Can We Cure Aging?

Controlling inflammation could be the key to a healthy old age

They say aging is one of the few certain things in life. But it turns out that they were wrong. In recent years gerontologists have overturned much of the conventional wisdom about getting old. Aging is not the simple result of the passage of time. According to a provocative new view, it is actually something our own bodies create, a side effect of the essential inflammatory system that protects us against infectious disease. As we fight off invaders, we inflict massive collateral damage on ourselves, poisoning our own organs and breaking down our own tissues. We are our own worst enemy.

This paradox is transforming the way we understand aging. It is also changing our understanding of what diseases are and where they come from. Inflammation seems to underlie not just senescence but all the chronic illnesses that often come along with it: diabetes, atherosclerosis, Alzheimer's, heart attack. "inflammatory factors predict virtually all bad outcomes in humans," says Russell Tracy, a professor of patheology and biochemistry at the University of Vermont College of Medicine, whose pioneering research helped demonstrate the role of inflammation in heart disease. "It predicts having heart attacks, having heart failure, becoming diabetic; predicts becoming fragile in old age; predicts becoming fragile in old age; predicts cognitive function decline, even cancer to a certain extent."

The idea that chronic diseases might be caused by persistent inflammation has been kicking around since the 19th century. Only in the past few years, though, have modern biochemistry and the emerging filed of systems biology made it possible to grasp the convoluted chemical interactions involved in bodywide responses like inflammation. Over a lifetime, this essential set of defensive mechanisms runs out of bounds and gradually damages organs throughout the body.

When you think about aging as a consequence of inflammation, as Tracy and many gerontologists now do, you start to see old age in a much more hopeful light. If decrepitude is driven by an overactive immune system, then it is treatable. And if many chronic diseases share this underlying cause, they might all be remedied in a similar way. The right anti-inflammatory drug could be a panacea, treating diabetes, dementia, heart disease and even cancer. Such a wonder drug might allow us to live longer. More to the point, it would almost surely allow us to live better, increasing the odds that we could all spend our old age healthy, vibrant and vital. And unlike science fiction visions of an immortality pill, a successful anti-inflammatory treatment could actually happen within our lifetime.

For the last century and a half the average life span in wealthy countries has increased steadily, climbing from about 45 years to more than 80 years. There is no good reason to think this increase will suddenly stop. But longer life today often simply means taking longer to die – slowly, expensively, and with more disease and disability. "If you talk to many old people, what they are really desperate about is not the fact that they are going to die but that they are going to be sick, dependent, have to rely on others," says Luigi Ferrucci, chief of the longitudinal studies section at the National Institute on Aging and director of the Baltimore Longitudinal Study of Aging, the nation's longest running study of old age.

Biologists have known for a while that inflammation increases with age, but until recently, given everything else that slumps, spikes, or goes off the rails as we get old, it didn't seem especially important. Some researchers on aging still think that way.

A big clue linking inflammation with aging came in the late 1990s, when Tracy and his colleagues showed that C-reactive protein (CRP), an inflammatory protein, is an amazingly accurate predictor of a future heart attack – as good as or better than high blood pressure or high cholesterol. At least in heart disease, inflammation is not just a bystander. What's more, we could do something to decrease it. Aspirin, which was already known to help people with heart disease, seems to work primarily by reducing inflammation.

So why should our own immune system rely on such an apparently dangerous mechanism? The answer, researchers say, lies in the fact that infectious disease has historically been the number-one killer of human beings and responding to this threat has profoundly shaped our biology. Possessing a fierce and ferocious immune response primed to keep us alive long enough to reproduce was an evolutionary no-brainer.

Inflammation is what gives us that response. It serves as all-purpose protection against invaders and traumatic damage. To take a simple scenario, suppose you are bitten by a cat. First, coagulation factors promote clotting in order to stanch bleeding and prevent germs from spreading from the wound site. A menagerie of phagocytes, which swallow and destroy pathogens, surge out of the bloodstream and squeeze into the affected tissue, engulfing bacteria and secreting cytokines – messenger proteins that send out the call for more responders. The phagocytes also generate reactive oxygen species, unstable compounds that chew up bacteria as well as damaged human tissue.

At the same time, other switches get flipped throughout the body, modifying everything from metabolism to cell growth, via other cytokines (such as IL-6 and tumor necrosis factor-alpha) and things like CRP, which mark bacteria for destruction. The specialized adaptive immune response eliminates any remaining germs. So far, so good. But the inflammation response can kick in even when there is no invader. Atherosclerosis, or hardening of the arteries, is classic example. In response to fatty deposits on the walls of the arteries, a type of phagocyte called macrophage identifies the growing lesions as trouble spots and infiltrates them, swelling and destabilizing the deposits. Those lesions can then break open, resulting in the formation of a blood clot that can clog blood vessels and cause heart attacks. The more active the macrophages are, the more CRP is in the bloodstream, and the more likely it is that the lesions will break open, block your arteries, and kill you.

The evidence that inflammation is behind other diseases is indirect, but it is mounting. Researchers have long known that in patients with Alzheimer's, the areas of the human brain clogged with senility associated plaques also bristle with inflammatory cells and cytokines. Modern research has found that cytokines block memory formation in mice. In diabetes, inflammation and insulin resistance apparently track together, and drugs that effectively restore insulin sensitivity also appear to reduce inflammatory factors like IL-6 and CRP. Inflammation is also being investigated by a group at Leiden University in The Netherlands as a culprit in declining lung function, and in old-age depression. Tracy's recent research

indicates that HIV, too, does major damage through inflammation; he calls AIDS an example of 'accelerated aging,' in which the body's response to the infection increases the risk for heart disease, bone loss, cognitive impairment, cancer and other problems. Even the weakness of old age may have an inflammatory cause: Ferrucci has found that inflammatory activity breaks down skeletal muscle, leading to the loss of lean muscle mass. Being fat makes all these diseases strike earlier, and that seems to be at least in part because fat cells spur more inflammation.

