IMPACT

Chew on This:

By Kevin Rayburn

Dental Researchers are Looking at Teeth in a Whole New Way

"Imagine what (smoking) could do to your teeth," went an old slogan advertising a brand of smoker's toothpaste.

(The advertisement conveniently failed to mention the effects of smoking on the heart and lungs.)

Dental researchers today might well lay claim to a reverse version of that ad: "Imagine what unhealthy teeth and gums could do to you."

That's because what a lot of people don't know, and a lot of dentists are finding out, is that your teeth and gums may influence disease throughout your entire body.

Researchers have found strong links between unhealthy mouths and everything from pre-term birth, heart disease, diabetes, stroke, pneumonia and more.

"Our research supports the link between oral health and systemic disease," says Denis Kinane, Professor of Periodontology and Professor of Microbiology and Immunology and UofL's Delta-Dental endowed professor in the School of Dentistry.

Kinane is part of a large team of UofL dental researchers exploring oral health by looking at larger issues such as the body's immune system, genetics and environmental aspects such as smoking.

Today's dental scientists are just as likely to use words and terms such as "gene polymorphisms", cytokines, and macrophages as they are to mention bicuspids and molars.

In one study, for instance, Kinane's team examines how periodontal disease, which causes receding gums and bleeding in the mouth as well as destruction of tooth-supporting bone, can release bacteria that travel through the bloodstream and may cause disease in other parts of the body.

"Around teeth there are sites where the epithelium of the gums is inflamed and ulcerated and the bacteria are close by. When we brush our teeth we perturb that balance ... and it's feasible that the bacteria can then enter the bloodstream and create the bacteremia that then causes problems

elsewhere such as the heart, placenta or liver."

One possible effect could be an increase in the atheromatous plaque in heart blood vessels, which can break off and cause heart attacks. Yet, what Kinane's team found during the study is the sort of thing that can drive researchers bonkers.

"We found that patients with inflammation (of the gums) have less bacteremia than patients with no gingival inflammation due or gingivitis (gum disease)."

If that sounds counterintuitive, Kinane would agree.

What it means is that the body is complex and does seemingly contradictory things.

"Ultimately it means that normal inflammation appears to be protective and that a lack of normal inflammation may be problematic," he explains.

As Kinane is finding, genetic variations among people mean that they react differently to disease.

"We normally expect the adaptive immune system to show individual variance, but now we're finding that the innate immune system, which is our basic defense against bacteria, also shows marked differences between subjects."

So if bad bacteria in the mouth could get into our bloodstream, should we stop flossing and brushing?

No, says Kinane.

"What we may eventually see is that high quality dental care will not only improve oral health, but may reduce the risk of cardiovascular and other serious diseases."

The rise in periodontal disease

The stereotype of the toothless Kentucky bumpkin is just that, and offensive.

Even so, statistics do show that Kentuckians and neighboring West Virginians are more likely than other Americans to have lost all or some of their teeth to untreated gum disease.

Studies and surveys have shown that dental health rates tend to decrease among people with lesser educational levels and socio-economic status.

Kentucky's high rates of gum disease and tooth loss are one reason why the internationally respected Kinane was recruited in 2002 to conduct his research in Louisville. His hiring was supported through Kentucky's Research Challenge Trust Fund. A native of Scotland, Kinane collaborates with some of the world's best dental researchers on three continents.

And his work has broader implications beyond the state.

That's because 15 to 20 percent of Americans suffer from periodontal disease. And those rates are increasing as the overall population ages.

In periodontal disease infected gums go untreated and inflammation spreads to the tissues that support the teeth, eventually causing tooth loss.

Why older people are more susceptible to gum disease—and the bleeding and receding gums, underlying bone loss and loosened teeth—also interests UofL associate professor Georgios Hajishengallis. Like Kinane, he and colleagues are looking to the human immune system for answers to such dental problems.

Outwitting wiley bacteria

Hajishengallis is trying to answer a fundamental question: Why does the aging immune system gradually lose its ability to fight the P. gingivalis bacteria—commonly found in the mouth—that plays a key role in causing gum disease?

