THE BODY ON FIRE

Illness can result when our natural disease-busting powers go awry

BY KATHERINE HOBSON

It's a classic case of too much of a good thing.

When the body is injured or infected by a germ, the immune system's first line of defense is a process called inflammation. It's sometimes painful, often itchy—and certainly familiar to anyone who has sprained an ankle or been bitten by a spider. While its effects may be uncomfortable, inflammation in these instances is a good thing. It is helping the body get rid of trespassers and heal from trauma.

But this same natural healing process, if it spins out of control, can become an adversary and cause serious health problems. Indeed, researchers are now tying inflammation to a host of common but serious diseases, including cancer, diabetes, heart disease, and even obesity. This new avenue of research is not only illuminating the nature of these diseases; it's also offering new hope for ways to prevent and treat them.

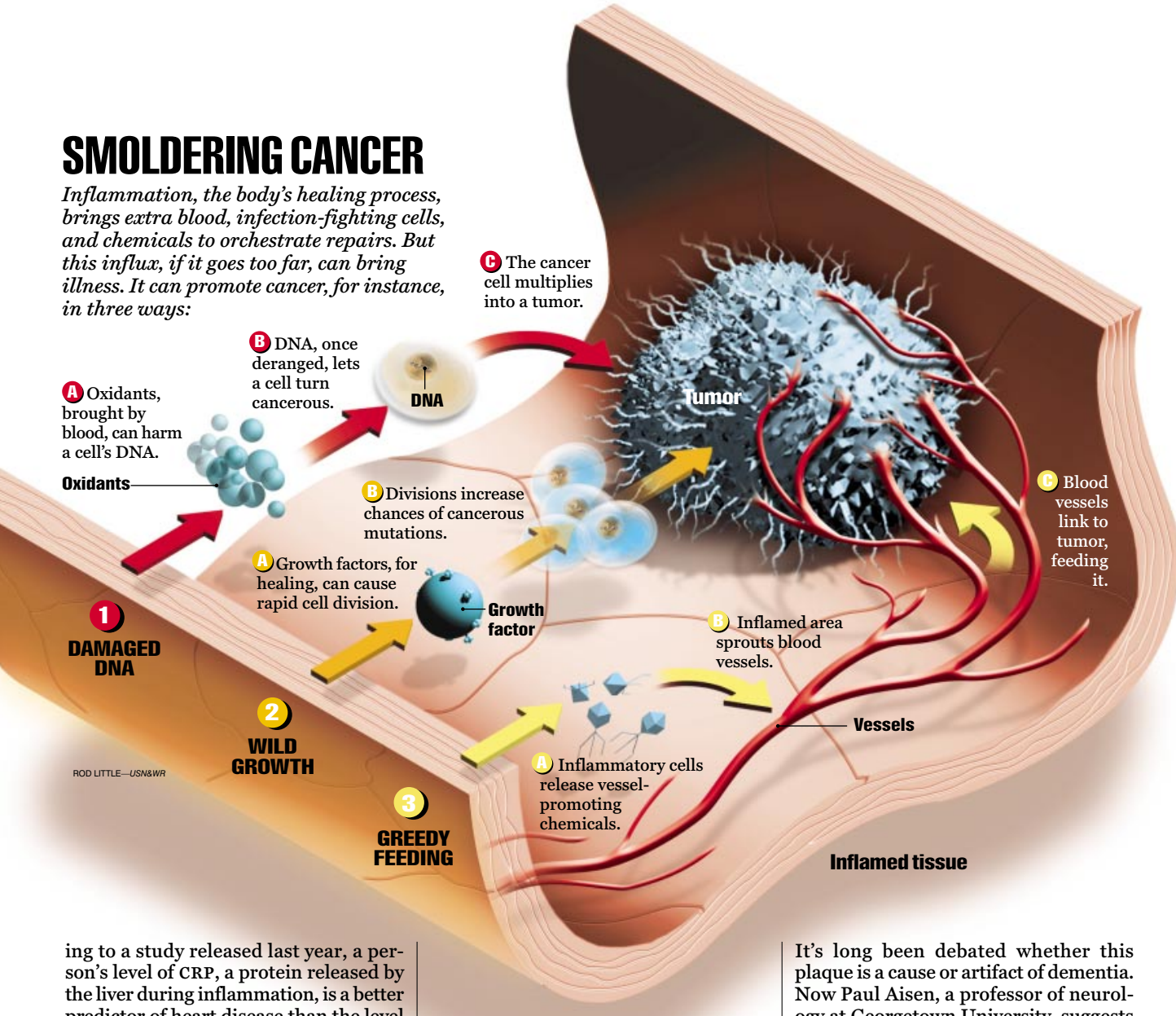
Under the skin. While the external symptoms of inflammation are easily recognized—the pain, redness, swelling, heat—the biological process going on beneath the skin is very complex and still not totally understood. We do know that blood vessels dilate and become "leakier" to allow infection-fighting white blood cells to reach the damaged tissue. This initial inflammatory response unleashes a cascade of chemical messengers that can in excess have damaging effects on the body.

