You and I know that the white sticky stuff that accumulates on teeth during the day and overnight is made up of millions of bacteria, but since patients don’t see the bugs (unless you have a microscope in your office) they don’t get excited about it. They think it might just be some leftover donut. No one likes the taste or smell of morning mouth, so strongly flavored mouthrinses and toothpastes are popularly used to cover up the nasty taste – neither actually removes the source of the nastiness. If your patients really knew what lived in that white sticky stuff, they just might be more compliant with your admonitions to remove it daily. In 1676, Antonie Philips van Leeuwenhoek, “the Father of Microbiology,” was curious enough about the white sticky stuff on his teeth that he scraped some off to examine under his primitive microscope. He observed “animalculi” living in a microbial community on his teeth and understood the impact these bacteria would have on the body, without really understanding the chronic inflammation of periodontal disease.

Since then, researchers have revealed the sophistication of oral bacter-
Ial communities, how they protect themselves while triggering infection, the complexity of the body's immune response and most recently, ways to stimulate the resolution of inflammation and return the tissues to homeostasis.

Plaque

The term plaque was first used by Dr. G.V. Black 100 years ago to describe accretions on tooth surfaces. His work with plaque focused on dental decay and ways to repair the loss of tooth structure. In 1943, Dr. Charles C. Bass, dean of the School of Medicine at Tulane University, published the first of many papers and research reports demonstrating the value of brushing and flossing to prevent periodontal disease. Loosing all your teeth as you aged was common in his day. Having lost a tooth or two to periodontal disease, Dr. Bass examined them under the microscope to learn why they were lost and find a way to save the rest. From his work came the “Bass” toothbrushing technique and unwaxed “Right Kind” dental floss. Brushing and flossing remain the primary means of removing the plaque, but still patients don't grasp the idea that this white sticky stuff, sometimes dyed red with disclosing solution, is actually a microcosm of millions of bacteria.

In 1965, the experimental gingivitis studies published by Dr. Harold Löe demonstrated that allowing plaque to accumulate in a healthy mouth produced gingivitis. Reinstating oral hygiene measures reversed the gingivitis within seven days. These early plaque studies showed a sequential development of marginal plaque beginning with Gram-positive coccoid bacteria and moving to a more complex, Gram-negative, anaerobic mixture of bacteria. As Dr. Niklaus Lang stated in a July 2009, *Journal of Clinical Periodontology* article: "These and other studies came to be the ultimate documentation that bacterial plaque was something very different from food debris, something much more colorful than Material Alba, and much more interesting than just 'Schmutz.'"

Biofilm

Adding the work of engineers to the study of bacterial plaque took it to another level – that of biofilm. While periodontists were focused on identifying bacterial species in dead plaque under the microscope, engineers lead by of Dr. J. William Costerton at the Center for Biofilm Engineering at Montana State University, were more interested in how the bacteria lived and worked together. Did they have single family dwellings or high-rise condos? Did they have highways and bridges to expedite travel? How did they bring nutrition in and get rid of waste materials? Did bacteria communicate by electrical, chemical or mechanical means? Engineers and microbiologists answered these questions using laser confocal microscopy and producing digital imagery to evaluate living plaque colonies in a fluid environment. Their work has provided information about a very complex, living bacterial community with inherent resistance to antibiotic and antimicrobial agents. Thus, we have a transition from Dr. G.V. Black’s term, *plaque*, to Dr. Costerton’s term, *biofilm*, and with it brings a greater understanding of the complex ecosystem in which the bacteria live and multiply.

Communication is a vital part of biofilm formation. Single, planktonic cells use both chemicals and energy to communicate. Through signaling molecules, the planktonic cells measure the number of other bacteria in the area. When they have the right number of cells to form a biofilm – a quorum – the bacteria communicate with each other and at the appointed moment, they all produce a polysaccharide slime that will form the matrix of the biofilm and hold them together as they grow into a tower or mushroom shape. This cell-to-cell communication allows bacteria to adapt to their complex and ever changing environment. Biofilms provide a protected mode of growth that allows bacteria to survive and multiply, even in a hostile environment. Channels within the biofilm carry nutrients in and toxic waste out of the organized community. Bacteria make up approximately one-third of the biofilm with the other two-thirds being slime and water. Gene expression by bacteria in one section of the biofilm is often different from bacteria in other sections. The structural complexity of biofilm and the communication among bacteria give the appearance of a single entity rather than millions of individual bacteria. It’s not surprising that many chronic infections are caused by bacterial biofilms.

