OF THE CALIFORNIA DENTAL ASSOCIATION

Journal

APRIL 2010

PERIO-SYSTEMIC LINK

RICHARD T. KAO
DDS, PHD

Vol 38 No04

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Journal

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CDA JOURNAL, VOL 38, Nº4

Personalized Medicine

KERRY K. CARNEY, DDS

Genetics has replaced linguistics as a marker for migration patterns and intermarriage in the ethnohistory of human populations.

Another good thing about CDA membership is the ease with which one can download federally and state-required forms and posters. The Equal Employment Opportunity poster is a good example. In the December 2009 issue of *CDA Update*, there was news brief about the most recent revision to the EEO poster. The section titled "Equal Employment Opportunity Is the Law" has been updated. The new version includes and describes the prohibition of genetic discrimination as mandated by the Genetic Information Nondiscrimination Act, GINA.

President George W. Bush signed GINA into law on May 21, 2008. After 13 years of debate, it was passed overwhelmingly in both the Senate and the House. It was designed to protect Americans against discrimination in their insurance and employment based on their genetic information. The intent of the law is to allow the public to access personalized medicine without fear of discrimination. GINA prohibits employers from collecting genetic information from employees, and using this information to make decisions regarding employment terms.

The issues of privacy, genomics, ethics, governance, and personalized medicine are all wound up together. We used to think about genetic counseling in terms of some rare genetic defect. Counseling was part of geneticist's specialty training. It was a science and an art. It involved educating the subject and/or family members to the meanings of genetic variation in terms of risk, severity of expression, social ramifications, and their own very personal context. However, now these counselors are sometimes cut out of the loop entirely. Now, there is direct-to-consumer, genomic profiling and interpretation. These DTC profiles are the result of an astounding acceleration in technological innovation, cost reduction, and a concomitant retargeting of diagnostic information from physician to consumer.

The Human Genome Project began in 1990. The planned completion date was 2005 but the spectacular advances in sequencing shortened the timeframe by two years. Gene sequencing and genomic profiling have become insinuated into our everyday experience. How is the public exposed to most genetic terminology? Rather than scientific journals, courtroom or forensic dramas are more likely the source. Some common uses of genetic testing have become as familiar as our commute to work. Genetic testing for paternity has given rise to billboard advertizing in Memphis proposing to answer the question: "Who's your daddy?"[1]

Genetics has replaced linguistics as a marker for migration patterns and intermarriage in the ethnohistory of human populations. A genomic boutique industry has sprung up around profiling one's ancestry. A Mountain View, Calif., company that provides DTC genomic profiles proclaims in its mission statement to be the world's trusted source of personal genetic information. On their Web site, the consumer can choose the "Ancestry Edition" at $399, the "Health Edition" at $429, or the "Complete Edition" at $499. Some profiling services portray themselves as genomic versions of visa and entry stamps in traditional passports; they offer up a picture of where your genome has been.

Having access to an individual's genome could provide a wealth of information and allow the tailoring of personalized medicine. The real breakthrough in personalized medicine will come when the cost of whole genome sequencing drops low enough that consumers start to demand treatment based on their own personal genomes. At that point, both research and clinical practice will be transformed.

James Watson and Francis Crick described the double helix structure of DNA in 1953. Watson has become the first human to have his personal genome made public and available on the Web. He reports that he is not troubled by the lack of privacy.[2] He describes how his heterozygous lactose intolerance gene allows him to ingest the occasional ice cream cone without gastric repercussion. However, he goes on to say that he did not have his APOE, an Alzheimer's predisposing gene, sequence revealed to him nor to the public. He said he wanted to live as if he would not be victimized in his 90s, as was one of his grandparents.[2] In this instance, Watson chose privacy over knowledge for very personal reasons.

Watson goes on to describe genomic pharmacology. He is homozygous for CYP2P6 (an allele of a drug metabolizing gene) and based on that information, he successfully reduced his β blocker regimen from one a day to one a week. It is easy to imagine that the pharmaceutical industry will at some point begin to incorporate genome-based warnings into their package inserts.

The inevitable tsunami of information from personal genomes will impact our understanding of genomic variability and the variability of our responses to medicines.[3] Based on personal genomes, individuals may choose to modify their lifestyles. They may choose to stay abreast of experimental therapies for conditions they are at risk to develop in the future. They may choose unnecessary or ineffective medical procedures based on inaccurate data or poor interpretations of data.

So what will be the role of the physician? The American Society of Human Genetics recommends, "Professional organizations should educate their members regarding the types of genetic tests offered DTC, so that providers can counsel their patients about the potential value and limitations of DTC testing."[4] Physicians are no longer gatekeepers to genomic information. They will be responsible for integrating that information into a personal treatment plan and making the information understandable in a practical, clinically relevant way for the patient.

Studies have recently shown that gene expression and biological pathways involved with healing are important in understanding the onset and healing process associated with gingivitis. The identification of biomarkers for individuals at risk for periodontal disease could make possible the design of advanced, personalized treatment options and preventive care. In a future not far away, a patient's genomic profile will be as important and accessible as his or her blood pressure is today. ■■■■

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Editorial Hits Close to Home; Formocresol Article Questioned

I thought the editorial, "Struggle," by Ruchi K. Sahota, DDS, CDE, (*Journal of the California Dental Association*, 38(2):81-2, February 2010) was a wonderful and introspective article. As I was reading, I found myself nodding and laughing with all her struggles as they are mine also.

As a working mom, I struggle with managing my new office, balancing my associateship at another office, volunteering with the Rotary club, managing my husband and 2-year-old son, and still trying to make home-cooked meals every night. In the last two years, I have learned to "say no." I totally understand how Dr. Sahota feels.

WANLAN XIAO, DDS
Livermore, Calif.

More Kudos for 'Struggle' Editorial

What a wonderfully written editorial, "Struggle." Those of us who are busy do indeed struggle with the balance of life. Like you, my wife and I find it challenging to spend the time with our four boys as well as run our practice, other investments, and our nonprofit volunteering.

There is an incredible dental organization that not enough dentists are aware of that addresses these issues. Our exposure to programs by Stephen Covey, Rev. Schuller, and others have helped us stay grounded in what we do. For example, the most powerful message we heard was from a former *National Geographic* staff photographer. He taught us that no matter how you look at or see things, there is always another way to look at it. And, often, the alternative way is the best!

The American Academy of Dental Practice Administration (aadpa.org), although a bit of a misleading name, is an incredible group of "positive on life and practice" dentists and consultants.

Lastly, I will close with information about another passion of mine. Boy Scout councils and troops need dentists and dental team members to support scouting by signing up to be a merit badge counselor. The dentistry merit badge is the most obvious, but most dentists also have knowledge and skills that apply in other areas as well. I am happy to provide more information about this to anyone.

Thanks for all you do.

WM. RANDY JUNGMAN, DDS
Escondido, Calif.

Assertions on Formocresol Challenged

Editor's note: *In response to the publication of Dr. Bradley Lewis' "The Obsolescence of Formocresol"* (Journal of the California Dental Association, *38(2):102-7, February 2010), we received three incisive letters. Dr. Ana Planells took issue with the author's claim that "Clinicians should be advised that using formocresol is not recommended by the American Association of Endodontists and the American Academy of Pediatric Dentistry." Dr. Planells documented that, "Nowhere in the AAPD guidelines do they state that formocresol is not recommended." A review of the guidelines and position papers published on the AAE Web site found that "the AAE does recommend* ***against*** *the use of paraformaldehyde-containing materials" with regard to filling materials and sealers, but there is no official position concerning formocresol. Dr. Lewis did not respond to requests for explanation or clarification of his statement. The* Journal *regrets any confusion that the author's statement may have caused.*

Information on the AAE and AAPD positions can be found in the following documents:

- *Guideline on Pulp Therapy for Primary and Immature Permanent Teeth. www.aapd.org/media/Policies_Guidelines/G_Pulp.pdf*
- *AAE Position Statement: Concerning Paraformaldehyde-Containing Endodontic Filling Materials and Sealers. www.aae.org/NR/rdonlyres/14F3726F-DA2D-4155-97E9-D0201E690B17/0/paraformaldehydefillingmaterials.pdf*

The following letter reflects the majority of the comments received by the Journal *in response to Dr. Lewis' article:*

I read with interest your lead article on "The Obsolescence of Formocresol." I would like to reflect on both the structure and substance of the author's argument for doing away with the use of formocresol in primary tooth pulpotomies.

In his "conclusion," the author uses the statement that due to formocresol's "harmful effects and lack of scientific support," its use should be eliminated from dental practice. This immediately reminds me of the type of arguments that I have routinely heard from anti-fluoridationists and anti-amalgam advocates, i.e., "everyone knows there's a problem." I would make the point that if an advocate or author begins with a highly biased point of view, it is my experience that they can find any number of additional points of evidence to support that original bias. I submit that an open mind is a most important attribute in finding truth. By way of example, my original training equated acid etching of the dentin with tooth death and malpractice; it was only through openness to possibilities that mainstream dentistry has incorporated acid-etching techniques into daily practice.

The author references Caceda [in his article] and notes while he/she has developed a pulpotomy technique using no formocresol and yet he/she still routinely employs the old standby formocresol pulpotomy. I sense in the article's tone a surprise and incredulity that any learned dental practitioner could still use formocresol. Let me suggest that, like myself, Caceda may have a reservoir of experience (thousands of successful procedures) as a body of evidence supporting formocresol's continued usage for pulpotomies. When I consider the length (70 to 80 years?) and breadth of clinical experience (millions of successes?), this dwarfs the rather miniscule number of cases of clinical experiences with MTA and makes me somewhat uneasy about the author's adamant certainty of MTA's superior performance.

While my use of MTA is admittedly limited (approximate three dozen cases, all permanent teeth), I will say I am impressed with my successes so far. My concerns with these uses of MTA is twofold:

1. The difficulty of clinic techniques is real and dramatic in my experience, especially in usage with "limited cooperation" pediatric patients.

2. The rather outrageous cost per patient. This in my view presents a real issue as far as pediatric patient access to care.

I do wish to echo the author's lament about the lack of standardization of care, i.e., why isn't a standardized preparation of formocresol of a known percentage available? As with every medication, dosage obviously creates a widely variable set of affects BOTH positive and negative.

Finally, these types of articles taunting the "obvious superiority" of a technique tend to limit accessibility to an unbiased assessment of available information and result in fear becoming the prime mover in decision-making. As an added example, I have detected an undercurrent of concern from some of my colleagues about eugenol's possible deleterious effects, e.g., toxicity and genotoxic possibilities, which the author's Table 1 seems to echo. With both eugenol and formocresol, I feel it is necessary to look at the whole picture and not rely solely on empiric evidence of the millions of successfully and apparently safe usage of these medicaments BUT on the other hand don't cavalierly ignore those. We need to look at treatments and patients in a complete way, balancing safety, effectiveness, time, and cost to deliver the best possible dental treatment to the most patients.

At a time of increasing concerns about access to care, I would hope that something like MTA with its added cost and technique limitations does not become the "standard of care." Let us rather look for improvements without abnormally raising the specter of fear as a reason for change.

ROBERT J. VENN, DDS
Modesto, Calif.

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Deborah Zemke

Club Ethics

BY DAVID W. CHAMBERS, PHD

When greeted in public with the question, "How are you," the proper response is "I'm fine. How are you?" To say that you are "superb" is presumptuous; it is an imposition to begin a list of ailments and complaints. Violating a confidence would be terribly bad form for a friend and unforgivable, and perhaps even legally actionable in a priest, health care provider, or attorney. On the other hand, in politics and the entertainment industries, failure to pass on the well-placed leak would jeopardize one's status in the network.

Club ethics regulate the way we behave in groups. Politicians can be elected while in jail, serving sentences for bribery, while others have their re-elections sabotaged for voting their

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Toothbrush Time, Oral Health Education Now Included in Massachusetts' Preschool Schedule

The Bay State is the first in the country to include toothbrushing and oral health education to the routine of children in day care.

In late January, the regulations — geared to curtail dental disease — went into play and require that children who eat at least one meal at a day care facility or attend for more than four hours are required to brush their teeth as well as learn about good oral health habits.

While the directive brought smiles to many dental professionals and parents, some were not as pleased. "I don't want someone's hand in my child's mouth," said one teacher and mother of a 5-month-old baby, according to a newspaper interview. "It's a little too much government intervention."

However, parents can opt out, said Sherri Killins, commissioner of the Department of Early Education and Care, the agency that watches over day care centers.

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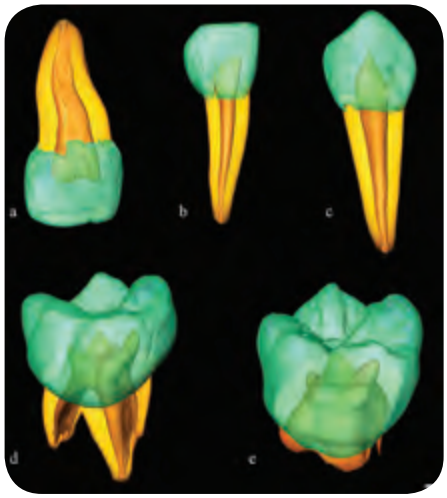

Courtesy of the University of Bristol

Virtual 3-D reconstruction of four deciduous and one permanent teeth assessed for linear, surface, and volumetric tissue proportions.

Ancient Dentition Offers Clues to Man's Evolution

The dentition of a child is helping researchers illuminate modern man's evolution. A team of international scientists are using the remains of a 30,000-year-old youth, excavated in 1998-1999 in Portugal and classified as a "modern human" with Neanderthal ancestry, to compare the child's milk teeth and nearly all of its permanent teeth to those of Neanderthals, later Pleistocene humans, and modern humans.

"This new analysis of the Lagar Velho child joins a growing body of information from other early modern human fossils found across Europe (in Mladeč in the Czech Republic, Peştera cu Oase and Peştera Muierii in Romania, and Les Rois in France) that shows these 'early modern humans' were 'modern' without being 'fully modern.' Human anatomical evolution continued after they lived 30,000 to 40,000 years ago," said João Zilhão, PhD, a professor at the University of Bristol, who is on the international team, in a press release.

The child's dentition has evoked questions about the degree Neanderthals and modern human groups of African descent bred when they came into contact in Europe. With anatomy basically comparable to today's human race, early modern humans emerged more than 50,000 years ago. A long-held, universal opinion is that little has changed in human biology since early modern humans.

Using X-rays to create cross-sections of 3-D objects, scientists were able to research the relative stages of formation of the developing teeth and proportions of crown enamel, pulp in the teeth and dentin, according to the study published recently in the *Proceedings of the National Academy of Sciences*.

Their findings were that for a set stage of development of the cheek teeth, the front teeth were relatively delayed in their degree of formation, according to a press release.

Tighter Controls on Drugs Keeps Risk for Abuse in Check

To thwart the dental office being used as a proverbial candy store, stricter control policies should be put in place, according to an author in a recent issue of *Anesthesia Progress*.

Dentists who are too trusting of their employees are actually putting themselves at risk when it comes to controlled substances, said Joel M. Weaver, DDS, PhD, adding, dentists who regulate drug access and distribution are protecting more than their practice, they're also protecting their patients, employees, and reputation. While it's often easier to stick with the way things have traditionally been done, making a few changes to drug access policies makes good business sense.

"Although change is difficult and usually meets with resistance, the thoughtful practitioner who can step back and observe his or her practice for potentially fatal weaknesses will be much less likely to succumb to a disaster," wrote Weaver. "Accredited hospitals already have strict rules to help prevent drug theft, but private unaccredited offices without mandatory controls are highly vulnerable to drug theft and deception."

By taking sole responsibility for storing, filling, and handling syringes with controlled substances, dentists reduce the chance for illegal drug use and mistaken dosages. It's important to rely only on those licensed to handle medications, Weaver said, singling out dentists, pharmacists, nurses, and medical doctors. Errors with dosages and concentrations may occur by certain employees who only have on-the-job training.

To read the entire article, "Who Should Have Access to the Controlled Substances in Your Office?" go to www2.allenpress.com/pdf/anpr-56-4fnl.pdf.

Timeline Suggested to Optimize Treatment of Cleft Lip/Palate

The sooner a child receives treatment for orofacial cleft, the better their psychosocial and medical well-being. The American Cleft Palate-Craniofacial Association recently presented some guidelines indicating the best time the primary surgery should be done, based on the child's type of orofacial cleft.

A retrospective study was carried out to verify whether children with orofacial clefts receive surgery for primary repair within the time suggested by the guidelines, according to a press release. The study was published in an issue of *The Cleft Palate-Craniofacial Journal*.

"Children whose mothers received maternity care coordination, received prenatal care at a local health department, or lived in the southeastern or northeastern region of the state were more likely to receive timely cleft surgery," said the authors.

The study, conducted in North Carolina, involved birth defects registries, Medicaid files, and vital statistics of those affected children for a seven-year period starting in 1995. Categories, according to a press release, ranged from perinatal care region to place to residence, and the characteristics of maternal, child, and system. The results found that 78 percent in the study obtained primary repair surgery by the age recommended in the association's guidelines. Other percentages included 90 percent for children with cleft lips; 58 percent for those with cleft palates; and nearly 89 percent for those with cleft lip/palate. Additionally, blacks and non-Hispanics, as well as those residing in the southwestern area of the state, were not as apt to receive surgery, per the recommended guidelines. Distance to the craniofacial center and the various services provided by the facilities likely were factors.

To read the entire article, "Timeliness of Primary Cleft Lip/Palate Surgery," go to www2.allenpress.com/pdf/CPCJ46.6_fnl.pdf.

The American Cleft Palate-Craniofacial Association recently presented some guidelines indicating the best time the primary surgery should be done, based on the child's type of orofacial cleft.

CLUB ETHICS, CONTINUED FROM 223

conscience against the party caucus. In extreme cases, gang members must demonstrate conspicuous flaunting of the public good (as in tagging), and mafioso or CIA agents might kill to demonstrate their good ethical status. What we are dealing with is cases where a positive bond between members and the group demands behavior that is independent of or in some cases antithetical to ethics generally.

Professional ethicists have focused almost exclusively on the nature of moral acts. It also matters who is affected by moral behavior and the style in which it is done. I have heard stories of dentists whose treatment of patients was so alarming that the profession vigorously sought to curb their practices, only to be blocked or equivocated by the legal system. But when the minor restraints imposed by justice were tampered with, the same dentist gets the "contempt of court" book thrown at them. It matters which club's rules are violated.

The challenge of club ethics exists in the American Dental Association Code, most notably in Section 4C: "Patients should be informed of their oral health status without disparaging comment about prior service." This standard from the section labeled "Professional Conduct" is at odds with the statement in the "Ethics" section that "the benefit of the patient (is the dentist's) highest goal." There is a conflict here between club ethics and ethical responsibility to the public.

In many years of leading case discussions with students and practitioners, there have been a surprising number who place the club ethic higher than the general one. Several practitioners who have been officers in organized dentistry have strongly stated there are no circumstances whatsoever that justify challenging the work of colleagues. One told me recently, "Patients come and go; I have to live with my colleagues throughout my career."

These same practitioners find it troublesome that dental students pretty rigorously enforce the club ethic of not ratting on colleagues who are known to cheat in dental school.

The nub:

1. In ethics, it matters what is done, but also whom it is done to and how.
2. Following the norms of one's group is often easier and more highly rewarded than being ethical in general.
3. Choose your friends carefully: they define what it means to be good.

David W. Chambers, PhD, is professor of dental education, Arthur A. Dugoni School of Dentistry, San Francisco, and editor of the Journal of the American College of Dentists.

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UPCOMING MEETINGS

2010	
April 11–17	United States Dental Tennis Association, Amelia Island Plantation, Fla., dentaltennis.org.
April 26–28	National Oral Health Conference, St. Louis, Mo., nationaloralhealthconference.com.
May 13–16	*CDA Presents The Art and Science of Dentistry*, Anaheim, 800-CDA-SMILE (232-7645), cda.org.
May27-29	Canadian Academy of Periodontology 55th annual general meeting, Vancouver, BC, cap-acp.ca.
Sept. 9–11	*CDA Presents The Art and Science of Dentistry*, San Francisco, 800-CDA-SMILE (232-7645), cda.org.
Nov. 7–13	United States Dental Tennis Association, Grand Wailea, Hawaii, dentaltennis.org.
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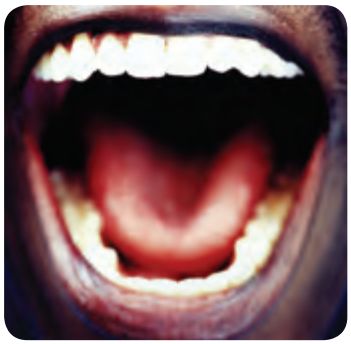
To have an event included on this list of nonprofit association continuing education meetings, please send the information to Upcoming Meetings, CDA Journal, 1201 K St., 16th Floor, Sacramento, CA 95814 or fax the information to 916-554-5962.



Bring 'MouthPower' to Your Office

A CD-ROM of the National Museum of Dentistry's ever-popular oral health education program, MouthPower, is now available to hygienists and dentists, thanks to a partnership between the museum and United Concordia Dental.

"The secret to a healthy smile is simple — taking good care of your teeth," said Jonathan Landers, executive director of the National Museum of Dentistry. "The MouthPower program shows kids how to do that in a fun and educational way."

The CD can be used by dental professionals to relay the importance of good oral health habits to patients, according to a press release. One of the highlights is the character Mouthie, in an interactive setting, who teaches children to floss and brush, make healthful food decisions, as well as avoid the use of tobacco. Bilingual lessons and handy activity sheets make it fun for kids to learn and put into practice good oral health routines.

The CD can be obtained by making a request through the museum; it also will be sent to the participating 45,000 United Concordia dentists across the country.

"We are excited to partner with the National Museum of Dentistry to share this outstanding oral health education program with our participating dentists," said Karen A. Whitesel, vice president, United Concordia Dental Corporate, professional relations. "Our hope is that this exciting tool will help dentists teach their young patients lifelong habits that maintain healthy smiles."

Protein Holds Promise to Kill Cancer Cells

A recently discovered protein may spell RIP to cancer cells.

Researchers at the University of Michigan studied a protein, receptor-interacting protein, that acts as a toggle that sets off the cell death process, which may help eradicate cancer cells, according to a press release.

Yvonne Kapila, an associate professor, Department of Periodontics and Oral Medicine at the university's School of Dentistry, said the RIP plays a role in mediating both the life and death of squamous cell carcinoma cancer cells. Additionally, Kapila said, the finding is important because cancer cells can dodge the typical cell death process. If that process could be activated artificially by a targeted introduction of RIP into cancer patients, those cells could be destroyed before they circulate out of control in the body.

"The cell must analyze multiple signals and say, 'OK, am I going to die or am I going to live,'" Kapila said. "We felt there must be some kind of communication between pathways of life and death otherwise the cell will be confused and not know what to do."

In looking at squamous cell carcinoma cells from head and neck tumors, as well as fibroblasts in mice, researchers discovered applications to other types of cancers and that RIP was "the communicator," according to a press release.

Healthy cells connect to a matrix in order to survive; if detached, the cells die. Cancer cells can detach from a matrix and circulate freely, permitting them to spread and metastasize in the body, said Kapila.

