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Fariba S. Younai, DDS

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DEPARTMENTS

FEATURES

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The Price of Soft Drinks

BRIAN K. SHUE, DDS

Americans love soda. It is a 14 billion-gallon-a-year industry in the United States, including sugar-sweetened beverages and sports drinks.

John Stith Pemberton continues to have an enormous impact on our world. It wasn't because of his services in the Civil War as a lieutenant colonel in the Confederate Army. Nor was it because he used his pharmacy skills to create a laboratory and pharmaceutical business, that even to this day still functions as a branch of the Georgia Department of Agriculture. He achieved greatness by concocting a sweetened syrupy drink that sold for 5 cents a glass at Jacobs' Pharmacy in Atlanta.

For it was on that day, May 8, 1886, Pemberton, a pharmacist, invented Coca-Cola.[1] The world has never been the same.

Americans love soda. It is a 14 billion-gallon-a-year industry in the United States, including sugar-sweetened beverages and sports drinks. On a more personal level, this amounts to about 506 12-ounce servings of soft drinks annually per person.[2] That's almost 1-1/2 cans of soda pop each day, per person, or about 50 gallons per person per year. And that's not counting diet soft drinks.

The impact of soft drinks hits children especially hard. The California Center for Public Health Advocacy reported in the "Soda Fact Sheet" that the average boy drinks more than 700 12-ounce cans of soda each year.[3] That's about two cans a day of Coke, Pepsi, 7-Up, Mountain Dew, or other ubiquitous carbonated caloric time bomb. In fact, each 12-ounce can of an average soda contains 10 teaspoons of sugar (or, most likely, high fructose corn syrup) and more than 140 calories. Imagine trying to eat 10 teaspoons of sugar one after another.

Consider how this weighs in on our health. The California Center for Public Health Advocacy stated, "Scientific evidence consistently supports the conclusion that drinking soda and other sugar-sweetened beverages increases a person's risk of being overweight or obese."[3]

Another article stated, "Sugar-sweetened beverages, soda sweetened with sugar, corn syrup, or other caloric sweeteners and other carbonated and uncarbonated drinks (such as sports and energy drinks) may be the single largest driver of the obesity epidemic."[4]

Almost one-third of American adults are obese.[5] The National Health and Nutrition Evaluation Survey from 2003-2004 stated that 66.3 percent of adults age 20 and older are either overweight (body mass index between 25.0-29.9) or obese (BMI ≥ 30.0), while 17 percent of adolescents age 12 to 19 and 19 percent of children from 6 to 11 are overweight.[6]

The California Center for Public Health Advocacy stated, "Reducing the amount of sugar-sweetened beverages people drink is an important strategy to reverse the obesity epidemic in California and across the country."[3]

We need to decrease soft drink consumption to improve overall health, but what can be done to reduce this addiction? Anticipatory guidance? Nutritional counseling? Scolding? How about a financial disincentive?

In "Ounces of Prevention — The Public Policy Case for Taxes on Sugared Beverages," Kelly D. Brownell, PhD, and Thomas R. Frieden, MD, MPH, argue just that point. They wrote in the April 30, 2009, *New England Journal of Medicine*, that taxing soft drinks may be justified because of the indirect impact on our country, because "an estimated $79 billion is spent annually for overweight and obesity alone — and approximately half of these costs are paid by Medicare and Medicaid, at taxpayers' expense."[4] They also argue an increase in revenue can be used to promote health.

This argument is not new. David Patterson, governor of New York, proposed an increase in fees in his 2009 budget to balance a multibillion dollar deficit, including a fee aimed at soft drink consumption.[7] He proposed a 18 percent fee on soda and other sweetened drinks, but it excluded diet sodas and drinks with more than 70 percent natural fruit juice. Patterson and his staff believed such a fee would decrease soda consumption by 5 percent because of the extra cost to the consumer. Patterson believed it would battle the obesity epidemic and also generate an additional $404 million the first year and more than a half-billion dollars each year thereafter. Critics and the public lambasted the "fat tax" proposal. It had no chance, no public support, and was basically dead on arrival. It has since been withdrawn.

California's Legislature has tried a fee on sodas and soft drinks in the past.[8] In 2002, SB 1520 began as a fee of $2 per gallon of sweetening syrup and $0.21 per gallon of bottled soft drinks or powder mixes, with the money generated to go directly to the battle of obesity. The bill stalled but was reborn without the fee the next year as SB 677, but required only nutritional beverages to be sold at elementary to junior high public schools during school hours. It became law. The concept extended further as SB 965 succeeded. It defined such beverages and included high schools in the new law, and Gov. Arnold Schwarzenegger signed it in 2005.

As recently as May 2009, the subject received attention, this time by the U.S. Senate Finance Committee that evaluated a proposal to add a 3-cent tax on soft drinks but not on diet sodas, in order to generate $24 billion in four years for use in funding a small part of the much-debated universal health care goal.[2,9] It didn't get far and was never heard again.

One key factor that has been largely forgotten from the soft drink controversy is this: The problem of tooth decay. It's the 800-pound gorilla (BMI ≥ 30). It largely is avoided, and, rarely, if at all, registers on the radar screen. The *New England Journal of Medicine* doesn't, nor do 90 percent of the articles and links that talk about fees and taxes on soft drinks. The focus is usually exclusively on calories instead of caries.

The negative effect of soft drinks on the oral health of America should be brought to the forefront. We shouldn't just focus on improving BMIs, but also DMFTs.

Oral health prevention and treatment programs like the Children's Dental Disease Prevention Program (CDDPP) can benefit from a manufacturer syrup fee as such state programs do not always receive the necessary revenue support

The negative effect of soft drinks on the oral health of America should be brought to the forefront.

from the state budget. During the California legislative budget negotiations this summer, all remaining funding was eliminated for the already decimated CDDPP program. The fee would make it possible to create an oral health screening, prevention, and treatment program to at-risk children throughout California with a dedicated, stable funding source. It is a positive step in improving oral health.

The momentum on placing fees on soft drinks is gaining. On Sept. 17, 2009, a group effort by the California Center for Public Health Advocacy and the UCLA Center for Health Policy Research posted the report "Bubbling Over: Soda Consumption and Its Link to Obesity in California" and provided links to the latest specific data on soft drink consumption and obesity in each California county and many cities.[12]

By individual city, the study reported the highest percent of children ages 2 to 17 that have had one or more sodas each day is Merced at 61.9 percent, San Francisco at the lowest with 36.9 percent, and the California average at 49.4 percent. The study further broke down the data between children and adolescents in the individual county statistics. For example, the highest percent of children ages 2 to11 that have had one or more sodas each day is my own: Imperial County at 60.7 percent, the lowest is Marin County at 18.4 percent, and the California average by county at 41.2 percent while the highest percent of children ages 12 to 17 that have had at least one soda per day is San Joaquin at 77.8 percent.

This study makes bold conclusions, including recommending the California Legislature to "impose an industry fee on soda and other sugar-sweetened beverages and earmark funds for community-based prevention programs" and wants the U.S. Congress to "tax soda and other sugar-sweetened beverages" for the same purposes.

Such a fee would be a huge step forward to ensuring revenue for use in state programs to improve health, whether it is used to address the problem of obesity or tooth decay. The cause and effect would be directly related — one can of soda at a time.

Pemberton never fully realized the significance of his invention. But with a fee on soft drinks to improve the oral health of the community, it would give new meaning to the phrase, "Have a Coke and a smile." ■■■■

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Address comments, letters, and questions to the editor to kerry.carney@cda.org.

Steve Dininno

What Is Trust Worth?

BY DAVID W. CHAMBERS, PHD

Human interactions are never perfectly articulated. He is late for the first meeting; she gave you the wrong information; they needed a little extra time to pay; the dentist said the sensitivity would stop soon. What a stupid, low-level, uptight world we would deal for ourselves if we failed to extend the trust necessary to grease the inevitable and random irregularities of interpersonal relations. Imagine a monetary system that constrained credit.

Individuals in America exhibit a range of trust as a basic personality characteristic. Some folks are trusters and some are not. Research has shown that those who by nature trust more are happier, wealthier, and less likely to be the victims of misplaced trust. Trust is a skill and those who practice get good at it.

CONTINUES ON 763

airBUG by Edge Medical Technologies Inc.

The airBUG e1 from Edge Medical Technologies, Inc. is an extraordinary new dental device that allows the dentist, hygienist, and dental assistant to aspirate, isolate, and provide tongue and cheek retraction during most dental procedures.

With the airBUG e1, the entire dental team can shorten procedure times, creating a more productive, efficient, and profitable practice. More importantly, patients will experience a higher level of comfort during treatment procedures without the added cost of new and expensive technology. For more information call, 866- 979-3343, or go to air-bug.com.

Digital Radiography Sensors Donated for West Africa Mission

Mercy Ships, a global charity that operates vessels that provide dental and medical care to residents in developing countries, has recently received donated Kodak RVG digital radiography sensors by PracticeWorks Systems, LLC.

Already in use onboard the world's largest charity hospital ship, Africa Mercy, the intraoral sensors are already in use at mobile clinics providing digital X-rays for patients receiving dental care during the ship's ten-month deployment to Benin, West Africa.

The Africa Mercy ship has six operating rooms, an intensive care unit, and ward space for up to 78 patients. Volunteer dentists, physicians, surgeons, and medical staff from more than 30 nations are delivering desperately needed health services by mobilizing people and resources around the globe.

With this donation, Mercy Ships was able to convert its dental operatory from radiographic dental film to a digital environment, allowing the volunteer staff to achieve greater productivity and deliver better patient care. Its arrival also eased the difficult logistics and environmental impact of managing film chemistry and processing in remote regions.

Mercy Ships also operates portable clinics to serve residents unable to travel to the ship. For more information, go to mercyships.org.

Deborah Bell © 2009 Mercy Ships

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"Redheads really do require more anesthesia, and by a clinically important amount."

DANIEL I. SESSLER, MD

Tressed Out: Redheads Are More Sensitive to Pain

Would the love of Charlie Brown's life demonstrate more anxiety in the dental chair than the famous blockhead's friends, Peppermint Patty and Lucy Van Pelt?

According to new research recently published in the *Journal of the American Dental Association:* yes.

Anesthesiologist Daniel I. Sessler, embarked on a study of hair color after listening to many of his colleagues comment that more anesthesia is required for their red-headed patients.

"The reason we studied redheads in the beginning, it was essentially an urban legend in the anesthesia community saying redheads were difficult to anesthetize. This was so intriguing we went ahead and studied it. Redheads really do require more anesthesia, and by a clinically important amount," said Sessler, MD, who also is chairman of the Department of Outcomes Research at the Cleveland Clinic.

Previous research has found that redheads require, on average, 20 percent more anesthesia than blonds or brunettes.

It was discovered that scarlet-tressed people were more often resistant to Novocaine or other local pain blockers, and it was common for redheads to be nervous about dental procedures, as well as twice as likely to skip going to the dentist than those with locks of brunette or blond.

Following the publication of his research, Sessler reported being contacted from other redheads who complained of fears going to the dentist and dental pain. That pain, researchers believe, is because of a mutation in a gene that is known to affect hair color. In those with blond, brown, or black hair, the gene for the melacortin-1 receptor, or MC1R gene, results in the production of melanin. However, a mutation in this gene produces pheomelanin, resulting in paler skin and a cherry mane.

Furthermore, it also has been found that carrot tops are more resistant to the effects of local anesthesia and other various numbing drugs that dentists use.

While this gene mutation can occur in darker-haired individuals, it is not a common occurrence.

Equal Success Rate With Different Bone Reconstruction Methods

Following autogenous bone grafting or distraction osteogenesis, endosseous implants do equally well, according to authors in a recent issue of the *Journal of Oral Implantology*.

After alveolar reconstruction, endosseous implants support and retain the prosthesis. Therefore, it is imperative for the method of alveolar reconstruction to be very compatible with the subsequent implantation. The authors, in a report in the September 2009 issue of the *Journal of Oral Implantology*, conducted a retrospective analysis to determine whether distraction osteogenesis or autogenous bone grafting offers a greater chance of clinical success.

Eighty-two consecutive patients from the patient population of Loma Linda University in a retrospective analysis of the two alveolar reconstruction techniques and the subsequent endosseous implantation were included in the authors' study. Every patient had been evaluated for implant success in a 36- to 61-month follow-up. There was a 97 percent success rate of implants preceded by autogenous bone grafts, and a 98 percent success rate of those preceded by distraction osteogenesis. There was no statistical difference between the two methods.

To read the entire article, "Implant Success in Distracted Bone Versus Autogenous Bone-Grafted Sites," go to 2.allenpress.com/pdf/orim-35-04-196-200.pdf.

Dexmedetomidine Hydrochloride: Has Propofol Met Its Match?

Dexmedetomidine hydrochloride may be useful for sedation in dental treatment, according to a new report published in the July–September 2009 issue of *Anesthesia Progress*, the publication of the American Dental Society of Anesthesiology.

Sedation is commonly induced with propofol, but use of this agent is often marked by high respiratory depression and the sedative actions are less sleeplike than is preferable. In an attempt to determine a reasonable alternative, the authors of the current study compared the effects of propofol with those of dexmedetomidine hydrochloride.

Fourteen patients scheduled for surgery at Matsumoto Dental University Hospital in Nagano, Japan, were randomly divided into two groups. One group received propofol, the other received dexmedetomidine hydrochloride.

