A Novel Approach to Resolving Inflammation

Understanding how the body naturally "turns off" inflammation may yield new treatments for periodontal disease and other inflammatory conditions

By Thomas E. Van Dyke and Charles N. Serhan

Scientists have known for almost 50 years that periodontal disease is caused by bacterial infections. However, the tissue damage that occurs in periodontal disease—destruction of the bone and ligaments that hold teeth in place—cannot entirely be explained by the action of infecting organisms. Instead, the real culprit seems to be the patient's own inflammatory response to that infection.

Inflammation evolved as a protective response to infection and to traumas such as wounds and insect bites. Yet inflammation can also be deleterious—especially when it persists, instead of fading away as it should. Our research collaboration over the past nine years indicates that periodontal disease results mainly from the body's failure to turn off its inflammatory response to infection. The result is chronic inflammation, which causes much of the tissue damage that we observe in periodontal disease.

Why, for some of us, does this inflammatory response to oral bacteria persist rather than subside? The answer may lie in our genes: Studies indicate that much of our susceptibility to periodontal disease is genetically influenced. But fortunately, it may be possible to rein in runaway inflammation and the tissue destruction it causes.

We and our colleagues have identified powerful compounds, produced naturally by the body, that put the brakes on the inflammatory response. If we can manufacture these novel anti-inflammatory chemicals and use them as medicines, they might offer safe and effective treatments—not only for periodontal disease but also for heart disease, arthritis, Alzheimer's disease and other health problems where chronic inflammation appears to play an important role.

Much of our work on inflammation in periodontal disease has focused on its cause: the immune reaction that the body mounts against infection. This attack triggers the classic signs of inflammation including heat, redness, swelling and pain. We've been particularly interested in the innate immune response—the body's first line of defense. This response is initiated by neutrophils, a type of white blood cell crucially important in eliminating infectious organisms by engulfing them through a process called phagocytosis—which literally means "cell eating."

As they congregate at the site of infection or trauma, neutrophils secrete "proinflammatory" chemicals that cause the first, or acute, phase of inflammation. Normally, in the next step, neutrophils cease their chemical onslaught and inflammation subsides. But in periodontal disease there is a glitch: neutrophils continue churning out proinflammatory chemicals, which create a complex, chronic lesion that destroys the gum and bone holding teeth in place.

Clearly, inflammation's failure to enter its last or "resolution" phase can have serious consequences. This final

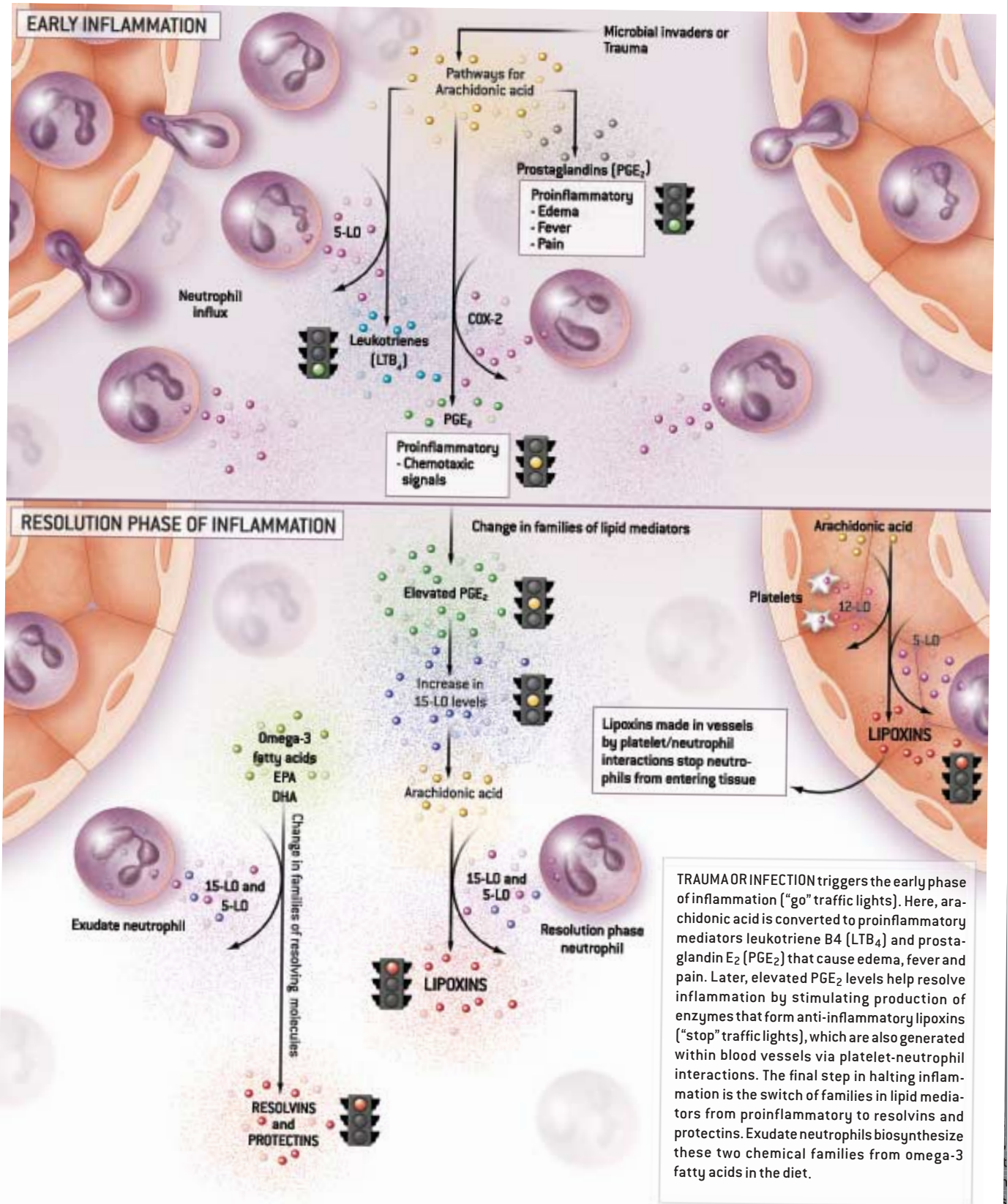
CAN GUM DISEASE CAUSE HEART DISEASE?