CDA JOURNAL, VOL 38, Nº4

Parents Cautioned to be Mindful When Their Young Children Use Fluoridated Toothpastes

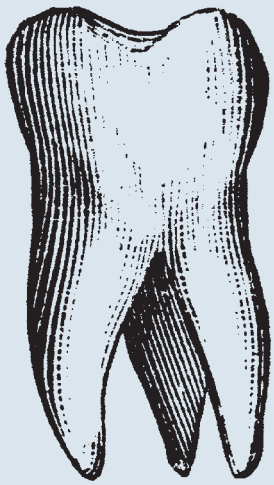
While a study has determined that fluoride-containing toothpastes (a minimum concentration of 1,000 parts per million) can help prevent tooth decay in children, researchers advocate parents talk to their dentists about concerns of fluorosis, which is caused by swallowing excessive fluoride.

Cochrane Oral Health Group researchers conducted a study that involved 73,000 children around the globe and nearly 80 trials. In studying the outcomes of various toothpastes used by the participating children, it was learned that toothpastes containing fluoride concentrations less than 1,000 parts per million were only as effective as nonfluoride toothpastes at preventing tooth decay, according to a press release. The concentration of fluoride toothpastes in the study ranged from 100 ppm to 1,400 ppm. Previous research, also conducted by the Cochrane Oral Health Group, had shown that compared to nonfluoride toothpastes, those with fluoride decreased dental decay by 24 percent.

In the recent study, it was found that use a fluoride-containing toothpaste on children under the age of 1 may boost the risk of mild fluorosis. What's more, fluorosis is still a factor in children up to the age of 6 who swallow larger amounts. Using small amounts of fluoride toothpastes reduces this risk, said the authors, adding that after age 6, teeth are fully developed and the risk of mottling diminished.

"It is very confusing for parents to know how to strike the right balance, which isn't helped by the fact that different companies use different concentrations of fluoride in their toothpastes aimed at children," said Anne-Marie Glenny, PhD, one of the authors.

"From a public health point of view, the risk of tooth decay and its consequences such as pain and extractions is greater than the small risk of fluorosis. Children would have to swallow a lot of toothpaste over a long period of time to get the severe brown mottling on the teeth," said Glenny.



New Study: Tooth Enamel Growth Due to Proline Repeats

University of Illinois at Chicago researchers have discovered that a tooth's structural integrity is due to a repeat of a basic amino acid in the middle of proteins in tooth enamel.

"Proline repeats are amazing," said Tom Diekwisch, DMD, PhD, professor and head of oral biology in the UIC College of Dentistry and lead researcher on the study. "They hold the key to understanding the structure and function of many natural proteins, including mucins, antifreeze proteins, Alzheimer amyloid, and prion proteins. We hope that our findings will help many other important areas of scientific research, including the treatment of neurodegenerative diseases."

Researchers looked at proline repeats in animal models and amphibians. In frogs, when the repeats are abbreviated, teeth don't have the enamel prisms responsible for the strength of human enamel, according to a press release. On the other hand, when the proline repeats are longer, they contract groups of molecules that enable the growth of enamel crystals.

The findings were published in the December 2009 online version of the *Journal PLoS Biology*.

Diekwisch said that when tooth enamel is grown, it is bathed in bubble-shaped groupings of proteins. The protein bubbles' size ranges in various animals; for example, in cows, it's 5 nanometers; 40 in frogs; and 20 in mice. The study also revealed that the more elongated the stretch of proline repeats, the more the protein bubbles contracted, he said. Additionally, research indicated that the smaller protein bubbles were associated with longer enamel crystals, according to a press release.

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Bag and Lanyard Pickup

Hilton Anaheim Hotel	Friday, 7 a.m.–3 p.m. Saturday, 8 a.m.–noon

Programs

Anaheim Convention Center and Hilton Anaheim Hotel	Symposia Thursday, various times Lectures/Workshops Thursday–Sunday, various times
Anaheim Convention Center	Dental Assistant Student Table Clinic Viewing Friday, noon–2 p.m. Military/Resident Table Clinic Viewing Saturday, noon–2 p.m. Student Table Clinic Viewing Sunday, noon–2 p.m.

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Kid Zone Hours	Friday and Saturday, 9:30 a.m.–5:30 p.m. Sunday, 9:30 a.m.–2 p.m.

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Hilton Anaheim Hotel	Child Care Thursday and Sunday, 8 a.m.–6 p.m. Friday and Saturday, 7 a.m.–6 p.m.
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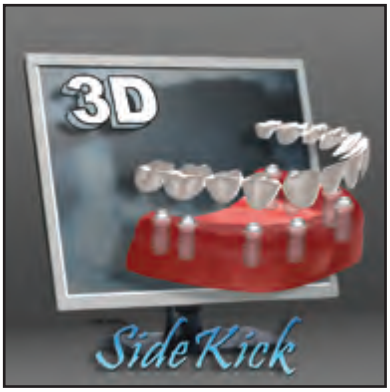

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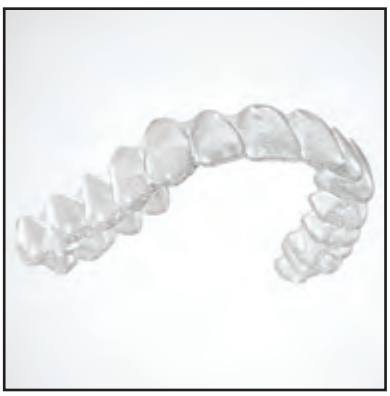

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IT'S 'PERIO-SYSTEMIC LINK'; *'Oral-Systemic Link' Is a Misnomer*

RICHARD T. KAO, DDS, PHD

During the past five years, there has been a plethora of publications touting the importance of how inflammation in the mouth may be linked to systemic health and disease. Some of these articles have labeled this link as the oral-systemic link. In this issue, the case is argued that these interactions should more appropriately be labeled as the perio-systemic link.

GUEST EDITOR

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Why argue this distinction? Improperly applied terminology always contributes to misinterpretation of the literature and scientific confusion. Since the tooth is the only structure that penetrates the integrity of the epithelial barrier, it is the point of access for a myriad of microbial invasions. It is the periodontium, the investing organ of the tooth that is the site of interactions between the host immune system and the microbes. In the past few decades, it has become increasingly clear that periodontal diseases are the result of both bacterial activities and the host's immune response to the infection. It is this inflammatory host response and resulting proinflammatory mediators that are responsible for the tissue changes that occur in periodontal diseases. Furthermore, this is the predominate source of the inflammatory load from the oral environment. In recent years, numerous epidemiological studies have suggested the association between chronic periodontitis and several systemic diseases.

Evidence now suggests that the proinflammatory mediators in periodontal disease are the same mediators involved in pathologic process such as myocardial infarction, stroke, diabetes, rheumatoid arthritis, and Alzheimer's disease. In this issue, the authors help dental practitioners understand the new paradigm of periodontal disease and its relationship to systemic health. Furthermore, these articles make it clear that dental care does not start and end in the mouth, but rather proper clinical management of a patient's health requires us to be definitive and vigilant in the management of our patient's periodontal conditions. Guidelines and recommendations are discussed.

In the first article, Dr. Michael Rethman examines how our understanding of inflammation has changed since our dental school immunology courses. He updates us on the current understanding of inflammation and summarizes the findings from the American Academy of Periodontology conference on inflammation. Utilizing this informational foundation, Dr. Rethman discusses several key aspects of the periodontal inflammatory response that may be related to several systemic diseases.

In the second article, Dr. David Richards interviews Dr. Kenneth Kornman, editor of the *Journal of Periodontology*, on the

association between cardiovascular disease and periodontal inflammation. This article details how our understanding of this association has evolved, what is the necessary evidence to demonstrate the relationship is causative, and explore some of the practical and theoretical implications. This discussion will help the readership understand the important difference between an association versus a causative or etiologic role. The cost and the study design may prohibit the definitive answer. Nevertheless, it is important for clinicians to understand this issue since it will be an important conversation topic when our patients approach us with their understanding/misunderstandings on this subject.

Given these associations between periodontal inflammation and systemic disease, why are periodontal diseases misdiagnosed or underdiagnosed? In the third article, colleagues and I discuss some of the clinical challenges in the diagnosing and monitoring of periodontal inflammation. Potential diagnostic problems and possible resolutions are discussed.

Lastly, Dr. Steven Schonfeld reviews effective strategies for managing periodontal inflammation. He provides a master clinician's view of practical strategies for periodontal therapy, as well as reviews the issue of statistically versus clinically significant approaches to therapy. Dr. Schonfeld wraps up his discussion with some insights as to emerging technology for controlling inflammation.

These *Journal* articles mark a pivotal time in our profession. Our professional responsibilities have clearly been expanded such that we now more than ever need to work with physicians in helping our patient control their inflammatory load. By doing so, we contribute to our patient's overall health. As our understanding of the perio-systemic link expands and interceptive therapy emerges, it imperative that as responsible health care providers we stay abreast of this topic. ■■■■

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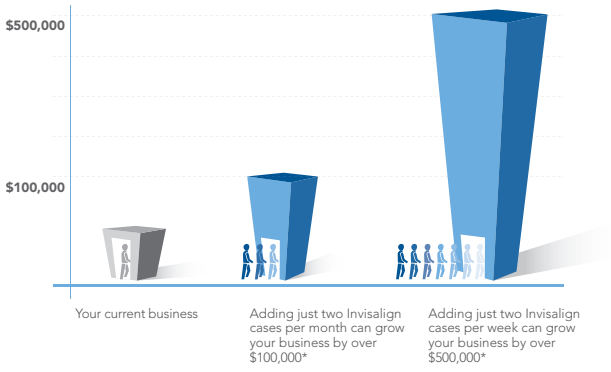

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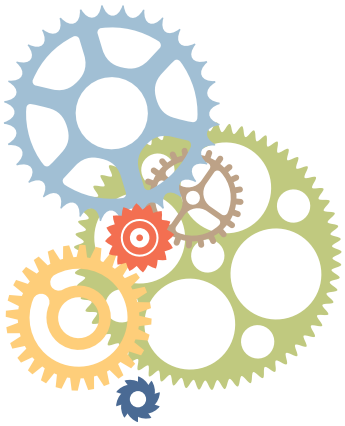

Inflammation in Chronic Periodontitis and Significant Systemic Diseases

MICHAEL P. RETHMAN, DDS, MS

ABSTRACT Endogenous chemical mediators play seminal roles in the initiation, persistence, and resolution of inflammation. Recent studies have revealed parallels between inflammatory mediators and mechanisms common to oral and systemic diseases. These relationships imply that novel therapeutics that profoundly modulate inflammatory mediators may improve clinical outcomes. Key source for this article is a 2008 conference reported in a *Journal of Periodontology* supplement titled *Proceedings of the 2008 Workshop on Inflammation; Inflammation and Periodontal Diseases: A Reappraisal.*

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The Immune System[1-3]

Inflammation consists of biochemical and cellular processes initiated by tissue irritation, injury, or infection. Nearby capillaries, soluble proteins and inflammatory cells respond to chemical signaling and edema results. Inflammatory cells are attracted from nearby tissues and blood. Complex cascades begin that are aimed at facilitating the destruction and removal of foreign organisms, removal and replacement of necrotic cells and damaged structural components, all aimed at the eventual restoration of tissue homeostasis and health.

Inflammation also activates other components of the immune system and may provide functional capabilities for these systems. Indeed, many of the more primitive mechanisms of the inflammatory response, such as lytic proteins collectively named complement, are tools that are used by more targeted immune mechanisms that developed later in evolution. Unfortunately, some of these tools, although usually adequate to the task at hand, are often not ideal. Many aspects of inflammation are nonspecific in their actions and can damage or destroy important host tissues while attempting to restore homeostasis. Examples include the periodontal ligament in periodontitis, and joint components in rheumatic arthritis. Furthermore, inflammation may never fully succeed at restoring tissue health/homeostasis and chronic inflammation may result.

To better understand the context for inflammation as part of the immune system, it's important to recall a basic understanding of entire immune system itself. Therefore, two general divisions of the immune system will be described, namely the innate, or nonspecific, and adaptive, or specific, components.

The innate immune system consists of evolutionary older mechanisms that respond locally and immediately to infection or trauma. A key feature of the innate immune system feature is complement. The soluble protein components of complement circulate in the serum and may be activated by numerous pathways. Bacteria themselves can directly activate the complement. When activated, complement proteins self-assemble into pore-like tubular structures that can penetrate bacterial membranes causing them to perish. Although bacteria themselves can activate the complement, the complement is also an important example of an innate capability that can be activated or amplified by other immune system components.

Using chemical signals called cytokines, the innate system recruits immune cells, activates complement, facilitates the removal of foreign substances, and activates the adaptive immune system. Phagocytic immune cells such as neutrophils, monocytes, and macrophages release cytokines termed interleukins that in turn play other roles including the clearing of pathogens or marking them for destruction by other cells.

The adaptive immune system amplifies the capabilities of the innate immune system because it is able to distinguish between host and foreign substances. This system is highly adaptable because of an exquisitely refined genetic mechanism that permits a small number of genes to generate a vast number of different antigen receptors, each of which is uniquely expressed on individual lymphocytes. When challenged by a specific antigen, such lymphocytes are activated. However, there are functionally and anatomically distinct T-lymphocyte (T-cell) and B-lymphocyte (B-cell) systems. B-cells originate in bone marrow, inhabit the spleen, and circulate in the blood. T-cells originate in the thymus and reside in the lymph nodes.

B-cells produce antibodies and remain quiescent until becoming fully activated by a specific antigen whose molecular structure docks with a unique antigen receptor complex on the B-cell surface.

Once a B-cell encounters its matching antigen and receives an additional signal from a T-helper cell, it can further differentiate into a plasma B-cell or a memory B-cell. The former produces prodigious amounts of antibodies that quickly bind to invading cells that display a matching antigen and thereby facilitate their elimination via a number of mechanisms, including facilitated phagocytosis and complement-mediated lysis. Memory B-cells are long-lived and function as prompt-responders to assure a quick and overwhelming antibody response should the same antigen be detected again. Most vaccines take advantage of this aspect of B-lymphocytes.

WHEN ACTIVATED, complement proteins self-assemble into pore-like tubular structures that can penetrate bacterial membranes causing them to perish.

Unlike B-cells, T-cells fail to recognize antigen in the absence of a formalized antigen presentation, with the important exception of superantigens that can trigger a T-cell response much more directly. (Many bacteria produce superantigens, including the normally nonoral *Staphylococcus aureus* and *Streptococcus pyogenes*. Superantigens may cause serious acute and chronic diseases including toxic shock syndrome, rheumatoid arthritis, diabetes and several types of skin disorders.) T-cells are more typically activated by the presentation of a processed antigen.

Although many cell types can present antigens, dermal dendritic cells, certain B-cells, and macrophages play key roles. Dendritic cells are commonly found in the epithelium, including the oral mucosa. Presentation cells process antigenic proteins and present peptides to T-cells residing in nearby lymph nodes. When a proper match is made, T-cells proliferate and attack invaders that display the specific antigenic peptides on their cell membranes. Unfortunately, this exquisite system is not always perfect. This is because processed antigens similar to proteins displayed by a host's cells are thought responsible for many autoimmune diseases (e.g., rheumatic heart disease).

Genes, Epigenetics and Gene-Environment Interactions in Inflammation and Disease

Genes, also known as alleles, function as the primary blueprints for proteins responsible for the anatomy and functionality of each organism. The 30,000 human genes consist of deoxyribonucleic acid (DNA) polymers. DNA molecules contain three-unit nucleotide sequences that code for the 20 amino acids used to produce all human proteins. Only a small fraction of each DNA molecule is known to contain genes, the remainder appears to have other physiological functions that are as yet not well understood.

Human DNA's iconic double helix is usually coiled around protein complexes called histones. DNA-histone complexes form chromatin packaged into 23 pairs of chromosomes. The genes themselves, epigenetic factors, and gene-environment interactions all have roles in inflammation and disease.

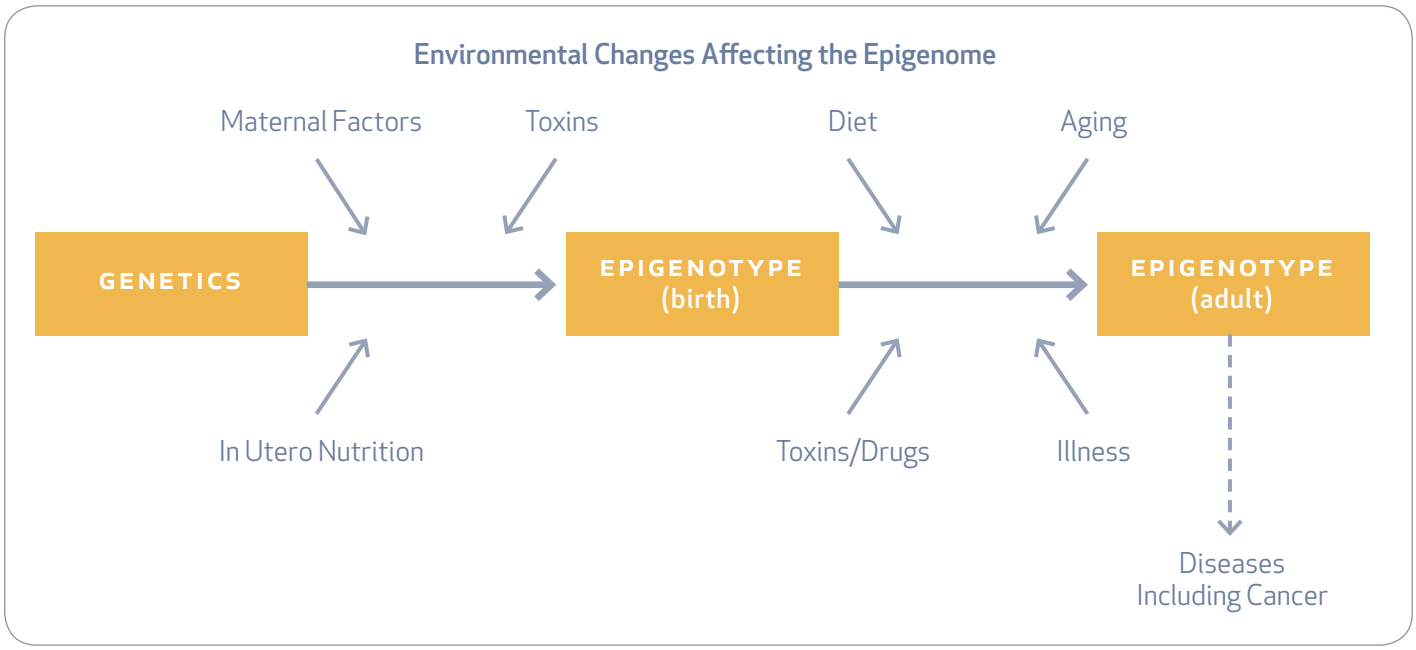

FIGURE 1. The epigenome changes in response to various environmental stimuli. Smoking, illnesses, drugs, diet, age, and in utero nutrition may affect the epigenetic signature to varying degrees at different points in development. Induced epigenetic modifications may be passed on to subsequent cell generations with potentially detrimental effects. *Reprinted with permission from the American Academy of Periodontology 79:1517, 2008.*

Gene-Caused Diseases

There are dozens of gene-caused disorders such as hemophilia A and sickle cell anemia. The latter is a gene-caused disease that results from a single nucleotide variation that appears in certain individuals in whom the amino acid valine replaces glutamate in a component of hemoglobin. Individuals who inherit this genetic variation from both parents lead shorter lives and are prone to serious vascular problems when their red blood cells assume sickle shapes. However, consistent with evolutionary pressures that affect human genes, children who inherit the variant allele from only one parent are substantially less likely to incur life-threatening malarial infections.[4]

Epigenetics and Disease[5]

Every cell with a nucleus contains all of an organism's genes. However, for cells to specialize as nerve cells, epithelial cells, muscle cells, etc., gene activity must be regulated. Epigenetics considered certain types of chemical modifications relevant to how genes are activated.[6] What this means is that every human cell has the same instruction manual, but different cell types are using different "chapters." For example, the secretory cells in the parotid gland contain the DNA instructions necessary to make bone, but for these cells and most others, the "bone genes" are turned off. Epigenetic changes are preserved when cells divide but most epigenetic changes only occur within the course of an individual organism's lifetime.[7]

New evidence suggests key roles for epigenetics in human pathologies, including inflammatory and neoplastic disorders. The epigenome is influenced by environmental factors throughout life. Nutritional factors can have profound epigenetic effects on the expression of specific genes and these traits can be passed on to subsequent generations of cells. Some cancers are associated with altered epigenetic profiles that lead to altered expression of genes involved in cell growth or differentiation. Epigenetic changes are necessary for the inactivation of one of the two X chromosomes in females and the monoalleic expression of certain regulatory genes (e.g., insulin growth factor-2 expressed from the paternal gene only).

Epigenetic changes are likely causes of the increased frequency of autoimmune and neoplastic with increasing age. Indeed, studies in aging monozygotic twins reveal increasing epigenetic differences apparently resulting from environmental influences (**FIGURE 1**).

Acetylation of histone proteins and methylation of DNA are two central epigenetic mechanisms. The former relaxes histone structures thereby encouraging gene expression by making the DNA more accessible for gene transcription. On the other hand, DNA methylation inhibits transcription.

Although epigenetics is an emerging field of study in inflammation research, some activities have been identified. Experiments examined the gene-specific control of lipopolysaccharide (LPS) -induced tolerance by chromatin.[8] (Many bacterial species associated with

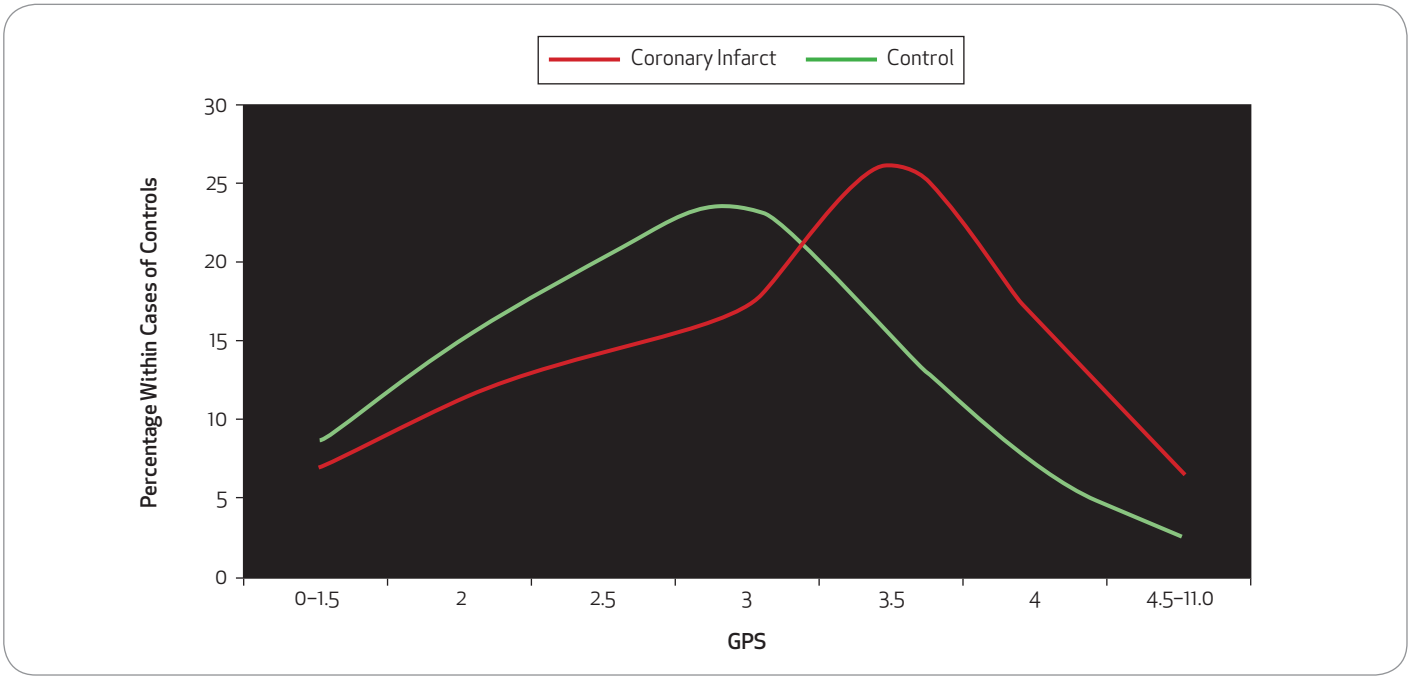

FIGURE 2. Distribution of cases with coronary infarct and control subjects by GPS. The subjects with coronary infarct (red line) had a GPS distribution that skewed toward the higher values, whereas the distribution of the control subjects (green line) was skewed toward lower values. Data from Trichopoulou et al.[10] *Reprinted with permission from the American Academy of Periodontology 79:1510, 2008.*

periodontitis produce LPS.) Although macrophages responded to LPS stimulation, they become hyporesponsive upon repeat LPS stimulation. Two distinct patterns of chromosomal modifications occurred during this hyporesponsive state. A group of genes responsible for inflammatory molecule production (e.g., TNF∝ and IL-6) was transiently silenced (i.e., tolerized). A second group of genes that includes various anti-microbial capabilities remained nontolerized. Of note is that tolerization seems to limit additional pathology associated with excessive inflammation, whereas nontolerized genes continue to produce anti-microbial enzymes that can do more harm than good.

