Chronic inflammation underlies many of the illnesses we dread, including cancer and heart disease. Can nutrition help put out the fire?

By Julie Flaherty  Illustration by James O'Brien

The immune system is supposed to be our great defender, the army that protects us against invading pathogens and rebuilds tissues damaged by injury. One of its master tactics is inflammation, where the body floods an injured or infected site with plasma and white blood cells, causing the familiar swelling, redness and don’t-touch-me-there tenderness. Without it, wounds would never heal, and germs would win the war.

But sometimes the inflammation-signaling cells that are supposed to fall back at the end of their mission keep fighting, attacking an enemy only they can perceive. What keeps the battle going? Recurring irritants, such as cigarette smoke, for one. Or, as we now know, carrying too much extra weight, or simply getting older.

It doesn’t mean your insides swell and throb the way your toe does when you stub it. Chronic, low-grade inflammation is not the kind you can feel, or even something you can see under a microscope. Instead, inflammatory molecules circulate at such low levels that only very sensitive tests can detect them. A full-blown infection, for example, might shoot your blood levels of C-reactive protein (CRP), a molecule released by the liver as part of the immune response, from 0 milligrams per liter up to 1,000 mg/L. Chronic inflammation, on the other hand, might register a benign-looking 3 mg/L. “It’s very subtle,” says Professor Joel Mason, M.D., director of the Vitamins and Carcinogenesis Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCRA) at Tufts. “It’s inflammation on a biochemical level.”
But even at such a slow burn, this silent war takes a toll on the body. A CRP level of 3mg/L is enough to triple your risk of heart disease. In fact, chronic inflammation is connected to many of the illnesses we see more often as we age.

“[Inflammation] is thought to be an important basis not just for cancer, but for insulin resistance and diabetes and atherosclerotic disease and any number of other conditions,” Mason says. “There is a lot of research going on into what role inflammation plays in a lot of the chronic degenerative diseases that our society falls prey to.”

If inflammation is the common denominator, then finding a way to dampen it through nutrition could have far-reaching health consequences. (See “The Search for Foods that Soothe,” below.) Research already suggests that inflammatory cooling properties may be what makes the fish-and-oil-rich Mediterranean diet effective in preventing cardiovascular disease and explain part of the heart-healthy power of oats. Eating fruits and vegetables, which we already know decreases the risk of cancer, persist for months and years, as it does apparently in obesity. Everyone knows that weight gain and diabetes are closely linked. It is only more recently that researchers have seen how inflammation may be one of the bridges that connect them.

“With obesity, there is a release of fatty acids and other factors that fuel inflammation and insulin resistance,” says Atkins Professor in Metabolism and Nutrition Andrew Greenberg, M.D., director of the HNRCA’s Obesity and Metabolism Laboratory.

For a long time, scientists thought that the extra fat we carry on our bodies was fairly inert stuff—just more baggage to slow us down. But more recent studies, including groundbreaking research by Greenberg, have shown that fat is actually a hormonal powerhouse. As people gain weight, their fat cells grow larger. When that happens, the cells churn out several inflammation-inducing proteins, known as cytokines. And they do it at a surprising rate. One of these cytokines is Interleukin-6. You usually find IL-6 when the body’s immune system is doing its day job, fighting an infection or trying to heal a burn, for example. But one study found that obese people had 10 times as much IL-6 in their fat tissue as normal-weight people. IL-6 and other inflammatory factors “block insulin’s ability to signal in the cell,” Greenberg explains, which is one way insulin resistance, the precursor to diabetes, can develop. This

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The Search for Foods that Soothe

There is some evidence that what we eat can affect inflammation. Perhaps not coincidentally, many of these foods are the same ones you’ve heard recommended as defenders against heart disease and cancer.

Some studies have shown that eating a meal high in saturated fat or trans fat causes inflammation markers to shoot up, if only temporarily. But unsaturated fats, and omega-3 fatty acids in particular, seem to be protective. Studies that look at groups of people over a long term have seen connections between omega-3 intake and inflammation-causing molecules in the blood. For example, a study of 727 postmenopausal women in the Nurses’ Health Study found those who had the highest consumption of omega-3s, found in fatty fish, walnuts, flaxseed and canola oil, had lower levels of CRP, that immune responder, and IL-6, that inflammation producing protein. Why would omega-3s fight inflammation? At least one study has shown that omega-3s reduce the expression of inflammatory proteins in cells that line our blood vessels.