SEVERAL PROVOCATIVE STUDIES suggest that people with periodontal disease have an increased risk of heart disease. To further investigate this link, we induced periodontal disease in rabbits by tying a thread around some of their teeth and treating their gums and teeth with a bacterium known to cause periodontitis in humans. Six weeks later, after the rabbits had developed periodontal disease, we examined their major blood vessels. The rabbits with periodontal disease had much more atherosclerosis—fatty plaque deposits in their major blood vessels—than the healthy control rabbits.

But which component of periodontal disease—the infection or the inflammation—was the culprit? To find out which had caused the atherosclerosis, we once again tried inducing periodontal disease. This time, besides ordinary rabbits, we used "inflammation-resistant" rabbits that we genetically engineered with Larry Chan (Baylor Medical College) to have abnormally high lipoxin levels in their blood. The resistant rabbits not only failed to develop periodontal disease—their arteries were almost completely free of plaque, compared with the nonresistant rabbits that developed periodontal disease.

This study adds to mounting evidence that periodontal disease may contribute to atherosclerosis. It further suggests that periodontal inflammation plays a key role in the potential periodontal disease–heart disease connection.

— TVD



TRAUMA OR INFECTION triggers the early phase of inflammation ("go" traffic lights). Here, arachidonic acid is converted to proinflammatory mediators leukotriene B4 (LTB_4) and prostaglandin E_2 (PGE_2) that cause edema, fever and pain. Later, elevated PGE_2 levels help resolve inflammation by stimulating production of enzymes that form anti-inflammatory lipoxins ("stop" traffic lights), which are also generated within blood vessels via platelet-neutrophil interactions. The final step in halting inflammation is the switch of families in lipid mediators from proinflammatory to resolvins and protectins. Exudate neutrophils biosynthesize these two chemical families from omega-3 fatty acids in the diet.

TAMI TOLPA

phase has traditionally been considered a passive event—a petering out of immune activity that paled in comparison to the acute phase's neutrophil attack. That assumption required drastic revision after one of us (Serhan) carried out the first systematic study of the natural history of inflammation by examining inflammatory pus in skin lesions of rabbits and mice.

We observed that neutrophils, which lead the white cell onslaught during inflammation's acute phase, secrete two compounds well known for provoking inflammation and attracting additional white cells to the area: leukotriene B_4, followed by prostaglandin E_2. But at the end of the acute phase, we saw something surprising: neutrophils stopped secreting classic inflammatory chemicals and instead began collaborating with other cells to synthesize compounds that halted inflammation.