Gene-Environmental Interactions[9]

This section will discuss the effects of the environment on genetic expression relevant to maladies linked to oral inflammation, namely type 2 diabetes, cardiovascular diseases, and metabolic syndrome, MetS.

Numerous studies have shown that individuals respond differently to drugs and diet. Despite tightly controlled conditions, dietary interventions to reduce serum cholesterol demonstrate wide-ranging yet modest average effects. The wide range of effects is encouraging, especially for those with a genotype that is highly responsive. However, the middling average response suggests significant genetic complexity underlying common clinical phenotypes such as "those with high cholesterol." In recent years, the complexity of genetic bases for type 2 diabetes has suggested that many genes play roles making it nearly impossible to study the effects of any single gene because of each gene's relatively small effect.

A recent study scored and ranked individuals by genetic predisposition scores (GPS) based on certain candidate genes, some of which produce cytokines involved in inflammation (e.g., IL-1β IL-6 and TNF).[10] The incidence of myocardial infarction was assessed. These results suggest a "genetic threshold" for predisposition to myocardial infarction. This study was also important because it revealed that a diet high in plant foods, olive oil, and moderate wine intake (but low in meat and dairy products) was cardioprotective even in individuals with high GPS scores (**FIGURE 2**).

MetS is a constellation of abnormalities, generally considered to include abdominal obesity, high blood glucose/impaired glucose tolerance, dyslipidemia, and high blood pressure. Together these increase the risk for type 2 diabetes and cardiovascular disease. A growing body of evidence from experimental and epidemiologic studies suggests that a nexus of all these abnormalities is a proinflammatory state. The hypothesis that chronic low-level inflammation underlies the pathophysiology of MetS is supported by the finding that as the characteristics of MetS rise in a population, plasma concentrations of proinflammatory markers, high sensitivity C-reactive protein (CRP) and IL-6, also increase, as the concentration of adiponectin (an adipocyte-derived protein important in glucose regulation and fatty acid (FA) catabolism) decreases.

A number of gene-environmental interactions have been surmised from an ongoing study that examines how gene-environmental interactions influence susceptibility to MetS. Known as the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study, it aims to characterize the genetic bases for the variable response of triglycerides (TG) levels following two dietary challenges, one that acutely raises TG via a fat-laden diet versus lowered TG resulting from fenofibrate administration.[11] Twelve hundred genetically homogeneous subjects with and without MetS were compared:

- Waist circumference, saturated fatty acid levels in erythrocyte cell membranes, levels of CRP, IL-6 and TNF∝ were all higher in subjects with MetS. Levels of polyunsaturated fatty acids (PUFA) were lower.
- Not only was MetS associated with higher levels of IL-1β, but the risk for MetS was also associated with several genetic variants of the genes that encode IL-1β.
- In light of the above, investigators wondered if diet could counter increased risks among those with differing alleles. Data indicated that diets high in certain forms of PUFA could do just that.[12]

Other reports derived from the GOLDN data investigated the effects of TG-lowering fenofibrate treatment on risk factors for cardiovascular diseases. Fenofibrate (eg., brand-name pharmaceuticals Antara, Fenoglide, Lipofen, Lofibra, TriCor, Triglide) lowers serum lipid levels and targets the atherogenic "lipid triad" (high serum TGs, low high-density lipoprotein levels with small and dense low-density lipoprotein particles) and inflammation. Because both phenotypes are important components of diabetes and MetS that potentially link these metabolic disorders to cardiovascular disease, fibrates were hypothesized to be therapies that might reduce cardiovascular disease risk in these patients.

Unfortunately, the study results were mixed. Some individuals with certain CRP alleles responded well. (CRP's role in atherogenesis, independent of lipid-based risk factors has been associated with multiple risk factors for cardiovascular disease including obesity, insulin resistance, and high blood pressure, and is a predictor of MetS.[13]) These data suggest that resistance to the anti-inflammatory drug fenofibrate depends on variable CRP genetic expression among MetS subjects. Similar to CRP expression, differences in alleles associated with proinflammatory IL-6 gene appear responsible for modulating serum levels of IL-6 and also modulate various serum lipid levels associated with MetS.

ALTHOUGH INCOMPLETE, research encouragingly indicates that genetic predisposition to MetS and other disorders can be substantially decreased via dietary changes.

Another aspect of lipid metabolism is that the perilipin proteins coating intracellular lipid droplets in fat cells have numerous allelic variants that appear to play roles in lipid metabolism. These have been linked to postprandial TG levels, body weight, obesity, risk for MetS, and serum inflammatory levels.

Although incomplete, research encouragingly indicates that genetic predisposition to MetS and other disorders can be substantially decreased via dietary changes.[14]

Cytokines in Periodontal Tissue Destruction[15,16]

Between the initial infection and the tissue destruction characterizing periodontitis is the production of numerous cytokines that mediate inflammatory mechanisms. Cytokines are functionally subdivided into chemokines, innate immune cytokines, and acquired immune cytokines. Animal experiments have suggested roles for all in periodontitis.

Chemokines are chemotactic cytokines, such as interleukin-8, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1. Chemokines are produced by cells normally present noninflamed tissue and recruit leukocytes and modulate osteoclast formation. Numerous cell types in the periodontium produce chemokines, including fibroblasts, endothelial cells, macrophages, osteoclasts, epithelial cells, neutrophils, monocytes, lymphocytes, and mast cells. Some stimulate osteoclast formation and survival.

Neutrophils, monocytes, and other cells produce innate immune cytokines such as IL-1, IL6, IL-11 and TNF∝ after being summoned to the site of injury or infection by the chemokines.

Experimental suppression of IL-1 appears to slow periodontal destruction; IL-6 appears pro-destructive; IL-11 appears protective. TNF∝ spurs osteoclast formation and accelerates periodontal breakdown as experiments in a murine model infected with periodontal pathogen *Aggregatibacter acitomycetemcomitans* (Aa) have shown. Indeed, greater numbers of Aa were observed in test mice genetically modified to decrease TNF∝ reactivity. However, despite higher bacterial levels, lower levels of bone-resorption-inducing cytokines were detected compared with control mice.

Acquired immune cytokines are produced by antigen-activated T- and B-cells as described above. They include IL-1,

IL-6 and TNF∝ in addition to IL-17 and nuclear factor-kappa B ligand (RANKL). IL-1 and IL-6 play roles in bone resorption via stimulation of RANKL, although lymphocytes also secrete numerous osteoclast-formation inhibitors such as osteoprotegerin (OPG), IL-4, IL10, IL-13 and interferon. RANKL, which binds to RANK, is one of the most potent inducers of osteoclast formation and activity. OPG binds to RANKL and inhibits osteoclast activities. It seems clear that various immune cytokines can inhibit or enhance periodontal destruction.

Cytokines, such as IL-1, are also involved in a phenomenon termed bone decoupling. Bone decoupling is the unbalancing of osteoblastic bone formation with osteoclastic bone destruction as is seen in the bone loss that characterizes periodontitis. Experiments in diabetic mice have suggested that TNF∝ plays a role in inducing an increased morbidity among osteoblasts that may lead to decoupling.[17] Similar evidence in primates has been reported.[18]

Multiple lines of evidence clearly indicate that increases in RANKL production raise the RANKL/OPG ratio and stimulate the differentiation maturation and longevity of osteoclasts leading to net bone loss. On the other hand, lowering of the ratio by either reducing RANKL or increasing OPG results in osteoclast apoptosis and is thereby osteoprotective.

Historically, periodontal practitioners have focused almost entirely on mitigating the bacterial etiologies of periodontitis. Although such tactics remain reasonable, it seems that reduction of inflammation and attenuation of the host's immune reaction to the microbial plaque, leading to a decrease in the ratio of RANKL to OPG resulting in a decrease in bone loss would be clinically useful as well. Future periodontal therapeutic tactics may directly target the RANK/RANKL/OPG axis.

The Relationship of Inflammation to Important Systemic Diseases That may be Associated With Chronic Periodontitis

Diabetes[19]

Diabetes is a serious health care concern. Its worldwide incidence is predicted to increase in concert with increased prevalence of obesity. Diabetes is a major individual and public health burden because of its serious microvascular sequelae. These include nephropathy, retinopathy, neuropathy, cardiovascular disease, and periodontitis. Total annual costs exceed $132 billion in the United States alone.

THESE FINDINGS suggest that inflammatory processes may play a greater role in the long-term progression of type 1 diabetes than in its onset.

Many factors, such as genetics, diet, sedentary lifestyle, the perinatal environment, age, and obesity are associated with diabetes. Nevertheless, an inflammatory basis for diabetes and its complications is gaining traction. Inflammation is associated with both type 1 and type 2 diabetes.

Type 1 diabetes is typically found in adolescents and young adults and arises from the autoimmune destruction of pancreatic islet cells that produce insulin. The increasingly common type 2 diabetes occurs mainly in adults, although its prevalence among young people is increasing in concert with childhood obesity rates. Type 2 diabetes is characterized by increased cellular nonresponsiveness to insulin (known as insulin resistance) that overwhelms the ability of pancreatic beta cells to secrete sufficient insulin.

Although there is controversy surrounding the precise role of inflammatory processes in type 1 diabetes, intriguing findings have emerged from studies of the inflammatory biomarker, CRP. Although CRP concentrations in individuals with the new onset (within days of diagnosis) of type 1 diabetes were similar to those observed in healthy controls, levels in individuals with long-term type 1 diabetes were significantly higher (P=0.04).

These findings suggest that inflammatory processes may play a greater role in the long-term progression of type 1 diabetes than in its onset. To wit, increases in inflammatory markers are observed in conjunction with the complications of type 1 diabetes. For example, increases in circulating levels of CRP, soluble vascular cell adhesion molecule-1, and nitrotyrosine were seen in patients with microvascular disease compared to those without diabetes.[20] Increases in monocyte release of interleukin (IL)-1β and superoxide anions were also reported in patients with type 1 diabetes.

Type 2 Diabetes

Increases in inflammatory markers have appeared in apparently healthy individuals who later developed type 2 diabetes.[21-23] This suggests that inflammation ramps up early in the disease process. For example, in adult Pima Indians (epigenetically prone to type 2 diabetes), individuals with higher white blood cell (WBC) counts (an indicator of greater inflammation), were more likely to develop type 2 diabetes over a 20-year period compared with those who had lower WBC counts. Similarly, in a prospective study of apparently healthy, middle-aged women, inflammatory markers IL-6 and CRP were associated with an increased risk for developing type 2 diabetes over a

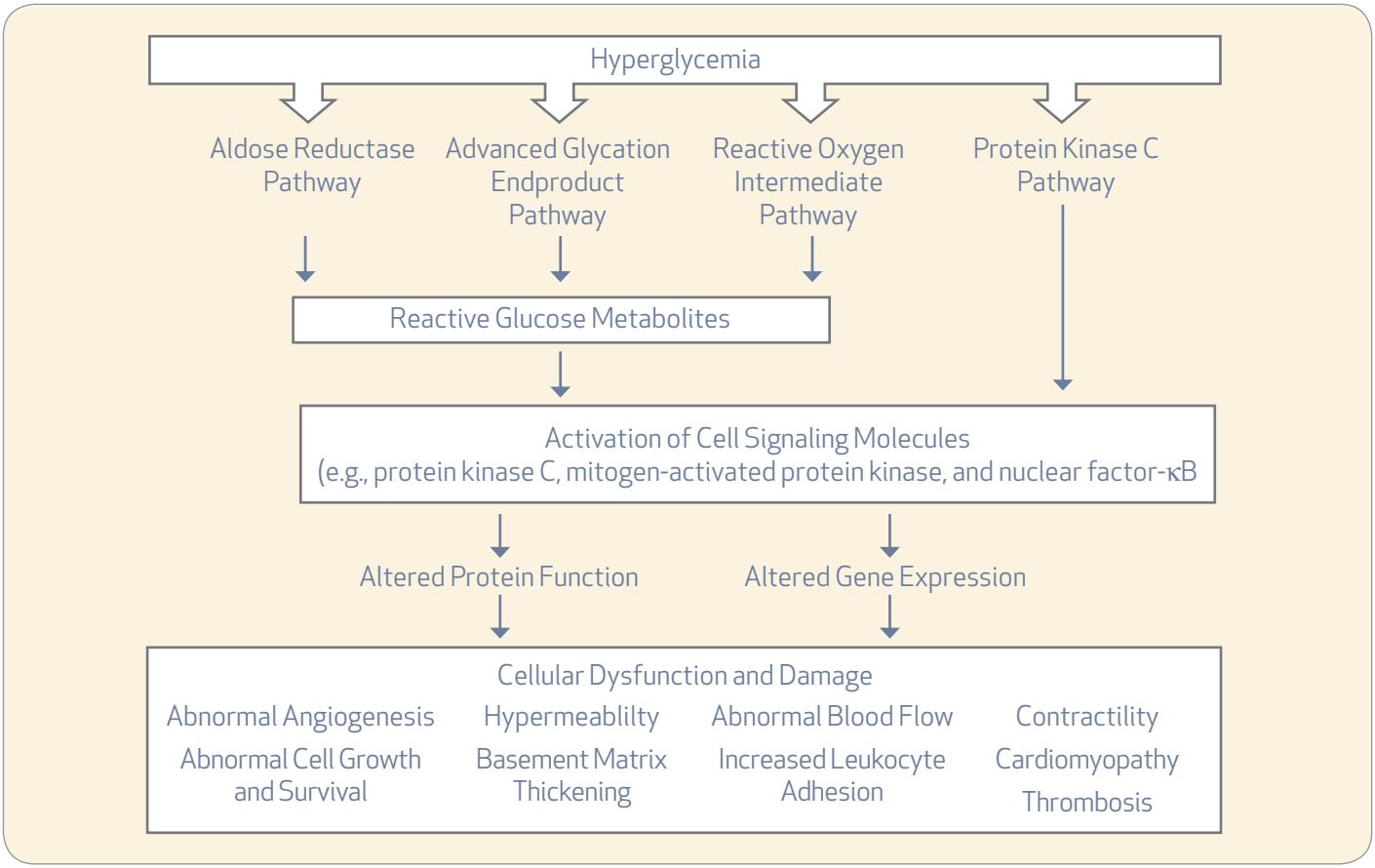

FIGURE 3. Major pathways initiated by hyperglycemia that contribute to complications of diabetes. *Reprinted with permission from Blackwell Publishing.*

four-year period. These findings are similar those seen in healthy, middle-aged men.

Type 2 diabetes is linked to obesity. Obesity and MetS have been linked to higher levels of inflammatory markers as discussed earlier. However, other data indicate that type 2 diabetes may develop in some independent of such associations. Nevertheless, evidence from both animal and human studies suggest possible roles for TNF∝, other inflammatory mediators, circulating markers of obesity (free fatty acids), bacterial lipopolysaccharides, protein kinases and/or oxidants in the development of insulin resistance in obesity and type 2 diabetes.

In this model, nuclear factor-kappa B is activated by these mediators and results in the transcription of genes that promote insulin resistance and the production of even more inflammatory markers. Furthermore, both animal and human trials have shown that pharmacological disruption of this pathway improves insulin sensitivity and lowers inflammatory load.[24]

The hyperglycemia that characterizes poorly controlled diabetes is considered a major risk factor for the development of diabetic complications including cardiovascular disease. **FIGURE 1** schematically represents pathways and mechanisms.

The actions of inflammatory pathways at the local tissue level are key to understanding their contribution to the pathogenesis of diabetic complications. Evidence suggests that increases in systemic markers of inflammation, such as CRP and IL-6, are associated with complications such as diabetic nephropathy. However, systemic inflammatory factors are only weakly associated with the development of diabetic retinopathy, and the relationship remains unclear for periodontitis.

As noted in **FIGURE 3**, altered gene expression and altered protein function are thought to play roles at local levels where diabetic complications are manifested. Among numerous other cytokines, kinase beta (PKCβ) is thought to play a key role in microvascular complications. The promising drug ruboxistaurin may inhibit this pathway and is in human clinical trials.

Although the most widely studied diabetic complications share a microvascular component adversely affected by hyperglycemia, periodontitis may be different. Indirect evidence linking periodontitis to obesity among individuals who are nondiabetic supports this distinction.

Nevertheless, it's not unlikely that obesity and insulin resistance enhance periodontitis risk and that hyperglycemia of diabetes worsens periodontitis. Additional

studies that tease out the relative contributions of the proinflammatory effects of obesity alone versus the effects of insulin resistance and hyperglycemia would be helpful to better understand these relationships.

Inflammation and Alzheimer's Disease[25]

Alzheimer's disease is the most common cause of progressive intellectual failure and a major cause of dementia. As demographics in the developed world shift toward more aged populations, Alzheimer's may become even more prevalent. The classic pathologic hallmarks of Alzheimer's are two: β-amyloid plaques and the neurofibrillary tangles. In an Alzheimer's patient, these are profusely distributed in the frontal neocortex and limbic system. These brain regions are associated with the higher mental functions that Alzheimer's impairs. Furthermore, a recently recognized aspect of Alzheimer's pathology is inflammation, specifically, an innate inflammatory response that may reflect attempts to remove amyloid deposits from the brain.

In recent years, numerous innate inflammatory mediators have been reported to be upregulated in pathologically vulnerable regions of the brain in Alzheimer's disease. These data led to a re-examination of the dogma of brain immunologic privilege and new studies that examined the roles of the innate inflammatory response in a number of other neurologic disorders, particularly Parkinson's disease and human immunodeficiency virus dementia.

Discoveries about neuroinflammation are beginning to move to the clinic. More than 20 epidemiologic surveys have demonstrated that common nonsteroidal anti-inflammatory drugs (NSAIDS) may protect against the development of Alzheimer's. By contrast, anti-inflammatory treatment trials for existing Alzheimer's have typically shown little to no effect on halting or reversing the disorder, although the drugs tested have often not been those suggested by epidemiological or other scientific results.

The extensive literature on innate inflammation and neurologic disease aside, key questions remain. First, are innate inflammatory responses a cause of neurologic disease or merely an effect? Second, can anti-inflammatory agents effectively treat existing neurologic disease, or is a protective strategy in high-risk patients the only reasonable option? Third, whether for protection or treatment, what is the best choice of anti-inflammatory agent?

ALZHEIMER'S DISEASE has not been associated with serum levels of proinflammatory mediators or with chronic periodontitis.

Of interest to dental practitioners, Alzheimer's disease has not been associated with serum levels of proinflammatory mediators or with chronic periodontitis.

Inflammation, C-reactive Protein, and Atherosclerosis[26]

Cardiovascular events, such as myocardial infarction and stroke, remain leading causes of morbidity and death in the United States. Evidence suggesting etiologic links between chronic periodontitis and cardiovascular disease exists. Data derived from a meta-analysis of five prospective cohort studies, five case-control studies, and five cross-sectional studies suggested a positive correlation between periodontitis and coronary heart disease.[27] After adjusting for risk factors, such as smoking, diabetes, alcohol intake, obesity, and blood pressure, subjects with periodontitis had a 1.14- to 1.59-fold greater risk for developing coronary heart disease compared to those without periodontitis.

Although the mechanisms underlying this association are not clearly understood, it was reported that certain colonizers of periodontal pockets (*Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*) have been detected in atherosclerotic plaques.[28,29] These pathogens produce lipopolysaccharides, that, in turn, induce macrophages to secrete cytokines (interleukin [IL]-1α and -1β and tumor necrosis factor [TNF]) that can play important roles in atherothrombogenesis.

Elevated cell- and cytokine-mediated markers of inflammation, including CRP, fibrinogen, and various cytokines, are associated with periodontitis.[30] The same elevated proinflammatory factors in periodontitis have also been linked with atherothrombogenesis. The connection between vascular events and periodontitis is also supported by evidence that oral bacteria enhance the expression of platelet aggregation-associated protein.

Atherosclerosis appears to be a chronic inflammatory disorder, suggesting that plasma markers of inflammation would be useful for vascular disease risk assessment. For example, in a large prospective study involving healthy men, IL-6 levels were elevated among men who subsequently experienced a myocardial infarction compared with age-matched controls.[31] In another large prospective study, healthy middle-aged women who subsequently developed cardiovascular events exhibited increased levels of soluble P-selectin, soluble CD40L, or macrophage-inhibitory cytokine compared with matched controls.[32-34]

TNF-α is another factor associated with cardiovascular disorders. Plasma concentrations of TNF-α were measured from 272 patients who developed recurrent nonfatal myocardial infarction or another cardiovascular event.[35] TNF-α levels were persistently elevated among postmyocardial infarction patients at increased risk for recurrent coronary events. These data indicate that changes in baseline levels of the inflammatory biomarkers discussed above may be potential biomarkers indicative of future risk for cardiovascular events, and may even be therapeutic targets aimed at cardiovascular disease prevention.

The high-sensitivity CRP (hsCRP) assay more accurately measures CRP than older assessment techniques. Increased hsCRP appears to be independent predictor for cardiovascular events. The relative risk for a first myocardial infarcation and ischemic stroke increases as baseline concentrations of hsCRP rise (suggesting strongly that atherothrombosis — a typical precursor to myocardial infarcation and stroke — is, at least in part, an inflammatory disorder).[36]

Elevations of other biomarkers significantly associated with vascular events include Lp(a) lipoprotein, homocysteine, IL-6, total cholesterol, serum amyloid A, apolipoprotein B-100, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and the ratio of total cholesterol/HDL cholesterol.[36] In 2002, data derived from a longitudinal study of nearly 30,000 healthy women also supports CRP as a cardiovascular risk indicator.[37] CRP is also a stronger predictor for cardiovascular events and death than are measures of LDL. Indeed, women in the high CRP/low LDL subgroup were at higher absolute risk than those in the low CRP/high LDL subgroup.

After adjusting for components of the Framingham risk score, including age, smoking status, blood pressure, presence or absence of diabetes mellitus, and HDL and LDL levels, quintiles of CRP remained an independent prognostic factor for risk. Moreover, increasing levels of CRP were associated with an increased risk for cardiovascular events at all levels of estimated 10-year risks (**FIGURE 4**).