Choosing carbohydrates that take longer to digest and do not cause spikes in blood sugar, such as vegetables, beans and whole grains, seem to be beneficial in reducing inflammation. One study, published this year in the Journal of Nutrition, found that overweight people who ate a diet of such foods reduced their CRP levels, whether they lost weight or not.

Oats are one whole grain that seem to have special health properties. The consumption of oats, oatmeal and oat bran, even for a short period, has been shown in most studies to reduce total blood cholesterol and LDL cholesterol (the bad kind), the main risk factors for cardiovascular disease. Scientists mostly credit this to
“Age-associated inflammation has been identified as an important contributor to many of the age-associated diseases, including Alzheimer’s, osteoporosis, loss of muscle mass and infection, in addition to cancer and cardiovascular disease.” —Simin N. Meydani

increase in inflammation appears to be a necessary step on the path to diabetes.

Enlarged fat cells bring on inflammation for a number of reasons. Engorged fat cells release fatty acids into the blood, which seem to spur an inflammatory response. People who carry a lot of weight also tend to have high numbers of macrophages in their fat. Macrophages are immune system weapons that normally gobble up pathogens or dead cells. Researchers believe the body sends the macrophages to clean up dead fat cells, the numbers of which increase dramatically with obesity. Once there, the macrophages infiltrate the fat and start sending out pro-inflammatory signals. In laboratory studies, obese mice that had excess macrophages started making a lot more insulin, and eventually developed insulin resistance.

GATEWAY TO CANCER
Inflammation might also explain, in part, the connection between being fat and getting cancer. Scientists have long known that if you carry extra weight, you are more likely to get cancer. And you don’t need to be obese. “Being obese increases your risk of developing colon cancer by two- or threefold,” says Mason, who has done numerous studies on colon cancer. “But just being overweight increases your risk by 20 percent.”

Now scientists suspect that it is the inflammation brought on by obesity that contributes to that risk. Certain cancers have a direct connection to inflammation. Cigarette smoking, for example, irritates the lungs, which leads to inflammation and lung cancer. The human papillomavirus causes a chronic infection, and the subsequent inflammation leads to cervical cancer. And people with chronic inflammatory bowel disease have a five- to sevenfold increase in their risk for developing colon cancer.

But obesity in and of itself seems to promote cancer. Take liver cancer. The number of cases of liver cancer in the United States has doubled in the past 25 years, although researchers are unsure why. The usual causes—excessive alcohol use and viruses such as hepatitis B and C—have not increased. One thing has, though: obesity. When a person gets fatter, so does oats’ soluble fiber, which interferes with the reabsorption of bile acid in the gut and reduces cholesterol levels.

But oats also contain special compounds called avenanthramides that seem to play a role in reducing inflammation. Avenanthramides are not found found in other cereal grains—they are a part of the oat plant’s own defense mechanism, produced in response to environmental stresses such as harsh weather. Professor Mohsen Meydani, D.V.M., Ph.D., director of the HNRCA’s Vascular Biology Laboratory, discovered that oat extract that was high in avenanthramides could reduce the number of inflammatory signals put out by cells that line blood vessels. Add in the fact that oats also have been shown to improve the function of blood vessel cells (which help regulate blood pressure and blood flow), and it seems oats have the potential to not only decrease plaque that causes bad cholesterol in the blood, but dampen the inflammation that leads to atherosclerosis. Meydani has also looked at a possible mechanism by which oats may reduce the risk of colon cancer. He looked at the cells that line the colon, and found that avenanthramides, in part because of their anti-inflammatory properties, inhibited the growth of cancer cells, but left healthy cells alone.

Fruits and vegetables are the cornerstone of any healthy diet. Yet more evidence for their power comes from a 2008 study by the HNRCA’s Vitamin K Laboratory. Looking at data from 1,381 participants in the Framingham Offspring Study, the Tufts researchers
his liver, and that fat infiltration can cause the liver to become inflamed. In laboratory studies of rats that were given a small amount of a liver-specific carcinogen, obese rats showed more inflammation markers and more precancerous lesions in their livers than regular-weight rats, says Professor Xiang-Dong Wang, M.D., Ph.D., N92, director of the HNRCA’s Nutrition and Cancer Biology Laboratory, which performed the experiments.