Doctors have long suspected a connection between inflammation and disease, based on their clinical observations. For example, when the bacterium *Helicobacter pylori* invades the gut, it causes inflammatory ulcers in some people; those same people are also more likely later to develop stomach cancer. Similarly, lung cancer is now thought to develop at least in part from the body's inflammatory response to the tiny foreign particles contained in cigarette smoke.

But researchers are just beginning to tease out exactly how inflammation encourages tumor growth. There are at least three likely pathways (diagram). First, says Lisa Coussens of the University of California–San Francisco's Cancer Research Institute, "we know that inflammatory cells are full of growth factors that are used by various cell types to help them proliferate." Such regeneration would obviously be helpful in healing damaged tissue. But by increasing the rate of cell division, it might also speed up the development of cancer. Second, molecules called oxidants, also produced by inflammation, can damage DNA and produce malignant cells. And finally, tumor cells can hijack certain inflammatory cells and in effect force them to labor on behalf of the tumor—building a blood supply, for example.

Heart of the matter. Inflammation is also suspected as the culprit behind another big killer: heart disease. The fatty plaques that gum up arteries were once thought to be the result of too much low density lipoprotein—LDL, the "bad cholesterol"—hanging around and clogging the vessels, much like a hairball in a drain. Now there's a more complex theory, involving inflammation. When those LDL particles sit around for long enough, they oxidize and cause the blood vessel walls to become "sticky." The sticky walls in turn attract specialized white blood cells—monocytes and T cells—and suck them into the inner wall of the artery. A complicated cascade of chemical events follows, but the bottom line is that it's the immune system's inflammatory response—not just the bad cholesterol itself—that gums up the works, causing strokes and heart attacks.

This new view of heart disease is already changing the way doctors look for warning signs in their patients. Accord-



ing to a study released last year, a person's level of CRP, a protein released by the liver during inflammation, is a better predictor of heart disease than the level of LDL itself. Intriguingly, doctors have also found higher levels of CRP in people with Type II diabetes, a disease that often travels in tandem with obesity and heart disease. In fact, Type II diabetics have two to three times the risk of atherosclerosis that nondiabetics have.

In parallel. Such correlations have researchers rethinking the link between heart disease and diabetes. John Pickup, a physician with Guy's Hospital in London, theorizes that both heart disease and diabetes are connected to the activation of the immune system associated with inflammation. So rather than diabetes causing clogged arteries or vice versa, he says, "they occur in parallel."

Obesity most likely plays a big role as well in the inflammation underlying these diseases. Pickup conjectures that the fat that accumulates around your middle—the proverbial spare tire—produces the same damaging chemicals seen in an inflammatory response to infection. An excess of those chemicals could exacerbate diabetes, heart disease, or both. This would also explain why obesity can be a vicious circle, says Michael Meguid, a surgeon and neuroscientist at SUNY Upstate Medical University in Syracuse, N.Y. "To counteract that local inflammation, the same fat cells also begin to produce the anti-inflammatory steroid cortisol," which makes you hungry, he says. So the more belly fat you have, the more food you crave. Meguid has performed gastric bypass operations on rats and shown that after the fat is removed, the levels of inflammatory chemicals in the blood decrease.

The list of inflammation-related diseases goes on. For example, researchers have now linked an aberrant immune response to Alzheimer's disease. A telltale sign of this debilitating dementia—postmortem—is the accumulation in the brain of a protein called amyloid peptide. It's long been debated whether this plaque is a cause or artifact of dementia. Now Paul Aisen, a professor of neurology at Georgetown University, suggests that the loss of cognitive function may actually be due to the body's inflammatory response to the protein, which destroys brain cells. Similarly, inflammation appears to cause the damage in autoimmune diseases like multiple sclerosis and rheumatoid arthritis and is even suspected of contributing to muscle weakness in old age.

But if inflammation is behind all these diseases, what's behind the inflammation itself? It could be a lot of things, researchers say. It might be a microbe like *H. pylori,* or a virus, or an environmental toxic substance like smoke. Age, diet, genetics, and prenatal nutrition probably all influence the sensitivity of an individual's immune system, says Pickup.

Then, of course, there's stress. The idea that stress contributes to heart ailments is an old one, but it may be even more influential than previously thought. Both acute and chronic psychological stress can produce the same

inflammatory response as a foreign microbe, says Paul Black, a microbiologist at Boston University School of Medicine, and stress can even lead to a chronic state of inflammation. It makes sense, if you consider the evolution of the "fight or flight" response. "An animal gets stressed when there's a predator coming at him, and he mobilizes his entire physiology within milliseconds," says Black. "Part of that mobilization is to prepare the inflammatory process—it's preparing for bacteria that may enter in a wound from a fight." Though humans today rarely encounter predatory animals, they do experience prolonged stress from intolerable bosses at work, rude drivers on the interstate, and other hazards of modern life.