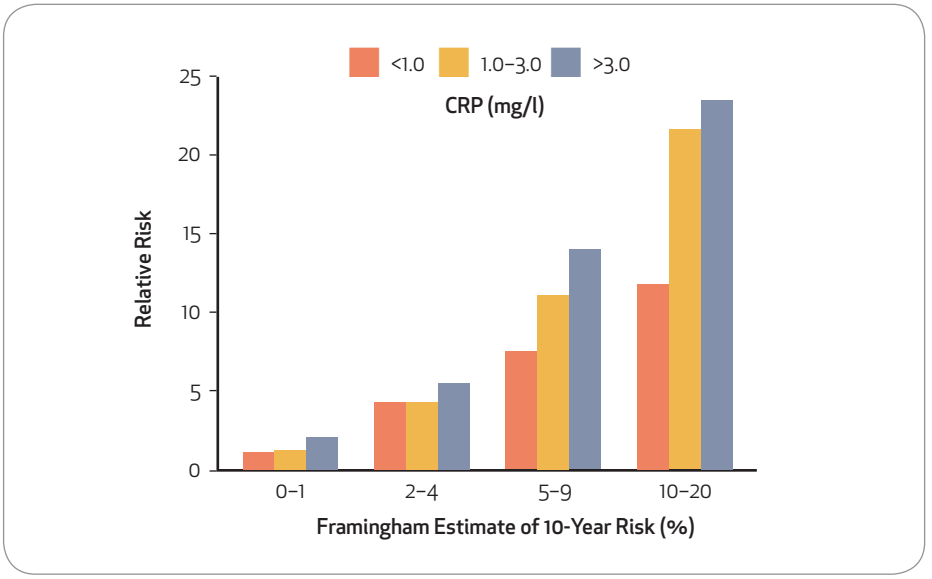

FIGURE 4. CRP levels are a stronger predictor of cardiovascular events than are LDL levels and add to prognostic information supported by the Framingham risk score. A) Event-free survival among women (N=27,939) with CRP and LDL levels above or below the median for the study population.[14] B) Multivariable-adjusted relative risks for cardiovascular disease according to CRP levels and the estimated 10-year risk based on the Framingham risk score, currently defined by the National Cholesterol Education Program and according to CRP levels and categories of LDL.[19] *Copyright 2002 Massachusetts Medical Society. All rights reserved. Ridker PM, Rifai N, et al, Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 347(20):1557-65, Nov. 14, 2002.*

Since these reports, studies based on at least a dozen more population cohorts around the world have corroborated the usefulness of hsCRP as a predictor of myocardial infarction, ischemic stroke, and cardiovascular death. A recent, large, prospective, randomized, double-blind, placebo-controlled multicenter trial (the JUPITER trial) compared the effects of an oral statin drug versus a placebo in apparently healthy patients with elevated hsCRP levels and nonelevated levels of LDL cholesterol. This study was terminated early because of the beneficial effects of the statin drug rosuvastatin in reducing in reducing the rate of serious cardiovascular events.[38]

Stroke and Ischemic Events

Inflammatory processes also appear to heighten the risk for stroke and cerebral small-vessel disease. In a sample of elderly people, ages 60 to 90, hsCRP levels were associated with the presence and progression of white matter lesions in the brain presumed to be the result of ischemia.[39] In another study, CRP levels were compared to the likelihood of ischemic strokes or transient ischemic attacks.[40,41] After adjusting for other risk factors, those in the highest quartiles of CRP levels had a two- to threefold greater risk for stroke. Overall, these data support the hypothesis that CRP, as a marker of low-level inflammation, predicts an increased risk for cardiovascular events in apparently healthy individuals.

Inflammation Appears to be a Risk Factor for Diabetes

As noted earlier, evidence supports roles for inflammation in the pathogenesis of diabetes. Similar to cardiovascular disease, increased hsCRP is a predictor of risk

for type 2 diabetes. In a large prospective cohort study in women initially free of diagnosed diabetes, baseline levels of hsCRP and IL-6 were significantly higher among cases than controls.[42] Later studies investigating a direct association between hsCRP levels and diabetes used exogenous injections of recombinant human CRP (rhCRP). Following injections of rhCRP, numerous cytokine markers of inflammation became significantly elevated compared with controls.[43] In a follow-up study by the same group, rhCRP injections administered to healthy males resulted in increased plasma glucose levels and decreased insulin production. Additional evidence implicated CRP as a prognostic marker for MetS. Collectively, this evidence suggested the need to develop strategies aimed at decreasing vascular risk among individuals with elevated levels of CRP.

Reynolds Risk Score Improves on Framingham Risk Score

Whether to add hsCRP assessment to traditional risk-prediction models, such as the Framingham risk score, remains a topic of current research. To address this issue, a series of 35 risk factors were evaluated at baseline among 25,558 initially healthy women over age 45 who were followed for future cardiovascular events over a 10-year period. Using these data, a new risk-prediction algorithm, the Reynolds risk score, was developed and validated. In brief, of the new biomarkers of risk, the most important additions were hsCRP and parental history of myocardial infarction before age 60. When these two factors were added to the usual risk markers, the Reynolds risk score proved to be more accurate than the Framingham risk score, particularly for those at "intermediate risk" where 70 percent of all events occur.

Furthermore, among those at intermediate risk, almost half of all participants were predicted to be at higher or lower risk than anticipated when the Reynolds risk score was used, and in almost all cases, this reclassification was correct.[44] Since the January 2008 AAP workshop (that is the seminal basis for this article), additional evidence has been published validating the Reynolds risk score as an improved risk-prediction system in men.[45] Treatment guidelines recommend statins for patients at higher risk. The Reynolds risk score should facilitate more effective and efficient use of these drugs.

FOLLOWING
injections of rhCRP, numerous cytokine markers of inflammation became significantly elevated compared with controls.

Statins

Statins possess potent lipid lowering and anti-inflammatory properties. When 3,745 patients with acute coronary syndrome (an umbrella term used to cover clinical symptoms compatible with acute myocardial ischemia) were treated with statins, the levels of LDL cholesterol and hsCRP were decreased.[46] Treated subjects who achieved a target level of hsCRP ≤2 mg/l had a significant improvement in event-free survival, independent of levels of LDL cholesterol. Subjects who achieved LDL cholesterol levels ≤70 mg/dl and hsCRP levels ≤2 mg/l did even better. These findings were corroborated in a second multinational trial that reinforced the significance of hsCRP as an indicator of risk and inflammation.[47]

Genetics and CRP

A number of studies have linked variances in hsCRP to genetic differences. Moreover, a recent genome-wide assessment of >6,400 women, data suggested close genetic links among CRP, diabetes, and early atherothrombosis.[48] However, analysis of these studies has suggested that only between 20 percent and 40 percent of the population variance in CRP has a genetic basis.

Therapeutic Implications

Thus far, it is unproven that inhibiting inflammation in general or CRP in particular will decrease the rate of vascular events. However, early research is promising. For example, a CRP inhibitor resulted in smaller infarcts and less cardiac damage (in rats dosed with rhCRP). Other approaches include the use of novel IL-6 or TNF inhibitors. Alternately, low-dose methotrexate, often used to treat rheumatic arthritis, is known to decrease parameters linked with systemic inflammation in humans, including erythrocyte sedimentation rate, CRP concentrations, and signs of clinical inflammation. An early study was promising.[49] In light of the similarities between rheumatic arthritis and atherosclerosis (such as the involvement of cytokines and elevated levels of CRP), conducting a trial comparing low-dose methotrexate to placebo in the secondary prevention of cardiovascular disease would contribute significant understanding in this arena.

Conclusion

The human immune system, the epigenome, the environment and cytokines play complex and interwoven roles in the myriad processes of inflammation. Inflammation is now known to be a common feature of many diseases associated with aging such as chronic

periodontitis, type 2 diabetes, cardiovascular disease, and Alzheimer's disease. Furthermore, there is increasing evidence that chronic oral inflammation and the resulting systemic increases in inflammatory mediators may enhance the morbidity of certain systemic diseases commonly associated with advancing age. Therefore, it will behoove dental practitioners to remain alert in coming years for the advent of improved predictive, preventive, and mitigative tactics that will emerge from this exciting and dynamic field of study. As of now, there remains much to be learned, but the benefits will likely be profound. ■■■■

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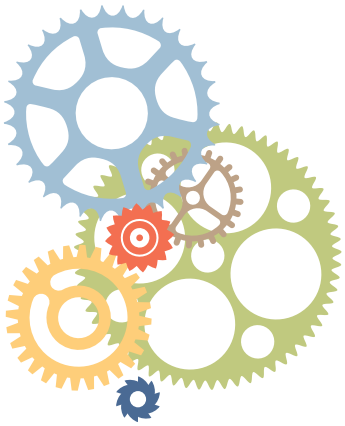

An Interview With Dr. Kenneth Kornman

DAVID W. RICHARDS, DDS, PHD

ABSTRACT Inflammation is recognized as the major underlying contributor to a number of chronic diseases, amongst them periodontitis and cardiovascular diseases. The relationship between these diseases is explored and commented on in this question-and-answer session between Ken Kornman, DDS, PhD, the editor of the *Journal of Periodontology* and David Richards, DDS, PhD, a former student of Dr. Kornman's. Practical suggestions and guidelines for the dentist are also examined.

AUTHOR

David W. Richards, DDS, PHD, has been in private practice in San Diego since 1997 when he left the University of California, San Francisco, School of Dentistry, as an associate professor.

In the past decade, there has been a focus on inflammation in the cardiovascular medicine discipline. This has resulted in a beginning to understand what may be an association between cardiovascular disease and inflammation due to periodontitis. In this interview with Kenneth Kornman, DDS, PhD, we have explored some of these associations in a practical and theoretical way. Kornman wrote in a dedication to his 1999 textbook, "To those who will provide most periodontal care in the future: the general dentists and hygienists." He is very interested in general dentistry understanding this disease.

Kenneth Kornman, DDS, PhD, is founder and chief scientific officer of Interleukin Genetics, a biotechnology company focused on genetic variations that influence immunoinflammatory and metabolic mechanisms involved in chronic diseases. He holds more than 20 U.S. patents on gene variations that regulate chronic diseases and on software methods for modeling complex biological mechanisms, and currently retains an academic appointment at Harvard University. Kornman has published more than 100 peer-reviewed manuscripts, authored three textbooks on treatment of periodontal diseases, and is editor-in-chief of the *Journal of Periodontology*.

Q: Please give us a give us a brief history of the association between cardiovascular disease and inflammation due to periodontitis.

A: In the early to mid-1990s several epidemiologic studies emerged from throughout the world suggesting an association between periodontal disease and cardiovascular disease. Although these observations initially received limited attention, a few periodontal researchers pursued details of these associations in adequately sized databases. In addition, studies of biological mechanisms that might explain the observed associations were reported and were intriguing.

These studies involved three potential explanations for the epidemiological associations. The first suggested that bacteria migrating through the blood from the periodontal area attached to injured vascular endothelium and uninitiated or accelerated atherosclerotic processes. This theory was supported by the demonstration of periodontal pathogens in atheromas taken from coronary and carotid arteries. A second line of investigation linked inflammatory mediators from periodontal disease to the increased risk for cardiovascular disease. And finally, others suggested that risk factors common between the two diseases may be acting as a confounder in the analysis of association.

In the past few years, sufficient studies were finally available to perform a meta-analysis, which is basically an analysis to determine whether the preponderance of evidence supports or denies an association between the two diseases. The meta-analyses concluded that periodontitis is a significant and independent risk factor for atherosclerotic cardiovascular disease. At the same time, impressive evidence emerged from the cardiovascular field to suggest that the most reasonable explanation for this association with any chronic inflammatory disease, such as periodontitis, appears to involve the role of systemic inflammatory mediators that have been strongly implicated in atherosclerotic cardiovascular disease events.

PATIENTS WITH MODERATE to severe periodontitis should be informed that there may be an increased risk of cardiovascular disease.

Of course the definitive test of this association is a prospective intervention study in which patients with periodontitis are treated and monitored for several years to see if that treatment reduces the incidence of cardiovascular events as compared to individuals who do not have periodontal treatment. Although such prospective treatment studies have not been done with cardiovascular events as the end point, intervention studies have demonstrated a significant effect of periodontal treatment of moderate to severe periodontitis on reducing intermediate biomarkers such as endothelial dysfunction as an outcome.

Q: Last summer there appeared in the* American Journal of Cardiology *and simultaneously in the* Journal of Periodontology *a consensus paper on clinical recommendations for managing patients with cardiovascular disease and periodontitis.[1] Tell us how this was accomplished?

A: A "consensus paper" relative to the association between cardiovascular disease and periodontitis evolved from a collection of activities initiated from various directions. In some ways it represents a very good example of how forward-looking individuals and organizations may influence the environment, but it certainly does not happen until lots of pieces are in place. The American Academy of Periodontology held a conference on inflammation that included numerous experts in periodontal disease, medicine and inflammation; a venue for discussions across several disciplines that may be united by inflammation.

Shortly after that conference, the editors of the *American Journal of Cardiology* held a consensus meeting on psoriasis and cardiovascular disease. Based upon the enthusiasm following that meeting, some of the participants, who had also attended the AAP inflammation conference, suggested periodontitis as a possible area for consideration relative to a consensus meeting on inflammation and cardiovascular disease. This suggestion was rapidly followed up by the editors of the *American Journal of Cardiology* who contacted the AAP.

Q: Could you summarize dentistry's role as outlined by these recommendations?

A: The consensus report recommends some very specific actions by both dentists and cardiologists. First of all, patients with moderate to severe periodontitis should be informed that there may be an increased risk of cardiovascular disease. Secondly, patients with moderate to severe periodontitis who have known cardiovascular risk factors should be advised to consider a medical exam on a regular basis to evaluate their cardiovascular status and risk management.

Patients with both periodontitis and a history of cardiovascular disease should be informed that periodontitis may raise inflammatory markers in the blood that have been associated with a significant increased risk for cardiovascular events. Dentists should also encourage patients with periodontitis to assess the risk for future cardiovascular disease events using one of the online risk algorithms, such as the one developed by the National Cholesterol Education Program or the Reynold's Risk Score. More effort to control standard risk factors that affect both diseases is encouraged. For example, all patients with periodontitis who smoke should discontinue.

We should also encourage dentists and physicians who are managing patients with periodontitis and cardiovascular

disease to closely collaborate on the treatment to optimize risk reduction and periodontal care. It is important to emphasize that periodontal treatment to assist in reducing cardiovascular risk should be focused on reducing and controlling the bacterial accumulations and eliminating inflammation.

If inflammation has not been eliminated, it should be assumed that the potential added risk for cardiovascular disease may remain. It is important to emphasize as noted above that there is currently no direct evidence that treating periodontitis prevents either primary or secondary cardiovascular events. However, as clinical decisions must be made daily in practice while waiting for more definitive evidence, it is, in the judgment of the consensus team, appropriate for dentists and cardiologists to act on the currently available information.

Q: Could you summarize the current understanding of inflammation in periodontitis with special regard to the conversion of gingival inflammation to attachment loss? Could you indicate which risk factors and diagnostic tests are the most useful in detecting this shift?

A: Most inflammation is primarily protective. Acute inflammation usually resolves nicely if the stimulant is removed and if the resolution is not interrupted. Gingivitis is a perfect example of this process. The inflammatory response however may be quite destructive under certain circumstances. If the stimulant is chronic, such as continued bacterial presence or continued sun exposure on the skin, the inflammatory response may not be allowed to resolve and complete the repair phase.

The same outcome may result in some people if the inflammatory response is exaggerated when it's activated. Such exaggerated inflammatory responses may result from genetic differences among individuals or may result from other inflammatory diseases throughout the body. Inflammation may also be destructive if the normal repair processes are disrupted, for example as a result of smoking. There are currently no good indicators of the transition from the simple reversible phase of gingivitis to the earliest stages of more irreversible destruction. We can, however, use risk factors to help identify patients who are more likely to have future destructive periodontal disease. The most well-documented risk factors for future progression of periodontitis are smoking, diabetes, and certain genetic variations.

THE MOST WELL-DOCUMENTED risk factors for future progression of periodontitis are smoking, diabetes, and certain genetic variations.

Q: What we have seen in the literature reviews about the association of periodontal inflammation and other systemic diseases are generalities about the 'inflammatory burden' placed on the body by periodontitis. Are there more specific hypotheses developed explaining linkages or causality of systemic diseases thought to be affected by periodontitis?

A: I agree that using the term "inflammatory burden" is the result of not having a definitive explanation for what is causative. I am also guilty of using that nonspecific terminology. The evidence does support however an increase in systemic inflammation associated with moderate to severe periodontitis. Since treatment of periodontitis lowers systemic inflammation, it is reasonable, in my opinion, to start with the statement that inflammation connects periodontitis and other conditions that are inflammatory. Today, we know that complex processes, such as inflammation, cannot be attributed to one causative chemical entity, but are best defined by pathways. If we are fortunate to determine the critical pathways involved in disease, this may ultimately lead to a better understanding of causation, but at this stage we really are speaking in nonspecific terms.

Q: As periodontists we have all been aware of the role of inflammation and disease. Now the focus seems to be largely on inflammation alone and seems to be 'dumbing down' our outlook and simplifying what we know to be a very complicated disease. What about the role of bacteria and genetic misadventures such as PMN adhesion defects?

A: For more than 20 years, many of us have defined periodontal disease as a bacterially induced chronic inflammatory disease. More than 10 years ago, Roy Page and I discussed how genetic and environmental factors may modify this inflammatory response to the bacteria and attempted to provide some context to some of the specific biologic mechanisms. We certainly should not discount the critical role played by bacterial complexes in initiating this disease and in disease progression.

We also should not lose sight of various mechanisms that are in the critical paths leading to tissue destruction, such as polymorphonuclear leukocytes, macrophages, and antibodies. Multiple cell types are involved and some destructive mechanisms are well-studied, such as matrix-metalloproteinases. The added emphasis in the past 10 years on inflammation is primarily the result of the tremendous evidence on inflammation in diseases

such as cardiovascular disease. Those findings shape our knowledge and research in the periodontal area, but inflammation is just part of that broader discussions on risk factors, pathogenic mechanisms, and interactions among multiple diseases.

Q: Could you give us some guidance on the few recent clinical intervention studies that have not resulted in an apparent effect of periodontal treatment on pregnancy outcomes and cardiovascular disease events?

A: In recent years, some clinical trials designed to evaluate the effect of periodontal treatment on systemic conditions, such as preterm delivery, have been either disappointing or unimpressive. We, of course, must start by considering the possibility that periodontal disease has no or minimal effect on preterm delivery, or that the treatment was inadequate to have a clinically meaningful effect. The general concerns that I have with some studies is that the treatment has been protocol driven rather than endpoint driven. This means that for example the protocol may define treatment as scaling and root planing for 30 minutes per quadrant. All patients would then be treated as specified by that protocol. This is very different then specifying that all patients should be treated by whatever procedures are necessary to eliminate all inflammation.

My second concern is that periodontal treatment studies continue to be modest in size and may well be too small to evaluate treatment effects in such complex conditions.

Q: Is it possible that the associations between these systemic diseases and periodontitis are due to the same or similar abnormalities in the immune systems of individuals with each disease that results in the inflammatory mediation of the diseases and that is where the association ends not involving direct causality?

A: One of the plausible explanations for associations between periodontal disease and other conditions is that there are common underlying defects that lead to different diseases in different tissues. Underlying defects may be genetic or environmental, such as smoking. As indicated, this would mean that the causality arrow may not go from periodontitis to cardiovascular disease, but the arrow may go from some specific mechanism to both diseases. I am comfortable with that possible explanation. So far there has been limited evidence to support that concept.

Q: What are some of the population effects of this information? What should dentistry be doing to promote better overall health? Do you have recommendations for strategies that dentists can use when dealing with our medical colleagues?

A: As we indicated earlier, short-term inflammation is good and protective. It is chronic inflammation that is not healthy and has been implicated in most diseases of aging. As the individuals responsible for managing one of the most common chronic inflammatory diseases, it is reasonable for us to assist our patients in controlling their inflammation. In my opinion, this involves educating them about inflammation and guiding better control of chronic inflammation on a systemic basis. In my opinion, the discussion with our medical colleagues may be well-served at this time by focusing on cooperation to control inflammation in our shared patients. This is a very different discussion than arguing that periodontal treatment will reduce heart attacks.

IN MY OPINION, the discussion with our medical colleagues may be well-served at this time by focusing on cooperation to control inflammation in our shared patients.

Q: What do you see to be the future of this information and its practical application?

A: Medical specialties for many years have been organized by organs and tissues based on anatomic observations. Such distinctions have less and less relevance as we better understand the broad mechanisms such as inflammation that may affect multiple tissues. The future application of this knowledge requires prospective treatment studies that define whether or not periodontal treatment makes a substantial difference in the expression of certain diseases. If it does, the world changes because periodontal treatment then becomes a central part of overall health maintenance.

As we wait for such studies it seems very reasonable for us to educate patients about what is known and to help them manage their own health by assisting in the reduction of inflammation. ■■■■

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ADDITIONAL INFORMATION

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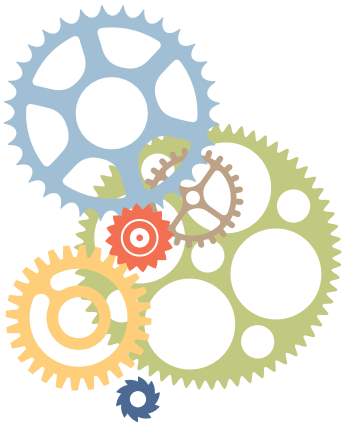

Clinical Challenges in Diagnosing and Monitoring Periodontal Inflammation

RICHARD T. KAO, DDS, PHD; STACEY LEE; AND LISA HARPENAU, DDS, MS

ABSTRACT An understanding of the new paradigm that periodontal disease may have a relationship to various systemic inflammatory conditions of aging reinforces the importance of monitoring oral inflammation. As oral health care providers, it is important to accurately assess, monitor, and manage our patients' inflammatory load. This review examines some of the clinical challenges associated with diagnosing and monitoring periodontal inflammation. Given these difficulties, patient management may be more effective when these patients are co-managed with a periodontist.

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During the opening ceremony at the 2009 Annual Meeting of the American Academy of Periodontology, keynote speaker and renowned cardiologist Paul Ridker, MD, MPH, challenged dental professionals to consider their potential role in preventing many of today's systemic diseases. Ridker described a paradigm shift that is occurring in medicine. Recent evidence suggests that chronic inflammation plays an important role in metabolic diseases, such as atherosclerosis, type 2 diabetes, stroke-ischemic events, and Alzheimer's disease. The incidence and amount of inflammation that patients experience, or their "inflammatory load," may be critical to the onset and progression of these diseases.

Recently, considerable research has focused on the immunomodulatory effects of several nutrients, such as fatty acids, antioxidants, carbohydrates, amino acids, micronutrients, and alcohol, which play a crucial role in maintaining an "optimal" immune response.[1] New evidence now suggests that if the inflammatory load an individual experiences can be minimized, the onset of these diseases may be retarded.[2] In his presentation, Ridker suggested that dentists have a role in contributing toward the general health of patients by monitoring and managing oral inflammation, thereby decreasing their inflammatory load.

Are We Measuring the Correct Parameters?

Inflammation in the oral cavity is common due to the ever-present microbial flora inhabiting this part of the body and the fact that teeth regularly come in contact

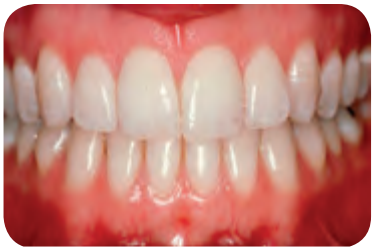

FIGURE 1A. The clinical presentation of a healthy periodontium with no signs of inflammation.