How does it happen? Joel Mason has discovered one route by which obesity-induced inflammation spurs cancer, at least in the colon. The lining of the colon is one of the most rapidly proliferating tissues in the body, producing tens of millions of new cells every day. “About every four or five days, you have an entirely new lining in your colon,” Mason says. The destruction of old cells and the creation of new ones is orchestrated by cascades of intercellular signals. One of them, the Wnt signaling pathway, is integral to colon health. But when this pathway is overactivated, it can lead to the uncontrolled cell growth that is cancer. “More than 85 percent of all human colon cancers are thought to arise because of overactivation of this pathway,” Mason says.

What triggers the overactivation? The inflammation brought on by obesity, for one. In studying the colons of obese mice, Mason saw elevated levels of pro-inflammatory cytokines, lots of Wnt signaling and an accompanying increase in cellular proliferation.

Mason says he is not trying to argue that Wnt signaling is the sole way in which obesity increases the risk for colorectal cancer, but he does believe it could be a substantial, biologically plausible pathway.

“It takes a number of different pushes from different directions to finally get the ball rolling where cells just finally decide that they are going to become cancerous,” he says. “Some of us think that they get nudged a little bit by these pro-inflammatory cytokines.”

Another theory about how inflammation leads to cancer has to do with oxygen free radicals, molecules that the inflammatory response signals to kill such intruders as bacteria or viruses. Unfortunately, these free radicals tend to destroy anything they come in contact with, including healthy cells. Sometimes a free radical damages a healthy cell just enough to mutate its DNA, which can trigger a cycle of abnormal cell growth.

Typically, cells have built-in mechanisms to prevent damaged DNA from being copied. But the inflammatory response, in its good-hearted attempt to promote the creation of healthy tissue after an injury, can work against those mechanisms—and even spur new blood supplies that help to fuel the growth of the abnormal cells.

It makes sense, then, that people who eat lots of fruits and vegetables have a lower risk of cancer; colorful produce is rich in carotenoids and other antioxidants, which neutralize free radicals. But sorting out which antioxidants are actually dampening inflammation has been tricky. In studies of obese rats, Wang’s laboratory supplemented the rats’ diet with either lycopene—an antioxidant found in tomatoes—or tomato extract. Both helped dampen inflammation, but the tomato extract did a better job.

In this case, the purified compound was not as effective as the whole food. To Wang, this means people are better off eating more tomato sauce and leaving the lycopene supplements on the shelf. “You better get this protection from your diet,” he advises.

His lab is also looking at whether consuming certain nutrients can block the cancer-inducing inflammation caused by cigarette smoke. They started by looking at a Harvard analysis of dietary intake studies, which showed that smokers who ate foods rich in a carotenoid called beta-cryptoxanthin (found in pumpkin, sweet red peppers, papayas, oranges and carrots) had a lower incidence of lung cancer.

measured blood levels of vitamin K as well as dietary intake. They then looked at 14 inflammation markers. Those people who had the most vitamin K in their blood and who reported eating more vitamin K rich foods showed lower levels of inflammation. The researchers point out that vitamin K is found in such leafy greens as spinach, lettuce and kale, as well as in cabbage, cauliflower, broccoli, Brussels sprouts, carrots, milk and soybeans—all foods that contain an assortment of micronutrients that could depress inflammation. So it is possible that vitamin K isn’t itself the inflammation fighter, but some of the other micronutrients and plant chemicals it keeps company with in those foods might be.

Of course, a combination of nutritional factors could be working together to fight inflammation. A 2008 study published in the American Journal of Clinical Nutrition found that people in Japan who ate a diet high in vegetables, fruit, soy, fish and yogurt had lower CRP levels.

The Mediterranean diet, which features olive oil, fish, complex carbohydrates and nuts, has been reported to be associated with a lower risk for most common chronic diseases, José Ordovas says. In the case of cardiovascular disease, this protection was attributed to the monounsaturated fats in olive oil. “However, more recently, we have learned that most of the effect could be related to the minor components present in extra virgin olive oil that confer its antioxidant and anti-inflammatory capacities,” Ordovas says. “Moreover, other components of the Mediterranean diet, such as the omega 3 present in fish or found in nuts, as well as some commonly used herbs and spices, act synergistically to reduce inflammation and oxidation and thus the risk of chronic diseases. Overall, these effects translate into healthier aging.”

Whether these foods make up an “anti-inflammatory diet” remains to be proven. But all of these findings support many of the current recommendations for what we should be eating anyway to stay healthy.