Blood pressure, heart rate, arterial blood oxygen saturation, and the bispectral index were measured initially for control and then at prescribed intervals throughout the treatment. Patients also completed a questionnaire the day after treatment to determine memory presence or absence both at the injection of local anesthesia and at the start of treatment, and to determine the comfortableness of sedation.

No significant differences were noted between the two groups in any of the parameters; however, the group given dexmedetomidine hydrochloride was marked by hemodynamic changes, so close monitoring is recommended. Furthermore, evaluation methods other than the bispectral index must be developed because this method makes it difficult to evaluate intraoperative sedation levels.

To read the entire article, "Psychosedation With Dexmedetomidine Hydrochloride During Minor Oral Surgery," go to http://www2.allenpress.com/pdf/ANPR56.3FIN.pdf.

Smile Tokens by TokensDirect

Smile Tokens are an effective way to reward pediatric patients for taking care of their teeth through flossing and brushing, as well as for having good checkups. The tokens can be used to claim prizes or used in on-site machines such as video games or gumball dispensers. Smile Tokens can be easily customized with the practice name, logo, or other marketing message. For more information go to tokensdirect.com.

TRUST, CONTINUED FROM 761

Trust means voluntarily making oneself vulnerable with the anticipation of greater rewards from cooperation than are likely from noncooperation. Sometimes the anticipated benefit from trust is a greater reward. Sometimes the anticipated benefit from trust is reducing the cost of transactions.

The phrase "I trust him about as far is his self-interests extend" makes perfect sense. Mutual self-interest, rather than presumed altruism or a sense of fairness, is the correct basis for trust. When agreements benefit all parties concerned, they can be counted on to be adhered to. These are referred to as self-enforcing agreements. They make possible things that could not be accomplished alone; they smooth out the random irregularities in social intercourse; and they reduce the costs of making contracts, monitoring them, and paying third parties.

Self-enforcing, mutually beneficial interactions are one of the hot new areas in moral philosophy. These contractarian theories of ethics turn out to successfully predict human behavior and explain us at our best. They also help identify where things can go wrong. The best places to look for abuses of trust are deception, coercion, and reneging. The con game, which depends on an assumption of both trust and greed, works by appealing to unrealistic self-interests. A dentist would be unethical in the trust sense of the term if he or she deceived the patient regarding what work needed to be done, offered only some treatment alternatives (coercion), or changed the conditions of the treatment plan midtreatment. Patients could violate trust by misstating their health condition or financial condition, threatening suit over things that did not happen, or failing to pay for care.

The concepts of what is ethical and what is legal in dentistry are sometimes blurred. One way to distinguish them is to ask how much trust is involved. Legal settlements, even including arbitration in some cases, bleed all the trust out of the relationship. Ethics puts trust back in.

The nub:

1. Don't expect relationships to last if there is not something of value in it for each party.
2. High trust increases the size of the pie; low trust decreases it — no matter how it is divided.
3. Practice the skill of trust building.

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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HemCon Dental Dressings by HemCon Medical Technologies

HemCon Dental Dressings are designed to seal an oral wound and offer relief of pain after a tooth extraction, for soft tissue wounds, and more. These dressings are designed to stay in place with sealing properties without the use of sutures, are safe, effective on anti-coagulated patients without the use of medication, and the dressings provide a barrier for tissue pain relief and dissolve within 48 hours. For more information go to hemcon.com.

Children's Dental Health Focus of New Patient Forms by The Dental Record

The Dental Record has produced two new forms for new pediatric patients: a caries risk assessment form and a preventive recommendations form. The caries risk assessment form highlights possible risk factors through a series of questions that are to be completed by the parent and the dentist. The preventive recommendations form provides a step-by-step plan for the parent to implement to improve the child's oral health. For more information, call 800-243-4675, or go to dentalrecord.com.

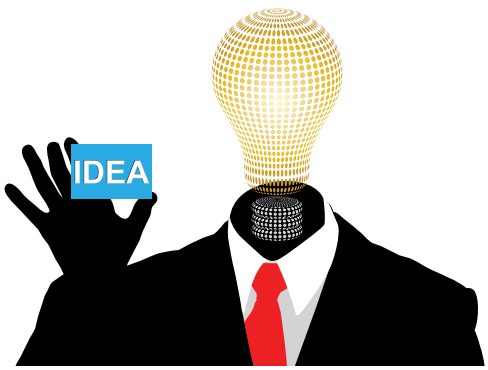
AGD Encourages Patients and Dentists to Work Together

The Academy of General Dentistry has issued an opinion to the American Academy of Implant Dentistry's advice that patients should elect not to save a tooth, but have an extraction and replace the tooth with a dental implant.

"It is important to note extracting a tooth and replacing it with a dental implant, while best for some, may not always be the best type of treatment for all patients," said David Halpern, DMD, FAGD, AGD president. "The state of oral health and the needs of each patient are unique as his or her fingerprint."

Last year, the AGD's House of Delegates issued a policy supporting dental implants as an accepted mode of treatment to replace a lost tooth. In 2009, the AGD's house passed guidelines for educational providers to use toward the development of curricula that will prepare dentists, regardless of generalization or specialization, to provide safe and appropriate dental implant treatment planning, placement, and restoration, according to a press release.

"In my practice, I encourage patients to save the natural tooth when possible," Halpern said. "Doing so can many times preserve the supporting bone, maintain the proper contacts to the adjacent and opposing teeth, and allow the patient to use the tooth for as many years as their other teeth. It used to be common practice to remove injured or diseased teeth. Maintaining a tooth through a root canal treatment can help people keep their natural teeth for life. Depending on your area that you live in, restoring and saving a tooth may cost less than replacing a tooth with a dental implant supported replacement."



Prototype Face Mask Makes Smile Visible, Improves Communication

San Francisco nurse Jeanne Hahne has designed a face mask made of cloth and clear plastic so that patients can see health care providers' most essential communication tool: their smiles.

Hahne, a nurse at California Pacific Medical Center, had the idea for the mask several years ago and recently took the time to make it a reality by designing the "ClearVision," a mask with cloth on the bottom half and clear plastic on top. It fits just like a regular medical mask, covering the nose and chin, with strings to tie in the back or loop over the ears.

"There are a lot of studies about what this portion of the face conveys. A lot is said in facial expressions," Hahne recently told the *San Francisco Chronicle* newspaper. "We like to see the smile and reassurance. Anxiety is decreased when you can feel connected to somebody."

The mask will be the subject of extensive studies to prove that it is as hygienic as the masks currently used by health care professionals. California Pacific Medical Center has already helped Hahne run some preliminary tests of the see-through face mask and so far, doctors, nurses and patients seem receptive. It is especially useful, she said, for young patients — children getting dental care seem particularly excited by the mask.

Hahne still needs a manufacturer for the mask, according to the *Chronicle*, but initial support for the product has been enthusiastic, especially from the deaf community. The mask is helpful when caring for patients who have some hearing loss.

Originally, Hahne's idea was geared toward easing patient anxiety, but now that doctors and nurses have actually tested the mask, a surprising aspect has emerged. The mask can help improve communication between health care workers because it's easier to see exactly what is being said when the mouth is visible.

Surgical Suites Refurbished at Dugoni School of Dentistry

The oral and maxillofacial surgery department at the Arthur A. Dugoni School of Dentistry hosted an open house recently to reveal its refurbished operatories and demonstrate its new video streaming capabilities.

The clinic, which underwent construction in May and was finished in mid-July, features expanded operatories that allow more space for students to view procedures, as well as permit wheelchair access. There also is a postsedation recovery area.

State-of-the-art audiovisual equipment has been installed in the surgical suites, including high-definition plasma screens and remote-controlled cameras, allowing for videoconference procedures to be televised to classes throughout the San Francisco campus or to record procedures to be used in continuing education classes.

From left to right are Bahram Javid, BDS, DMD, associate professor; Anders Nattestad, DDS, PhD, professor and director of Undergraduate Oral and Maxillofacial Surgery; Remy Lagman, a registered nurse; Rowena O'Connor, manager, Oral and Maxillofacial Surgery; A. Thomas Indresano, DMD, professor and chair, Oral and Maxillofacial Surgery; and Len Tolstunov, DDS, assistant professor.

Hospital-grade operating lighting, which is low maintenance since there are no bulbs to service, also was installed. The LED light source provides more than ample light for procedure yet without heat.

"Our whole department is very proud of this new state-of-the-art clinic and excited about the potential this gives us to treat patients and to educate students in a hands-on way," said Anders Nattestad, DDS, PhD, professor of oral and maxillofacial surgery. "This is a unique oral surgery facility among dental schools due, in part, to its technical and audiovisual capabilities. We're glad to see the new surgical suites open and in use to benefit our students and patients from the community."

The remodel was made possible, in part, through alumni and friends' support of the Dean's Fund for Excellence, the school's annual fund. This fund allows Dean Ferrillo the flexibility to enhance the institution and the opportunity to meet any challenges that arise without using student tuition, according to a press release. Nearly half of the funding was provided from a federal facilities improvement grant and special care funds, which were raised through the Pacific Center for Special Care, under the direction of Paul Glassman, DDS, MA, MBA, and Christine Miller, RDH, MHS, co-directors of the center. This money was raised for the purpose of improving oral health for people with disabilities who face multiple barriers in obtaining oral health care.

UPCOMING MEETINGS

2009	
Nov. 2–4	National Network for Oral Health Access National Primary Oral Health Conference, Nashville, Tenn., Luana Harris-Scott (619) 279-5879 or nnoha.org.
Nov. 8–14	United States Dental Tennis Association fall meeting, Scottsdale, Ariz., dentaltennis.org.
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.
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.

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.

Oral Health Care Project in the Works for Rwanda

A dentist in North Carolina is looking for adventurous and caring dental professionals for an outreach project in Rwanda.

Having completed a feasibility study on a successful model in Kenya, Richard T. Reckmeyer, DDS, MBA, would like to take the project west to help meet the demand for oral health care in Rwanda.

Reckmeyer met with Kigali Health Institute faculty, students and administrators. (The school is Rwanda's only dental facility.) He also met with other governmental officials and administrators of nearly a dozen community health centers in Musanze District as part of his feasibility study. The results were eye-opening. Following the 1994 genocide, in which 1 million people were killed in 100 days, oral health care is in high demand but scarce.

Some of the statistics, according to a press release:

- The ratio of oral health care providers to the total population of Rwanda is 155/10.5 million.
- Simple extractions are the second most common service (second to lower respiratory disease) in the community health centers in Gakenke District, Northern Province, Rwanda.
- For 987 patients, 95.5 percent of the oral health care needs in Nyabihu District, Northern Province, Rwanda, are simple extractions and basic cleanings.

Dental professionals and students interested in a life-changing experience can contact Richard T. Reckmeyer, DDS, MBA, at richard.reckmeyer@cox.net or 623-979-7555. More information can be seen at http://members.cox.net/richard.reckmeyer/RROHC.pdf.

Honors

Rachel R. Johnson, DDS, has passed the American Academy of Cosmetic Dentistry's accreditation written examination, the first step in the accreditation process. The program is for dentists and laboratory technicians that tests their foundational knowledge in cosmetic dentistry. The three-part process consists of written, clinical case, and oral exams, and each part of the process must be completed in sequence. Dentists and laboratory technicians have up to five to complete the process after passing the written exam.

Harold C. Slavkin, DDS, is the 2009 recipient of the American Dental Association's Gold Medal Award for Excellence in Dental Research.

The award honors individuals who have contributed to the advancement of the profession of dentistry or who help improve the oral health of the community through basic or clinical research.

"Dr. Slavkin's impact on public policy and dental research has been considerable," said John S. Findley, DDS, ADA immediate past president. "In addition to contributing substantially to the peer-reviewed literature, his exceptional national and international leadership has served to advance dentistry in countless ways."

Harold C. Slavkin, DDS

Anders Nattestad, DDS, PhD

Slavkin received $25,000 and a gold medallion at a formal presentation last month during the ADA's 150th Annual Session in Honolulu. He also can serve a three-year term on the ADA Council on Scientific Affairs.

Slavkin was dean of the School of Dentistry at the University of Southern California from August 2000 until his retirement in December 2008. Presently on sabbatical, he plans to return to USC next year to resume being part of the Center for Craniofacial Molecular Biology, of which he is founding director, and teaching in the graduate school and dental school.

The Arthur A. Dugoni School of Dentistry has named **Anders Nattestad, DDS, PhD,** as the school's director of Global Initiatives.

While continuing to maintain his current responsibilities as professor and director in the school's oral and maxillofacial surgery department, Nattestad will help manage and review opportunities for global partnerships and initiatives for the school, as well as work closely with the dean, administration, faculty, and students. Prior to joining the San Francisco campus, Nattestad was professor and head of oral and maxillofacial surgery at the University of Nevada, Las Vegas School of Dental Medicine. He previously held the position of chair of the department of oral and maxillofacial surgery at the University of Copenhagen, Denmark, where he also earned his DDS degree, PhD, and specialization in oral and maxillofacial surgery, according to a press release.

Additionally, Nattestad served the last 10 years on the executive committee for DentEd, an extensive European Union project, and served as secretary general of the Association for Dental Education in Europe for five years. He is fellow of the American Dental Education Association Leadership Institute, a reviewer for the *Journal of Dental Education* and the author of more than 40 published articles.