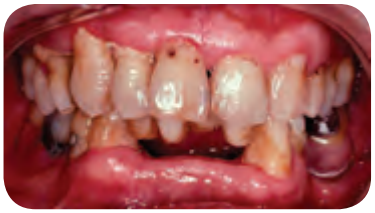

FIGURE 1B. In this presentation of chronic periodontitis, marginal redness, gingival enlargement, and some localized bleeding on probing are present in response to localized plaque.

with the external environment. The periodontium provides a barrier that prevents microbial influx into the body. Consequently, the immune system is very active in the periodontium. Not surprisingly then, periodontal inflammation represents the predominant form of oral inflammation. Whether one believes in Ridker's thesis or are simply trying to maintain their patients' oral health, it is important to recognize that clinical monitoring and control of periodontal inflammation should be key tasks of all oral health providers.

But are dentists doing a good job monitoring and identifying periodontal inflammation? Most members of the dental team have a general appreciation of healthy gingiva (**FIGURE 1A**). Oral changes associated with inflammation include altered gingival appearance (e.g., edema, enlargement, color changes, lack of a knife-edged and scalloped shape) (**FIGURE 1B**); gingival bleeding; discomfort/pain; unpleasant taste; and halitosis. One problematic issue is that for many patients, these are common occurrences so complaints are infrequent. For clinicians, these clinical parameters are difficult to document or quantify. As a result, these inflammatory signals are seldom recorded at and between dental visits.

This commentary will review various ways in which clinicians assess inflammation. Some of the factors complicating the accurate measurement of inflammation also will be discussed. Finally, some possible solutions to these problems will be offered.

Factors That Compromise the Accurate Discrimination of Periodontal Inflammation

Gingival Inflammation and Bleeding

Though gingival bleeding is an obvious manifestation of inflammation, monitoring of this clinical symptom is inconsistent. Slight gingival bleeding occurs so frequently that it is seldom fully appreciated by both patients and dental health care providers. Unless it follows an acute traumatic episode, bleeding should always be recognized as a sign of pathosis. Unfortunately, however, most clinicians merely comment on this observation, leaving patients with little means to compare how well they are controlling their inflammatory load.

Several indices are used to clinically assess gingival inflammation. The two most frequently used measurements are the gingival index, GI, and the papilla bleeding index, PBI.[3,4] The GI can be used to accurately compare gingival inflammatory status at recall visits and active-maintenance therapy sessions. The PBI is an easily reproducible assessment of the gingival status that can be used to enhance patients' appreciation for plaque control. Unfortunately, these two tests are relegated to clinical research and are not often used in clinical practice.

Some practices, however, are more diligent, incorporating the gingival index simplified, GI-S, or gingival bleeding index, GBI, into their examinations.[5,6] Both methods are similar in that each tooth is divided into four segments, and each segment is scored as either positive or negative for bleeding on probing. The percentage of sites with bleeding can then be calculated (**TABLE 1**). In an adaptation of the GI-S, this TiME charting of the upper right quadrant records a possible of six possible bleeding points per tooth. In this case, there are 17 bleeding sites out of a total of 42 sites. This gives a bleeding index of 40 percent. The goal over each maintenance visit is to decrease the percentage bleeding index. Though collecting these data takes time, this can effectively be accomplished at the recall appointments. These indices are advantageous because they provide patients with a quantifiable score that enables them to determine how well they are doing in controlling periodontal inflammation.

When interacting with patients, clinicians should explain that bleeding is simply a reflection of the level of inflammation that exists at the dental epithelial-connective tissue interface and it can be reversible. Bleeding on probing does not necessarily predict future disease activities. Lang et al. studied bleeding on probing as a predictor for the progression of periodontal disease and found that it had low positive predictive value for the progression of periodontitis.[7] In fact, they found that the consistent absence of bleeding over several visits was an excellent predictor of periodontal stability.

Therefore, patients need to understand that bleeding is a useful indicator of the presence of periodontal inflammation at a particular point in time. Second, they should be counseled that it is reversible with improved oral hygiene and therapy. Lastly, if dentists are conscientious about gathering these data and sharing results with patients, this can be an effective way to improve a patient's oral inflammatory load status.

TABLE 1

TIME for Periodontics - [Joe Perio Session - 10/22/2009]

Furcation Classification	- - -	- - -	- - -		- -			
Bleeding - Suppuration		BBB	- B -	- - B	B-B	B - -		
Gingival Width	- - -	334	444	444	444	444	444	444
Attachment Loss	- - -	744	2 >6	534	434	432	- - -	- - -
Recession/Enlargement		-7-4-4	-2-5-3	-4-3-3	-3-3-4	-3-3-2	- - -	
Buccal Pocket Depths	- - -	323	376	424	423	423	323	323
Maxillary Arch	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Palatal Pocket Depths	- - -	> 7 >	629	426	726	623	323	323
Recession/Enlargement		-3-3-4	- - -	-3-3-3	-3-3-3	- - -	- - -	
Attachment Loss	- - -	> 8 >	3·3	436	736	3 - -	- - -	- - -
Bleeding - Suppuration		BBB	B-B	- - B	B-B	B		
Tooth Mobility	-	II+	I+	-	-	-	-	-
Prognosis	-	Hpls	Poor	Guard	Poor	Guard	Fair	Fair

Periodontal Pocketing and its Measurements

Probing depth has become the standard by which most practitioners monitor periodontal disease. Unfortunately, this is not really a good indicator for periodontal inflammation. Attachment loss, reflected by increased probing depth and changes in gingival crestal levels, demonstrates periodontal breakdown. However, it only yields the amount of periodontal breakdown at that point. It cannot be determined whether the disease occurred in the past and has been managed, or whether there is current disease activity simply by looking at one set of data. This is akin to looking at a single frame of a cartoon strip and trying to figure out what came before or will come afterward. It is difficult to follow the storyline.

Only with multiple chartings of attachment level (probing depth and gingival crestal change in relationship to the cementoenamel junction) can the practitioner detect periodontal breakdown over time. Unfortunately, most clinical practices measure only the probing depths, paying little or no attention to gingival recession and enlargement. While monitoring attachment level is an essential part of periodontal diagnosis, it must be interpreted together with gingival inflammation and swelling, and radiographic evidence of alveolar bone loss.

Even in rare situations where both probing depths and gingival recession are monitored over time, inter- and intra-examiner variability may account for a 2.5 to 3 mm difference in probing depth measurements, and it may take one to two years before periodontal destruction can be accurately determined.[8,9] This is not a very effective strategy for monitoring and managing periodontal inflammatory load.

A number of factors can affect the accuracy of periodontal probing. These include probe size, probing angulation, tooth anatomy, probing force, and the inflammatory status of the periodontal tissue. Several studies have shown that periodontal probing often fails to record the true pocket depth.[10,11] Though probe size and angulation can be controlled, errors are more frequent due to probing force and the severity of inflammation in the tissue. Probing forces of 25 g have been suggested as appropriate; however, inter- and intra-examiner probing forces have been shown to vary from 3 to 130 g.[12,13]

Although several electronic probes have been developed for research purposes, only the Florida electronic probe is clinically available.[12] The reproducibility of the Florida probe is superior to manual probing, but its incorporation into clinical practice is not prevalent. Even more critical than probing force is the altered position of the probing depth in the presence of inflammation. At an inflamed site, the friability of the tissue often results in easy penetration, even with a relatively light probing force. In some instances, the probe may penetrate to the bone margin. This results in an overestimation of the true pocket depth.[14,15] Due to these factors that affect the accuracy of periodontal probing, it can take some time before periodontal breakdown can be ascertained.

Though much of the clinician's focus is on periodontal pocket depth, one should be attentive to the measurement of clinical attachment level, the presence and prevalence of gingival inflammation, and radiographic evidence of alveolar bone loss. If a clinician subscribes to the concept that decreasing oral inflammatory load promotes oral and systemic health, they must also recognize that it may take considerable time to detect changes, and the process may be fraught with technical difficulties.

Periodontal Biotypes

Historically, Ochsenbein and Miller have discussed the importance of "thick versus thin" gingival biotypes and how this distinction can influence restorative treatment.[16] More recently, this concept has been expanded. The gingival biotype is a description of the soft and bony tissue surrounding a tooth. Thick and thin gingival biotypes respond differently to inflammation, restorative trauma, and parafunctional habits, and the resulting defects dictate different types of treatment modalities.[17] For example,

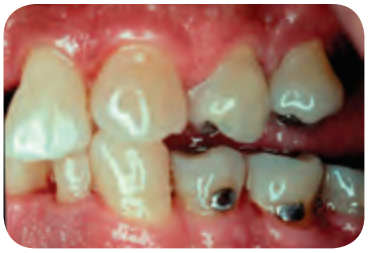

FIGURE 2A. The clinical presentation of thick gingiva. Note that with chronic inflammation, the tissue becomes fibrotic and pocket formation occurs.

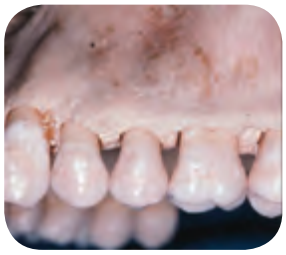

FIGURE 2B. The type of osseous architecture associated with this gingival tissue type.

when teeth are extracted, these tissue biotypes react with different healing bone remodeling responses, necessitating variable approaches in implant site preparation.[18] This section will present inflammatory changes associated with these periodontal biotypes and the difficulties in monitoring these changes.

Thick gingival tissue is probably the image most associated with periodontal health (**FIGURES 2A-B, TABLE 2**). The tissue appears dense with a relatively large zone of attached gingiva and a thicker underlying bony architecture. Thin gingival tissue tends to be delicate and almost translucent in appearance (**FIGURES 3A-B, TABLE 3**). It appears friable with a minimal zone of attached gingiva. The soft-tissue topography is highly accentuated with thin or minimal bone over the labial roots. Each of these gingival biotypes responds differently to inflammation.

Early in the inflammatory process, thick periodontal biotypes often exhibit marginal inflammation, cyanosis, an enlarged edematous appearance, and bleeding on probing. In the presence of long-standing chronic inflammation, the gingival tissue will become more fibrous. It may remain firm and pink, but the tissue appears thicker with increased pocket depth. Bleeding on probing may be less obvious. In patients with poorly controlled diabetes, there may also be chronic subclinical abscess formation where the gingival margin is highly thickened and rolled. Whereas early inflammatory changes are easy to reverse, chronic inflammation usually results in pocket formation and changes in the osseous architecture that often will require surgical intervention.

It is more challenging to monitor inflammation in the thin gingival biotype. Early signs are often reflected in subtle marginal redness. Since the interdental embrasure is the site of greatest plaque accumulation and more difficult to maintain, inflammation tends to initiate in the papilla area. Subsequently, the inflammation spreads around the gingival margin. In thin biotype, the healthy appearance of a knife-edged gingival margins and scalloped papillae. With inflammation, the papillae become slightly enlarged and edematous, with blunted margins (**FIGURES 3A**). Two hallmark responses to chronic inflammation are gingival recession and loss of interproximal tissue, resulting in a visible space at the apex of the interproximal embrasure.

As previously noted, patients with this gingival biotype will usually have very shallow pocket depth. With chronic periodontal disease, attachment loss is often evidenced not by increasing pocket depth, but by increasing gingival recession. Olsson and Lindhe found that approximately 15 percent of the Scandinavian population has thin gingival biotypes.[19] It is not enough to monitor only probing depths in these patients since this may give the illusion that there is no change. In these

TABLE 2

Characteristics of Thick Gingival Biotype

- Relatively flat soft tissue and bony architecture
- Dense fibrotic soft tissue
- Relatively large amount of attached gingiva
- Thick underlying osseous form
- Relatively resistant to acute trauma
- Reacts to disease with pocket formation and infrabony defect formation

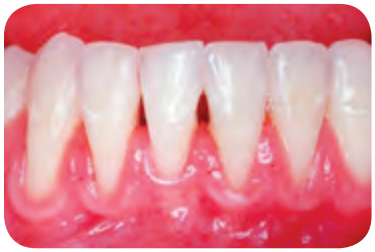

FIGURE 3A. The clinical presentation of thin gingival biotype. Note the gingival recession and in areas of advanced periodontal breakdown, there is loss of interproximal papilla.

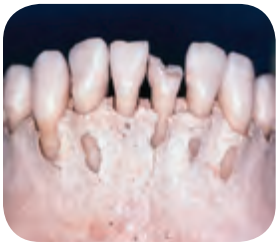

FIGURE 3B. The osseous architecture associated with thin gingival biotype.

TABLE 3

Characteristics of Thin Gingival Biotype

- Highly scalloped soft tissue and bony architecture
- Delicate friable soft tissue
- Minimal amount of attached gingiva
- Thin underlying bone characterized by bony dehiscence and fenestration
- Reacts to insults and disease with gingival recession

cases, the inflammatory response is reflected in the continued breakdown of the thin buccal bone, clinically visualized as gingival recession. In these patients, it is necessary to document at least once a year the attachment loss that has occurred.

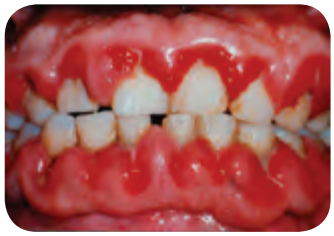

FIGURE 4A. Dilantin-induced gingival enlargement is multilobulated with deep clefts such that maintaining good oral hygiene is difficult. *(Case treated and contributed by Dr. G. Pieroni.)*

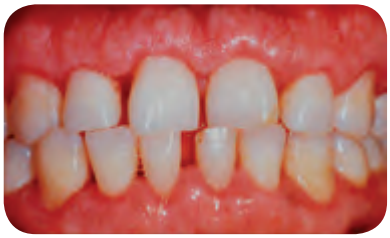

FIGURE 4B. Even after gingivectomy, marginal inflammation is still present despite improved oral hygiene. (*Case treated and contributed by Dr. G. Pieroni.)*

Drug-Influenced Gingival Overgrowth

A number of medications have been found to alter the gingiva's immune response to plaque biofilm. These include anticonvulsants (phenytoin), immunosuppressive medications (cyclosporin), and calcium channel blockers (nifedipine, amlodipine, and diltiazem). These medications modulate the immune system such that, when combined with poor plaque control, gingival enlargement occurs. The gingiva on the labial aspect of the anterior teeth is usually more severely affected than the gingiva of posterior teeth. The swelling is mainly fibrous tissue and may appear lobulated/multilobulated (**FIGURES 4A-B**).

This gingival enlargement is mostly due to increased deposition of extracelluar matrix material. With good oral hygiene, the enlargement is less proliferative or absent altogether. Interestingly, the amount of enlargement does not correlate to the medication dosage. The threshold dosage that elicits this clinical response is very individualistic. This, coupled with the observation that good oral hygiene tends to minimize gingival enlargement, suggests that each patient's immune system has its own threshold.

Oftentimes changing medications is not possible, as in the case of epileptic patients who are taking anticonvulsants and organ transplant patients taking immunosuppressive medications. It is known that calcium channel blockers are critical in the management of cardiac angina, arrhythmias, and hypertension. However, 60 percent of patients placed on an alternative calcium channel blocker showed regression in their nifedipine-induced gingival enlargement.[20] Therefore, since gingival enlargement is associated with calcium channel blockers, it may be reasonable for patients to inform the supervising cardiologist about their oral situation and request a switch to another calcium channel blocker if necessary.

Gingival enlargement can create clefts and more areas for plaque accumulation, making it more difficult for patients to maintain good oral hygiene. This eventually can require that a gingivectomy be performed to remove the hyperplastic tissue. Patients should always be informed that the frequency of surgical retreatment is highly dependent on the rate of regrowth. Therefore, proper oral home care and periodontal recall appointments are essential.

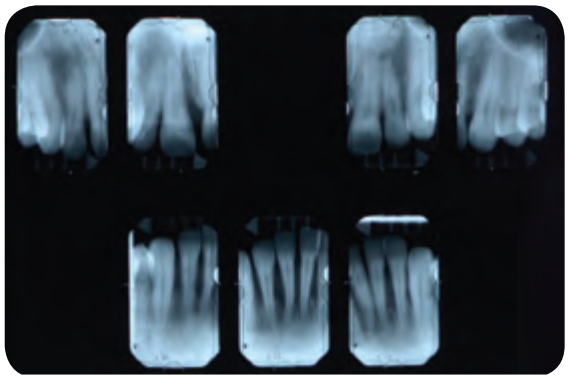

FIGURE 5A.

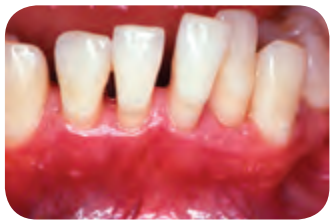

FIGURE 5B.

FIGURES 5A-B. A case of localized aggressive periodontitis where there is rapid localized bone loss primarily associated with anterior teeth. The patient had minimal level of dental care during adolescence. With the first comprehensive dental examination during the patient's mid-20's, advanced bone loss was a new revelation. Radiographs of the patient's anterior dentition are provided (**FIGURE 5A**) and clinical presentation of lower anterior (**FIGURE 5B**), which the patient had no sense that there was a problem. Dental history revealed prior dental visits did not include anterior periapical radiographs and the rapid periodontal attachment loss was not diagnosed in a timely fashion.

Aggressive Periodontal Disease

An altered immune system, as noted in the previous section, can result in an unusual inflammatory response. Similarly, altered immune cell function can result in rapid periodontal destruction as demonstrated in patients with aggressive periodontitis who are otherwise healthy. The most common forms of these aggressive diseases are localized aggressive periodontitis (previously called localized juvenile periodontitis or prepubertal periodontitis) and generalized aggressive periodontitis (previously called rapidly progressive periodontitis).

Unlike periodontitis that is a manifestation of systemic disease or necrotizing periodontal disease where the inflammation is very dramatic and visible, aggressive periodontitis can be clinically

subtle. This is especially true of localized aggressive periodontitis where the disease occurs during adolescence (**FIGURES 5A-B**). There are two forms: localized aggressive periodontitis, in which bone destruction is limited to the first molars and incisors, and a generalized form where destruction is not limited. The prevalence of this disease is approximately 0.2 percent in whites and Asians and 0.8 to 2.9 percent in blacks in the United Kingdom.[21] Similar findings were found in the United States.[22]

Despite the rapid and aggressive nature of bone destruction associated with these diseases, the gingiva usually shows few, if any, signs of inflammation. Also, there is seldom any notable amount of gingival bleeding, plaque, or calculus. Thus the condition often escapes detection until adulthood. By that time, bone destruction has ceased, but the deep periodontal defects lead to the development of periodontal abscesses with associated pain and swelling.

Unlike drug-influenced gingival overgrowth where the immune system is modulated to produce an exacerbated response, the genetically transmitted neutrophil dysfunction associated with aggressive periodontitis suggests that the immune system can be modulated to result in very rapid bone destruction with less obvious gingival inflammation. Periodic periapical radiographs and periodontal probing are essential for early detection of this form of periodontal disease.

Smoking

Smoking has been long recognized as a risk factor for cardiovascular and pulmonary disease. Though early studies of smoking and increased periodontal disease discounted its etiologic contribution as the result of poor oral hygiene and accumulation of local factors, studies in the 1900's clearly indicate that tobacco use increase the risk for periodontal disease.[23-27] These studies established that cigarette smoking increases the overall risk for severe periodontal disease by 2.8 times independent of confounding factors of dental plaque and calculus.[23-27] Additionally, the severity of attachment loss is directly relation to both the amount (packs) and the length of history for smoking.[24,26]

Today, this is discussed in terms of either pack-years or number of cigarettes per day. Though the first and foremost effect of smoking is immunosuppressive effect on the host, there is increased bacterial adhesion, higher levels of putative periodontal disease associated microflora, and inflammatory cytokines.[28-31] Since smoking is proinflammatory, clinicians should consider either providing or referring patients to smoking cessation programs.

IT IS IMPORTANT TO measure both the probing depth as well as the gingival recession on a regular basis for this is the only way to monitor changes in attachment level.

Conclusions: Possible Solutions

A paradigm shift has occurred in our understanding of periodontal disease. As we learn more about perio-systemic links, it becomes clear that our former reliance on monitoring probing depths and attachment loss is no longer enough. If periodontal inflammation results in an increased inflammatory load that is interrelated to serious and widespread systemic diseases, attention should be paid on the accurate detection, monitoring, and reversal of gingival inflammation. This paper has argued this is a difficult task that will require some new approaches.

First, clinicians must be more effective in monitoring gingival inflammation, incorporating effective mechanisms such as the GI-S or GBI into the periodontal maintenance programs. By recording bleeding sites and determining the percentage of total sites that bleed on probing, inflammation can be measured over time and clinicians can offer their patients quantifiable data that illustrate how effective their efforts at home are in eliminating inflammation.

Second, it must recognize that probing depth information when measured singularly is useless. It is important to measure both the probing depth as well as the gingival recession on a regular basis for this is the only way to monitor changes in attachment level. If one simply measures the probing depth, patients with thin biotype may have a stable probing depth but the recession may progress. For periodontal risk management, periodontal destruction can be only be followed by interpreting changes in attachment level and not just probing depth.

Third, given all the difficulties in accurately monitoring and managing periodontal inflammation, it is crucial the dental team work together. The hygienist's effectiveness in educating and motivating patients can be increased considerably when bleeding sites are measured via the GI-S or GBI. Gathering this information also permits the dentist to assess changes in a patient's periodontal inflammatory load.

Finally, considering all the factors such as gingival tissue biotypes, drug interaction, aggressive periodontitis, and smoking that can compromise the accurate assessment of periodontal inflammation, it would be greatly beneficial for the dental team to involve a periodontist to help co-manage cases that are not stable. ■■■■

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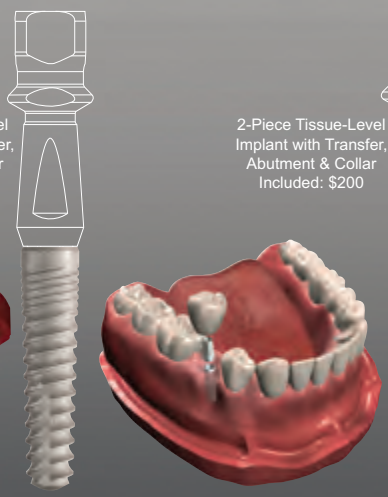

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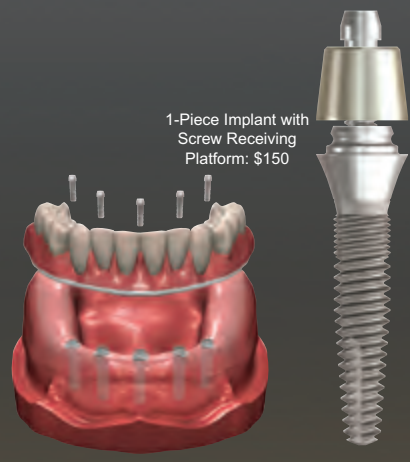

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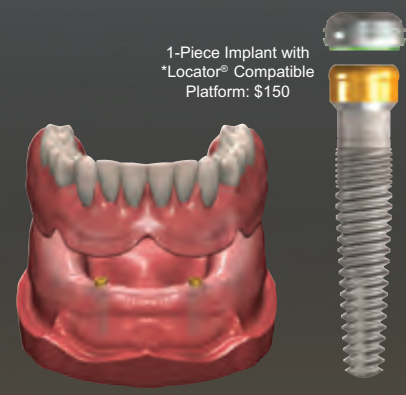

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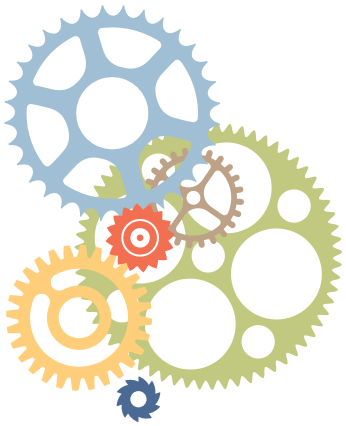

Strategies for Managing Periodontal Inflammation

STEVEN E. SCHONFELD, DDS, PHD

ABSTRACT Most of the tissue destruction in periodontal disease is caused by the patient's inflammatory response. Classical approaches to controlling inflammation rely on attempts to eliminate pathogenic bacteria that incite the inflammatory response through mechanical or chemical means. This approach still has a place in treating periodontal inflammation today. Emerging and future approaches will rely more on modifying the inflammatory response itself, by limiting the activity of proinflammatory pathways and by amplifying pathways that resolve inflammation.

