It’s a jungle in there

Oral ecologists find the warm, moist human mouth a microhabitat in which benign creatures dominate and terrible ones lurk

Since 1959, when scientists isolated a species of infectious bacteria that causes most cavities, a national campaign to reduce tooth decay has focused on brushing, flossing, and adding fluoride to water supplies, toothpaste, and mouthwashes. Fluoride, a chemical that often appears naturally in groundwater, acts quickly to restore the tooth’s smooth crystalline surface so that bacteria have a difficult time gaining a foothold.

These dental hygiene methods have worked so well that today, 50% of US children under 12 have no tooth decay. However, of the remaining 50% of children with cavities, many have severe forms that are difficult to control, even with the best dental hygiene. Sealants painted over pits and fissures have limited success, because the bacteria are extremely good at hiding and will emerge as soon as the sealant wears off. And periodontal disease, infection of the gums that is caused by approximately a half dozen bacterial species, affects millions of people, mostly adults.

During the last 20 years, modern biological technology, including genetic engineering and techniques to study anaerobic bacteria—those that live without oxygen and cause most periodontal disease—has enabled oral ecologists such as Socransky to identify some of the organisms. They have determined that the mouth’s microorganisms have evolved with the human species, probably for as long as it has existed. In exchange for living in their tropical paradise, the mostly beneficial bacteria help fend off disease-producing bacteria from the outside world that attempt to infiltrate the mouth via the nose, the fingers, or the air. For example, some beneficial bacteria produce organic acids, such as propionic and butyric acid, that kill bacteria that cause intestinal problems.

However, researchers funded by the US National Institute of Dental Research have pinpointed approximately a dozen species of bacteria and yeast that live in the mouth and can cause infections in the teeth and gums of virtually every human in the world. In the last five years, researchers have made significant strides in understanding how these organisms are transmitted from one person to another, and they are in the initial stages of developing startling new methods of dental care to prevent the spread of infection. These methods include varnishing mothers’ teeth to prevent the spread of bacteria to their babies, infecting mouths with less harmful strains of bacteria that crowd out the harmful organisms, and developing medications that prevent undesirable bacteria from sticking to teeth and gums so that they are sluiced out of the mouth by saliva, through the digestive system, and to the sewer system and out to sea.

Humans born with sterile mouths

When human babies pop into this world, their wails of greeting burst from sterile mouths. “Within minutes to hours, they are colonized with organisms that stay with them until they die,” says Socransky. The mostly harmless bacteria, yeast, viruses, and protozoa enter from anything that makes contact with a baby’s mouth, such as the air, a breast or bottle nipple, or a finger.
The growth of organisms in the mouth follows the classical pattern of ecological succession, the same way that bare land eventually turns into a thick jungle. A few pioneer species settle first, creating a habitat friendly to other species, which then move in. When the first baby teeth push through the gums, another set of species—including the dreaded Streptococcus mutans, the bacteria believed responsible for most tooth decay—slips in. During puberty, the composition of saliva changes, so that another group of organisms immigrate and flourish.

By the time humans reach adulthood, their mouths harbor what is known as a climax community—a complex group of organisms, each with its own preferred microhabitat. Some species live only on the cheeks. Others prefer the back of the tongue over the front, especially the group of anaerobic bacteria that lives in the crevices of the tongue and emits hydrogen sulfide, the origin of most severe bad breath. Another group will survive only on the palate. The teeth themselves provide a plethora of living options—surfaces that face the outside world, sides with a view of the back of the mouth, a strip along the edge of the gums, or the gloomy, wet, oxygen-deprived spaces between the gums and teeth.

"Seeing all these different forms of life and figuring out what they do and where they live is fascinating," says Socransky. "You get a sense of what kind of world is living with you."

Saliva, the magic fluid that keeps this ecosystem in balance, harbors its own collection of bacteria, as well as a host of other substances. Bicarbonate ions buffer the tooth-decaying acids that are produced by harmful bacteria such as S. mutans. Phosphate and calcium ions supersaturate saliva and continually repair the microscopic chinks made in the crystal structure of the teeth by the bacteria's acid. Saliva contains antibacterial agents, such as lysozyme, which kills bacteria by opening up their cells walls. Approximately 60 proteins float around in saliva. Some of them actually provide nutrients for bacterial growth, while others lubricate the mouth and cause bacteria to stick together in such large clumps that they cannot stick to tooth surfaces and are easily washed away. Saliva also contains antiviral components, including a substance as yet unidentified that kills the HIV virus.