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DENTISTRY *and* MEDICINE— *A New Crossing Point*

FARIBA S. YOUNAI, DDS

GUEST EDITOR

Fariba S. Younai, DDS, is a clinical professor of oral medicine and orofacial pain in the Division of Oral Biology and Medicine at the University of California, Los Angeles, School of Dentistry.

This issue is dedicated to exploring some of the most important current areas of interaction between dentistry and the biomedical sciences. Each article focuses on one exciting topic in the realm of craniofacial and medical research and sets out to describe the latest findings in the field and their potential impact on oral health and care. Progress in the biomedical sciences is exponential, and increasingly, the translation of major discoveries into clinical practice is redefining the approach to patient care. As we gain more insight into the reciprocal relationship between systemic and oral health, the gap between medicine and dentistry fades and patient treatment needs to span both disciplines.

We, as dental professionals, must maintain great appreciation for our patients' medical conditions and treatments as they can significantly impact our oral health treatment decisions. Physicians must also be cognizant of the role of oral health, especially among their medically complex patients, in achieving optimal general health goals. In this issue, two articles present evidence for these congruent points. M.A. Vanderlinde and R. Mulligan in their article "Treating the Older Adult Dental Patient: What Are the Issues of Concern?" discuss several dental management issues in complex geriatric patients and present a diagnostic rubric for clinical assessment. They describe how, in geriatric patients with multiple diagnoses, attention to coexisting medical, psychosocial, and behavioral conditions are relevant to planning for dental care.

In his paper "Destructive Periodontal Disease, Systemic Inflammation and Atherosclerotic Complications," R.G. Craig describes the role of periodontal disease in chronic systemic inflammatory conditions. He reviews the compelling evidence for the association between periodontitis and chronic conditions such as diabetes, renal disease, rheumatoid arthritis and even Alzheimer's disease, and goes on to explain, in detail, the relationship between periodontal inflammation and atherosclerotic diseases.

Although oral health clinicians are fully educated on the medical issues of concern during their dental education, remaining current in the field is no small feat. However, today, more than ever, knowledge of latest medical advancements is critical and necessary to their ability to gather the appropriate information on their patients, to communicate with other medical and nonmedical providers, and to deliver safe patient care. Similarly, as physicians gain better

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understanding of the potential systemic roles of oral diseases, they seek professional expertise of dental professionals involved in their patients' care. This is especially true for chronic illnesses that require a lifetime of disease management and support. Our profession's readiness to accept this new and evolving relationship between medicine and dentistry is of paramount importance.

In their article "Oral Health and HIV Infection: a Chronic Disease Model," F.S. Younai and C. Vincent-Jones describe the latest medical discoveries in HIV disease management and provide an update for oral health implications of HIV infection. They describe the role of oral care providers in a spectrum of HIV care that is fully integrated into medical care, psychosocial support, and is outcome-based.

Finally, craniofacial research itself has expanded to a point where scientists in oral biological sciences are making remarkable contributions to other branches of science. Three articles describe examples of these types of scientific advancements. K. Gilmore, P. Chen, and K. Leung, in the article "Anti-Microbial Peptides for Plaque Control and Beyond," provide a comprehensive overview of the natural anti-microbial peptides found in the oral cavity and their protective role against oral infections. They further explore the potential application of these natural compounds in developing new preventive and therapeutic approaches to oral infections, to systemic bacteremia, and to infectious diseases.

A. Bhatt and A.D. Le's "Craniofacial Tissue Regeneration: Where Are We?" discusses the potential oral tissue sources for stem cells and how they are currently used, in experimental animal models, for dental and osseous regeneration. They also discuss the possibilities of tissue regeneration in humans using tooth-derived stem cells.

D.V. Messadi, P. Wilder-Smith and L. Wolinsky's "Improving Oral Cancer Survival: The Role of Dental Providers" critically examine several adjunctive diagnostic tools, some already in commercial use and some in development, in their effectiveness for diagnosing oral premalignant and malignant lesions. One of such approaches they discuss is the exciting field of salivary diagnostics and its broad application from early detection of precancerous oral lesions to diagnosing systemic conditions. They also introduce natural and pharmaceutical agents currently in chemoprevention trials for head and neck cancer and their more broad potential applications in cancer prevention.

The overarching goal of this issue is to present a wide range of topics across several disciplines and to reflect the ever-growing extension of our field into arenas such as medicine, basic sciences, and public health. All the topics discussed represent the evolution of a greater role for oral health providers in the biomedical field. ■■■■

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Destructive Periodontal Diseases, Systemic Inflammation, and Atherosclerotic Complications: The Emerging Role of the Dental Profession

RONALD G. CRAIG, DMD, PHD

ABSTRACT An emerging body of evidence has associated moderate to severe periodontitis with atherosclerotic complications. The contribution of periodontitis to systemic inflammation may account for this association in view of the pivotal role inflammation plays in atherosclerotic complications. Periodontal therapy has been shown to decrease systemic inflammation and to improve early atherosclerotic events; however, to date, periodontal therapy has not been shown to decrease subsequent atherosclerotic complications although aggressive treatment in at-risk populations appears warranted.

AUTHOR

Ronald G. Craig, DMD, PHD, is an associate professor, Department of Basic Sciences and Craniofacial Biology, Department of Periodontology and Implant Dentistry at New York University College of Dentistry.

Over the past two decades, an ever-increasing number of studies have reported an association between destructive periodontal diseases and atherosclerotic complications, including myocardial infarction and stroke.[1] In addition, destructive periodontal diseases have also been found associated, to varying degrees, with other chronic systemic diseases or conditions including type 2 diabetes mellitus, preterm low birth weight infants, chronic kidney disease, rheumatoid arthritis, and possibly Alzheimer's disease.[2-9]

These seemingly disparate chronic diseases are united by the discovery that increased systemic inflammatory burden is an underlying risk factor for all of these diseases. Of interest, destructive periodontal diseases, along with several other chronic infections and/or inflammatory conditions, have been shown to contribute to systemic inflammation and destructive periodontal diseases, although apparently decreasing in prevalence over the past decade mainly due to the decreased prevalence of smoking in the United States, are still relatively common in the adult population.[10-13]

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These findings, therefore, raise the question of what is the role, if any, for the dental profession in the prevention or management of these commonly encountered systemic chronic diseases?

To address this question, the intent of this paper is to provide an overview for the dental health care professional of the contribution of destructive periodontal diseases to systemic inflammation. Using reports primarily published within the last five years, emphasis will be placed on the role destructive periodontal diseases may play in atherosclerotic complications since the greatest body of evidence has been assembled for this oral-systemic disease association.

Specific questions to be addressed in this overview are:

- What is the strength of the association between destructive periodontal diseases and atherosclerotic complications?
- What biologically plausible explanations have been forwarded to account for this association?
- How may destructive periodontal diseases contribute to systemic inflammation?
- Can the treatment or eradication of periodontal diseases reduce the risk of subsequent atherosclerotic complications?

The significance to the dental profession, if destructive periodontal diseases are indeed shown to contribute to atherosclerotic complications, is that periodontal therapy may become a medically necessary component of care in the prevention and management of atherosclerotic complications in the future.

Destructive Periodontal Diseases Are Associated With Myocardial Infarction and Stroke — Strength of the Association

Despite recent advances in health care and prevention, atherosclerotic complications, including myocardial infarction, stroke, and thromboembolic events, continue to be a major cause of mortality in the United States. From 1995 to 2005, the national death rate due to cardiovascular diseases decreased by 26.4 percent. However, in 2005, the latest year complete data are available, the overall death rate from cardiovascular diseases was 278.9 deaths per 100,000 individuals, still a very prevalent rate of death. Preliminary data from 2006 also reports that cardiovascular diseases accounted for 34.2 percent of all deaths or for one of every 2.9 deaths in the United States.

PERIODONTAL THERAPY may become a medically necessary component of care in the prevention and management of atherosclerotic complications in the future.

Stroke accounted for one out of every 18 deaths.[14] These data highlight that although considerable progress has been made in prevention and management in the last 10 years, death from atherosclerotic complications continues to be a major public health concern in the United States. Therefore, the search continues for additional means to decrease mortality from atherosclerotic complications.

In addition to conventional risk factors for atherosclerotic complications that include age, gender, lipid profiles, hypertension, smoking, diabetes mellitus, exercise, body mass index, and family history, nonconventional risk factors such as periodontal diseases have been increasingly associated with atherosclerotic complications.[1] The initial reports of an association between periodontitis and atherosclerotic complications came from Scandinavia in 1989. Mattila and co-workers reported that oral infections including caries, periodontitis, periapical lesions, and pericornitis were more frequent in subjects with recent myocardial infarctions than in healthy populations.[15]

Syrajanen and co-workers reported poor oral health was more frequently found in subjects with recent strokes than in stroke-free controls.[16] Since 1989, an ever-growing body of evidence has linked periodontitis and atherosclerotic complications. Perhaps the most conclusive study to date is a comprehensive meta-analysis of prospective cohort studies, case-control studies, and prevalence studies.[17] In this report, a meta-analysis of five cross-sectional studies that included 17,724 subjects found the prevalence of cardiovascular disease to be 1.59 times greater (confidence interval of 1.33-1.91) in subjects with periodontitis than in those subjects without periodontitis.[17] This meta-analysis, encompassing several cross-sectional studies, suggests periodontitis is significantly, although moderately, associated with atherosclerotic complications. The clinical significance of these findings is that, since destructive periodontal diseases are treatable, they may comprise a reversible risk factor for atherosclerotic complications.

However, both adult periodontitis and atherosclerotic complications share several common risk factors including age, gender, BMI, smoking, diabetes mellitus, and socioeconomic status. Therefore, the possibility exists that the association between the two diseases may merely be due to common risk factors, also termed confounding factors. But this hypothesis fails to be supported by the results of prospective studies that suggest periodontitis may precede, and therefore, may contribute to atherosclerotic complications. A meta-analysis of five prospective cohort studies that together included 86,092 subjects reported subjects with periodontal disease, defined using a range of criteria,

were 1.14 times (confidence interval of 1.07-1.23) more likely to experience a subsequent cardiovascular disease event.[17] Five prospective case control studies from the same meta-analysis comprising 1,423 subjects reported a 2.22 times greater risk (confidence interval of 1.59-3.12) of a subject with periodontitis experiencing a subsequent atherosclerotic complication.[17] Therefore, results of prospective as well as cross-sectional studies support a positive, although modest, association between adult periodontitis and atherosclerotic complications.

It should be noted that a variety of factors can contribute to the variance observed in the results from the above cited studies, including the criteria used to define an atherosclerotic event and, perhaps more importantly, the criteria used to define periodontitis exposure. It has been suggested that periodontal indices such as pocket depth more strongly associate with acute serum markers, such as C-reactive protein and fibrinogen (discussed below), and that indices that record past periodontitis activity such as clinical attachment level and tooth loss more strongly associate with chronic markers, such as early signs of atherosclerosis such as arterial media thickness.[18]

In addition to atherosclerotic complications, periodontitis has also been reported to precede two additional chronic diseases: chronic renal disease and type 2 diabetes mellitus. A cross-sectional study of 5,537 subjects that participated in the Atherosclerosis Risk in Communities study, ARIC, found subjects with severe periodontitis to be twice as likely to have early renal insufficiency when compared to periodontally healthy controls.[19] An analysis of the third National Health and Nutrition Survey, NHANES III, found a positive association between the presence of periodontitis and edentulism with decreased renal glomerular filtration rate, a precursor of chronic renal disease.[20] A longitudinal study of Pima Indians found periodontitis to be predictive of death from both ischemic heart disease and diabetic nephropathy, and also to be predictive of overt nephropathy and end-stage renal disease in subjects with type 2 diabetes mellitus.[2,3]

In addition to chronic renal disease and type 2 diabetes mellitus, maternal exposure to periodontitis has also been associated with preterm, low birth weight infants.[5,6] Therefore, the question arises, what is the biologic mechanism responsible for the association between periodontitis and these chronic systemic diseases?

A LONGITUDINAL STUDY of Pima Indians found periodontitis to be predictive of death from both ischemic heart disease and diabetic nephropathy.

Elevated Systemic Inflammation Predicts Atherosclerotic Complications

Although several mechanisms have been forwarded to account for the association between periodontal disease and atherosclerotic complications, the contribution of moderate to severe periodontitis to systemic inflammatory burden is particularly attractive. Nearly half of the patients diagnosed with myocardial infarction and stroke do not present with the characteristic altered serum lipid profiles reported in the Framingham risk for cardiovascular disease studies. These lipid profiles include increased total cholesterol, low-density lipoprotein (LDL) and triglycerides, and decreased high-density lipoproteins (HDL). Therefore, clinical studies conducted in the past decade have expanded to examine other atherosclerotic risk factors such as increased systemic inflammation.[21] In sites of acute or chronic infection/inflammation, proinflammatory cytokines such as tumor necrosis-α (TNF-α), interleukin-1 (IL-1) and IL-6 are locally synthesized and released. If the local inflammatory response is particularly severe, the serum level of these proinflammatory cytokines also increases.

In response to infection/inflammation, the elevated level of proinflammatory cytokines, in turn, regulate the hepatic synthesis of a set of serum proteins, termed acute phase proteins. Acute phase proteins are thought to be a primitive host response to infection and trauma but have also been identified as risk factors for atherosclerotic complications. In particular, C-reactive protein (CRP), an acute phase protein and systemic marker of inflammation, has been identified as a major risk factor for atherosclerotic complications and supplements traditional serum lipoprotein profiles in the prediction of myocardial infarction and stroke.[22-25] Most importantly, statin therapy that decreased levels of CRP below 2 mg/l resulted in a decreased incidence of cardiovascular events and mortality in the 3,745-subject "Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction" study.[26] The results of this study suggest inflammatory processes play an active role in atherosclerotic complications.