In research funded by the National Institute of Dental and Craniofacial Research, Hajishengallis has found that P. gingivalis, may be circumventing the body's immune system by "tricking" white blood cells and then hijacking the cells.

"Our research suggests that P. gingivalis has evolved, learning to use the human immune system for its own survival," Hajishengallis says.

The researchers found that P. gingivalis uses a receptor, CR3, on the bacteria-eating white blood cells of our immune system to circumvent the body's defenses and flourish in dental plaque.

They discovered that the sticky fringes—fimbriae—that cover P. gingivalis interact with CR3 and tell it to reduce production of a substance that keeps infection at bay. This interferes with the body's immune defense and may also allow other microbes that live with P. gingivalis in dental plaque to survive.

Moreover, P. gingivalis may actually be targeting the CR3 receptor to pass into white blood cells, because, unlike other immune receptors, it does not vigorously promote killing of bacteria. This makes P. gingivalis better able to survive and could also allow the harmful bacteria to use white blood cells as "trojan horses" that carry them into vulnerable cells in other parts of the body, Hajishengallis said.

Hajishengallis and his team speculate that blocking CR3 could be one way to control human periodontitis and associated diseases. This has already been shown by the Hajishengallis team using a mouse model of periodontal disease and a CR3 inhibitor. Similar inhibitors may also be useful in other inflammatory or autoimmune diseases such as psoriasis and forms of cardiovascular disease.

vaccinating against tooth decay

In another study, Hajishengallis and a research fellow colleague, Shuang Liang, have found that removing the toxic part of an E. coli protein renders it harmless yet still able to tell the body to begin an immune response.

That finding, Liang says, "lays the foundation for vaccines against a variety of diseases that begin in the mouth and mucus membranes."

It also demonstrates a common theme of much UofL dental research: the link between the immune system and dental health.

Tooth decay begins when sugars and starches are left on the teeth. Bacteria in the mouth thrive on these foods, producing acids that destroy tooth enamel and lead to tooth decay and cavities.

Theoretically, a vaccine supplemented by an effective adjuvant— an added substance that alerts the immune system to the organism's presence—could prevent cavities by keeping decay-causing bacteria from gathering on the teeth.

the role of inflammation

Michael Martin, an assistant professor of dentistry at UofL, is part of the research team in the Oral Health and Systemic Disease Research Group, established by Kinane.

In previous work, Martin had found that a protein called GSK3 appears to regulate inflammation.

Now, Martin is studying how GSK3 regulates the disease process and whether it can be used to control the inflammatory response and tissue destruction that occurs with periodontal disease.

At first, inflammation can be protective, helping to kill invading bacteria. Sometimes, however, the immune system's inflammatory response over-reacts, causing damage to the body's tissues. This mechanism is thought to be at the heart of many auto-immune disorders. "Our indirect evidence suggests GSK3 will work well to control periodontal disease and may have applications to many inflammatory diseases," he added.

A better understanding of the protein's role in controlling inflammation also could lead to treatments for diseases such as rheumatoid arthritis, celiac disease and lupus. It may also lead to new ways to stop sepsis, a life-threatening immune response to infection that often leads to organ failure and death.

A thriving center

For a recent period, UofL announced this past summer that it had received nearly $6 million in dental research grants.

That and other trends, such as the dental school's ascendency to 17th among the nation's 56 schools that receive NIH funding (up from 37th in 2002), bode well for its research efforts.

"There's no reason Louisville could not become a Mecca for oral health research internationally," Kinane says.

"One thing that's interesting about all this work we're doing is that it could increase people's perception of the importance of dental health and dental research. With the appreciation of the systemic effects of gum disease, you might find that dentists are more aware and make diagnoses of other diseases such as heart disease."

In one five-year study of systemic disease, Kinane is looking for markers of cardiovascular disease in the blood.

"We've found nearly all the markers found in blood can also be detected in saliva and with the new technologies the group is developing we can detect these markers within ten minutes."

The classic dental phrase, "rinse and spit," takes on a new meaning.

"Imagine if we can use saliva to diagnose heart conditions rather than having to take blood," Kinane says. "No needles. Patients at risk can do it themselves; just spit in a bottle."

UofL staff writer Anne Eldridge contributed to this article.