Ecological conditions in the mouth are never stable. People change their diets, they lose teeth,
they have crowns or false teeth put in, or they go on medications that affect certain microorganisms. "For example, an epilepsy medication causes overgrowth of gums," says Socransky, "and that changes the microbiota. But, for most medications, we're not entirely clear what they do. No one has systematically studied what happens to the organisms in the mouth when people take medications such as insulin, anti-inflammatory drugs, or cancer drugs. I'm sure that they have an effect."

Changes also occur after every meal, every brushing and flossing, even after every time we swallow, as millions of bacteria lose their hold on teeth and tumble down the throat. During night's sleep, when saliva production drops to nearly zero, bacteria, like the minions in the movie Fantasia's "Night on Bald Mountain," revel in their freedom and multiply with abandon until the dawn.

Most of the time, however, the inhabitants of the mouth live in more or less perfect harmony. "Congress should take lessons from the mouth," says Yolanda Bonta, manager of clinical research in the Department of Research and Development at Colgate Oral Pharmaceuticals in Piscataway, New Jersey.

But, like last winter's breakdowns in budget talks that led to the shutdown of the federal government, sometimes things go to hell in a handbasket in the mouth, too. Abundant sugar can power some strains of S. mutans into a frenzy of activity. The bacteria seep acid as they gobble up sugar and overtake saliva's ability to buffer the acid, which eats away at the minerals of tooth enamel. Without adequate brushing and flossing, plaque grows, producing calcified deposits and a cozy home for more species that do more damage. Sticky opportunistic bacteria gain a foothold in the newly formed holes and crevices, and no amount of salivary flow will wash them off. A microscope reveals that the bacteria-laden plaque you scrape off your tooth with your fingernail is a daunting tangle of thick vines ending in corncobs winding in and around a slowly writhing mass of lumps and wormlike creatures.

Stress, medications, and unknown factors can throw the ecosystem of the mouth out of whack, causing a species of bacteria that keeps periodontal disease-producing bacteria under control to disappear and the gums to turn red with infection. More than 200 types of medication, as well as radiation of the head and neck for cancer treatment, cause a drastic drop in saliva production, and bacteria run rampant.

Bacteria, yeast, and protozoa can dive down tiny cracks in a tooth to infect the blood- and nerve-rich root to cause ice pick–like stabbing pain. During a dental procedure, bacteria can infiltrate the bloodstream or the brain. If the body's immune system does not act quickly enough to stop them, they infect the heart or brain tissue and eventually can cause death or madness.

In fact, because bacterial infections to tooth roots were so difficult to contain in the days before antibiotics, dentists were not allowed to do root canals in the United States until after World War II, even though root canal procedures had been known for hundreds of years. The direction in which infection spread also gave names to particular teeth. "That's why eye teeth are called eye teeth," says Kathleen Olender, an endodontist at the University of California at San Francisco School of Dentistry. "If that particular tooth gets infected, the bacteria can easily travel to infect the eye."

Bacteria find their opportunities

In the last few years, researchers have made significant strides in better understanding how oral bacteria are transmitted from person to person. At the University of Alabama School of Dentistry, Page Caufield, a professor of oral biology, found that humans are colonized by S. mutans—the cavity-causing bacterium—during a "window of infectivity" at around two years of age. At that time, S. mutans is passed from the primary caregiver—usually the mother—probably through saliva transmitted when droplets are spewed by talking or sneezing into the face of a child whose teeth are emerging. "The window opens and closes," says Caufield. "If children aren't infected by S. mutans then, another bacterial species colonizes and uses that niche. People don't exchange S. mutans as adults."

Another important discovery was that S. mutans comprises thousands of different strains, some more harmful than others, which partly explains why some people have more, or more severe, cavities than others. However, recent studies indicate that bacteria that cause periodontal disease are passed between spouses and "significant others," says Ernest Newbrun, a dental researcher at the University of California at San Francisco Department of Oral Biology. "It isn't clear that that's the only way those bacteria are transmitted, but it seems to require direct mouth-to-mouth contact, in other words, kissing."

This knowledge is leading scientists to develop new methods of preventing diseases of the teeth and gums. "Instead of trying to kill all the microorganisms, we're targeting specific interactions," says Irwin Mandel, recently retired from decades of research at Columbia University School of Dental and Oral Surgery. "It's more of a magic bullet approach than a shotgun approach."