These findings have provided researchers with a totally new appreciation of how subtly inflammation can work and how wildly awry it can go over time. It is not about "a massive infection or a welt the size of an egg because you got hit in the head with a two-by-four," Tracy says. "Inflammation also goes on at a much lower level." As it simmers in the background, over years and decades, collateral damage accumulates in the heart, in the brain, everywhere. Harvey Jan Cohen, chairman of the department of medicine and director of the Center for the Study of Aging at Duke University Medical Center, likens inflammation to "little waves lapping on the shore. It's a relatively low level of activity, one that sustained over time wears away at the beach and stimulates other bad events."

Evolution has designed into us a cruel trade off: What saves us in the short term often kills us over the long haul. As we get older, acute episodes of inflammation tend to turn into chronic ones, perhaps because the regulation of the immune system becomes less efficient. Inflammatory factors in the blood can increase two- or fourfold. Chronic infections may be partly to blame. Although we usually do not know it, nearly all adults are infected with the Epstein-Barr virus, and around 60% of us with cytomegalovirus. These two pathogens can stay in our bodies in a latent state, hiding out in our cells. But Ronald Glaser, a viral immunologist at Ohio State University Medical Center, and his research partner psychologist Janice Kiecolt-Glaser, think that these viruses are not fully dormant. They have found evidence that with age, antibodies to the Epstein-Barr virus increase, indicating a reawakened virus and an active immune response.

Early experiences may also influence the way that inflammation affects an individual's aging, says Caleb Finch, a neurobiologist and gerontologist at the University of Southern California. Analyzing historical birth and death records from 19th-century Europe, he and Eileen Crimmins, a gerontologist and sociologist at USC, found that longevity is directly related to exposure to childhood disease. Children born during years of high neonatal mortality who survived to adulthood did not live as long as those born in healthier years. The reason, Finch says, is inflammation: A high infectious burden in childhood results in a high inflammatory burden in adulthood, which results in a shorter, sicker life. Conversely, he believes that people in affluent countries now live so long because their childhoods are free from diseases like measles, typhoid, malaria, whooping cough, and worms. Without these diseases, people grow bigger and stronger, and live much longer.

Looking beyond provocative findings like those in Finch's study, Tracy and other researchers on aging say that it may be too simplistic to think of inflammation in terms of straightforward cause and effect. Instead we must think of human biology as a group of interdependent systems. "Is inflammation a response to aging, or is it causing aging or disease?" Tracy asks. "My answer is: Yes. It does all those things. There is no other way to think about it – it is both cause and response to what is going on."

Inflammation is not uncontested as a theory of aging. There are many competing hypotheses. Yet inflammation reinforces some of these ideas more than others, potentially establishing a plausible constellation mechanisms responsible for aging.

For example, according to the free radical hypothesis of aging, we get older because of constant cellular damage caused by reactive oxygen compounds that are a natural product of metabolism. Inflammation can partly explain how this might work. Macrophages, as part of the inflammatory response, produce reactive oxygen species in order to attack bacteria. Oxidative stress and inflammation clearly egg each other on, and calming one can inhibit the other.

To take another prominent example, a low calorie diet is known to increase the life spans of creatures ranging from flatworms to rats, but no one knows why, or whether it would help humans live longer. Inflammation provides a clue: Dietary restriction sharply inhibits the inflammatory response, and that may be part of why it promotes longevity at the same time that it reduces insulin resistance and slows dementia. Yet another widely discussed theory of why we age blames the shortening of telomeres, chromosomal structures that, in most cells, dwindle with each division and may ultimately limit the number of times any cell can divide. It is possible that inflammation could play a role a role here, too, because it prompts the faster turnover of cells in the immune system and other tissues.

Still, nobody thinks that there is a single root cause of aging. Different species may age in different ways, and multiple mechanisms are probably at work. “I think it would be a mistake to suggest that inflammation is the cause of aging, or that all theories of aging must tied to it,” Cohen says. Then again, it may not ultimately matter whether inflammation is the most significant cause of our decay. More important is that inflammation offers an unparalleled opportunity to do something about it. Some ways to reduce inflammation are elementary, like healthy food, exercise and a good attitude. Those of us without it, can turn to drug companies, which are exploring new anti-inflammatories like flavonoids. The diverse efforts to develop new therapies that might prevent the chronic debilitating diseases of aging share one thing in common, says Nir Barzilai, a molecular geneticist and director of the Institute for Aging Research at the Albert Einstein College of Medicine in New York. “If I develop a drug, it will have a side effect, which is that you will live longer.” Researchers are also looking at new uses for old drugs, trying to prevent Alzheimer’s by using ibuprofen, for example. The evidence on anti-inflammatories and Alzheimer’s is mixed, but in one recent study, older people who used ibuprofen for over five years were more than 40% less like to develop Alzheimer’s disease.

Some of this research stretches the boundaries of what we know. Rudi Westendorp, head of the department of gerontology and geriatrics at the Leiden University Medical Center, is trying to treat old age depression with drugs that are currently used for autoimmune conditions like RA. Harvard University researchers are considering a vaccine against atherosclerosis, which may provoke a reaction that suppresses inflammation.

The caveat with these experiments is that by modifying inflammation, we are playing with fire. After all, fighting off infection is an absolutely essential bodily function. “The danger of monkeying around in a system like that is that you may do more harm than good,” Cohen says. But humans finally appear able

to renegotiate the ancient evolutionary bargain in which we accepted frail old age in return for robust reproductive health.