Destructive Periodontal Diseases Contribute to Systemic Inflammation

Although systemic inflammation can arise from many sources, moderate to severe periodontitis has been shown to be associated with elevated serum CRP levels and an acute phase response. The initial observation of a positive association between serum CRP levels and the severity of periodontitis was reported in 2000 from an analysis of the NHANES III data.[27] Since 2000, a series of studies have focused on periodontitis and acute phase proteins,

especially CRP. A recent meta-analysis of 18 reports, culled from more than 448 reports in the literature, found a consistent positive association between elevated CRP and periodontitis.[28] Severe periodontitis, in addition to elevated CRP levels, has also been associated with hyperglycemia and altered serum lipid profiles consistent with an acute phase response.[29] Increased systemic markers of inflammation including CRP, IL-6, fibrinogen and TNF-α were found in patients with acute coronary syndrome and periodontitis, while the severity of coronary artery disease, as determined by the number of occluded coronary vessels at angiography, correlated with the number of missing teeth, clinical attachment loss, and total bacterial burden of *Porphyromonas gingivalis*.[30]

Periodontitis has also been found associated with early atherosclerotic events, such as atherosclerotic plaque progression. A study of 657 subjects without a history of myocardial infarction or stroke had levels of 11 periodontal pathogens measured by DNA hybridization. In addition, carotid intima-media thickness, IMT, an additional marker of atherosclerotic plaque progression, was measured by high-resolution ultrasound. The overall bacterial burden was found to correlate with cardiovascular IMT but no relationship was found for CRP.[31] It is therefore plausible that increased systemic inflammatory burden, contributed perhaps in part by destructive periodontal diseases, may increase the risk of subsequent atherosclerotic complications.

Effect of Periodontal Therapy on Systemic Inflammation and the Incidence of Atherosclerotic Complications

If destructive periodontal diseases in fact contribute to systemic inflammation and therefore increase the risk for atherosclerotic complications, effective periodontal therapy and the eradication of periodontal infections should decrease levels of systemic inflammation and the incidence of subsequent atherosclerotic complications. Recent reports have shown that effective periodontal therapy can decrease several markers of systemic inflammation and may also improve early pathologic events associated with atherosclerotic disease progression. Full-mouth extraction in patients with severe periodontitis has been shown to decrease levels of CRP, plasminogen activator inhibitor-1, fibrinogen, and total white cell counts, all systemic markers of infection/inflammation that have also been associated with atherosclerotic complications.[32]

RECENT REPORTS have shown that effective periodontal therapy can decrease several markers of systemic inflammation.

Aggressive, nonsurgical periodontal therapy, including the use of locally applied subgingival antibiotics, has been reported to decrease serum CRP levels in those subjects responsive to treatment.[33,34] Aggressive, nonsurgical periodontal therapy has also been reported to improve serum lipid profiles and to decrease systolic blood pressure.[35]

However, not all intervention studies have observed a decrease in CRP with periodontal therapy.[36,37] It should be noted that elevated systemic inflammation may arise from many sources including chronic diseases, such as rheumatoid arthritis, and commonly encountered conditions, such as obesity. Studies reporting a decrease in CRP after periodontal therapy have generally enrolled subjects that had severe periodontitis and elevated (>3.0 mg/L) CRP levels without other overt sources of systemic inflammation, such as elevated BMI. Studies that have shown a decrease in inflammatory markers with periodontal therapy have also followed rigorous maintenance and recall protocols.

Several periodontal intervention studies have also reported improvement in early pathologic events associated with atherosclerosis. Aggressive, nonsurgical periodontal therapy has been shown to decrease endothelial dysfunction, a systemic vascular disorder characterized by decreased local expression of vasodilators, particularly nitric oxide, and an overexpression of vasoconstrictors by endothelial cells.[38,39] Endothelial dysfunction has been identified as an early marker for atherosclerotic complications and is thought to reflect overall systemic inflammatory burden.[40]

As compelling as the results of the above studies appear, no studies to date have demonstrated that effective periodontal therapy can decrease the incidence of atherosclerotic complications. Several explanations may account for this. Periodontal intervention trials for atherosclerotic complications, such as myocardial infarction, are difficult and expensive to conduct. The low rate of incidence for atherosclerotic complications in the general population implies a large study population would need to be recruited and followed for extended periods of time to capture a significant number of cardiovascular events. In addition, an intervention study would need to focus on and recruit subjects with severe periodontitis who would also comply with aggressive periodontal therapy and maintenance and recall regimens. In addition, subjects recruited into the study would need to be free from other sources of inflammation such as rheumatoid arthritis and high BMI. Also, multiple risk factors have been identified for atherosclerotic complications of which periodontitis may be only a single factor. Since the strength of

the association between atherosclerotic complications and destructive periodontal diseases is modest, large subject numbers would need to be recruited in the face of the large number of confounding factors.

Conclusions

At present, evidence from a large number of clinical studies supports an association between destructive periodontal diseases and atherosclerotic complications. The association is greatest for moderate to severe periodontitis, but, overall, the strength of the association is modest. Several mechanisms have been forwarded to account for the association but the contribution of periodontitis to systemic inflammation is particularly attractive in view of the role inflammation plays in atherosclerotic complications in addition to several other chronic systemic diseases that are also associated with periodontitis.

Intensive periodontal therapy has been shown in several studies to decrease systemic markers of inflammation, such as CRP, as well as to improve early events associated with atherosclerosis such as endothelial dysfunction. However, to date, periodontal therapy has not been shown to decrease the risk of subsequent atherosclerotic complications in at-risk populations. Nonetheless, since destructive periodontal diseases are readily amenable to treatment, it appears prudent to remove this reversible risk factor from the array of risk factors for atherosclerotic complications that include myocardial infarction and stroke. ■■■■

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TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT

Ronald G. Craig, DMD, PhD, Department of Basic Sciences and Craniofacial Biology, Department of Periodontology and Implant Dentistry, New York University College of Dentistry, 345 East 24th St., MC 9436, New York, N.Y., 10010.

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Anti-Microbial Peptides for Plaque Control and Beyond

KATHERINE GILMORE, BS; PING CHEN, PHD; AND KAI P. LEUNG, PHD

ABSTRACT Anti-microbial peptides perform many functions in the oral cavity. They may provide protection against microbial pathogens, assist in oral biofilm control, and function as an important part of the innate immune system in response to local and systemic infection. Synthetic versions of these peptides may be useful to supplement natural anti-microbial peptides or as therapeutic agents.

AUTHORS

Katherine Gilmore, BS, is with the Microbiology Branch, U.S. Army Dental and Trauma Research Detachment, Walter Reed Army Institute of Research, Great Lakes, Ill.

Ping Chen, PHD, is with the Microbiology Branch, U.S. Army Dental and Trauma Research Detachment, Walter Reed Army Institute of Research, Great Lakes, Ill.

Kai P. Leung, PHD, is with the Microbiology Branch, U.S. Army Dental and Trauma Research Detachment, Walter Reed Army Institute of Research, Great Lakes, Ill.

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Multicellular organisms have developed many defenses against pathogenic microorganisms. Some of the most ubiquitous innate defenses are anti-microbial peptides, AMPs. These compounds are found throughout the animal and plant kingdom, suggesting that they have provided an evolutionary advantage, and, in some species, may be the only anti-microbial defense.[1,2] In humans, AMPs are found primarily within surfaces that contact the outside world, such as skin, eyes, the lining of the gut and lungs, and the oral cavity.[3-8] AMPs can protect these surfaces in cases where the physical barrier has been disrupted. For example, β-defensins and the human cathelicidin LL-37 protect against skin infections in psoriasis patients, burn patients, and inflammatory lesions in gingival tissue.[9-11]

To date, more than 900 different AMPs have been identified.[12] In addition to the inhibition of microbial growth, AMP functions include chemotactic activities, cytokine and chemokine induction, angiogenesis, endotoxin neutralization, and promotion of wound healing.[7] To carry out these functions, these peptides can interact with multiple targets, including toll-like receptors, lipopolysaccharide (LPS), and lipid II.[13] AMPs remain effective despite their longevity as anti-microbials, and the development of microbial resistance remains low.[14]

Though no causative link between oral disease and systemic disease has been firmly established, bacteremia originating in the oral cavity has been associated with many systemic problems, most notably bacterial endocarditis.[15] Poor oral hygiene and oral diseases, such as periodontitis, may increase these risks.[16,17] The correlation between natural AMP

FIGURE 1A. α-helix.

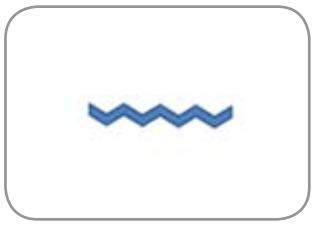

FIGURE 1B. Extended structures.

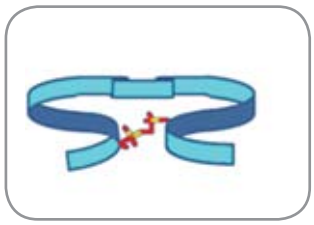

FIGURE 1C. Loop structure stabilized by disulfide bonding.

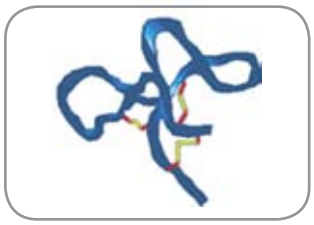

FIGURE 1D. β-sheets stabilized by disulfide bridges .

FIGURES 1A–D. Anti-microbial peptides and basic peptides structures. *Adapted from Weinberg A, Krisanaprakornkit S, Dale, BA, Epithelial anti-microbial peptides: review and significance for oral applications. Crit Rev Oral Biol Med 9(4):399-414, 1998. Copyright holder is SAGE Publications. Reprinted with permission from SAGE Publications.*

expression levels in the oral cavity and susceptibility to oral disease has been clearly demonstrated, though the disease process is extremely complex.[18-20]

A recent study showed that in children, increased expression of human neutrophil proteins (HNP) -1, -2, and -3, all in the α-defensin family of AMPs, was correlated with a decrease in dental caries, though there was no correlation between caries formation and the expression of other AMPs such as β-defensins or LL-37.[18] Other studies show that deficiencies in LL-37 are associated with severe periodontal inflammation and increased susceptibility to pathogenic microorganisms.[20] There is a great deal of variability in individual AMP expression, which may be under genetic control.[18] The use of synthetic AMPs to supplement natural peptides in patients with low expression levels warrants further investigation.

An increase in dental caries and periodontal disease has also been correlated with an increase in age.[18,19,21] As the patient's age increases, susceptibility to periodontal disease and dental caries increases.[18,19] Susceptibility to *candida spp* also increases with age. This correlates with a decrease in anti-microbial peptide expression.[18,22] This suggests AMP supplementation may help to decrease these risks.

In this review, the authors will describe various applications of some anti-microbial peptides, with special emphasis placed on the role of anti-microbial peptides in protecting the oral cavity.

Major Classes of Natural Human Anti-Microbial Peptides in the Oral Cavity

The vast diversity among AMPs makes them difficult to categorize except by their secondary structure. Most AMPs contain a net positive charge of +2 or greater and have an amphipathic design, with hydrophobic and cationic regions spatially segregated in different regions of the peptide.[12,14,23] This arrangement allows for either an α-helical or β-sheet secondary structure. Some linear AMPs, like magainin, only form these structures within a membrane or membrane-like environments. Most AMPs begin as larger precursors that are post-translationally modified through glycosylation, proteolytic processing, amino acid isomerization, or carboxy-terminal amidation. Though sequences are rarely similar between species, there is significant conservation within a species, further highlighting the evolutionary importance of these molecules.[14,23]

In the oral cavity, it has been hypothesized that AMPs expressed by oral epithelial cells create a chemical barrier that prevents oral pathogens from taking hold.[7,24] Saliva is critical to the protection gained through AMPs as it protects and transports the peptides to gingival tissue, and particles in saliva can promote AMP activity.[9,24,25] Some of the more commonly expressed AMPs are human cathelicidins, histatins, and α and β-defensins (hBd).[24] Basic AMP structures are illustrated in **FIGURE 1**.