Remedies. So if you believe that inflammation is behind these diseases, you might wonder why sufferers can't just take an aspirin. Indeed, many already do: Now a regular part of many people's diet for its cardiac benefits, aspirin not only thins the blood but also reduces inflammation. And research indicates that aspirin, ibuprofen, and other anti-inflammatory drugs like the new COX-2 inhibitors can cut the risk for certain kinds of cancer. Cholesterol-lowering statins are also being studied for their anti-inflammatory properties. But don't expect to see these drugs replacing chemotherapy anytime soon. Some anti-inflammatory drugs can be hard on the stomach and may actually contribute to other, more rare forms of cancer. They are also probably better for preventing cancer or a recurrence than for treating existing tumors, says UCSF's Coussens.

"Psychological stress can produce the same inflammatory response as a foreign microbe."

Scientists are only beginning to figure out which old—or new—remedies might prevent the inflammation now associated with so many diseases. But lifestyle changes, like losing weight, exercising, eating antioxidant-containing fruits and veggies, and avoiding tobacco can help cut the unwanted invisible inflammation—without leaving the body unprotected from the next marauding germ. ●

BREAST CANCER

Searching for the next tamoxifen

BY KATHERINE HOBSON

Tamoxifen is the drug of choice to treat postmenopausal women with breast cancer, but it's neither a perfect nor a permanent solution. It carries a small risk of uterine cancer and blood clots, and taking it any longer than five years actually increases the chance the disease will come back. That leaves patients with no options for further treatment. "One of my patients has told me that it's like she's walking on a tightrope, and after five years you take away the net," says oncologist Larry Norton of New York's Memorial Sloan-Kettering Cancer Center.

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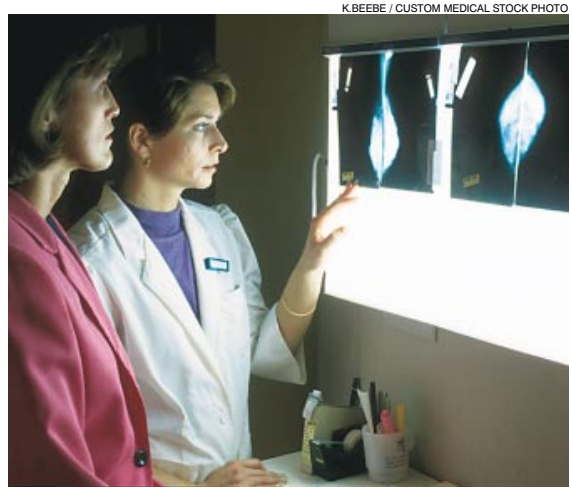

DIAGNOSIS. New drugs may offer new options for women.

Now those women may have a new lifesaver. Researchers reported last week that patients who followed up their tamoxifen with a newer drug, called letrozole (brand name: Femara), had fewer recurrences of tumors than those who took a placebo. The distinction was so striking that the researchers, who reported their results in the *New England Journal of Medicine,* stopped the trial early. After 2.4 years, 5.1 percent of women who got no treatment after tamoxifen had a recurrence of cancer, compared with only 2.9 percent of women who took tamoxifen and then letrozole. In the world of cancer recovery, where incremental gains are the norm, those numbers are major.

The study also showed that letrozole—made by Novartis, which helped fund the study—prevented new tumors in the opposite breast. This adds to the evidence that this class of drugs—called aromatase inhibitors—might someday replace tamoxifen, or even be prescribed to prevent cancer in high-risk women.

Full stop. The female hormone estrogen is a major culprit in many kinds of breast cancer. Tamoxifen, in use for more than 25 years, blocks the hormone's path to breast cells. By contrast, the newer aromatase inhibitors stop estrogen from being made in the first place. Earlier results from other studies have shown them to be more effective than tamoxifen when taken as a first-line treatment directly following surgery. But experts have been reluctant to recommend that they replace the older, proven drug until more is known about their longer-term side effects, which include osteoporosis.

Because this study was stopped early, it lacks that kind of long-term information about either side effects or actual survival rates, says Harold Burstein, an oncologist at the Dana-Farber Cancer Institute, who wrote an editorial accompanying the study. And many other questions remain. For example, should aromatase inhibitors be prescribed indefinitely for women following surgery, replacing tamoxifen? And will they help women who stopped tamoxifen therapy months or years ago?

Those questions will be answered only by future study results. Meanwhile, this latest study provides an option that doctors can offer today to women finishing tamoxifen and wondering what comes next. ●