote the growth of blood vessels carrying nourishment to a tumor. They can also help dangerous pre-cancerous cells, which might otherwise eliminate themselves, avoid cell suicide.

Cytokines can modify behavior of some cells in other ways, prompting them to reproduce faster and thereby heightening their risk of acquiring mutations. “Most of the data would suggest they are the biggest player,” Peek says.

Other prominent players include prostaglandins, substances that mediate inflammation and are products of a cyclooxygenase, or COX, enzyme, which is activated by inflammation. Research has indicated that long-term use of non-steroidal anti-inflammatory drugs can inhibit this enzyme and stifle a key cancer-promoting process.

Studies by DuBois and others have focused on the COX enzyme and colorectal cancer—including research showing that the drug Celebrex (celecoxib) and similar anti-inflammatory medicines, known as COX-2 inhibitors, can reduce pre-cancerous colon polyps.

Levels of the COX-2 form of the enzyme are elevated in about 85 percent of colon cancers, DuBois says, which suggests inhibiting COX-2 could lower cancer risk. Unfortunately, the research by DuBois and several others on the COX-2 inhibitors, in which patients took the medicines over an extended period of time, led to a highly publicized finding that the popular painkillers were associated with rare but serious cardiovascular side effects, including heart attacks and strokes.

But their anti-cancer effect was clear: In a study led by Monica Bertagnolli, MD, of Harvard Medical School, among patients who had pre-cancerous polyps detected and removed during colonoscopy, those given Celebrex for three years experienced about a two-thirds reduction in the number of polyps likely to become cancerous, compared with patients given a placebo, DuBois says, adding

that there is still some hope that COX-2 inhibitors can have a place in cancer prevention. For one thing, people at highest risk for cardiovascular side effects in Bertagnolli's study turned out to be those who already had significant cardiovascular disease. For another, her study used very high doses of the drugs; lower doses are accompanied by fewer side effects, research has shown.

### Does Everyone Need Prevention?

Prevention is also complicated when it comes to stomach cancer and the chronic inflammation caused by *H. pylori* infection, the prevalence of which is on the decline in the United States and worldwide.

Physicians, aware of the bacteria's role in ulcers as well as cancer, treat the infection with antibiotics and in some cases are probably preventing stomach cancers. But many people may be receiving treatment unnecessarily, says Peek, director of Gastroenterology, Hepatology and Nutrition at Vanderbilt.

"The pendulum has swung just a little too far. A lot of patients who don't have ulcers but have nonspecific symptoms are getting tested and treated," Peek says. "We don't know the consequences." He notes that only a portion of infected people will get ulcers, and a smaller fraction will develop gastric cancer.

One area of concern is that while *H. pylori* infection is declining in developed nations, the prevalence of cancer related to Barrett's esophagus, a condition caused by severe acid reflux, is rising. Research has suggested that *H. pylori* provides a protective effect against acid reflux disease and Barrett's esophagus. "The message is that there may be unintended consequences of indiscriminately treating patients," Peek says. Patients treated for *H. pylori* infection should be those for whom the bacteria poses a specific risk: for instance, people with documented ulcer disease, a personal or family history of gastric cancer, or pre-malignant changes in the stomach, Peek says.

Genetic variations among individuals may also help explain why only a certain percentage of those who are infected get cancer, says Sloan-Kettering's Shah. He and colleagues at Sloan-Kettering are studying genes that are activated when *H. pylori* infects a person, focusing on subtle variations in certain immune response genes.

"Maybe a specific, unique immune response [to *H. pylori*] leads people down the path to get cancer," Shah says. "Maybe those are the people who need not only treatment of the infection but also a drug that will turn down their immune response."



Lou D'Andrea's liver cancer was likely tied to chronic inflammation caused by hepatitis C. Photo by Ryan Ashby.

What it comes down to for patients is that even though symptoms vary—or may not be present at all—for different inflammatory conditions, being diagnosed with a certain condition can prompt close monitoring of at-risk patients for cancer. D'Andrea's doctors are still keeping an eye on both cancer sites, and so

far, so good.

D'Andrea never saw either of his cancers coming, but he's now well-aware of how insidious a chronic infection can be. "As far as the hepatitis goes, I have no clue how I wound up with this," he says of the bloodborne infection. "The doctor had no clue. He said, 'You could have had it for 40 years.' "