Cathelicidins

The only human AMP in the cathelicidin family is the human cathelicidin anti-microbial protein hCAP18, which consists of two regions: the conserved prodomain, cathelin, and the nonconserved C terminal peptide. After hCAP18 is secreted, the active portion in the C terminal region known as LL-37 is cleaved.[26-28] LL-37 has a +6 charge and is amorphous in aqueous solutions, but folds into an α-helical structure in a nonpolar environment, such as that found in the lipid membrane.[27] LL-37 has been detected on the tongue, buccal mucosa, and in saliva in response to the presence of bacteria.[18] Expression of LL-37 can also be stimulated through exposure to vitamin D and in response to trauma.[27] Like many AMPs, LL-37 was originally studied for its anti-microbial properties, but since has been shown to be multifunctional.[4,28] These functions include chemotaxis, chemokine induction, angiogenesis, regulation of immune response, and wound healing activities.[27]

Histatins

Histatins are another group of AMPs that are expressed in the oral cavity. They are characterized by histidine-rich homologous amino acid sequences, and contain multiple arginine and lysine residues, giving the peptides a basic nature.[29,30] Histatins are expressed in saliva from the submandibular and sublingual parotid glands. In healthy adults, histatins are present in ranges from 50 to 425 μg/ml.[31] These peptides are a part of the acquired pellicle and have been shown to inhibit

the growth of oral pathogens such as *Porphyromonas gingivalis, Streptococcus mutans,* and *Candida albicans*.[29] Histatins may be an important part of natural protections against fungi and dental caries.[22,32]

α-Defensins

α-defensins are a large subfamily of cationic AMPs that are rich in arginine and effective against a variety of bacteria and fungi. They are characterized by three-stranded, anti-parallel β-sheets stabilized by six cysteine residues forming three disulfide bonds. These peptides are the most prevalent protein in human neutrophils and are expressed by neutrophils as part of a nonoxidative anti-microbial mechanism during an inflammatory response.[18,33] They are usually 29-36 amino acids (aa) long and are stored in their preproform (93-95 aa long) in neutrophils since the mature peptide is cytotoxic to many host cells. α-defensins are usually expressed in tissue distinct from those that express β-defensins, suggesting a different role in host immunity. It has been speculated that α-defensins evolved to work intercellularly, while β-defensins were evolved to be secreted locally.[9]

β-defensins are short, cationic peptides with a β-sheet structure and two to three disulfide bridges.[9] They are expressed along the surface of oral stratified epithelia in gingival tissue and are known for their anti-microbial properties.[34,35] Ten forms of β-defensins (hBD-1-10) are found in the oral cavity.[36] hBd-1, which ranges from 36 to 47 aa in length, is continuously expressed by oral epithelial cells. In contrast, hBD-2 (41 aa in length) and hBD-3 are expressed in response to specific microorganisms and proinflammatory cytokines.[34,36,37] While all forms are detected in response to inflammation, hBD-3 is the primary defensin induced by periodontal disease.[36]

There appears to be a great deal of heterogeneity in the basal expression of hBDs, and studies suggest that some individuals may be genetically predisposed to express a higher basal level of hBDs, making it easier to maintain mucosal and gingival health.[35,26] When hBD levels were compared between healthy and diseased gingival tissues, lower levels of hBD-2 and hBD-3 were expressed in diseased tissues. Likewise, lower levels of hBD-2 were detected in the saliva of individuals with candidiasis.[36] hBDs can act as chemoattractants for T cells and may also stimulate the acquired immune response through the activation of dendritic cells via the CCR6 receptor.[35,36,38]

Synthetic Anti-Microbial Peptides

Biologically active natural AMPs have several challenges to overcome before they can be used for clinical treatments. Native peptides tend to be expensive to manufacture and are often easily degraded. Many of them are also toxic in their active form.[7,12,39] To overcome these issues, synthetic AMPs are being designed.[40] Synthesizing peptides also allows the flexibility to modify the properties of natural peptides to increase their anti-microbial and other biological activities.[41] For example, by increasing the amphipathicity of the native histatin 5 in the synthetic peptide Dhvar 5, the anti-fungal activity is increased.[26,41]

Two methods for developing potential anti-microbial peptides are the derivation of peptides from combinatorial libraries and construction based on sequences from the active regions of naturally occurring anti-microbial peptides.[26,41,42] The authors' laboratories used a synthetic peptide KSL (KKVVFKVK-NH2) developed by combinatorial chemistry and its analog, KSL-W (KKVVFWVK-NH2), as anti-microbials.[42] These peptides demonstrated activity against selected oral and nonoral pathogens, fungi, herpes simplex virus type 1 (HSV-1) (personal observation), and oral biofilms.[42-45] Other examples of AMPs developed from combinatorial libraries include the dermaseptin derivatives S4(1-15) and NC12-S4(2-15).[46] A recent example of synthetic peptides derived from natural AMPs is a 12-amino-acid histatin-based peptide (P-113), formulated in a mouthrinse that was tested in humans with experimental gingivitis. A significant reduction in bleeding on probing was reported in treatment groups.[47] Other examples include the lactoferricin hLF-1-11, magainin analogs MSI-751 and MSI-774, and protegrin IB-367.[33,46,48] By using synthetic AMPs, it may be possible to supplement natural peptide action, especially in patients with increased risk of caries and oral diseases.

AMP Activity Against Pathogens

Mechanisms of Action

AMP responses to a bacterial challenge can take place very quickly, often within a few hours, and in many cases, the killing time of bacteria by peptides occurs in minutes.[42] One of the most characterized AMP killing mechanisms against bacteria is its selective membrane-lytic action. Multicellular eukaryotic membranes are less affected by AMPs due to the neutral charge on the headgroups of the majority of lipids facing the outer layer, while most of the negatively charged headgroups are segregated to the inside leaflet of the membrane. Cholesterols also help with stabilization of the membrane and may interact with lipids to prevent AMP integration into the cell membrane, further protecting the eukaryotic cells from AMP action.[14,49]

In bacterial membranes, the outer membrane layer is rich in negatively

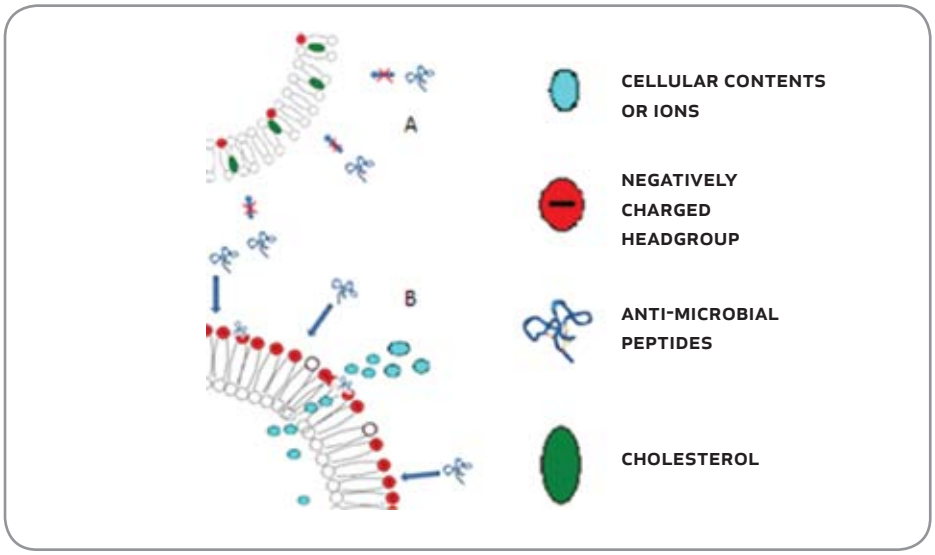

FIGURE 2. Perturbation of cellular membranes by AMPs. AMPs are unlikely to interact with mammalian cells because the majority of negative charge is sequestered to the inner leaflet. Cholesterols also stabilize the membrane **(A).** Bacterial cell membranes carry a negative charge, allowing the interaction with positively charged AMPs, leading to membrane perturbation and leaking of cellular contents **(B)**.

charged phospholipid headgroups, giving the membrane an overall negative charge. This negative charge allows for electrostatic interactions between the bacterial membrane and the positively charged AMPs. Hydrostatic interactions (a combination of hydrophilic and hydrophobic interactions) between the peptide and the membrane can also occur.[2,14] These interactions are demonstrated in **FIGURE 2**. Interactions between AMPs and bacterial membranes can result in the displacement of the lipids, disruption of the membrane layer, or, sometimes, the entry of the peptide into the bacterial cell. This can lead to cell death through membrane depolarization, degradation of the cell wall, development of a physical hole in the membrane, and disturbance of normal membrane functions. In some cases, peptides will enter the cell and damage critical internal macromolecular structures.[14,49]

Microbial Resistance

Bacteria are often able to adapt to conventional antibiotics and develop resistance.[50,51] It has been reported that bacterial resistance to AMPs is less prevalent. This is perhaps due to the needs of the target bacteria to restructure the membranes, a potentially highly energy-dependent process, in order to resist the mechanical actions of the peptides.[14] For example, multiple passages in growth medium containing one-half the minimum inhibitory concentration, MIC, value of protegrins did not induce resistance in methicillin-resistant organisms, though these organisms did develop resistance to antibiotics such as gentamycin and norfloxacin after a similar number of passages.[9,13] Likewise, using a similar procedure, the authors tested the microbial resistance induced by a synthetic peptide KSL-W against *S. mutans*. The MIC of KSL-W did not change after 15 passages (personal observation).

While AMPs have a low propensity in inducing microbial resistance, some species of bacteria can demonstrate resistance to AMPs. For example, species such as *P. gingivalis* can secrete digestive peptidases that degrade the peptides.[14] Additionally, some species of gram-negative bacteria can develop resistance to peptides by decorating the outer membrane with positively charged moieties of 4-amino-arabinose and ethanolamine. This leads to a collection of a positive charge along the outer membrane, making it more difficult for AMPs to target the bacteria.[14]

Bactericidal Activity Against Oral Pathogens

It has been demonstrated that hBD-1 and hBD-2 are primarily effective against gram-negative oral bacteria, such as *Fusobacterium nucleatum*, while hBD-3 is more effective against gram-positive oral bacteria. The proposed mechanisms of action are pore formation and disruption of target bacterial membrane.[52] Genco et al. demonstrated that analogs of magainin, MSI-751 and MSI-774, possess strong antimicrobial activity against gram-negative anaerobic pathogens, including *P. gingivalis, F. nucleatum, Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), *Eikenella corrodens, Prevotella loescheii,* and *P. intermedia.*[48] In the authors' laboratories, they demonstrated that peptide KSL exhibits strong bactericidal activity against *S. mutans* and other cariogenic oral microorganisms including *S. sobrinus* and *Lactobacillus acidophilus.*[43]

Clinical Relevance

At present, there are several candidate anti-microbial peptides such as hLF-1-11 (a small peptide derived from human lactoferrin) in commercial development as anti-infective agents. Several other candidate peptides such as plectasin, HB-107 (19-amino-acid fragment of cecropin B) are in the preclinical stage of development for use in wound healing and the treatment of systemic infections.[33] The commercial development of peptides for use in controlling oral bacterial infections is limited.

One synthetic peptide, IB-367, a peptide derived from protegrin, has been in commercial development and

testing for treating oral mucositis.[46] Another study shows that the exogenous application of a gel (P-113) consisting of the 12-amino acid active region of histatin 5 significantly inhibited gingivitis in beagles, and maybe also in humans as measured by bleeding on probing.[29]

AMP Activity Against Oral Biofilms

Dental caries and periodontal diseases are clearly associated with the accumulation of oral biofilms.[21,53,54] It was hypothesized that uncontrolled growth of certain resident microbes or shifts in microbial composition due to changes of oral environment that favor the emergence of pathogenic bacteria in oral biofilms results in the development of diseases.[55,56] In fact, in germ-free animals, periodontitis and gingivitis do not occur. These disease conditions do occur in the presence of the biofilms and subside when biofilm accumulation is removed or when growth is under-controlled.[54] Oral bacteria associated with pathogenic oral biofilms, including cariogenic *S. mutans, S. sobrinus,* and *lactobacillus*, are essential for the development of caries.[21]

Other pathogens in biofilms, such as *A. actinomycetemcomitans*, have been associated with localized aggressive periodontal disease, while *P. gingivalis* is an oral pathogen associated with severe gingivitis and periodontitis.[18,54] Prevention strategies include the use of anti-microbial agents for biofilm growth control or interventions that could alter environments to prevent the emergence of pathogenic organisms in oral biofilms.

Oral Biofilm Development

Human oral biofilms are multispecies microbial communities formed on oral tissues of shedding and retentive surfaces.[57-59] They are highly structured and spatially organized.[58] Biofilm cells are embedded within a complex, extracellular matrix that is adhered to a surface.[32,44,60] Human oral biofilms are composed of an estimated 500 bacterial species and are formed through many steps.[53] First, the tooth must acquire a pellicle, a film derived from saliva consisting of various salivary proteins. Many of these proteins, such as proline-rich proteins and statherins, serve as host-derived receptors that make it possible for primary colonizers to attach to the tooth surface.[53,61,62]

AMPS CAN BE USED to either prevent bacterial colonization at early stages of biofilm development or to reduce the load of biofilm formed at later stages.