Infection

The infection is created when toxic waste products from the bacteria in a biofilm pass through the epithelial attachment and the non-keratinized sulcular tissue, triggering a response from
the blood vessels in the area, causing redness, heat and swelling. The body's first response to irritation, injury or infection is via rubor (redness), calor (heat), tumor (swelling), and dolor (pain). Researchers have discussed several possible theories to explain how bacterial biofilm actually causes periodontal disease. The ‘specific plaque hypothesis’ suggested just one bacteria was responsible, however periodontists have identified six to eight potential pathogens among 700 identified species in oral biofilm, and research hasn't confirmed one specific bug responsible for gingivitis or for converting gingivitis to periodontitis. In medicine, an acute infection is generally caused by a single species of bacteria and as such is susceptible to antibiotic therapy. Chronic infections are generally mixed bacterial biofilms and not easily eradicated by conventional antibiotic therapy.

Next came the ‘non-specific plaque hypothesis’ suggesting that all plaque was bad plaque and it was the amount of plaque that caused disease. Again, no research to prove this and you’ve probably seen patients with so much plaque they deserve disease, but don’t have any attachment loss. Then there are the others who have very little plaque on their teeth, but the connective tissue and bone seem to be melting away.

It's not just about the bacteria anymore, as smoking and diabetes were the first recognized risk factors that interfere with periodontal healing. The impact of genetics became clear with studies done on twins. Today, epigenetic differences, changes in gene expression can be influenced by environmental factors, stress, diet and bacterial accumulation. Although our original DNA doesn't change, the way the genes are expressed does, which impacts periodontitis as well as cancer and other inflammatory diseases. Alterations in gene expression can be reversed by eliminating the stressor, nutritional deficiency, bacteria or they can remain and be passed on to future generations with potential detrimental effects.

Variations between patients was acknowledged by Dr. Roy Page and his colleagues in 1997 when genetic, environmental and acquired risk factors were added to the description of pathogenesis. These findings led researchers to focus on the individual and the complexities of the immune response rather than the bacteria. Diet, genetic variations and immune response are now considered important aspects of the pathogenesis of periodontal disease and the focus of current research.

Inflammation

The study of inflammation began in ancient times as documented by Celsus with the four cardinal signs of inflammation: rubor (redness), calor (heat), tumor (swelling), and dolor (pain). The body's first response to irritation, injury or infection is via the blood vessels in the area, causing redness, heat and swelling. Pain results from the release of chemicals stimulating nerve endings. The arrival of defensive white blood cells to the area triggers a cascade of immune reactions.

Both innate and adaptive immune responses occur. The innate response will recruit immune cells to the area. Polymorphonuclear neutrophils, monocytes and macrophages are all phagocytic cells that release cytokines, triggering the complement system and acute phase response. These systems will assist in the targeting and removal of pathogens.

The adaptive immune response can distinguish cells of the body from the invading pathogens. These cells recognize antigens and organize a response to eliminate specific pathogens. Attempts to control the immune inflammatory response have used non-steroidal anti-inflammatory drugs to block the signs of inflammation. An exciting new direction in the research shows that the resolution of inflammation is an active process that can be modified and pushed, with newly derived substances, to return the tissue to homeostasis, without the side effects of anti-inflammatory drugs.

Resolution of Inflammation

Traditionally, it was thought that simply eliminating the pro-inflammatory mediators would be enough to turn off inflammation and allow the tissues to return to health. Evidence now confirms that resolution of inflammation is not a passive process, but an actively regulated process. The research team at Boston University led by Dr. Thomas Van Dyke, in collaboration with others, has identified resolvening lipid mediators that contribute to restoring the periodontal tissues to health. The body produces lipoxins from the metabolism of arachidonic acid and Dr. Van Dyke's team has derived a number of similar molecules from omega-3 polyunsaturated fatty acids. Resolvins and protectins are similar to lipoxins, acting to trigger the termination and resolution of inflammation and returning the tissue to homeostasis. Animal research with topical applications of omega-3 derivatives around periodontally involved teeth restored the connective tissues to health and prevented bone loss. Human studies are now underway to determine clinical effectiveness of activating the resolution of inflammation and repair of the tissues with omega 3 fatty acid derivatives.

The common denominator between periodontal disease and other systemic diseases and conditions is chronic inflammation. Diabetes, arthritis, cardiovascular disease, obesity and aging all share components of chronic inflammation. Identifying and targeting the mechanisms of infection, inflammation and resolution of inflammation are the challenges researchers now face. This research is multidisciplinary with periodontists, physicians, microbiologists and geneticists working together to understand chronic inflammation and how it impacts the body in so many ways. What started with a look at the white sticky stuff on our teeth, has led to a wealth of information and research about the complex immune response of individuals and the genetic influences responsible for the wide variation in responses, not just to periodontal disease, but many other diseases and conditions.