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Many dentists, especially of my generation, will probably remember the "three-ring" Venn diagram (**FIGURE 1**) used to explain the need for a susceptible host (patient), pathogenic bacteria and permissive environmental factors (in this case, the presence of sugars in the diet) to be present simultaneously in order for dental caries to develop. Caries can be prevented if any of the three factors can be eliminated or sufficiently modified.[1]

This diagram can serve as a simplistic paradigm for many infectious diseases by replacing "caries" with the name of another infectious disease (e.g., periodontitis) and "bacteria" with the name of the associated infectious agent(s). Of course, the chief drawback of this model is its lack of specificity in defining exactly what makes a patient susceptible to a particular disease or how environmental factors can influence the outcome of the interaction between the infectious agent and host. Fortunately, in the nearly five decades since the model was suggested, biomedical science has advanced considerably and there is a better understanding of some of the factors that can influence the outcome of host-parasite interactions. A more complex, but still simplified, scheme for periodontal disease that reflects our deeper understanding of the situation is shown in **FIGURE 2** and this figure will form the basis for this discussion.

The accumulation of pathogenic bacteria in the periodontal spaces is clearly the initiating factor in the development of inflammatory periodontal diseases (IPD).[2] It should be stressed that while a number of different bacteria can apparently cause gingivitis, a smaller number of bacteria seem to be capable of causing the chronic inflammation that leads to periodontitis.[2-4]

A seminal concept that has been evolving since the 1970s is that while pathogenic bacteria are the inciting factors for IPD, most of the tissue destruction seen in this disease appears to be related to the inflammatory response of the host rather than being caused directly by bacterial factors.[5-8] Hence, control of inflammation is paramount in the ability to successfully treat IPD. In a 2008 statement in its clinical resources for periodontal practitioners series, the American Academy of Periodon-

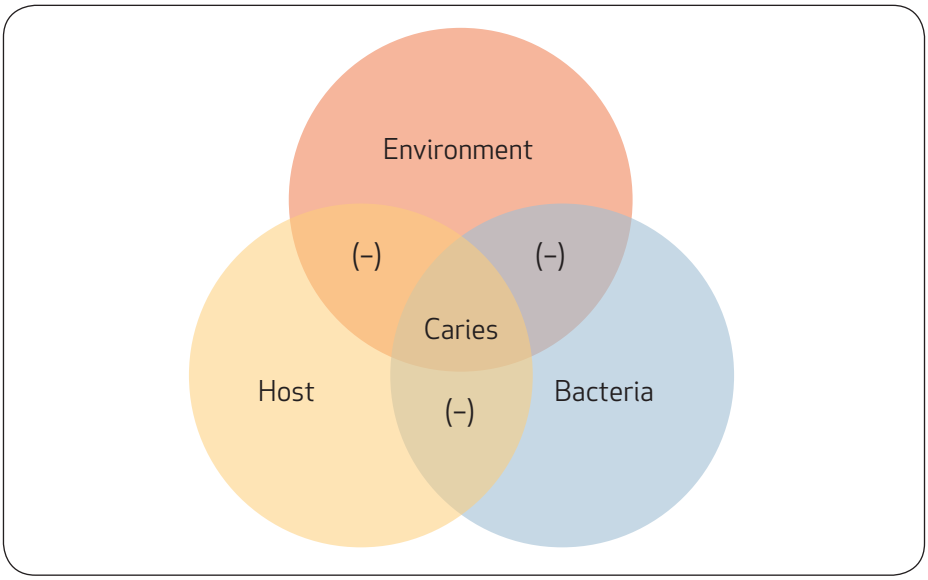

FIGURE 1. For caries to occur, a susceptible host (patient), pathogenic bacteria and permissive environmental factors (in this case, the presence of sugar in the diet) all need to be present simultaneously. If only two of the factors are present, caries does not occur (-).

tology observed that "periodontal therapy is primarily about elimination (of) or controlling inflammation through removal of local irritants and behavior modification."

It also is important to note that not every patient who harbors pathogenic species will go on to develop periodontitis.[9,10] Patients whose immune systems can effectively manage colonization of the periodontal spaces and tissues by mounting an acute inflammatory reaction that resolves relatively quickly (reflected by the bottom arrow labeled "Resolution" from the "Inflammation" box in **FIGURE 2**) seem to be at relatively low risk of developing IPD, while those patients who develop a chronic inflammatory response (right-pointing arrow from the "Inflammation" box) will be at much greater risk.[11]

As indicated in the upper right-hand box ("Genetics/Epigenetics/Drugs/Environment") in **FIGURE 2**, genetic and epigenetic factors, along with environmental factors such as smoking (see the contribution by Dr. Rethman in this issue for more details) can influence the nature of an individual patient's inflammatory response.[12,13] This will determine whether the initial inflammatory response resolves and the gingival tissue is restored to a state of homeostasis (bottom arrow labeled "Resolution" from the "Inflammation" box in **FIGURE 2**), or whether it converts to a state of chronic inflammation leading to tissue destruction (right-hand arrow from the "Inflammation" box).[11] The potential to modulate some aspects of the inflammatory response, mainly effector pathways, form the basis for some emerging treatments, and, more importantly, suggest avenues for the development of new approaches to treating IPD.

Classical and Contemporary Approaches to Managing Periodontal Inflammation

Periodontal disease has been recognized as a human affliction in various cultures for more than 2,000 years, and the ancients advocated various oral hygiene measures to prevent it.[14] The role of bacterial plaque in initiating gingivitis and the efficacy of plaque removal in resolving it was confirmed in pioneering, well-controlled clinical studies more than 40 years ago.[15,16] Hence, there is good reason to believe that adequate oral hygiene can prevent gingival inflammation in most people by preventing the accumulation of bacteria on and around the teeth, and that plaque removal can resolve gingivitis.

To return to the relatively simple caries model, caries can be prevented if one of the necessary factors required for its development is eliminated or modified. Likewise, the interruption, reversal, or sufficient modification of any events leading from "Healthy Tissue" through "Pathogenic Bacteria" and "Inflammation" as depicted in **FIGURE 2**, IPD and periodontal tissue destruction can be prevented. In fact, all current and emerging strategies for managing periodontal inflammation rely on this basic principle.

The upper left ("Oral Hygiene/Root Planing/Surgery/Anti-microbials") box in **FIGURE 2** lists most of the existing approaches to managing periodontal infections and inflammation. The mechanism involved in all of these approaches is to either prevent the colonization of the periodontal spaces and tissues by pathogenic bacteria, or to remove them if they have gained a foothold. This has been the underlying principle behind the treatment of IPD since the recognition of periodontal diseases by ancient peoples and remains an important approach, although executed in a somewhat more sophisticated manner, to this day. Of course, before the advent of modern microbiology and immunology, clinicians did not understand the basis for any success that their treatments may have had. Although still incomplete, the understanding of these processes has increased dramatically in the past 20 years and continues to increase with current research.

Not everyone practices perfect, or even adequate, oral hygiene on a consistent basis, and the fact is that plaque and calculus accumulates on and around the teeth of most people at one time or anoth-

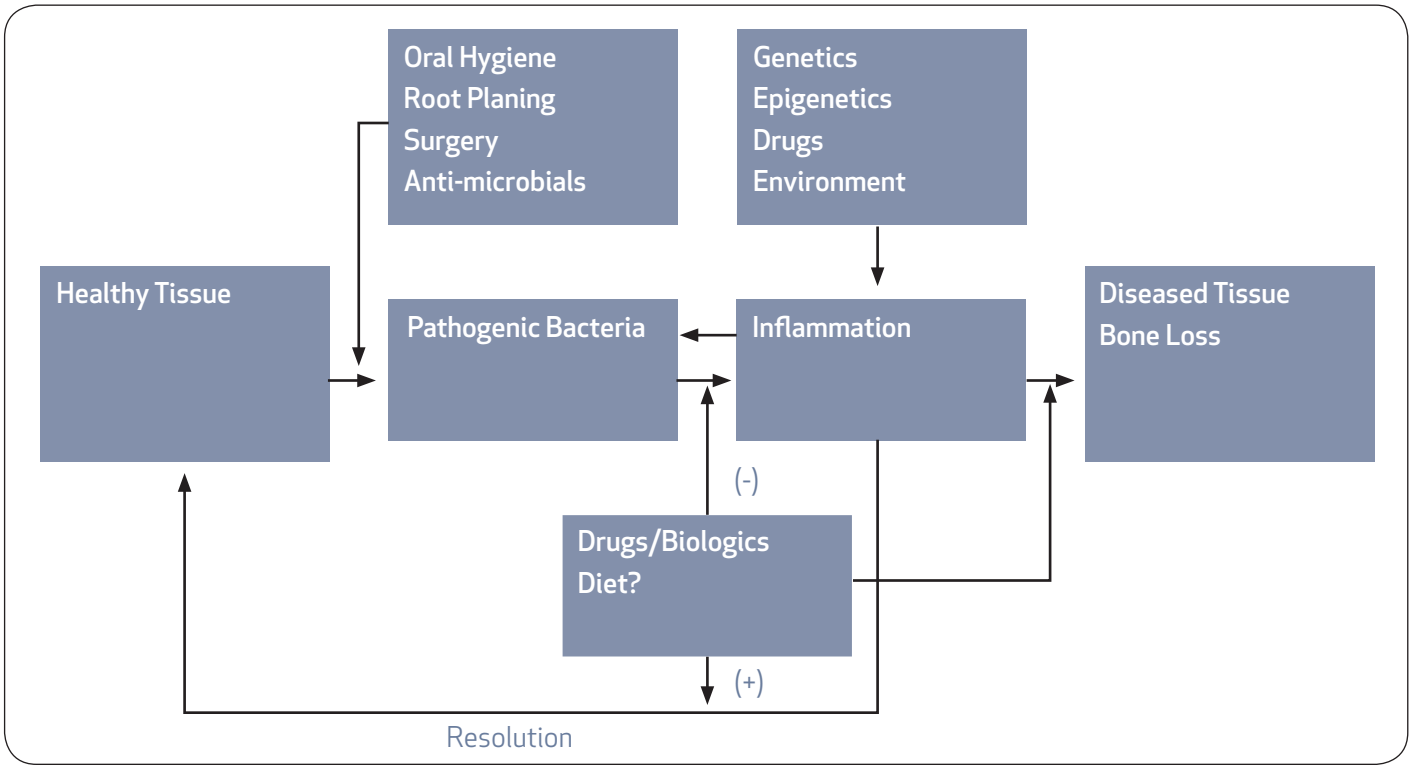

FIGURE 2. A simplified schematic showing various pathways leading to periodontal disease and bone loss by inflammatory events incited by the accumulation of pathogenic bacteria (horizontal arrows). Areas that offer opportunities for preventing or reversing these events are also represented (vertical arrows). See text for details.

er. Therapists have been removing these accumulations for at least 1,000 years.[14]

Nonsurgical mechanical debridement, scaling and/or root planing (SRP), physically removes bacteria and their products. It can thus interrupt the progression from healthy tissue through inflammation to a diseased state that is initiated and maintained by the presence of bacteria, as symbolized by the downward-pointing arrow from the upper left ("Oral Hygiene/Root Planing/Surgery/Anti-microbials") box in **FIGURE 2**. Indeed, root planing has been shown to improve the clinical health of tissues, as well as reducing the numbers of potential periodontal pathogens and some inflammatory markers.[16-19] SRP appears to be equally effective when done using hand instruments or mechanically driven devices, such as ultrasonic scalers.[20] It remains as a mainstay of periodontal therapy today and should generally be the first type of treatment provided for patients with periodontal inflammation initiated by bacterial plaque. However, there are limits to the effectiveness of SRP without surgical access, especially in pockets deeper than 5 mm.[21,22]

If clinical signs of inflammation are not resolved following SRP, e.g., there is continued bleeding on probing, clinically inflamed gingival tissues or inflammatory markers continue to be present, other modalities of treatment should be considered. Bleeding on probing, for example, has been shown to be correlated with the presence of putative periodontal pathogens and, hence, when present, suggests that the bacterial burden which incites inflammation has not been adequately reduced.[23]

The role of flap surgery in controlling periodontal inflammation is, like SRP, dependent on physical removal of bacteria and their products that incite a chronic inflammatory response. Flap surgery has repeatedly been shown to increase the efficacy of root debridement irrespective of any other possible benefits.[22,24,25] Numerous studies have shown that surgery results in a greater decrease in pocket depth compared with nonsurgical root planing, although the difference appears to become less significant with time.[26-28] Nonetheless, by increasing the chances of adequate root debridement, and thus decreasing the load of potential pathogenic bacteria that can lead to persistent inflammation, flap surgery still remains a part of the clinical armamentarium in treating IPD.

The history of topical medicaments and mouthwashes recommended to treat periodontal disease goes back to the ancient Babylonians and Assyrians.[14] In more contemporary times, there has been a wide variety of topical and systemic agents advocated to treat periodontal diseases.

Anti-infective therapy can be used locally by delivery into the mouth, e.g., via dentifrices and mouthrinses, or applied directly into the periodontal pocket. Alternatively, they can be used systemically, i.e., ingested. The local delivery agents

TABLE 1

Effects of Adjunctive Antibiotics or Anti-microbials on Pocket Depth and Clinical Attachment Levels When Used as Adjuncts to Scaling and Root Planing.

Intervention	Pocket Depths		Clinical Attachment Levels	
	#/+ Studies*	Effect sizes (mm): Range and Meta-analysis (MA)	#/+ Studies*	Effect sizes (mm): Range and Meta-analysis (MA)
Tetracycline, systemic	5/0	Range: NA MA : 0.15 (-0.29 - 0.58)	5/1	Range: 0.31 MA: none done
Tetracycline, local	16/5	Range: 0.40-0.93 MA: 0.47 (0.22 - 0.72)	16/2	Range: 0.15 - 0.48 MA: 0.24 (0.07 - 0.42)
Minocycline, systemic	2/0	Range: NA MA: none done	0/0	Range: NA MA: none done
Minocycline, local	8/4	Range: 0.30‡ – 1.10′ MA: 0.49 (0.40 - 0.58)	8/3	Range: 0.39 – 0.80 MA: 0.46 (0.32 - 0.60)
Metronidazole, systemic	8/3**	Range: 0.47¶ – 1.645 MA: none done	6/2	Range: 0.47¶ – 1.19# MA: none done
Metronidazole, local	11/4**	Range: 0.18 – 0.80 MA: 0.32 (0.20 - 0.44)	8/2	Range: 0.40 – 0.66 MA: 0.12 (0.01 – 0.24)
Metronidazole with amoxicillin, systemic	4/2**	Range: 0.7 MA: none done	4/1**	Range: NR MA: none done
Chlorhexidine, local	17/2	Range: 0.26 – 0.33 MA: 0.24 (0.13 - 0.35)	13/3	Range: 0.16 – 0.28 MA: 0.16 (0.04 – 0.28)
Other antibiotics, systemic	7/3**	Range: 0.47 – 0.87†† MA: none done	6/2**	Range: 1.30 MA: none done
Other antibiotics, local	1/1	Range: 0.44 MA: none done	1/1	Range: 0.37 MA: none done
Other antimicrobials, local	5/1	Range: 0.8 MA: none done	4/0	Range: NA MA: none done

(Adapted from Bonito A, Lohr K, et al Effectiveness of Anti-microbial Adjuncts to Scaling and Root Planing Therapy for Periodontitis, vol. 1, Evidence Report and Appendixes. Evidence Report/Technology Assessment No. 88; AHRQ Publication No. 04-E014-2. Rockville, Md., Agency for Healthcare Research and Quality, March 2004.)

* Number of studies/Positive studies. Positive studies are defined as those showing statistically significant effects in favor of the adjunctive therapy as contrasted with scaling and root planing alone.
† CI, confidence interval; MA, meta-analysis; mm, millimeters; NA, not applicable; NR, not reported.
‡ 0.30 mm PD reduction for baseline PD of 5 mm or greater.
′ 1.10 mm PD reduction for baseline PD of 7 mm or greater.
¶ 0.47 mm PD reduction and CAL gain for baseline PD of 4 mm to 6 mm.
1.64 mm PD reduction for baseline PD of more than 6 mm.
1.19 mm CAL gain for baseline PD of more than 6 mm.
** One of these studies did not report any specific data, only a significant difference.
††0.87 mm PD reduction for baseline PD of 6 mm or greater.

can be further divided into those that are capable of sustained release, either through inherent substantivity or by means of carriers providing for "controlled release" over time, and those that are not.

Anti-infective substances can also be classified either as antibiotics or as substances with anti-microbial properties such as chlorhexidine, citric acid, essential oils, hydrogen peroxide (both as a single agent and in combination with sodium bicarbonate and sodium chloride), iodine, quaternary ammonium compounds, sanguinarine, sodium hypochlorite, stannous fluoride and triclosan, all of which will be referred to as "anti-microbials."[29] All of these substances have been suggested as remedies for gingivitis or periodontitis, and are frequently used as adjuncts to mechanical therapy.[29] All of them exhibit some anti-bacterial activity against a variety of bacterial species in vitro when used at appropriate concentrations.

While the anti-microbials are generally only delivered locally, antibiotics can either be taken systemically or applied directly into the periodontal pocket, usually in some type of carrier.[29] Anti-microbials and antibiotics are usually used as adjuncts to conventional SRP, and, as with mechanical treatment, the mechanism of action is to reduce or eliminate the bacteria that incite inflammatory reactions.

Some studies have shown that a variety of antibiotics and anti-microbials have statistically significant positive effects when used adjunctively in this fashion. However, the clinical efficacy of most of these substances is hard to determine, as suggested by the data in **TABLE 1**, reproduced from the report "Effectiveness of Anti-microbial Adjuncts to Scaling and Root Planing Therapy for Periodontitis" from the Agency for Healthcare Research and Quality.[30] This report is a systematic review and meta-analysis of the literature related to use of anti-microbials and antibiotics in the adjunctive treatment of periodontal disease published in 2004.

There are various types of scientific evidence one can consider when trying to decide on the efficacy of a clinical intervention. Not all of these types of evidence have equal weight, though. In fact, there is a hierarchy of the quality of clinical evidence that can be used to support evidence-based decision-making in the health disciplines.[31] A typical hierarchy is as

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follows, listed from most reliable evidence at the top to least reliable at the bottom:

- Systematic review/meta-analysis of many randomized, controlled clinical trials
- Randomized controlled clinical trial
- Cohort study
- Case control study
- Case reports
- Expert opinions, editorials

A systematic review seeks to identify all studies addressing a specific clinical question. The reviewers then assess the quality of the studies and exclude those that fail to meet predetermined quality standards in terms of experimental design, power of the study, data analysis, and other factors. When trying to decide on whether to incorporate a new material or technique into one's practice, it is clearly wise to use the highest quality evidence available, according to the principles of evidence-based practice. Thus, a meta-analysis, an analysis that combines data from a number of different studies to give a single meta-analytic estimate of the actual treatment effect, or systematic review of many studies is much more powerful than anecdote, case reports, or individual studies, no matter how good the experimental design of the individual study may be.

The data in **TABLE 1** show how well antimicrobials or antibiotics work when used adjunctively with mechanical treatment. It comes from a review of 70 papers that met the inclusion criteria, i.e., they addressed the specific questions being asked and were deemed to be of sufficient quality to be included.[30] As the table shows, there is a high degree of variability in the study outcomes.

The majority of the studies did not show statistically significant positive outcomes. Moreover, even in those cases where there was statistically significant improvement with adjunctive anti-microbial or antibiotic treatment, it is not clear whether the incremental improvement over root planing alone was clinically significant, i.e., the amount of improvement makes a substantial difference in the clinical outcome. The authors include the following salient points in their conclusions: [30]

- "Adjunctive local antibiotics appeared to have more impact than adjunctive systemic antibiotics";
- "The major probing depth (PD) reductions were in the range of about one-quarter to one-half millimeter, and the major clinical attachment level (CAL) gains in the range of about one-tenth to one-half millimeter";

THERE IS A HIERARCHY of the quality of clinical evidence that can be used to support evidence-based decision-making in the health disciplines.

- "Combining PD and CAL results suggests that local minocycline might be the most promising adjunctive therapy, meta-analysis estimates of 0.49 mm for PD reduction and 0.46 mm for CAL gain; followed by local tetracycline, estimates of 0.47 mm for PD reduction and 0.24 mm for CAL gain. Local metronidazole and chlorhexidine results are well below these levels";
- "By and large, harms from these adjunctive therapies are relatively minor. We take note, however, of concerns about bacterial resistance from overuse of systemic antibiotics"; and
- "Some results of trials that we did review suggested that added effectiveness of adjunctive treatment was greater in circumstances of more severe periodontitis where supportive or self-care may be less well-executed. These situations may include patients with refractory periodontitis or who have deep pockets, defects or furcation involvement, or circumstances in which the modified Widman flap surgery is not done, which would enable proper debridement of otherwise hard-to-reach areas. Routine use of appropriate, i.e., efficacious, adjunctive therapies might arguably be reserved for patients such as these."
- "The improvements produced by adjunctive antimicrobials beyond those levels, produced by SRP alone ... (are) approximately one-quarter to one-third of the impact of SRP alone."

The results of the systematic review suggest that while there are some studies showing efficacy with the ajdunctive use of anti-microbials and antibiotics, the preponderance of the evidence does not support widespread use of these agents as adjuncts to mechanical therapy at this time.[30] Nonetheless, there may be certain situations in which patients would benefit from their use, especially in patients who present with more severe disease. Another relatively recent systematic review concluded that although benefits of adjunctive use were minimal, "in some populations, anti-infective agents in a sustained-release vehicle alone can reduce PD and bleeding on probing (BOP) equivalent to that achieved by SRP alone."[32]

Interestingly, certain antibiotics may be useful in the treatment of IPD, but work by mechanisms distinct from reducing or eliminating pathogenic bacteria. This will be discussed in the next section.

Emerging Approaches to Managing Periodontal Inflammation

The classical and contemporary interventions discussed above all depend on interrupting the chain of events leading from healthy to diseased tissue by removing accumulations of pathogenic bacteria and their

products or preventing their accumulation in the first place. Emerging approaches seek to limit tissue destruction by directly blocking proinflammatory pathways without affecting bacterial accumulations, although every attempt should still be made to reduce the bacterial burden. This is represented by the right arrow from the lower box labeled "Drugs/Biologics/Diet" in **FIGURE 2**.

