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Cancer Miracles

Robert Langreth 03.02.09

Charles Burrows noticed a strange lump on his stomach in the summer of 2005. By November the pain was so bad it felt like a knife was stabbing him in the stomach. A ct scan and a biopsy confirmed Burrows' worst fears: He had inoperable liver cancer.

Few cancers have a worse prognosis. His tumor, the size of a baseball, was already starting to strangle the portal vein going into the liver. Doctors at the Phoenix Veterans Affairs Health Care System told Burrows, then 56 years old, there was nothing they could do. "They said, 'Get your affairs in order because you have 30 days to live, maybe 60,'" recalls Burrows, who is divorced with three grown kids.

Burrows quit his carpentry job and spent the next two months in a fog. Then things got very strange. In February 2006 Burrows developed abdominal bloating, shaking, chills and nausea. Soon after that he noticed that the lump on his stomach was gone. By then his daughter had found a doctor in private practice willing to consider treating him. But the doctor couldn't find a tumor. He went back to the VA, where gastroenterologist Nooman Gilani was flabbergasted when computed tomography and magnetic resonance imaging scans showed no sign of cancer. Where the tumor had once been, there was "literally empty space," Gilani says.

Burrows remains free of cancer three years later and still seems dazed by the turn of events. "I won a lottery, and I don't understand why," he says. "I would like someone to explain to me what the heck happened."

Ole Nielsen Schou also looked like a goner. In 2002 the Danish pharmaceutical production manager (now 69 and retired) found out that his melanoma had spread to his liver, abdomen, lungs, bones and ten spots in his brain. The abdominal tumor was surgically removed, but doctors at Rigshospitalet in Copenhagen had no treatment for his other tumors. He took a strange cocktail of 17 vitamins and supplements, including shark cartilage pills, and imagined the metastases were rats and he was chasing them with a club. [**In Depth: 6 Miracle Cancer Survivors.**](#)

Four months later he went back for a new scan and found that 90% of his tumors had melted away. Soon they were gone. Co-workers hugged and kissed him when they heard the news. Plastic surgeon Vennegaard Kalialis, who detailed his case last year in *Melanoma Research*, doubts it was the vitamins. "It is a complete mystery," she says. "Nobody has seen anything like this."

Spontaneous tumor regressions are among the rarest and most mysterious events in medicine, with only several hundred cases in the literature that can be considered well documented. Regressions have most often been reported in melanoma and in kidney cancer. But the phenomenon may, in fact, be an everyday one, taking place beyond doctors' eyes. A recent study suggests that as many as 1 in 3 breast tumors may vanish on their own before being detected by a doctor.

Why do some patients get lucky? Scientists are finding tantalizing evidence that the immune system, the body's defense against disease-causing microbes, kicks in to play a critical role in combating cancer. If that's the case, then Schou and Burrows are more than just lucky patients. They are clues to how doctors may someday save thousands of lives.

The evidence includes the fact that some unexplained remissions have occurred after infections, which may propel the immune system into high gear--possibly attacking the cancer tumor as well as the infection. Burrows' remission seemed to begin after his strange illness. Schou's abdominal tumor when removed was swarming with white blood cells, the lead weapon in the body's immune system. It's also possible that ordinary cancer survivors, people who beat the disease after getting radiation, chemotherapy or surgery, get an assist from their own immune systems.

Big drug companies, including Pfizer, Bristol-Myers Squibb and Sanofi-Aventis, are doggedly pursuing drugs that aim to boost the immune system to fight cancer. GlaxoSmithKline is in final-stage tests of a vaccine to prevent lung cancer from coming back after surgery. In an early trial it slashed the probability of cancer recurrence by 27%. "It is all about educating the patients' natural defenses against cancer," says GlaxoSmithKline's Vincent Brichard. Easier said than done, of course. Some patients, apparently, need only a small trigger to propel a massive anticancer attack. With nearly all others, however, the cancer cells fight back successfully and even co-opt immune cells to aid their growth. Why some patients respond better than others to certain drugs is a focus of furious scrutiny.

The role of the immune system in controlling cancer has been hotly debated for decades--and indeed many scientists remain unconvinced. But Jedd D. Wolchok, an oncologist at New York's Memorial Sloan-Kettering Cancer Center, thinks there is a connection. A spontaneous remission, he says, is "either divine intervention or the immune system." While few researchers directly study such cases--they are far too rare--they provide hints of what the immune system might be able to do if we could harness it.