In Alabama, Caufield and his team will soon begin clinical trials on 250 women who carry harmful strains of S. mutans. Their teeth will be treated with an antiseptic and varnished during their children's window of infectivity. The scientists hope that the trials will result in 250 children who will live a life free of the S. mutans strains that have plagued their mothers.
At the University of Florida at Gainesville, molecular biologist and dentist Jeff Hillman has been using genetic engineering for the last ten years to develop a harmless strain of *S. mutans* that will replace the acid-producing strains that occupy most mouths. In the early 1980s, he and his research team isolated a strain that metabolizes sugar but did not produce acid as a waste product. However, no matter what he and his colleagues did, the *S. mutans* that already occupied a person's mouth would not be budged. Even trying to eliminate the original *S. mutans* with antibiotics and painting the teeth with iodine did not work. "They have hiding places," says Hillman. "Nobody found a way to wipe them out entirely."

So Hillman looked at hundreds more strains of *S. mutans* and found one that produces an antibiotic-like molecule that kills all other strains of *S. mutans*. Using genetic engineering, he modified this strain so that it would no longer produce acid. The so-called effector strain can colonize tooth surfaces, he says, and wipe out other strains of *S. mutans*.

Within the next few months, Hillman will begin clinical trials on laboratory rats, and if the bacteria perform as intended, he will conduct clinical trials on humans. He anticipates that, eventually, dentists will apply the bacteria during a typical cleaning. "In theory, the new strain should stay with people the rest of their lives," says Hillman. "And since *S. mutans* normally is transmitted from mother to child, this effector strain will also be transmitted and will prevent tooth decay in the children of those treated."

Unfortunately, says Socransky, this approach is not as simple in periodontal disease, which involves several species. Some live in the periodontal pocket and interact with a second set of microorganisms that colonize above the pocket. They seem to have complex interactions, even keeping each other in check. For example, *Streptococcus oralis* produces hydrogen peroxide, which prevents *Actinobacillus actinomycetemcomitans* from multiplying out of control. And *A. actinomycetemcomitans* produces a bacteriocin antagonistic to *S. oralis*. When something, such as stress, medication, or other unknown factors, causes *S. oralis* to die off, *A. actinomycetemcomitans* gains the upper hand and causes serious gum disease that dentists must perform surgery to cut away the gums and clean out the infected tissue.

Researchers at the Forsyth Dental Center have spent the last five years deducing how bacteria attach themselves to teeth, with the goal of developing substances that can prevent bacteria from sticking to tooth surfaces. "They appear to bond to specific salivary proteins absorbed on tooth surfaces," says Donald Hay, a protein chemist and associate director of the center's research institute. Hay worked with Forsyth microbiologist Ronald Gibbons, who discovered in the 1970s that bacteria have to stick to a surface to cause infection.

Hay and Gibbons have found that individual bacterial species bind to particular proteins. "*S. mutans* binds to a high molecular weight protein in mucin. Others bind to two other proteins. There's quite a lot of variation among species," says Hay.

The researchers have made good progress in identifying the salivary proteins and their structure, and they are now beginning to tackle the bacterial molecules. When they understand the interactions between the two, "then we'll be in a good position to interfere with the interaction," says Hay.

Other research in the area of oral ecology includes the development of saliva tests akin to blood tests, so that dentists can diagnose people at risk for oral disease. Efforts are also being made to develop artificial saliva for the 2 million people with Sjogren's syndrome, an autoimmune disease that causes severe drying of the mouth, eyes, and other mucosal surfaces. Others who would benefit from artificial saliva include those millions of people whose saliva glands shut down after radiation treatments or as the result of certain medications. Research is also continuing at the Forsyth Dental Center, the University of Washington, the University of Texas at San Antonio, and the University of Florida to develop vaccines against caries and periodontal disease.

Most of these new methods are still five to ten years away from seeing the inside of a dentist's office, say researchers. Until then, Bonta advises keeping this thought in mind. "You can afford NOT to brush for 72 hours," she says. "[However], if you pass that threshold, you may not be able to remove the plaque and bring the infected parts of the teeth back to health."

And it is best to brush for more than one minute, says Newbrun. Fifty or 60 seconds is not enough to clean the 150 tooth surfaces that most of us have, to bring that bacteria count down to a manageable and healthy 1000 to 100,000 per tooth.

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