We dubbed these anti-inflammatory compounds lipoxins, since they were derived from the lipids (fatty acids) released from neutrophils' cell membranes and from other cells that congregate early in inflammation. If it is prostaglandins and leukotrienes that give the "green light" that accelerates tissue injury and inflammation, then it is lipoxins that can be considered the "red lights" that help bring inflammation to a halt.

The synthesis of these inflammation-stopping compounds starts late in the acute inflammatory response. Before that, inflammation is in full swing: enzymes from platelets and other cells attracted to the area metabolize arachidonic acid (a major fatty acid in cell membranes) to create leukotrienes and other proinflammatory compounds. Then, once these inflammatory chemicals have crowded together, an abrupt shift occurs, and enzymes induced in neutrophils convert arachidonic acid into inflammation-dampening lipoxins. The inflammatory response ceases as lipoxins increase in quantity at the expense of proinflammatory compounds.

SERHAN RECENTLY discovered yet another family of inflammation-resolving compounds that we've dubbed "resolvins." In contrast to lipoxins, whose starting material is arachidonic acid, the resolvins are derived from fatty acids in the diet—specifically from omega-3 fatty acids that are especially plentiful in fish.

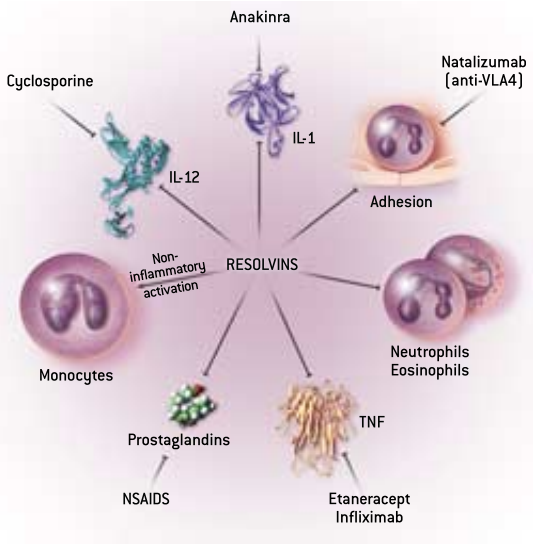
Several well-designed clinical studies indicate that diets rich in omega-3s help in treating and preventing arthritis, cardiovascular disease and other inflammatory conditions. We now suspect that the resolvins formed from omega-3s may in part account for the anti-inflammatory properties of these dietary fatty acids.

The actions of lipoxins and resolvins in the body are similar but not identical. Their net effect is to rapidly halt inflammation and minimize tissue damage. Furthermore, taking aspirin results in more potent and longer-lasting lipoxins and resolvins [*see box on page 45*].

In our federally funded Specialized Center for Oral Inflammation and Resolution, we are studying how the structure of resolvins gives them their potent anti-inflammatory ability. Based on our findings, we reasoned that the topical application of lipoxins and resolvins as medicines might prove useful in treating or even preventing inflammatory diseases like periodontitis. We also wondered if these compounds might help against other inflammatory problems such as cardiovascular disease and the complications of diabetes.

To test resolvins' ability to prevent periodontitis, we chose an established

UPPER PHOTO shows inflammation and erosion of gums in rabbits with periodontitis. In lower photo, topical resolvin prevents inflammation and tissue destruction of periodontitis.



ANTI-INFLAMMATORY DRUGS target only specific aspects of inflammation—and typically cause harmful side effects in doing so. Ibuprofen and other nonsteroidal anti-inflammatory drugs (NSAIDs), for example, curb prostaglandin production while increasing users' risk for gastrointestinal bleeding. By contrast, naturally occurring inflammation-resolving compounds, such as resolvins and lipoxins, affect all aspects of inflammation. They create a coordinated cellular and molecular response that brings inflammation to a halt. Drugs mimicking these natural compounds could potentially treat inflammation "naturally" and without side effects.

model of human gum infection—the rabbit model. We tied silk thread around certain rabbit teeth to trap bacteria and then added a disease-causing human bacterium, *Porphyromonas gingivalis,* to induce periodontitis. After dividing the rabbits into two groups, we swabbed a resolvin-containing solution on the gums of one group and an inactive solution on the gums of the other. The results were striking: rabbits receiving the topical resolvin solution were completely protected against periodontitis, whereas the placebo group developed severe gum disease [*see photos on page 44*].