In addition, salivary mucins and agglutinins, such as glycoprotein gp340, also adsorb to soft and hard tissue surfaces in the oral cavity and serve as receptors for the adhesion of early colonizers such as *streptococcus* and *actinomyces*.[63] *F. nuleatum* binds to the primary colonizers and acts as a bridge between primary colonizers and other bacteria such as *P. ginigvalis* and *Prevotella spp*.[61] The adhered bacteria proliferate and develop into mature microbial communities.[44,64] As the biofilm develops, the composition of the biofilm changes, with environmental conditions dictating the bacterial species present. Often, the proximal surfaces and fissures are dominated by gram-positive, acid-tolerant, facultative anaerobic species, while in the gingival crevice, biofilms are dominated by gram-negative obligate anaerobic bacteria.[53]

Treatment of Oral Biofilms

Biofilms present unique treatment challenges because cells embedded within the matrix tend to be less biologically active, making them 100 to 1,000 times more resistant than planktonic (free-living) bacteria to small-molecule antibiotics that generally target growing bacteria.[60] The matrix also structurally protects the bacteria by shielding cells from contact with treatments, reducing the diffusion of anti-microbials, and facilitating cell-to-cell signaling. Phenotypic adaptations also arise in response to attachment, such as changes in fatty acid and phospholipid composition of bacterial cell envelopes and the presence of persister cells.[32,65]

Control of biofilm growth through good oral hygiene has been traditionally associated with the prevention of caries and subginigval plaque-induced periodontal diseases.[53,66] Mechanical control of biofilms through toothbrushing is the most common form of oral hygiene. While brushing and flossing are effective in removing the bulk of oral biofilms from tooth surfaces, areas that are difficult to reach by mechanical removal are where most oral inflammation occurs. The problems are further compounded by individual behavior and motivation for practicing oral hygiene, prompting investigation into the chemical control of biofilms to supplement mechanical control.[53]

AMPs can be used to either prevent bacterial colonization at early stages of biofilm development or to reduce the load of biofilm formed at later stages.[67,68] When treating oral biofilms, it is important to control rather than eliminate the biofilms. Normal flora makes up the majority of the biofilm and plays a role in host defense by colonizing surfaces and excluding pathogens. Therefore, biofilm homeostasis is the desired outcome of treatment.[7,64] Naturally

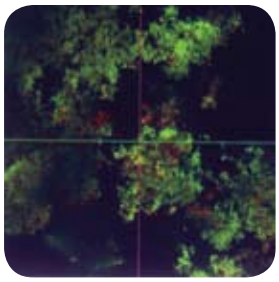

FIGURE 3A.

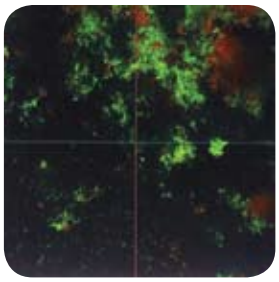

FIGURE 3B.

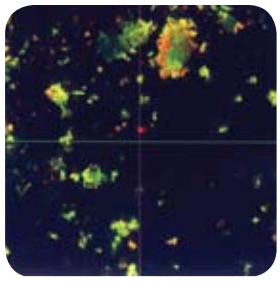

FIGURE 3C.

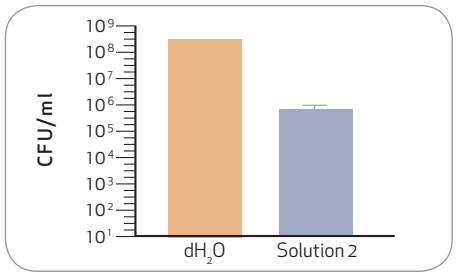

FIGURE 3D.

FIGURE 3. Synergistic effects of KSL-W and CPC. Unstimulated saliva was collected, and salivary bacteria was isolated and seeded onto saliva-coated hydroxyapatite discs as previously described.[43] Discs were treated after approximately 44 hours, 50 hours, and 67 hours of growth with treatment solutions. After the third treatment, discs were stained with Live/Dead BacLight Bacterial Viability Kit (Molecular Probes L7012), rinsed, and then imaged using a confocal microscope at 40X magnification. Biofilms were treated with **(A)** dH_2O], **(B)** 200 µg/ml KSL-W, or **(C)** KSL-W at 200 µg/ml and CPC at 0.0025 percent. CFU counts **(D)** demonstrated a significant ($P<0.001$) reduction in live cells between discs treated with a combination of 200 µg/ml KSL-W and 0.0025 percent CPC compared to discs treated with dH_2O over nine experiments. Statistical analysis of data was performed using a student's t test (two-tailed) with P value set at $P<0.05$.

expressed AMPs show selectivity in this area. Some pathogenic bacteria, such as *F. nucleatum* and *P. intermedia*, have a high susceptibility to AMPs, while some bacteria of the normal oral flora, such as some strains of *S. gordonii* and *Actinomyces naeslundii*, exhibit only weak susceptibility, suggesting that AMPs act to promote biofilm homeostasis. This suggests that AMPs show promise as therapeutic adjuncts used in the control of oral biofilms.[69]

Clinical Relevance

Histatin 5 and some of its derivatives such as Dhvar 5, as well as other synthetic peptides like KSL and its analog KSL-W, have been shown to reduce oral biofilms in vitro.[32,44,45]

The incorporation of the histatin-based peptide, P-113, in a mouthrinse for plaque control and treatment of gingivitis has been tested in a phase II multicenter study. The results indicated that P-113 mouthrinse is safe and reduces the development of gingival bleeding, gingivitis, and plaque in the human experimental gingivitis model.[47] The authors' laboratories have used the combination of KSL-W and cetylpyridinium chloride, CPC, to demonstrate a synergistic interaction against oral biofilms in vitro, with CPC serving as a surfactant and the peptide serving as an anti-microbial.

A reduction in live bacteria was confirmed by CFU count and confocal microscopy[45] (**FIGURE 3**). This is demonstrated in **FIGURES 3A-D**. A smaller amount of bacterial DNA was also recovered from treated oral biofilms grown on saliva-coated discs, with 1.3 µg per formulation treated disc compared to 15.6 µg per disc treated with distilled water. KSL-W and CPC have been incorporated into a gum formulation, and it is hypothesized that the mechanical actions of chewing will help to break up the biofilm, making bacterial cells more available for contact with the anti-microbials.[45,70,71]

At present, the longitudinal studies using AMPs, naturally occurring or synthetic, for caries control are lacking. The role of AMPs alone, or in conjunction with other treatment agents for active reversal of early caries lesions, has not been determined. While AMPs hold promise, there are potential limitations that must be overcome, such as safety, stability, and costs associated with the use of peptides as therapeutic adjuncts for promoting oral health.

AMP Activity Against Fungi

Candidiasis is the most common form of fungal infections. Fungal infections in humans tend to be opportunistic, infecting primarily those with suppressed immune systems.[1,31] In the oral cavity, denture-induced stomatitis, caused by microbial colonization of the denture surface, affects the palatal mucosa in greater than 50 percent of denture wearers. This infectious disease is prevalent among prosthesis users, particularly the elderly and institutionalized.[72] Treatment of this clinical condition is problematic due to incomplete disinfection of the acrylic surface and rapid microbial recolonization.

This constitutes an important concern in this population. Oral candidiasis might also be manifested in patients with xerostomia or patients undergoing chemotherapy, radiation therapy, and other treatments.[73] Clinical treatment can be difficult as both mammalian cells and fungal cells are eukaryotic, making selectivity difficult, and many anti-fungal drugs can be toxic. This means that there are limited anti-fungal drugs available, and resistance is quick to develop. Investigations into AMP actions against fungi have been performed in the hope of developing new anti-fungal drugs.[1]

Mechanisms of Action

Membrane perturbation is one of the mechanisms that AMPs use against fungi. Another proposed mechanism is that some AMPs may kill fungi in an energy-dependent manner.[39] Histatins have been one of the most characterized naturally occurring anti-fungal peptides, and have been shown to be effective against *Candida albicans* and other oral fungal pathogens without toxic effects to humans.[74,75] Histatins can interact with target fungal mitochondria, leading to the release of cellular components and cell death.[41,76]

Blocking mitochondrial activity leads to complete resistance of fungi to histatin

5, suggesting the activity of histatin 5 is dependent on the metabolic state of the fungal cell.[76] β-defensins show a similar mechanism of action and in one study, *C. albicans* was killed in an energy-dependent manner, but the peptide did not cause membrane perturbation.[39] Histatins and β-defensins cause small membrane defects to allow their entry into the cell. In contrast, LL-37 can severely affect membrane morphology, causing the membrane to break up into discrete vesicles and resulting in an almost instantaneous release of cellular contents.[77] Many of these anti-fungal activities exhibited by AMPs are salt or ion sensitive.[39,78]

The overlap of killing function, but difference in killing pathways demonstrated by histatins, β-defensins and LL-37 against *Candida spp,* suggests how natural AMPs in the oral cavity can work together to overcome fungal challenges in a variety of oral environments.[31,39,76,77] This also suggests how the supplementation of natural peptides with synthetic peptides can further support natural anti-fungal activities in patients with depressed immune systems, individuals prone to denture-induced stomatitis, and other patients with increased risks.

Clinical Relevance

There are a limited number of products using AMPs in the treatment of oral candidiasis. At present, an anti-microbial peptide PAC113, based on the active segment of histatin 5, is in commercial development for treating oral candidiasis.[33]

AMPs Activity Against Viruses

There are several families of viruses associated with the oral cavity including herpes viruses, papillomaviruses, picornaviruses, and retroviruses. They are most often associated with oral ulcers and erosions, and can also be associated with oral cancers, sialadentitis, and destructive periodontitis. The role of viruses in oral diseases is not fully understood, though there appears to be a synergy between periodontal herpesvirus infections and periodontopathic bacteria.[79] Herpes viruses may create conditions that favor bacterial infection through the suppression of the immune system or by generating new bacterial attachment sites in infected cells. Periodontopathic bacteria may also facilitate viral replication, possible through suppression of interferon-γ, which can act to suppress viral reactivation from latency, facilitate cell apoptosis, and inhibit viral replication. This synergistic interaction could be a critical component of oral pathosis, especially in periodontitis.[79]

Mechanisms of Action

Anti-viral effects of AMPs have been demonstrated against herpes simplex virus type 1 (HSV-1), one of the most prevalent oral viruses, and other enveloped or adenoviruses.[25,26,41,80,81] The mechanisms of these anti-viral activities are not as well understood as those of anti-bacterial and anti-fungal activity. Some molecules, like magainin, appear to have direct inhibitory effects against HSV-1 particles, while others, like polylysines, appear to competitively bind to virus receptors on host cells.[41,81]

Membrane depolarization caused by AMP formation of ion channels as seen in bacteria is not likely to take place in viruses because viral envelops do not maintain membrane potential. Other membrane disruption interactions with viricidal effects may be in play.[81] Defensins and synthetic histatins have been shown to directly inactivate HSV-1 and -2 through virolysis.[5,41] Another mechanism could involve the inhibition of the long terminal repeat promoter, which promote the expression of host pattern recognition receptors in the viral particle, and many studies show that AMPs can inhibit viral reproduction.[33,41]

AMPs can also yield protection against viruses through activation of the adaptive immune response. This is illustrated by LL-37, which can trigger plasmacytoid dendritic cells to release type 1 interferons through the activation of toll-like receptors.[82] Toll-like receptors are transmembrane proteins that recognize pathogen-associated molecular patterns in unique microbial features such as lipids, peptides, carbohydrates, and nucleic acid structures. Activation of toll-like receptors initiates the transcription of genes that regulate the inflammatory response to include the expression of defensins.[83]

Clinical Relevance

To the best of the authors' knowledge, there is no commercial development of AMPs for use in treating viral infections. A study done by the authors' laboratory has shown that synthetic peptide KSL-W may display anti-viral activities. Both a viral plaque reduction assay and quantitative PCR (qPCR) experiments, which quantify viral plaques and viral DNA, respectively, demonstrated that KSL-W shows significant anti-viral activity against HSV-1. With test concentrations ranging from 0 to 500 μg/ml, anti-viral activity was shown in an apparent dose-dependent manner in both assays. Data for these qPCR assays is summarized in **FIGURE 4**.

Although it has been shown that many AMPs have anti-viral effects, it is possible for AMPs to have adverse effects to the host. Groot et al. described a histatin 5 derivative, Dhvar 2, that may destabilize the HIV viral envelope, facilitating viral envelope and the host cell membrane fusion, and promoting viral entry into the cell up to 30-fold.[41]

Other Effects of AMPs

In addition to directly killing or inhibiting oral pathogens, AMPs play an important role in innate immunity in the oral cavity, and may have systemic effects by

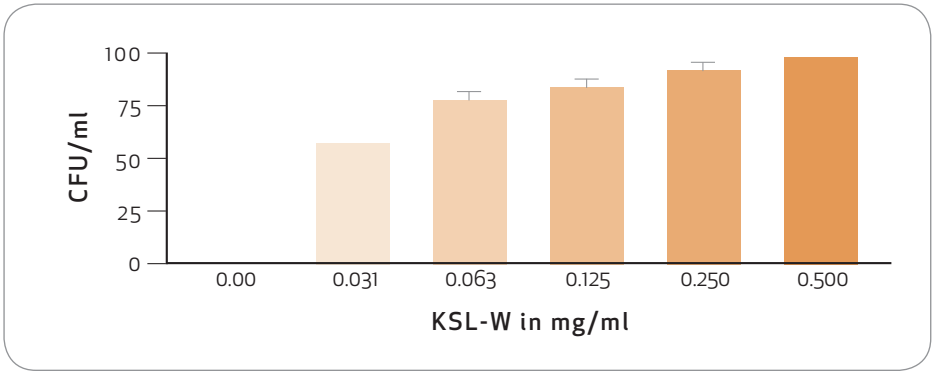

FIGURE 4. This figure represents the average data from four experiments that demonstrates possible anti-viral effects of the synthetic peptide KSL-W. Vero cells (ATCC CCL-81) were grown to a confluent layer in 24-well plates in Minimal Eagle Medium (MEM) supplemented with 10 percent fetal bovine serum (FBS). The supernatant was removed, and MEM supplemented with 2 percent FBS and containing viral particles and treatment solutions (inoculation medium) was added. KSL-W concentrations ranging from 31.25 µg/ml to 500 µg/ml were used in this experiment. Heparin was used as a control. Plates were incubated for one hour, then inoculation medium was removed and replaced with MEM containing 2 percent FBS and 0.8 percent agar (overlay medium). Plates were incubated for three days. After incubation, overlay medium was removed and qPCR analysis was done to quantify viral DNA. A significant reduction in the amount of viral DNA was shown in all treatment groups ($P<0.001$). Primers and probes used for qPCR were described by Hudnall et al.[94]

reducing bacteremia originating in the oral cavity. Human gingival tissues are responsible for secreting many of the natural AMPs. Some of the triggers for AMP expression and activity are inflammatory mediators, tumor necrosis factor-α, the presence of microorganisms, or through injury.[84]

AMPs display a variety of activities during inflammation. They can both stimulate and suppress the inflammatory response. Proinflammatory activities include stimulation of the production and release of several cytokines and chemokines. They also suppress expression of inflammatory mediators that are induced by endotoxins, including tumor necrosis factor α and the nuclear translocation of NF-κB subunits and stimulate cellular recruitment.[20,28,80,85] AMPs can also directly bind to and neutralize LPS.[85] In this manner, AMPs act as mediators to regulate and balance the inflammation response.