In the mid 1980s, Golub and colleagues discovered that tetracycline derivatives could inhibit mammalian collagenases.[33] They subsequently found that these drugs could be used to limit inflammation and bone destruction in periodontal diseases, even when given at doses too low to have an anti-microbial effect and which have not been reported to cause antibiotic resistance in bacteria.[34,35]

Collagenases are enzymes that degrade native collagen (the major structural protein of connective tissue and bone), and are members of the class of enzymes called matrix metalloproteinases (MMPs). MMPs are intimately involved in degradation of tissue and bone, bone remodeling, wound healing, and other important biologic functions.[36] In the gingivae, MMPs are secreted by polymorphonuclear leukocytes (PMNs) and fibroblasts in response to the presence of bacterial lipopolysaccharides (endotoxins) from gram-negative periodontal bacteria.

In addition to their direct effect on connective tissue and bone, MMPs are also involved in the regulation of the inflammatory response by cleaving and activating some cytokines.[36] These are molecules that carry signals between cells and have a variety of functions including recruiting inflammatory cells, regulating their functions, and stimulating the formation of osteoclasts.[8] Hence, the inhibition of MMPs by low-dose tetracyclines appears to result in both direct inhibition of tissue-destroying enzymes and interference with proinflammatory pathways and effector cells such as osteoclasts, signified

by the right-hand arrow from the lower box ("Drugs/Biologics/Diet?") in **FIGURE 2**.

In 1998, the Food and Drug Administration approved a formulation consisting of 20 mg of doxycycline hyclate (Periostat, CollaGenex Pharmaceuticals) to be taken twice daily as an adjunct to mechanical treatment for periodontitis. The drug is also available as a generic. Because this is a dose that is lower than that needed to inhibit bacterial growth, it is referred to as subanti-microbial-dose doxycycline (SDD).

A 2003 systematic review of seven randomized clinical trials concluded there was a statistically significant beneficial effect when SDD was used adjunctively to SRP.[37] Unlike the situation with locally applied anti-infective agents, however, the majority of these studies showed positive results with SDD. Nonetheless, the magnitude of these changes was still modest, with additional clinical attachment level gains being generally less than 1 mm over what was seen with SRP alone. As with the anti-infective agents, the beneficial effects were more pronounced in sites with deeper initial pocket depths.

The review also considered six studies that looked at the safety of SDD, with most of the studies looking at six to 12 months of use. No changes to the oral and subgingival flora were found (as would be expected if the dose of doxycycline was truly subanti-microbial). Adverse effects in the test groups were not different from those in the control groups, so SDD appears to be a safe treatment modality.

A more recent "proof of principle" study looked at SDD used adjunctively to flap surgery.[38] The results, which should be considered preliminary in nature, indicated that SDD may also be useful when used as an adjunct to flap surgery.

To summarize, it appears that SDD may be a useful adjunct to conventional mechanical therapy, especially in patients with more severe or refractory disease. While it is safe and apparently does not lead to the emergence of doxycycline-resistant bacteria, clinicians should consider whether the relatively small gains in clinical attachment are important enough to warrant its widespread use.

Since, as stated previously, "periodontal therapy is primarily about elimination (of) or controlling inflammation," it is probably not surprising that anti-inflammatory drugs have been considered for adjunctive use in the treatment of IPD. The primary class of drugs that have been investigated for this purpose are the nonsteroidal anti-inflammatory drugs (NSAIDs).

INTERESTINGLY, seven of eight studies also failed to find a decrease in gingival inflammation, measured by gingival index, in the NSAID-treated groups.

NSAIDs are a class of drugs that includes aspirin, diclofenac, diflunisal, flurbiprofen, ibuprofen, ketoprofen, ketorolac, meclofenamate, meloxicam, naproxen, and piroxicam. They act by inhibiting cyclooxygenases, which are enzymes in the pathway that generates proinflammatory mediators such as certain prostaglandins, thromboxanes, and prostacyclins.[39]

A systematic review of nine studies on the effects of NSAID therapy either alone or as an adjunct to mechanical therapy generally indicated no statistically significant decrease in the loss of clinical attachment when NSAIDs were used.[37] Ten studies looked at pocket depth measurements, and the vast majority (eight out of 10) could not find statistically significant benefits for NSAID treatment. Interestingly, seven of eight studies also failed to find a decrease in gingival inflammation, measured by gingival index, in the NSAID-treated groups.[37]

When alveolar bone levels were measured, there did appear to be a benefit to NSAID use. Six of the studies measured alveolar bone loss and these studies consistently showed statistically significant decreases in bone loss.[37] However, this benefit must be weighed against the potential hazards of moderate to long-term NSAID use, including "serious adverse GI events — bleeding, ulceration and stomach or intestine perforation — as well as increased risk for serious and potentially fatal cardiovascular thrombotic events (myocardial infarction and stroke)," as outlined in the black box warnings the Food and Drug Administration requires for all NSAIDs. There also is reason to believe that most of the NSAIDs may interfere with homeostatic mechanisms involved in the resolution of inflammation (see below).

In summary, most NSAIDs probably do not have much of a role in controlling periodontal inflammation, although there is clearly the potential for the use of new anti-inflammatory agents that may become available in the future.

Because bone loss is a generally irreversible consequence of IPD, investigators also have looked at "bone-sparing" agents, such as the bisphosphonates in treating the disease. The bisphosphonates, such as Aredia (pamidronate, Novartis), Fosamax (alendronate, Merck), or Reclast/Zometa (zoledronic acid, Novartis), are a class of drugs that decrease osteoclastic bone resorption and consequently bone turnover. They are commonly prescribed to treat osteoporosis, osteopenia, and Paget's disease of bone.[36]

While there have not been a lot of studies on the use of the bisphos-

phonates for treating IPD, those that were included in the 2003 systematic review mentioned above showed positive effects.[37] In one study, fewer sites lost bone as compared with the placebo (20 percent versus 40 percent). In another study, there was a decrease in the absolute amount of bone loss in the treatment arm compared with the placebo. More recently, a longer and larger study showed benefits in terms of CAL, pocket depths, and bleeding on probing with bisphosphonates.[40]

A rare but severe side effect of bisphosphonate therapy is bisphosphonate-related osteonecrosis of the jaw (BRONJ). This condition can occur when alveolar bone is exposed, usually during a dental extraction.[41] It is most frequently seen in cancer patients who are taking relatively high intravenous doses of bisphosphonates for palliative treatment of bone metastases or to treat hypercalcemia associated with certain malignancies, but patients taking oral bisphosphonates for osteoporosis have also developed BRONJ. While the incidence of BRONJ in patients taking oral bisphosphonates is hard to determine, some estimates range between 1:10,000 and 1:100,000.[41] However, "considering that millions of patients have been prescribed bisphosphonates for the treatment of osteoporosis, the relative prevalence of BRONJ in these patients was low" according to a 2007 systematic review.[42]

To summarize, treatment with bone-sparing medications may offer an approach to treating the inflammatory bone loss associated with IPD. However, while the existing data are promising, there is probably not yet enough evidence to recommend that these drugs be widely used for the treatment of IPD. Clinicians should also consider the risk of BRONJ, which although rare, can be a severe complication before prescribing these agents.

Future Approaches to Managing Periodontal Inflammation

As has been seen, contemporary approaches to managing periodontal inflammation largely center on reducing the burden of bacteria that incite the inflammatory response. Some emerging technology, e.g., SDD, inhibits inflammatory effector molecules or cells such as the MMPs and osteoclasts. Future approaches may work by modulating the inflammatory response earlier in the process, interrupting the initial cascade of mediators that increase inflammation and bone resorption, or by enhancing the resolution of inflammation.[8,39,43,44] These pathways are represented by the upper and lower vertical arrows from the lower right-hand box ("Drugs/Biologics/Diet?") in **FIGURE 2**.

Initial events in the inflammatory response to the presence of bacteria include binding of bacterial products such as endotoxins by molecules called "toll-like" receptors that are found on the surface of dendritic cells, monocytes/macrophages, mast cells, and some lymphocytes. This binding causes the cells to make and secrete a variety of inflammatory mediators, e.g., bradykinin, and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α).[8,39,43] Cytokines, as explained previously, are a class of molecular messengers that among other things, recruit and regulate inflammatory cells, and can also stimulate or block , depending on which cytokine, the formation of osteoclasts that are the cells responsible for bone resorption.

IL-1 and TNF-α affect osteoclast function by inducing the production of other cytokines by osteoblasts or stromal cells in bone.[43] One of these, the "receptor activator of nuclear factor-kappa B ligand"(RANKL), stimulates the differentiation and activation of osteoclasts, which is why it also is sometimes called "osteoclast differentiation factor" by binding to and activating the "receptor activator of nuclear factor-kappa B" (RANK) on osteoclast precursor cells. RANK, as the name implies, is an activator of nuclear factor kappa of B cells (NF-κB), which was originally found in activated B-lymphocytes but is found in other cell types as well. When activated, NF-κB turns on gene transcription and protein synthesis in responder cells, allowing them to perform effector functions in the inflammatory and immune responses.[45]

THERE IS NO DOUBT that a competent immune system and well-regulated inflammatory response are necessary to prevent severe periodontitis.

Other interleukins, e.g., IL-4, and some interferons can induce the production of osteoprotegrin (OPG), which is a competitive inhibitor of RANKL, and thereby reduces osteoclast activation. Thus, osteoclast activity seems to be regulated by the OPG:RANKL ratio; when more OPG is available, it binds to RANK (without activating it) and thus prevents binding of RANKL and subsequent osteoclast activation. This has the effect of inhibiting bone loss.[43]

Clearly, these complex proinflammatory pathways offer a number of points at which potentially therapeutic interventions could occur, by either inactivating effector cells or molecules themselves, or by limiting their activation or production. As discussed earlier, MMPs are involved in cleaving and activating some of the cytokines involved in the activation cascade, so inhibition of MMPs by SDD may affect this early stage in the inflammatory pathway by suppressing activation of certain cytokines.

A potential new intervention may come in the form of a new drug called Protelos (strontium ranelate, Servier Laboratories), which has been shown to stimulate osteoblasts to secrete OPG, thus preventing the activation of osteoclasts.[46] It has also been shown to upregulate the differentiation of osteoblasts from stromal cells in bone, so it seems to be able to both prevent bone resorption and enhance bone deposition.[46] Strontium ranelate is available as a treatment for osteopenia and osteoporosis in Europe, but it has not been cleared by the FDA for use in the United States as of this writing.

While this review has focused primarily on the deleterious effects of chronic inflammation in IPD, the inflammatory response clearly has protective functions as well. There is no doubt that a competent immune system and well-regulated inflammatory response are necessary to prevent severe periodontitis. For example, patients with defects in PMN numbers or function frequently exhibit aggressive periodontitis, as do patients with acquired immunodeficiency syndrome.[47,48] Hence, any intervention that alters proinflammatory responses at a basic level needs to be examined carefully for unintended consequences that could lead to more destruction instead of less, or which could affect other systems in the body that rely on intact inflammatory pathways.

The interventions discussed so far center on interrupting proinflammatory pathways or effector cells and molecules, but this may not be the only approach to controlling inflammation. Another potentially important avenue for managing IPD in the future may be by enhancing the mechanisms that resolve

inflammation and return the tissues to a state of homeostasis.[11,39] This is possible because recent research indicates that the resolution of inflammation relies not merely on the absence or diminution of proinflammatory pathways, but is an active process mediated by specific resolution pathways.[39] The tissue destruction seen in IPD may be the result of the inordinate persistence of inflammation in response to bacterial challenges caused by the failure of resolution pathways to restore homeostasis.[49]

Molecules that appear to be important in the resolution of inflammation are lipids made from fatty acids, as are many proinflammatory effectors, e.g., some prostaglandins, thromboxanes, and leukotrienes. Some anti-inflammatory lipids are made from omega-3 polyunsaturated fatty acids (ω-3 PUFAs) in addition to those made from omega-6 fatty acids such as arachidonic acid (AA), which is also the precursor of some proinflammatory lipids.[39,49-51]

Early gingival events in the inflammatory response to pathogenic bacteria include the binding of inflammatory agonist molecules, e.g., bradykinin, by cell surface receptors that activate the enzyme phospholipase A_2. This enzyme, in turn, liberates AA from phosphatidyl choline. AA is the substrate for a variety of biosynthetic pathways involved in the synthesis of proinflammatory lipid mediators such as the prostanoids (prostacyclines, prostaglandins and thromboxanes) via the cyclooxygenase pathways (COX-1 and COX-2), or leukotrienes via the 5-lipoxygenase (5-LO) pathway; the prostanoids and leukotrienes participate along with proinflammatory cytokines in inflammatory cell recruitment, edema, pain, and destruction of connective tissue and bone.[39,52]

Apparently, when the concentration of proinflammatory substances reaches a critical point, they can cause a change in PMNs

that induces other biosynthetic pathways for AA (a "class-switch") that eventually result in the production of lipid mediators called lipoxins.[53] Lipoxins are capable of promoting the resolution of inflammation by limiting the migration of additional PMNs into the site of inflammation, activating noninflammatory monocytes, and stimulating the removal of dead (apoptotic) PMNs by macrophages.[39,52] This pathway is represented by the lower arrow labeled "Resolution" from the "Inflammation" box which leads back to "Healthy Tissue" in **FIGURE 2**.

A consequence of this feedback loop may be that the use of NSAIDs other than aspirin can actually delay the resolution of inflammation by inhibiting the generation of the critical concentration of proinflammatory mediators needed for the class-switch to occur.[39,50] Aspirin (ASA) may also induce a switch from proinflammatory to proresolving AA metabolites.[51] Like other NSAIDs, ASA inhibits the production of the proinflammatory prostanoids by COX-1 and COX-2. However, ASA is the only NSAID that also induces the synthesis of 15-R-hydroxy-(p)-eicosatetraenoic acid, that is further modified by 5-LO to form 15-epi-lipoxins. These are known as "aspirin-triggered lipoxins" (ATLs). ATLs are more bioactive forms of lipoxins and hence have greater proresolving activity than the unmodified forms.[39,51]

Thus, the use of ASA to induce endogenous ATLs is a possible intervention to resolve chronic inflammation in IPD. Of course, the use of ASA needs to be balanced by potentially serious side effects such as GI bleeds. Another approach on the horizon may be to use exogenous synthetic lipoxin analogs, as it has become possible to chemically synthesize lipoxin analogs, which are more stable than the native molecules. These lipoxin analogs have been shown to have inhibitory effects on acute inflammation by activating proresolving pathways.[54,55] This type of intervention is represented by the downward-pointing arrow from the lower box labeled "Drugs/Biologics/Diet?" in **FIGURE 2**.

There is another group of endogenous anti-inflammatory lipid mediators that are synthesized from several ω-3 PUFAs, specifically eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) rather than from AA.[50,52] These metabolites are called resolvins (formed from both EPA and DHA) or protectins (from DHA).[50] As with the lipoxins, ASA seems to increase the stability and duration of action of these molecules.[50] The resolvins and protectins act by diminishing the attraction of inflammatory cells, increasing phagocytosis of apoptotic PMNs and blocking the production of proinflammatory mediators.

ASA IS THE ONLY NSAID that also induces the synthesis of 15-R-hydroxy-(p)-eicosatetraenoic acid, that is further modified by 5-LO to form 15-epi-lipoxins.

There is some evidence that increased dietary intake of ω-3 PUFAs can have beneficial effects in reducing morbidity from atherosclerosis, asthma, cardiovascular disease, and cancer.[51,56] There is an inflammatory component in all of these diseases and it has been postulated that increased dietary ω-3s can lead to increased synthesis of resolvins and protectins.[50,51] This leads to the possibility that increasing dietary intake of ω-3s, especially when taken with ASA, can be an effective strategy in controlling inflammation in IPD. This pathway is also represented by the downward-pointing arrow from the lower box labeled "Drugs/Biologics/Diet?" in **FIGURE 2**.

Finally, it has been shown that a chemically synthesized resolvin (RvE1) was effective in limiting or reversing periodontal disease in rabbits infected with *P. gingivalis*.[57] This opens the possibility of using exogenous pro-resolving mediators of inflammation such as lipoxins, resolvins, and protectins in the clinical treatment of periodontal disease at some time in the future.

Take-Home Lessons

Classical approaches to controlling inflammation rely exclusively on attempts to suppress pathogenic bacteria that incite the inflammatory response through mechanical (SRP, flap surgery) or chemical (anti-microbials and antibiotics) means. While this approach has roots going back at least 1,000 years, it still has a place in treating periodontal inflammation today.

Emerging and future approaches will rely more on modifying the inflammatory response itself, by limiting the activity of proinflammatory pathways, effector cells and mediators, as well as by amplifying pathways that resolve inflammation. Treatment with SDD is a start in this direction, but the future holds the promise of even more effective interventions.

Clinicians should always use the best available evidence when deciding when or whether to adopt new treatment modalities. This is best achieved by searching the clinical scientific literature for systematic reviews and meta-analyses that give a much better sense of the state of the art than individual articles or testimonials, especially from parties who stand to gain if you adopt their products. ■■■■

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ENCINO GP - 3 eq. ops., 1,200 sq. ft. suite, 7 story professional building. Collected approx. $514,348 for 2009. ID#2631. **Price Reduced!**
GLENDALE - Turn Key practice, 3 eq. ops., 5 plumbed not eq., 2,000 sq. ft. suite, two story Med/Dent bldg. ID#2591. **Price Reduced!**
***LANCASTER GP** - 3 eq. ops., 1,200 sq. ft. suite, one story shopping center. BUYER'S NET OF $123,769. ID#2691.
***LAWNDALE GP & Bldg** - Excellent practice w/8 eq. ops., 3,000 sq. ft., free standing bldg. NET OF $237K. ID#2901.
***LAWNDALE GP (New)** - Store front office w/parking behind bldg., 4 eq. ops., 2 plumbed not eq. NET OF $63,234. ID#1331.
LOS ANGELES GP - 4 eq. ops., 1,700 sq. ft. office, strip shopping center. Collected approx. $345,882 for 2009. ID#2621.
LOS ANGELES GP - Turn Key, 3 eq. ops., multi story Med/Dent bldg. Coll. approx. $197,238 in 2009. Great views. ID#2831.
MARINA DEL REY- Great starter location - LSHLD - 2 eq. ops., 1 plmbd, Only dental practice in bldg. ID#2791.
MONTEBELLO - Long established practice - Equip. & Charts Only! 2 eq. ops., in single story busy shopping center. ID#2701.
***REDONDO BEACH GP** - 3 eq. ops., in large remodeled shopping center. Collected approx. $276,831 in 2009. NET $85,477. ID#2821.
***ROLLING HILLS GP** - Long established practice w/5 eq. ops., 1,760 sq. ft. suite in a 2 story Med/Prof. bldg. NET $109K. ID#2981.
***SAN PEDRO GP** - 2 eq. ops., 1 plmbd., 1,400 sq. ft. office located on 2nd fl of strip center; visible location. ID#2851. **Price Reduced!**
SHERMAN OAKS GP - Excellent street visibility. 3 eq. ops., Med/Dent bldg. Collected approx. $404,565 for 2009. ID#2491.
***WILMINGTON GP** - A must see practice! 3 eq. ops., 1,400 sq. ft. office located in a 1 story free standing bldg. NET OF $387K. ID#2841.

ORANGE COUNTY

***GARDEN GROVE GP** - 7 eq. ops., 2,200 sq. ft. suite. 16+yrs of Goodwill. Collected $1,061,802 in 2009. NET $329K. ID#2891. **SOLD**
IRVINE GP/SPEC - Leasehold Improv. & Equip. Only! 3 ops., 1 plmbd not eq., suite in 2 story Med/Dent Bldg. ID#2661. **Price Reduced!**
SAN JUAN CAPISTRANO GP (New) - Well design & modern office w/4 eq. ops., 3 plmbd not eq., in a 2 story prof. bldg. ID#3021.
***TUSTIN GP** - Turn Key, state of the art office. 5 eq. ops., 3 chairs in open bay. Ready for multi specialty office. ID#2861. **SOLD**
WESTMINSTER GP - 2 eq. ops., 850 sq. ft. suite, single story strip mall. BUYER'S NET OF $44,326. ID#2711.

RIVERSIDE / SAN BERNARDINO COUNTIES

***INDIAN WELLS GP** - Long established practice, 5 eq. ops., 1,400 sq. ft. suite, 2 story prof. bldg. NET $151,585. ID#2801.
LA QUINTA (New) - Leasehold & Equip. Only! 3 eq. ops., 1,000 sq. ft. suite in a strip shopping center. Established in 1995. ID#3011.
ONTARIO GP (New) - Excellent growth potential office w/4 eq. ops. in a single strip plaza in major intersection. ID#2791.

SAN DIEGO COUNTY

EL CAJON (New) - Solo Practice, 3 eq. ops., 1 plmd not eq. 2,200 sq. ft. office, free standing bldg. Seller owns bldg. NET $123K. ID#3031.
OCEANSIDE - 4 eq. ops., 1,500 sq. ft. office, one story Med/Dent bldg. Collected approx. $345,049. ID#1641. Great Location!

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***SANTA BARBARA COUNTY GP (New)** - Long Establised Practice, 3 eq. ops.,1,010 sq.ft, 2 story strip mall. NET OF $219K. ID#2881.

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CONTINUES ON 286

CLASSIFIEDS, CONTINUED FROM 285

OPERATORY FOR RENT OR LEASE — Dentist with 25 years experience wants to rent or sublease an operatory on Saturdays in the Sacramento or Roseville area. E-mail drpreddis@gmail.com or call 916-517-9905.