“Diets rich in fruits and vegetables, whole grains and fish are associated with lower risk of cardiovascular disease and cancer,” says Alice Lichtenstein. With a nod to Shakespeare, she adds: “The diet you describe, by any other name, would be the same.” —j.f.
Wang’s lab took two groups of ferrets—one given beta-cryptoxanthan and one not—and exposed them to cigarette smoke. The animals that were given the supplement fared much better. “It almost totally blocked smoking-induced inflammation and precancerous lesions,” Wang says. A follow-up study went a step further: It found that beta-cryptoxanthan actually prevented the growth of lung tumors in animal lung cancer models. The research was presented at the American Association of Cancer Research annual meeting in April.

**HEART ATTACK TRIGGER**

Chronic inflammation gained its current notoriety when it was implicated in the number-one cause of death around the world: cardiovascular disease. The old, simplistic belief was that having a high concentration of cholesterol in the blood would cause it to build up in blood vessel walls until it decreased or totally blocked the flow of blood—a clog in the plumbing, so to say. Now researchers theorize that there is more to the relationship between blood cholesterol and arterial cholesterol, and that inflammation plays an important role in promoting these blockages, or plaques, as well as in triggering chest pain, stroke and heart attack.

The process works something like this: High concentrations of LDL, the “bad” cholesterol, lodge in the lining of blood vessels. Macrophages, those scavenger cells sent out by the immune system, recognize that the LDL isn’t supposed to be there, and ingest it. These cells, now puffed with cholesterol, embed themselves in the blood vessels and form the fatty streaks that are the first step in plaque formation. Inflammatory signals sent out by the macrophages encourage additional cholesterol buildup. Eventually, a fibrous collagen cap develops and seals off the plaque. These capped plaques can sit benignly for years. Only when the plaques rupture does trouble begin, and again inflammation seems to be the culprit. In laboratory tests, researchers have seen that macrophages can secrete enzymes that degrade the cap.

“Inflammation is thought to make atherosclerotic lesions less stable,” explains Gershoff Professor Alice H. Lichtenstein, D.Sc., director of the HNRCA Cardiovascular Nutrition Laboratory. “If they rupture, the surface becomes thrombogenic, making it more likely a clot will form and clog up a vessel.” If the clot blocks the flow of blood to the heart, you have a heart attack. To the brain, you have a stroke.

Simply getting older can also increase chronic inflammation.

“Age-associated inflammation has been identified as an important contributor to many of the age-associated diseases, including Alzheimer’s, osteoporosis, loss of muscle mass and infection, in addition to cancer and cardiovascular disease,” says Simin Nikbin Meydani, D.V.M., Ph.D., director of the HNRCA and its Nutritional Immunology Laboratory, who has worked on several studies looking at age-related inflammation over the past 25 years.

She has found that one of the important players in the aging game is a messenger chemical, prostaglandin E2, which normally helps activate the inflammatory response. As we age, our bodies tend to make more prostaglandin E2, and that excess has been associated with nerve pain, plaque rupture in the arteries, cancer and suppression of function in T cells, which are crucial to the immune system.

COX-2 inhibitors, a group of inflammatory drugs, can suppress prostaglandin production, but they can cause dangerous side effects such as stomach bleeding. So Meydani and her HNRCA colleague, Assistant Professor Dayong Wu, M.D., Ph.D., have been looking at foods or supplements that might do the same job as the drugs. For example, people who eat diets high in omega-3-rich fish produce less prostaglandin. Vitamin E was shown both in mice and humans to reduce prostaglandin E2 production and improve immune response. Studies also showed that restricting calorie intake lowers prostaglandin production while improving immune response.

So what can you do to keep inflammation at bay? The best defense may be keeping body fat in check. Weight loss has been shown to decrease people’s levels of C-reactive protein, one of the markers of inflammation. A 2002 study in the journal Circulation tracked 25 obese, postmenopausal women who went on a weight-loss diet. They lost an average of 30 pounds, and reduced their CRP more than 30 percent.

Then again, most Americans haven’t exactly excelled at keeping their bodies at a healthy weight. That’s why Greenberg, Mason and others have been looking at other ways to interrupt the obesity-inflammation-disease cycle.

“We have identified various factors, which, if we block their action, blocks inflammation and promotes improved insulin and glucose blood levels in obese animals,” Greenberg says. The next step will be identifying drugs—or nutrients—that can curb the inflammation and reduce the rate of obesity-associated diabetes, which is reaching epidemic proportions. **TN**

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