The immune system work is part of a new twist on the war on cancer. For decades cancer researchers have focused mostly on killing cancer cells with drugs and radiation, or removing them with surgery. But this is often impossible to accomplish. So scientists are studying the environment around tumors in order to invent drugs that will halt their spread. Such drugs, like Genentech's Avastin, would be the medical equivalent of cutting terrorist-cell supply lines or putting up security checkpoints to stop them from getting into vital areas.

One of the first scientists to try to trigger the immune system to attack cancer was the New York surgeon William Coley. He was inspired by a patient with sarcoma who recovered after suffering an acute bacterial infection. In the 1890s Coley started vaccinating other patients with killed bacteria. He claimed that his toxins spurred the immune system to destroy tumors in a minority of cases.

In the 1980s the natural immune protein interleukin-2 was touted as a breakthrough. But it turned out to help only a small minority of cancer patients and to sport an array of nasty side effects. Over the years numerous trials of anticancer vaccines designed to train the immune system to recognize cancer have shown mostly lackluster results. None of these new therapeutic vaccines is approved in the U.S.

But intriguing data suggest that the immune system can combat cancer sometimes. "To the body, a tumor looks like the biggest bacteria it has ever seen," says Robert Schreiber, an immunologist at Washington University School of Medicine in St. Louis. He has found that mice lacking key components of their immune system are far more likely to develop cancers. In one experiment 60% of mice missing something called the gamma interferon receptor on their cells got tumors after being exposed to a carcinogen, versus only 15% of normal mice.

Schreiber theorizes that many early cancers arising in the body are killed off by the immune system. Over time, however, some develop mutations that allow them to thwart the immune system, and a long stalemate ensues. Eventually some tumors escape the control of the immune system entirely.

Moreover, a 2006 study by the University of Paris Descartes' Wolf H. Fridman found that the number of certain kinds of white blood cells inside colon tumors is a stronger predictor of a relapse than criteria pathologists traditionally use, such as whether cancer cells have spread to the lymph nodes. He analyzed tumor samples from 415 people who had been operated on for early-stage colon cancer over the last two decades. Those with the highest number of these cells in their tumor rarely relapsed; those with few immune cells almost always did.

No broad-based anticancer antidotes have emerged from the immune system work yet. In trials to date, immune-boosting drugs have generally helped only a minority of patients, particularly those with melanoma. But when they do work, it can be spectacular.

By the odds, 27-year-old Sharon Belvin should no longer be alive. The North Carolina resident found out that she had melanoma in her lung a week before her wedding when she was only 22. That sort of tumor usually sprouts like a weed once it has migrated beyond the skin to internal organs, and it resists most chemotherapy. By the time she turned 24 the few standard treatments had failed, and she had tumors in both lungs.

But then Memorial's Wolchok put her on an experimental drug called ipilimumab that aims to trigger the immune system. Within four months her lung tumors started to shrivel. By late 2006 they were gone. Today Belvin remains free of cancer and off treatment. She spends her time caring for her husband and 1-year-old daughter, whom she calls "a miracle baby, after all we have been through." Her case is so unusual that during a recent appointment the radiologist called Wolchok in disbelief. "He said, 'What did you do for this patient? Am I reading the diagnosis correctly?'"

Seven years ago Los Angeles high school social studies teacher Joseph Rick spotted a purple pimple on the small of his back. Too late: The melanoma soon spread into his colon. Nine surgeries and 40 chemo rounds over two years failed to stop it. By fall 2004 dozens of tumors riddled his body. Doctors gave Rick, then 43, four months to live. Rick bought a grave site for himself and went home to his L.A. condo to die. By December his weight had plummeted to 90 pounds from 240. He could barely walk.

Then he heard about a new immune-system-boosting drug being tested at UCLA, similar to the one Belvin received. A week after his first infusion visible brown tumors on his neck and thigh began to fade and his appetite returned. By March his tumors had shrunk 25%, and by early 2006 they were gone. When he could go back to work, he broke into tears watching the sunrise. Says Rick: "I would have been dead [years ago] without this drug."

Belvin's drug, from Bristol-Myers Squibb and Medarex, shrank tumors in about 10% of melanoma patients in a 2007 trial--not enough to get approval without more study. A larger trial that could lead to approval will wrap up late this year. Rick's drug is being tested by Pfizer. In a recent final-stage trial it failed to beat chemotherapy, and Pfizer sent it back a grade; the drug will start over at an earlier stage of trials. Both drugs turn off a natural brake on immune system activity called CTLA4 (cytotoxic T-lymphocyte antigen 4). They are part of a new breed of drugs that hit specific molecular components of the immune system.