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- **CITRUS HEIGHTS:** *For Sale*-General Dentistry Practice. Well-designed 6 operatories with 1,500 sq. ft. office in professional building. Desirable location. 2-3 days hygiene. Owner is retiring.
- **DIXON:** *For Sale*-General Dentistry Practice. '08 collections were $122,894. 3 op 1,100 sq. ft. office. Owner has relocated out of state and is motivated. Good opportunity to build a practice in a growing community near Davis, CA. #14265 SOLD
- **EL SOBRANTE:** *For Sale*-General Dentistry Practice: Ideal for recent grad or DDS looking for satellite practice. 3 ops. w/potential of 5. '08 receipts $330K, adj. net income $124K. 3 days of hygiene, Pano, Easy Dental software. 1,300 sq. ft. Seller is retiring after 35years in same location. #14302 SOLD
- **FRESNO AREA:** *For Sale*-**Exceptional** General Dentistry Practice. This outstanding practice has annualized collections of $1,921,467, $798K adj. net income. The office has Dentrix, Laser, Intra-oral camera, digital x-ray and Pano. Bldg. may be avail. for sale. Owner is retiring. #14283
- **FRESNO:** *For Sale*-General Dentistry IV Sedation Practice. Collections $1,064,500. Seller looking for either an outright sale or a buyer to purchase 1/2 of the practice. Buyer will need IV sedation skills or have been trained to provide IV sedation. Facility 1,500 sq. ft. w/5 equipped operatories & 7 days of hygiene. #14250
- **FRESNO:** *For Sale*-General Dentistry Practice. Owner has practiced in same location 24 years. 3 TX rooms, 1,000 sq ft. Located in a Medical/Dental Bldg. Owner to retire. 2008 collections were $86K. Ideal for a new grad or satellite office. SOLD
- **FRESNO:** *For Sale*-**Office Space Only in North Fresno Area.** New fully equipped 3-op dental space avail. asking $115K. Equip. approx. 2 years old. Space avail. for 4th op. Office design contemporary & tastefully done. Asking price includes all leasehold improvements. SOLD
- **GRASS VALLEY:** *For Sale*-This Periodontal Practice is located in a very desirable growing community. Practice has been in its present location for the past 28 years. Office consists of 1500 sq ft 3 ops, Intral-oral camera. Practice has 5 days of hygiene.
- **GREATER AUBURN AREA:** *For Sale*-General Dentistry Practice 7 Dental Building. Outstanding opportunity to purchase well established, very successful, 4 op Fee for Service practice. 1,800 sq. ft. dental bldg. in the Sierra Foothills. No PPO or HMO. '08 Collections $763K on 3.5 days with 5.5 days of hygiene. Owner is retiring. #14304 SALE PENDING
- **LAKE FORREST:** *For Sale* - General Dentistry Practice. This 4 operatory, 1,200 sq. ft. office had gross receipts of 1.2 million in 2009. There are 5 days of hygiene and approx. 3,000 collective patients. Approx. 10% of receipts are from two HMO plans. Seller has practiced in the same location for approx. 30 years. Owner is retiring. SALE PENDING
- **MODESTO:** *For Sale* - General Dentistry Practice. 5 operatories, 32-years in practice. Gross Receipts $884K w/adjusted net income of $346. Dentrix, Cerec, and Intra-oral camera. Owner to retire. SALE PENDING
- **MODESTO:** *For Sale*-General Dentistry Practice. 12 Treatment rooms, Pano, Laser, Intra Oral Camera,10-years in same location. Three days of hygiene. Owner-32 years in practice willing to work a couple days of week to help transition the practice or as Role-Reversal.
- **MURRIETA/TEMECULA:** *For Sale* - 2009 receipts were $648,000. This 4 op, 1,500 sq. ft. office space with 4.5 days of hygiene. Average age of Dental Equip is 7 years.
- **NO. CA WINE COUNTRY:** **ENDO PRACTICE** For Sale-GR 958K adj net $673K 4 Ops, 1,500 sq ft. Overhead 29% Owner to retire #14296
- **OROVILLE:** *For Sale* - General Dentistry Practice. Owner dentist recently deceased. 2009 collections $770K. Very nice stand alone dental building with basement. 7 ops digital x-ray 5 days of hygiene. Bldg 3,000 sq ft Basement 540 sq ft. Temporary Dentist in place.
- **PALM SPRINGS:** *For Immediate Sale* - General Dentistry Practice. 2008 Gross Receipts $906K with adj. net income of $346K. Highly desirable location with 4 ops. Laser, and Intra-oral camera. 5 days of hygiene. Owner recently deceased. SOLD
- **PORTERVILLE:** *For Sale*-One of two partners is retiring in this highly successful General Dentistry Practice. Receipts $2Mil. adj. net $1,257,000. 2,000 sq ft 6 ops. Intra-Oral camera, Pano, Dentrix.10 days of hygiene. #14291
- **RANCHO SANTA MARGARITA:** *For Sale* - General Dentistry: *Office Space Fully Equipped*: Owner would like to sell existing dental equipment and have buyer take over lease in the 1,200 sq. ft. treatment room, office. Built by Henry Schein in 2005 with Pelton and Crane cabinetry and sterilization center. Excellent opportunityfor a low cost start up or satellite practice.
- **RED BLUFF:** *For Sale*-General Dental Practice **"REDUCED PRICE"** Facility overlooks the Sacramento River, 3,500 sq ft, has 8 ops, 10 hygiene days. Reduced price/Or Best Offer due to retiring doctor's health. Historically Gross Receipts have been over $1 Mil per year. 100% financing available. Sale of Building (optional) #14252
- **REDDING:** *For Sale*-Owner looking for Assoc. trans. into Partnership w/Buy-Out. GR $1 Million dollars income $436K. 5.5 days hygiene, 2,200 sq. ft. #14293
- **RENO: FOR IMMEDIATE SALE DECEASED DENTIST** - General Dentistry Practice. 2 ops, 17yrs. present location '07 GR $763K with adj. net of $263K w/65% overhead. Bldg. also for sale. Owner deceased. SOLD
- **ROSEVILLE:** *For Sale*-General Dentistry Practice. 2008 Receipts $834K with adjusted net income of $297,218. 64.4% overhead. Practice has been in this present location for the past 7 years. 13-15 New Patients a month. 6-treatment rooms in 2,100 sq ft. Laser, Intra-oral camera, and digital radiography. Owner relocating out of office. SOLD
- **SAN FRANCISCO:** Financial District 4 ops, 1,500 sq. ft. MERGER - Buyer needs to bring in Pt. base #14288 SOLD
- **SAN FRANCISCO:** *For Sale-Patient Base for Sale*-Owner passed away last June and the practice has continued on 4 days a week with an associate. Lease can't be renewed. There are approx. 1,000 acive patients in the practice. The patient base can be purchased at no risk to buyer since the purchase price is paid according to the receipts collected on the patients that transfer.
- **SOUTH LAKE TAHOE:** *For Sale*-General Dentistry Practice. Office is 647 sq ft. 2 ops. Practice has been in its present location for the past 26 years. Owner to retire. #14277 SOLD
- **YUBA CITY/ MARYSVILLE:** *For Sale*-General Dentistry Practice w/Bldg avail. Practice located in present (great) location over 30 years. 1,800 sq ft 5 ops 4 hygiene days. Owner to retire.#14273 SOLD

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Busy periodontal practice with a highly desirable location. 5 op, very profitable business with long term goodwill and a great staff. 2009 collections $900,000+. The seller is retiring.

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Long established, 4 op GP with an excellent location in a professional complex. Strong patient base developed over 34 years. 2009 collections exceeded $670,000. The seller is retiring.

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Well established 5 op GP with 14 years of goodwill and room for growth. The selling dentist is highly motivated and all reasonable offers will be considered.

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3011 MID-PENINSULA GP

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PENDING

2999 NO. CA COAST

Flourishing Pediatric Dental Practice. Well est. with seasoned staff. 4,000+ active pts., avg. 50-80 new pts/[illegible] over 2.2M in Gross Receipts. Fu[illegible]p. 1,600 sq. ft. office with open bay and 2 quiet areas Asking $1,542,000.

SOLD

2976 NORTH BAY SANTA ROSA GP

Beautiful, contemporary & pristine, state of the art office in a strip shopping ctr. with anchor retailers: Safeway, Starbucks, Baja Fresh, etc. Averaging 40+ new patients a month with 1,200+ active patients (all fee-for-service). 4 ops (3-fully-equipped) in 1,350 sq. foot facility. Located on a well-traveled intersection with incredible street signage and visibility. 2009 gross receipts $626K+ with an adj. net of $202K+. Owner willing to assist Buyer for a smooth transition. Asking only $498,500.00.

3006 MONTEREY COUNTY ORTHO

Est. Ortho practice in 2,668 sq. ft. office with 5 open bay chairs in a professional dental complex. Panorex and Cephlometric X-ray machines. Stable and loyal referral base. GR for 2008 were $340K+. Annualized GR as of Oct 2009 are $335K+. Owner retiring and willing to help for a smooth transition. Asking 227K.

2986 SAN JOSE FACILITY & EQUIP

A 1 1/2 year-old stunning facility with small pt. base that has all the bells and whistles. 2,000 sq. ft., state-of-the-art dream office. Located in desirable comm./residential neighborhood close to O'Connor Hospital & Valley Fair Mall. 6 ops and new equip. For the est. GP who is looking to move into a larger facility or for the assoc. GP who is ready to start out on their own. Asking $475K.

3022 MODESTO GP

Owner retiring from well est. friendly, family practice w/3 ops. in 1,150 sq. ft. office + spacious storage area. Avg. GR for past 5 years $379K w/44% overhead & great upside potential. Quality staff. Owner willing to help w/smooth transition. Partnership in building available. Asking $278K for practice.

3016 CONTRA COSTA COUNTY PERIO

Est. 1990 in desirable bedroom community 20 miles from SF. 1,068 sq. ft. beautifully remodeled office w/4 fully-equipped ops., & excellent staff. Assign[illegible]5 year lease w/5 year opti[illegible] to help in the transition [illegible]duce. 2008 GR $441K+, 2009 GR projected to $460K+ as of Oct. Terrific upside potential. Asking $275K.

PENDING

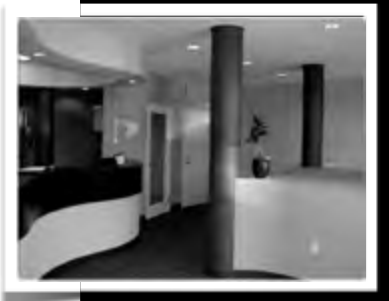
COMING SOON:

NORTH BAY GP

3 OPs, 2,000 sq. ft. office. Avg. GR $438K+

WINE COUNTRY GP

5 OPs Avg. 1,500 sq. ft. office Avg. GR $751K+



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BAY AREA

A-6781 SAN FRANCISCO - New equipment-hardly used. VIRTUALLY NEW practice! 1,000 sf/3 ops. **$65k**

A-7751 SAN FRANCISCO- ***Space Sharing.*** GP seeks DDS to share office in renowned 450 Sutter St bldg. ***Call Now!***

NEW! **A-807 SAN FRANCISCO -** Well-known Medical/Dental Prof bldg in heart of downtown financial district. Quality, state-of-the-art practice. 800sf w/2 fully equipped ops. Plumbed for 1 add'l **$250k**

A-817 BELMONT- Surrounded by dental specialties in a 2-story Prof. Bldg w/easy access to public transportation. 860sf w/ 2 ops & plumbed for 1 add'l. **$210k**

A-829 SAN FRANCISCO Facility– Attractive Office w/traditional décor. 1600sf & 2 fully equipped ops. **ONLY $49k**

B-7881 TRI VALLEY, CA - ***Facility Only -*** Location, Location, Location! 1070 sf, 4ops, ADEC chairs and equipment. Fully networked Dentrix computers. **$325k**

NEW! **B-846 OAKLAND-** Long-established, fee-for-service practice.Excellent reputation. Dental Prof Bldg. 2,100sf w/ 3 fully equipped ops **$325k**

NEW! **B-8531 W. Contra Costa** - Just blocks off I-80 commuter corridor. Multi-story Dental Prof Bldg. 1,212sf w/3 fully equipped ops. **$475k**

C-690 SANTA ROSA -1050 sf with 3 ops. One of the most prestigious areas in Santa Rosa. Very mature landscape & beautiful office. Emphasis on Crown & Bridge, esthetics dentistry & prosthetics **$345k**

C-787 SANTA ROSA - GP in very desirable area. 1700 sf , 4 fully equipped ops. Gross over $300k last year! Write your own success story here. **$150k**

C-7811 SOLANO CO - 2,997 sf w/6 fully equipped ops + 2 Hyg ops + 1 add'l op! Buy the whole practice for $1.3m or only 50% for $650k. **Call for Full Details!**

BAY AREA CONTINUED

NEW! **D-842 PLEASANTON** –General Dentistry. 1,488sf w/ 2 ops **$295k**

D-790 MORGAN HILL FACILITY - SPECTACULAR! Dental Prof Plaza on busy intersection. 1,730 sf/5ops, 3 of which are fully equipped. ***This is an Ideal Satellite Office for Specialty Practice!*** **$75k**

D-779 SUNNYVALE - Well established GP in heart of Silicon Valley! 4 ops, 1050sf. Call for more information! **$225k**

D-824 SANTA CLARA- GP - 35+ new pats/mo by word-of-mouth referrals. Retail Shp Ctr in heart of Silicon Valley. Just 6 years old w/ 1,500 sf & 3 fully equipped ops. Plumbed for 1 add'l op **$485k**

D-8301 SAN JOSE- FFS - "One Stop Shop" w/multiple Specialists under one roof. Exc Pt Base. Amazing opportunity in a highly desirable, family-oriented community. 2,400 sf & 8 ops, **$1.2m**

NEW! **D-845 SAN JOSE -** ***Facility*** **-** Attractive office. Traditional décor. Retail Plaza. 2,240 sf & 5 ops. **$150k**

NEW! **D-8521 SAN MATEO-Facililty -** SPECTACULAR office -Quality dental care - Modern facility. Just blocks off of Hwy. 92 and I-280. 2-Story Shp Plza. 2,076 sf & 4 ops + 3 add'l **$150k**

NEW! **D-8541 SANTA CRUZ-**Relaxed atmosphere. Well-established, modern practice. Free standing single story building. Affluent, desirable location. 1,650sf & 4 ops. Plumbed for 1 add'l. **$430k**

NEW! **D-8601 PALO ALTO—FACILITY-**Ideally Suited for a Specialist. Highly desirable upscale community. Significant leasehold improvements! 1100sf w/3 fully equipped ops **$390k**

NEW! **D-863 SAN JOSE-**Excellent location & Stellar Reputation! Professionally Decorated in Popular Retail Shopping Ctr. 1500sf & 3 fully equipped ops **$495k**

BAY AREA CONTINUED

NEW! **D-857 MOUNTAIN VIEW-** Quality practice. Busy traffic flow. Significant walk-in patients-continuous growth. Free-standing bldg w/ ample exclusive patient parking. 3,400sf - 11 ops **$620k**

NORTHERN CALIFORNIA

E-729 AUBURN - Busy retail shp ctr w/ excellent signage & good traffic flow. Well maintained FFS practice. 1750sf, 4ops. Plumbed for 2 add'l ops **$300k**

E-7121 SACRAMENTO AREA – Largely FFS. 1800sf, 4ops (+2 add'l plumbed). Highly visible,2-story Prof bldg. **$695k**

E-818 SACRAMENTO-Increase the part-time, relaxed workweek and watch the practice grow! Loyal Patient Base. Collections over $350k in 2007. 1,200sf & 4 ops. ***Building previously appraised @ $260k in 2004. $315k for Practice AND Building***

E-821 ***Facility*** **SACRAMENTO-**Attractive office—traditional décor. Well-maintained, highly visible, single-story bldg. Great area. 1,400sf, 3ops. Plumbed 4th op **$60k**

NEW! **E-849 SACRAMENTO-** Established community in distinct area. FFS Quality practice. Free-standing building. 3 fully equipped ops **$205k**

F-7651 COASTAL EUREKA AREA- Near Thriving University. Vibrant student/staff population. Seller retiring. 2700sf, 6 ops. **$480k**

G-751 RED BLUFF/CHICO- Known for special sense of community & small town living. Complete remodel ~5 yrs ago. FFS GP. 2350sf / 4 ops equipped. Plumbed for 2 add'l. **Current Lender Willing to Carry Qualified Buyer. Practice Offered at $175k / Real Estate $250k**

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NO. CALIFORNIA CONTINUED

H-634 WEST OF RENO—On the Feather River in Plumas Co. 1500 sf/ 4 ops, excellent location. Lease below market value. **$250k**

H-668 NORTHEASTERN CA– GP with over 30 yrs goodwill. 4 ops 1600sf office. 2007 gr rcpts exceed $650k **$395k**

H-831 SUTTER CREEK -"Buy-in" opportunity during Seller's eventual retirement plans. Dental Prof Bldg w/ ample parking on a busy scenic highway in desirable neighborhood. 4 ops. **$160k**

***NEW!* H-856 SOUTH LAKE TAHOE** Live and Practice in the Beautiful and Unique Tahoe Area! This GP accepts over 50 new patients each month! Respected and Growing! 1568 sf & 4 fully equipped ops **$425k**

CENTRAL VALLEY

I-685 TURLOCK - 1700sf, 7 ops. Avgs 14 patients & 11 Hyg Pats/day! Practice recently remodeled. Highly attractive free standing building. Mostly Adec Eqpmt. **$350k**

I-772 *Facility* STOCKTON-Desirable, affluent health care area. 2,140sf/4 ops **$250k**

I-802 MODESTO - Facility. ~ 1500sf w/4 ops & room for 1 more. State of the art facility directly in front of Vintage Faire Mall **$445k**

I-838 MODESTO- Retail Shopping Center adjacent to a popular Supermarket, drawing walk-in patients from traffic flow & word-of-mouth referrals. 1,200 sf & 4 fully equipped ops **$350k**

***NEW!* I-840 TRACY-** Must See to Appreciate! Major thoroughfare / desirable area. 2,165 sf & 6 ops. Plumbed for 1 add'l op. **REDUCED!! $345k**

J-801 FRESNO– Facility. ~ 1300sf and 4 ops. Traditional Décor. **ONLY $70k**

SOUTHERN CALIFORNIA

K-735 ALISO VIEJO FACILITY - Upscale 2 story Prof Bldg. 1,800sf/4 ops. $4k sublet income at this location too! **$225k**

K-762 INDIAN WELLS– Well Respected practice w/loyal patient base. Newly remodeled, 1400+ sf, 5 ops **REDUCED! NOW ONLY $475k**

K-793 SAN DIEGO-2500sf & 4 fully equipped ops w/ plumbing for an add'l 2 ops. Highly Desirable Neighborhood **$475k**

K-827 STUDIO CITY-Highly esteemed, 4 op fee-for-service practice setting the bar for excellence! Near Beverly Hills, W. Hlywood ,Westwood **$515k**

K-816 MISSION VIEJO-Reputation as one of the best dentists in this vibrant OC Comm. Top-notch office in popular Rtl Shp Ctr. Close proximity to Gov. amenities & schools. 1,300 sf & 2 ops. **$325k**

***NEW!* K-847 SANTA MARIA-** Spacious ops & picturesque windows capturing scenic views. 1,200+ sf/3 ops + 1 add'l **$425k**

***NEW!* K-858 CHATSWORTH**– Seasoned Staff supported by Excellent Specialists. Stable Loyal Patient Base. 2150 sf & 4 + fully equipped ops **$295k**

NEVADA

LV-756 LAS VEGAS-Brand new 1,600sf/ 3 op office (Plumbed for 1 addl op) Attractive & well-equipped in Rtl Shpng Ctr. **$150k**

LV-796 HENDERSON - Master-planned community! Excellent location & easy freeway accessibility. Spacious, like-new office. 2,080 sf w/3 fully equipped ops & plumbed for 3 add'l ops **$295k**

LV-694 LAS VEGAS - Well established, large GP. 2200 sf & 6 ops. Gross Receipts over $900k. Equipment less than 5 years old. Office was recently painted and carpeted. **$545k**

NEVADA CONTINUED

LV-800 LAS VEGAS-Well Established FFS practice. Emphasis on prevention. Seasoned Staff. 3350 sf & 6 ops. **$785k**

***NEW!* LV-850 LAS VEGAS-** Med Prof complex. 2,603 sf & 6 fully equipped ops, **$652,200**

***NEW!* LV-861 LAS VEGAS**– FFS Quality Practice—Stable Patient Base & Seasoned Staff. Professionally Remodeled 1750sf, 5 op office. Call for Info! **$180k**

R-810 DAYTON-Gross Rcpts over $1mil in 08! Amazing, quality, well-estab w/loyal, stable patient base & seasoned staff. Excellent signage, easy freeway accessibility, ample parking. 1,500sf & 5 ops. **$595k**

R-841 RENO –Long-established, quality practice committed to patient education, technology & self improvement. Wonderful, stable patient base. Excellent signage, Centrally located in desirable, upscale neighborhood. 1,750 sf & 5 ops. **$350k**

SPECIALTY PRACTICES

K-653 GARDEN GROVE—ORTHO - Desirable area. 2200 sf 4 chairs in open bay. 2 private ops. **$285k**

C-6821 SOLANO CO. PROSTHO- Personalized treatment in warm caring environment. 1040 sf with 3 fully equipped ops. **$325k**

I-7861 CTRL VLY ORTHO- 2,000sf, open bay w/8 chairs. Garden View. Antique Exam Room. 45 years of goodwill. FFS practice sees 60-70 patients daily. Prof Plaza. **$370k**

E-811 SIERRA FOOTHILLS ORTHO- Fast growing area. Patient Oriented, Well respected Ortho practice. Avg 30 pats/day. 1200 sf & 3 chairs in open bay. **$175k**

***NEW!* I-8481 TWO Perio Practices CENTRAL VALLEY -Office[1]**: 1,100sf & 2 ops. **Office[2]:** 1,660sf & 2 ops **REDUCED TO ONLY $90k**

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PRACTICE FOR SALE — Land, building and dental practice for sale in Woodburn, Oregon. Call 503-720-1714.

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DR. BOB, CONTINUED FROM 298

should be deliberately incorporated into daily activities just like exercise and vigorous consumption of Sarah Lee products.

To be effective, laughter should be indulged in concert with at least one other person, or perhaps a small animal. People who frequently laugh all by themselves are regarded with suspicion. This has sometimes resulted in their being summarily fitted with jackets featuring multiple straps or being shot. In either case, the spontaneity is effectively squelched and in the latter instance, the health benefits are dubious.

What we are looking for are ways to apply this research to the dental field where laughter is conceded to be in short supply. Obviously, no mention must be made of periodontal disease in the patient's presence. Nothing will kill an enjoyable session at the dentist's like a detailed description of his gum deficiencies. Likewise, words like extraction, decay, drill, root canal, and $600 should be avoided. Laughter is a delicate thing, easily quenched by some thoughtless remark from the dentist or a staff member.

We have decided to incorporate a laugh track in our speaker system similar to those that are a necessary part of every sitcom.

On the theory that laughter is contagious like yawning, an office suffused in giggling and guffaws could be second only to Disneyland as "The Happiest Place on Earth." It goes without saying that treatment plans involving anything other than prophylaxis should be written out and given the patient in a sealed envelope to be opened later at home while he is sitting, or better yet, laying down.

We are able to confirm the validity of the laughter researcher's hypothesis. It has been our observation that the really happy, bubbling-with-laughter people who visit our office never have anything wrong with their teeth. Admittedly, most of these people are either salesmen or UPS deliverymen, not that there is anything wrong with that. Those actual patients with multiple oral problems are depressingly glum, tending to cast a pall over the whole office.

So there is much work to be done if we are to successfully promote laughter as the best medicine. Sometimes little remarks like "Your teeth are OK, but your gums will have to go" will snap them out of their blue funk into paroxysms of hilarity, but you can tell their hearts aren't really in it despite the tears rolling down their cheeks.

We want *Readers' Digest* and the Center for Preventive Cardiology to understand we're doing our best. Further research is needed to find out what those people who are said to be "laughing all the way to the bank" are doing. And by the way, what do you hear from the morticians of America? ■■■■

CDA JOURNAL, VOL 38, Nº4

Giggle Your Way to Good Health

To be effective, laughter should be indulged in concert with at least one other person, or perhaps a small animal.

→ Robert E. Horseman, DDS

ILLUSTRATION BY DAN HUBIG

Laughter is the best medicine *Readers' Digest* has been proclaiming for the past 50 years or so in one of its feature departments. This small format periodical that is so handy for poking in a hip pocket and that lends itself so easily to pinching from doctors' waiting rooms without being detected, has always tried to be all things to all people.

Pathos, inspiration, tearful confessions, and spiritual conversions are all grist for the pages of the *Digest*. Interspersed are the *Humor in Uniform, College Humor, Humorous Remarks of Small Children,* and *Funny Things My Pet Did I Want to Tell You About* sections.

You may remember a few years ago when an undercover patient commissioned by the magazine visited dental offices around the country and came up with treatment plans that varied wildly in complexity and cost, all for the same mouth. Although this expose evoked much merriment among patients and dentists, the *Humor in Dentistry* section never made it big and has since been dropped.

The *Laughter Is the Best Medicine* department, however, is still going strong and recently received a sort of blessing from none other than the director of the Center for Preventive Cardiology at the University of Maryland. Dr. Michael Miller says research has proved having an active sense of humor influences heart and artery disease. He feels that laughter

CONTINUES ON 297

"Dr. Robin made a process I thought would be a nightmare quick and easy with a better result than I ever could have imagined!"

--Ruth Kalpins, D.M.D., M.M.Sc.

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