By using AMPs to promote good oral hygiene, it may be possible to help prevent bacteremia originating in the oral cavity. Though a causative link has not firmly been established, bacteremia due to the introduction or oral commensual bacteria into the bloodstream has been associated with cardiovascular diseases, such as bacterial endocarditis, and atherosclerosis and stroke, pulmonary diseases, such as aspiration pneumonia, low birth weight and preterm birth in pregnant patients, and systemic infections, such as disseminated candidiasis and septicemia.[15,17,86-89]

Transient bacteremia can be induced by dental procedures such as tooth extraction, and oral surgery, and there is growing evidence that everyday activities such as chewing and toothbrushing can induce bacteremia, especially in patients with periodontitis.[16,90] The use of antibiotic prophylaxis during invasive dental procedures is currently recommended, which can lead to bacterial resistance to antibiotics.[15] Increasing importance is being placed on factors associated with good oral health and hygiene.[17] Supplementing oral hygiene practices with AMPs may help to reduce the risks associated with bacteremia.

Conclusions

The scope of AMP action is complex and not yet fully understood. They form a chemical barrier to protect the host from bacterial, fungal, and viral pathogens; help to control the growth of oral biofilms; and may help to reduce the occurrence of dental caries and periodontal disease. By promoting good oral health and hygiene, the use of AMPs may also reduce the risks associated with bacteremia. AMPs play a crucial role in selectively upregulating the innate immune system and can also trigger adaptive immune responses. Using AMPs therapeutically faces many challenges, including cost of production, stability, and potential toxicity. To date, there are many AMPs being investigated for use in therapeutics, though there are none currently commercially available.

Our understanding of the roles AMPs play in the oral cavity is constantly expanding, and recent review articles have been written describing the roles of AMPs in oral cancer, wound healing, and the possibility for use as diagnostic agents.[91-93] Though caution is warranted, the study of natural and synthetic AMPs in the oral cavity, and the possibilities presented for use as supplements or therapeutics, remains an exciting and hopeful endeavor. ■■■■

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TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT Kai Leung, PhD, Microbiology Branch, U.S. Army Dental and Trauma Research Detachment, Walter Reed Army Institute of Research, 310B B St., Bldg. 1-H, Great Lakes, Ill., 60088.

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Improving Oral Cancer Survival: The Role of Dental Providers

DIANA V. MESSADI, DDS, MMSC, DMSC; PETRA WILDER-SMITH, DDS, PHD; AND LAWRENCE WOLINSKY, DDS, PHD

ABSTRACT Oral cancer accounts for 2 percent to 4 percent of all cancers diagnosed each year in the United States. In contrast to other cancers, the overall U.S. survival rate from oral cancer has not improved during the past 50 years, mostly due to late-stage diagnosis. Several noninvasive oral cancer detection techniques that emerged in the past decade will be discussed, with a brief overview of most common oral cancer chemopreventive agents.

AUTHORS

Diana V. Messadi, DDS, MMSC, DMSC, is with the Division of Oral Biology and Medicine at the University of California, Los Angeles, School of Dentistry.

Petra Wilder-Smith, DDS, PHD, is with the Beckman Laser Institute, University of California, Irvine.

Lawrence Wolinsky, DDS, PHD, is with the Division of Oral Biology and Medicine at the University of California, Los Angeles, School of Dentistry.

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Oral cancer is an important component of the worldwide burden of cancer. Although its incidence ranges around 3 percent of all cancers, relative survival rates are among the lowest of major cancers. An estimated 28,000 new cases of oral cancer were diagnosed in 2007 in the United States despite routine screening exams in current medical and dental practices. Oral cancer is the eighth most-common cancer among white males and the sixth most common cancer among black men in the United States.

Approximately 9,000 deaths occur as a result of these malignancies. More deadly than breast cancer, cervical cancer, and prostate cancer, it has been estimated that oral cancer kills one person, every hour, every day.[1,2]

Several studies suggest that head and neck cancer, particularly tongue cancer, is increasing in young adults both nationally and internationally.[3] Factors that contribute to this rise are still unknown, suspected etiologic agents include smokeless tobacco, various forms of drug abuse, environmental factors, and the human papilloma virus.[4]

The oral cancer survival rate after five years of diagnosis approximates 50-55 percent. In contrast to other cancers (e.g., breast, colorectal, and prostate cancers) the overall U.S. survival rate from oral and pharyngeal cancer has not improved during the past 50 years.[1,2,5] The five-year survival rate is 75 percent for those with localized disease at diagnosis, but only 16 percent for patients with late stages

because in the majority of cases, the cancer is diagnosed in stages 3 and 4 with lymph node metastasis.[6,7] Of all oral cancer cases documented by the National Cancer Institute Surveillance, Epidemiology and End Results Program, advanced lesions outnumbered localized lesions more than 2:1.[8]

Such dismal statistics seem perverse since the disease primarily arises in the surface oral epithelium that is readily accessible to direct visual and tactile examination. The conclusion that at least some lesions are ignored or missed by patients, health care professionals, or both, is inescapable. In part, this may be due to an incomplete understanding or awareness that even small asymptomatic lesions can have significant malignant potential. Health education programs aimed at motivating patients to present earlier have also been largely unsuccessful. A delay in diagnosis and presentation with late-stage disease may be due to patient delay or professional delay, although both may contribute.

The Importance of Early Detection

The prevention of oral cancer and its associated morbidity and mortality hinges upon the early detection of neoplastic lesions, allowing for histologic evaluation and treatment as necessary. Any tool that improves the detection of such lesions should improve the effectiveness of screening methodologies. Although basic oral cancer examination to achieve early detection requires only a 90-second visual and tactile examination, too few practitioners, and dentists in particular, are conducting these exams.[9] Moreover, the identification of high-risk individuals would permit the development and implementation of efficient chemoprevention and molecular targeting strategies.

There is general consensus that clinical stage at the time of diagnosis is the most important predictor of recurrence and death in head and neck cancer patients. The time to diagnosis is influenced by multiple clinical and sociodemographic variables, including patient reluctance to consult a health care professional, due to lack of access that is all too common, especially in patients with low socioeconomic status, SES, as well as professional delay in diagnosing and treating the disease.

THE PREVENTION of oral cancer and its associated morbidity and mortality hinges upon the early detection of neoplastic lesions.

Studies have shown that dentists and other health care providers are in desperate need of systemic educational updates in oral cancer prevention and early detection, as they are remiss in the provision of oral examinations and in the detection of early oral cancers.[10] Clinicians can increase survival rates if a cancerous lesion is detected at an early stage, or if a precursor lesion (dysplasia) is discovered and treated prior to malignant progression.[11] Recent models determining the value of a population-based oral cancer screening program show it to be a promising health promotion strategy (especially in high-risk individuals) with significant increases in quality adjusted life years saved, QALY, which await further economic appraisal.[12]

The Need to Educate Dental Health Professionals on Early Cancer Detection

The lack of prevention and early detection of oral cancer by health care providers is a worldwide problem. Most dentists claim to perform an oral cancer examination on their patients, but several studies indicate the dentists' lack knowledge in the area of oral cancer etiology and diagnosis.[11]

Despite the wide availability of several written guidelines, no noticeable progress has been made in achieving earlier diagnosis and prognosis of oral cancer in the past decade.[2] In 2000, Horowitz et al., in the conclusion of a nationwide U.S. survey conducted among practicing dentists, stated that there is a need for systematic educational updates in oral cancer prevention and early detection. The need is to reinforce the importance of 1) obtaining complete health histories, including history of risk factors such as tobacco and alcohol consumption; and 2) performing an increased number of oral mucosal examinations. Based on indications by a preponderance of the dentists surveyed, that the emphasis on oral cancer was not comparable to other content areas in their dental schools, the authors also concluded that greater emphasis on oral cancer prevention and early detection should be incorporated into the dental school curriculum. Dental boards should also include in the clinical portion of their licensure the performance by the applicants of an oral cancer examination.

The American Cancer Society recommends screening for cancers of the head and neck, including oral cancers, every three years in asymptomatic persons between the ages of 20 and 40, and yearly in asymptomatic patients after age 40. Smokers and alcohol users, who are considered high risk, should be examined every year regardless of

their age.[13] Dentists need to know that a comprehensive oral cancer examination only takes 90 seconds of their time — a minimal effort, given the resulting benefits to both the patient and the dentist if cancer is detected early.

Visual examination continues to be the gold standard for the detection of early epithelial changes. Criteria for suspicion of an oral leukoplakia or squamous cell carcinoma include changes in surface texture, loss of surface integrity, color, size, contour deviations, or mobility of intraoral or extraoral structures.[14]

Emerging New Clinical Modalities for Early Detection

Recent advancements in oral cancer research have led to the development of potentially useful diagnostic tools at the clinical and molecular level for the early detection of oral cancer. The gold standard for oral cancer diagnosis remains tissue biopsy with a pathologic assessment, but this technique needs a trained health care provider, and is considered invasive, painful, expensive, and time consuming. Recently, scientific research in the field of oral cancer has focused on finding alternative approaches to traditional biopsy, with high expectations in finding a test for oral cancer detection that mimics the Papanicolaou smear, Pap smear, which has significantly improved the early detection and subsequently lowered the mortality rate of cervical cancer.[15]

Recent clinical diagnostic tools developed for the early detection of oral cancer include tolonium chloride or toluidine blue dye, Oral CDx brush biopsy kits, ViziLite, salivary diagnostics, and several imaging devices such as Velscope and multispectral optical imaging systems. To date, none has shown equivalency or been confirmed to be superior to clinical examination.[16,17]

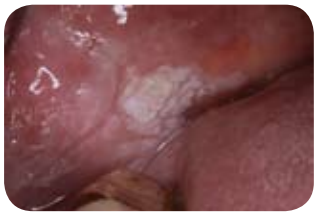

FIGURE 1A. Leukoplakia lesion on right buccal mucosa.

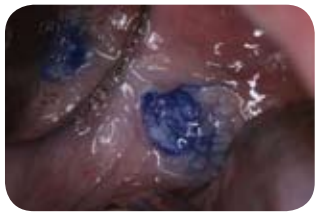

FIGURE 1B. Positive blue staining after TB rinse.

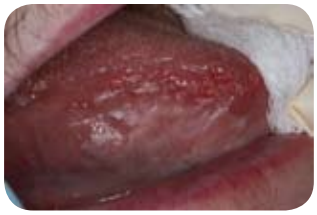

FIGURE 1C. Leukoplakia of R lateral border of tongue.

FIGURE 1D. Negative stain after TB rinse.

Vital Staining (Toluidine Blue)

Tolonuim chloride also known as Toluidine blue, TB, has been used for decades to aid in the detection of mucosal abnormalities of the cervix and the oral cavity. TB is a metachromatic dye that clinically stains malignant cells but not normal mucosa. Two mechanisms of toluidine blue staining have been proposed. The dye may be taken up by the nuclei of malignant cells manifesting increased DNA synthesis.

Another hypothesis is that the dye can penetrate through randomly arranged tumor cells. The clinical staining procedure involves patients rinsing their entire mouth with the dye, then the physician inspects for areas of blue staining. Malignant lesions stain dark blue; dysplastic lesions stain different shades of blue, depending on the degree of dysplasia.[14] Blue staining in a patient indicates the need for a biopsy. **FIGURE 1** depicts a clinical photograph of a positive TB stain (B) and a negative TB stain (D).

Occasionally, a small amount of dye may be retained in normal mucosa. This dye can be wiped away with acetic acid. Surfaces that are rough or keratinous will also retain stain (e.g., the dorsum of the tongue, gingival crevices). Nonmalignant areas of inflammation occasionally stain with toluidine blue; therefore, all positive lesions should be restained in 14 days to decrease the false positive rate. Toluidine blue can also be used to screen patients with previous carcinoma of the upper aerodigestive tract. These patients are known to be at high risk for a recurrence; therefore, clinicians may add toluidine rinses to their visual examination.[14,18]

From recent studies, a relationship between toluidine blue staining and genetic changes associated with the progression of potentially malignant lesions to oral cancer — such as allelic loss or loss of heterozygosity (LOH) — was demonstrated.[19] Furthermore, the authors demonstrated in a longitudinal study that toluidine blue identified LOH-positive lesions that subsequently progressed to oral cancer.