TO FURTHER EXPLORE this connection between inflammation and susceptibility to disease, we studied genetically engineered rabbits that have elevated levels of lipoxins when their white blood cells are activated. These rabbits also have a very low incidence of atherosclerosis [*see box on page 42*] in their major vessels. We tried to produce gum disease in these "inflammation-resistant" rabbits using the same silk thread and bacteria technique described above. With their elevated levels of circulating lipoxins, these rabbits proved resistant to periodontitis.

While we know that bacteria causes periodontal disease, it now appears that its progressive form may be primarily driven by inflammation—which could alter the way this condition is controlled and treated. In people susceptible to periodontal disease, for example, topical application of lipoxins or resolvins could possibly prevent or lessen its severity.

More broadly, our research has shown that inflammation involves the coordinated response of a large number of biochemical pathways. But today's anti-inflammatory drugs defuse only one pathway or another and can be risky to use. Consider two examples: by far the largest class of anti-inflammatory drugs are the NSAIDs (nonsteroidal anti-inflammatory drugs), which include naproxen, ibuprofen and many other compounds. The NSAIDs short-circuit just one inflammatory pathway (the one that converts arachidonic acid into prostaglandins). Moreover, NSAIDs cause thousands of deaths annually in the U.S., mainly due to gastrointestinal bleeding. Other, more powerful anti-inflammatory drugs, such as Remicade for treating rheumatoid arthritis, do so by dampening the immune response, which may increase vulnerability to infections as well as to cancer.

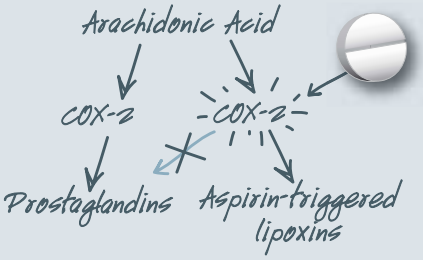
By contrast, lipoxins and resolvins might offer major advantages over existing anti-inflammatory drugs. They act by "centrally" defusing inflammation rather than just turning off one or another individual inflammatory pathway [*see sidebar on page 44*]. In addition, these natural compounds would be expected to produce few side effects.

Our studies have shown that lipoxins and resolvins may be ideally suited for treating periodontal disease. ●

REVVING UP LIPOXINS AND RESOLVINS WITH ASPIRIN

ASPIRIN'S POTENT ANTI-INFLAMMATORY PROPERTIES were recognized soon after it was introduced a century ago. But not until many decades later did Sir John Vane, Sune Bergström and Bengt Samuelsson—in research for which they shared a 1982 Nobel Prize—discover how aspirin actually works. Aspirin blocks the enzyme COX-2. This provides relief by preventing arachidonic acid in cell membranes from being converted into prostaglandins—the chemical messengers that cause the pain and swelling of inflammation.

By blocking the COX-2 enzyme, aspirin and similar drugs do a good job of shutting off the prostaglandins that fuel the early, acute phase of inflammation. But they may also set the stage for chronic inflammation by hindering the body's own attempt to heal: As the illustration on page 43 shows, prostaglandins are vital for producing the lipoxins that help to resolve inflammation.



This suggests a better strategy for quelling inflammation: Instead of halting acute inflammation, focus instead on helping the body in its effort to resolve the inflammatory response.

When we swallow aspirin, it not only inhibits COX-2 but also modifies its action. Research by one of us (C.S.) has shown that aspirin-modified COX-2 catalyzes the production of "new and improved" resolvin and lipoxin compounds that have more potent and longer-lasting anti-inflammatory effects than the naturally occurring variety.

These previously unappreciated aspects of aspirin's activity may help researchers develop truly anti-inflammatory compounds that would not just muffle acute inflammation but would actively resolve inflammation and heal wounds. These drugs would be especially useful against periodontal disease, heart disease and other important health problems that arise from chronic inflammation.

— TVD

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CHARLES N. SERHAN studies the cellular molecular mechanisms that resolve inflammation. He holds the Gelman Professorship at Harvard Medical School, is a senior biochemist and an endowed distinguished scientist at Brigham and Women's Hospital. Dr. Serhan is also chairman and professor of oral medicine, infection and immunity at the Harvard School of Dental Medicine.