Other treatments that aim to amplify the immune system report similar patterns--scattered amazing success stories combined with a failure on the broad stage. Last summer Cassian Yee at the Fred Hutchinson Cancer Research Center reported eradicating tumors in a 52-year-old man with advanced melanoma by plucking out the rare white cells from his blood that seemed to be active against cancer, painstakingly growing them in the lab and then injecting billions of them back into him. The man is free of cancer three years later. On eight other patients the procedure helped temporarily or not at all. "It's the hallmark of immune therapy--it doesn't happen often, but once it happens, those patients live years," says UCLA oncologist Antoni Ribas.

One famous researcher, the National Cancer Institute's Steven Rosenberg, says his immune cell therapy, roughly similar to Yee's, helps 72% of melanoma patients when given after chemo and radiation. Rosenberg, whose work was inspired by a patient whose stomach cancer vanished on its own, is now expanding the method to colon and breast cancer. But his procedure is far too complex for most hospitals to do.

What is special about the miracle survivors? Why do a minority of outliers live years longer than most? Is it something in their blood? Their genes? Are their tumors weaker than some? Or do they have unusually strong immune systems that just need a slight nudge?

The immune system is "phenomenally complicated," says oncologist Jeffrey Weber of the H. Lee Moffitt Cancer Center in Tampa. "Nobody knows how to pick out the patients that will respond." Complicating matters further: Some people get mysteriously delayed responses to immune-boosting drugs, as if a trigger has finally gone off. In the past some responses may have been missed because therapy was stopped too soon, says Bristol-Myers Squibb Vice President Renzo Canetta.

Some patients' tumors have mutations that make them particularly sensitive to one drug or another. Another reason that drugs get spotty results may be that some tumors are simply more visible to the immune system than others. Some 30% to 40% of melanoma tumors contain a rare protein called NY-ESO-1 that looks particularly suspicious to the immune system. Wolchok at Memorial has analyzed blood from eight patients for whom Bristol-Myers' CTLA4 drug worked; in five of them it appeared to rouse or amplify an immune response against this particular protein.

Another reason for perplexing results is that there are numerous molecular brakes inside the body that keep the immune system from rampaging out of control; cancer cells evade the immune system by manipulating these brakes. The drugs that Belvin and Rick took release one of those brakes (CTLA4), thereby allowing the fury of the immune system to be unleashed on the tumor. But tumors can quell the immune system by activating other brakes. Patients who don't respond to the CTLA4 drugs may have other brakes that are still engaged. Researchers may have to do many small trials of various combinations of immune-boosting drugs until they find which combos work best on which patients, says Dana Farber Cancer Institute's Glenn Dranoff.

Even as some researchers puzzle over the mystery of rare responders, others are finding that the immune system may play a crucial role in how patients react to bestselling antibody drugs. These drugs--such as Herceptin for breast cancer (Genentech) and Erbitux for colon cancer (Eli Lilly)--were designed to bind to signaling molecules on tumors and disrupt cell growth signals. But it turns out that they perform a second role, which drug companies have paid scant attention to until recently: flagging the immune system to kill cancer.

Rockefeller University researcher Jeffrey Ravetch has shown that antibody drugs like Herceptin no longer work well in lab mice when the portion of the antibody that flags the immune system is damaged--even though they still bind perfectly well to the tumor. Genetic differences in people's immune systems may also explain why some people respond much better to antibody drugs than others. Last year an Italian study of 54 breast cancer patients found that patients whose white blood cells had certain gene variants were far more likely to respond to Herceptin than those who had different variants. Similar results have been found with some other antibody drugs.

Biotech company researchers are now trying to devise second-generation antibodies that send stronger signals to the immune system, in hopes that far more cancer patients will benefit. "We are very intrigued by this," says Genentech biochemist Mark Sliwkowski, who cautions that the precise role of the immune system in the response to antibody drugs is unclear.

If the new thrust in immune system research goes somewhere, it could mean there will be more survivors like Barbara Bradfield of Puyallup, Wash. In 1992 her breast cancer came roaring back only two years after she'd had a double mastectomy. She had a marshmallow-size tumor on her neck and 16 spots in her lungs. She refused more heavy-duty chemotherapy and faced the fact she was going to die. Then she found out she qualified for a trial of a drug called Herceptin, which targets 25% of patients whose breast tumors have a certain mutation. She was one of the first patients to take it. Typically, it extends life by five months. But within six months of when she started Herceptin in 1992, Bradfield's tumors had all melted away. They have never come back, and now, at age 66, she is considered cured.