Chemiluminscence: ViziLite

Chemiluminensce is a noninvasive screening tool targeted at dentists to assist in the identification of suspicious superficial oral lesions. It consists of an acetic acid wash and a single-use "chemi-light stick" that generates a moderately short wavelength light with peak outputs near 430, 540, and 580 nm for illumination of the oral cavity (ViziLite). The use of acetic acid followed by chemiluminescent illumination for visual diagnosis is similar to speculoscopy (an adjunct to Pap smear of the

FIGURE 2. Chemiluminescence with ViziLite shows suspicious lesion on the right side of the tongue as white; normal epithelium is dark.

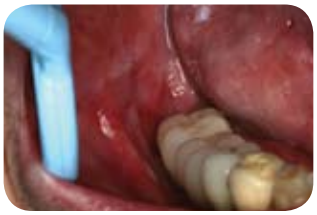

FIGURE 3A. Oral CDx brush application on a suspicious buccal mucosal lesion, with suspicious erythroplkia lesion on R buccal mucosa.

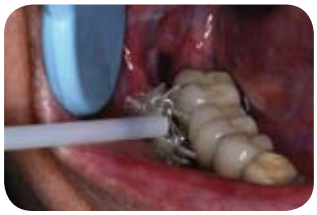

FIGURE 3B. Application of the Oral CDx brush for cytology testing.

uterine cervix), utilizing the same chemiluminescent light source for cervical diagnosis.[14] Based on the rationale that the visual presentation of cervical and oral/pharyngeal lesions, including SCC, is nearly identical under chemiluminescence, the cervical approach can be adapted to the diagnosis of any cancerous lesions of the oral cavity.

ViziLite is based on the typically greater nuclear content density and mitochondrial matrix of abnormal cells than that of normal cells. The increased nuclear density and the resulting increase in nuclear to cytoplasmic ratio reflect an increase in the proliferative rate and metabolic activity of precancerous cells. After the patient rinses with a dilute acetic acid solution, the dense nuclei of abnormal squamous epithelial tissue will reflect light and appear white when viewed under a diffuse low-energy wavelength light. Normal epithelium will absorb the light and appear dark.[20]

The majority of studies investigating chemiluminescence evaluate subjective perceptions of characteristics of intraoral lesions including brightness, sharpness and texture versus routine clinical examination. As these parameters are highly subjective, it is not surprising that results have been contradictory.[16,18] Recently a combination of both TB and ViziLite systems (ViziLite Plus with TBlue system) has been introduced. **FIGURE 2** demonstrates the use of ViziLite after a positive TB stain on the R-lateral border of tongue. The suspicious lesion is seen as a dense white lesion as compared to the adjacent dark normal mucosa. A new chemiluminescence device (MicroLux DL) has also recently been introduced on the market.[14]

Cytology (Oral CDx)

The brush biopsy (CDx) was designed for use on clinical lesions that would otherwise not be subjected to biopsy because the level of suspicion for carcinoma, based upon clinical features, was low. When an abnormal CDx result is reported (atypical or positive), the clinician must follow-up with a scalpel biopsy of the lesion, as brush cytology does not provide a definitive diagnosis.[21-23] The intent of the brush biopsy is to obtain cells from a suspicious oral site while avoiding the pain and discomfort of a tissue biopsy, similar to a Pap smear for identifying abnormal cervical cells in routine cervical cancer screening. The designed brush (Oral CDx) is used for epithelial cell collection and samples are eventually fixed onto a glass slide, stained with a modified Papanicolaou test and analyzed microscopically via a computer-based imaging system. Results are reported as "positive" or "atypical" when cellular morphology is highly suspicious for epithelial dysplasia or carcinoma, or when abnormal epithelial changes are of uncertain diagnostic significance respectively.[24] **FIGURES 3A** and **3B** illustrate the use of an oral CDx brush on a suspicious buccal mucosa lesion.

Controversy exists over the use of the Oral CDx product because some studies have indicated a high false-positive and a high false-negative rate.[23] There are multiple examples in the literature of studies with essentially opposite findings; therefore, most articles suggest further investigation of the product. A formal biopsy is still indicated if there is clinical suspicion of a lesion regardless of the Oral CDx result.[25,26]

In conclusion, further research with clear objectives, well-defined population cohorts, and sound methodology are required before promoting the extensive use of the brush biopsy or any other diagnostic tool for oral cancer detection.

Imaging Devices

- Photosensitizers
- Spectroscopy and fluorescence
- In vivo microscopy
- Optical coherence tomography

1. PHOTOSENSITIZERS

Topical or systemic application of photosensitizers can selectively render pathologic tissues fluorescent when exposed to specific wavelengths of light, this technique has extensively been used for skin and esophageal cancer.[27,28] This induced fluorescence can be used to identify and delineate areas of pathology. Although the fluorescence may be strong enough to be detected with the naked eye (**FIGURES 4A–4C**), usually some sort of fluorescence detection device is used to enhance fluorescence detection and assist with accurate lesion mapping. Whilst many agents are under investigation, or in clinical use outside of the United States, FDA approval for photosensitizing drugs remains limited. Some promising agents for photodetection include aminolevulinic acid (ALA) (Levulan), hexyl aminolevulinate (Hexvix), methyl aminolevulinate (Metvix), tetra (meta-hydroxyphenyl) chlorin (mTHPC), as well as porfimer sodium (Photofrin).[29-33]

FIGURE 4A. In vivo multiphoton microscopy images of the hamster cheek pouch. Healthy tissue, showing ordered and dense collagen fiber network in blue.

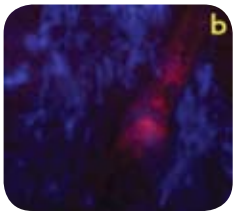

FIGURE 4B. Dysplastic lesion, showing engorged blood vessel, shortening of collagen fibers with reduced density and organization.

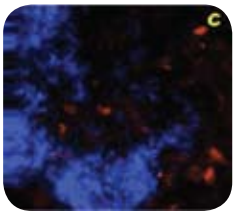

FIGURE 4C. Malignant lesion, showing further collagen loss and inflammatory exudates (red).

In a clinical study of 20 patients with oral neoplasms, three hours after the application of topical Photofrin solution, the photosensitized tissues showed a strong red fluorescence, with increasing fluorescence intensity correlating with increasing levels of pathology. Guided by their visible fluorescence, lesions were biopsied at four suspicious sites for each patient. The diagnostic sensitivity using unaided visual fluorescence diagnosis or fluorescence microscopy approximated 93 percent. Diagnostic specificity was 95 percent for visual diagnosis, improving to 97 percent using fluorescence microscopy. The differences between healthy tissue versus dysplasia versus malignancy were all significant ($p<0.05$).[33]

Advantages of a photosensitizer-based diagnostics approach include the capability for 3-D surface and subsurface mapping of lesion margins using available imaging technologies, the ability to inspect large surface areas, noninvasiveness, and the capability for subsequent photodestruction of the photosensitized lesion. Depending on the photosensitizer used and its mode of application (systemic versus topical), imitations include systemic photosensitization over prolonged periods of time, limited penetration depth, the need for specialized fluorescence detection and mapping equipment, and lack of specificity when inflammation or scar tissue are present.

2. SPECTROSCOPY

This term refers to the process of measuring the emission and absorption of different wavelengths (spectra) of visible and nonvisible light. Various types of optical spectroscopy have been investigated for oral diagnosis. All of these methods have one basic principle in common: the optical spectrum of a tissue contains information about the biochemical composition and/or the structure of the tissue, which conveys diagnostic information. Malignancy-related biochemical and morphologic changes perturb tissue absorption, fluorescence, and scattering properties. The biochemical information can be obtained by measuring absorption/reflectance, fluorescence, or Raman scattering signals.[34] Data is often in the form of graphs, some imaging devices that color code spectral characteristics of tissues also exist, such as the Velscope.

VELSCOPE SYSTEM

For decades the use of tissue autofluorescence has been described to screen and diagnose precancers and early cancer lesions in organs such as the lung, uterine cervix, skin, and, more recently, the oral cavity.[35-37] The concept behind tissue autoflorescence is that changes in the structure (e.g., hyperkeratosis, hyperchromatin, and increased cellular/nuclear pleomorphism) and metabolism (e.g., concentration of flavin adenine dinucleotide [FAD] and nicotinamide adenine dinucleotide [NADH]) of the epithelium, as well as changes of the subepithelial stroma (e.g., composition of collagen matrix and elastin), alter their interaction with light. Specifically, these epithelial and stromal changes can alter the distribution of tissue fluorophores and as a consequence the way they fluoresce after stimulation with intense light (typically, blue light excitation at 400 to 460 nm), a process called autoflorescence. The autoflorescence signal can be directly visualized by the clinician.[35-37]

One of the tissue fluorescence imaging system that have been marketed to dental offices is the Velscope system. In the oral cavity, normal oral mucosa emits a pale green autofluorescence when viewed through the instrument handpiece whilst abnormal tissue displays a decreased autofluorescence and appears darker with respect to the surrounding healthy tissue.[37-38] Studies have shown that Velscope can improve lesions contrast and therefore improve the clinician's ability to distinguish between mucosal lesions and healthy mucosa. Whilst preliminary data on Velscope's specificity and sensitivity are predominantly based on case series and case reports, full-scale clinical trials using different patient populations are needed to establish the diagnostic efficacy of this tool.[18]

Structural and morphological information may be obtained by spectroscopic techniques that assess the elastic-scattering properties of tissue.[39] Pursuant to encouraging preliminary data clinical trials of elastic scattering spectroscopy, sometimes in combination with fluorescence spectroscopy, or imaging, are under way.[34] Other studies combine spectroscopy with polarized light and/or fluorescence imaging, and/or in vivo microscopy. Devices under development and testing include the FastEEM4 System, the Indentafi and the PS2-oral. These clinical studies are still at a relatively early stage, and preliminary results are encouraging.[40-49]

Significant challenges to the use of diagnostic spectroscopy include the often low signal-to-noise ratio, difficulty in identifying the precise source of signals, data quantification issues, and establishing definitive diagnostic milestones

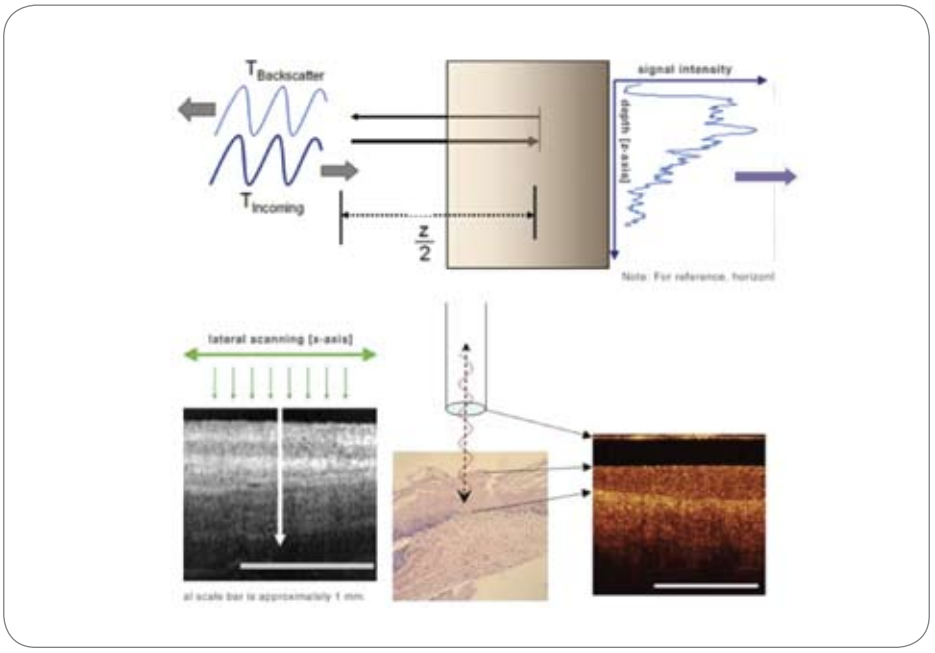

FIGURE 5. OCT performs 2-D imaging in biological tissues by projecting harmless near-infrared light onto the tissue and measuring the backscattered intensity of light as a function of depth (left). It is able to capture tissue substructure images in real-time using lateral scanning (middle). In-depth spatial resolution is 5-20 µm in air, and is typically able to visualize tissue to a depth of 2 mm (right).

and endpoints, especially given the wide range of tissue types contained within the oral cavity. Limited tissue penetration and concerns about mutagenicity when using UV light present further clinical challenges. The abundance of data/information generated in association with our incomplete understanding of the carcinogenesis process tend to render data analysis and interpretation very complex, however, the development of diagnostic algorithms may be able to mitigate this challenge.[39]

3. IN VIVO MICROSCOPY

In vivo confocal or multiphoton imaging resembles histological tissue evaluation, except that 3-D subcellular resolution is achieved noninvasively and without stains. In epithelial structure, resolution of 1 µm has been achieved with a 200–400-µm field of view. Confocal imaging of oral mucosa has resolved subcellular detail in the lip and tongue and oral squamous cell carcinoma from multiple sites.[50,51] While this technology can provide detailed images of tissue architecture and cellular morphology, a very small field of view and limited penetration depth of 250-500 µm considerably reduce the clinical usefulness of this approach. Multiphoton microscopy resembles confocal, but affords a greater tissue penetration depth, the use of many different wavelengths of light, and less tissue heating[52] (**FIGURE 4**). Because of high cost and the specialized expertise required to operate such systems, neither approach is clinically feasible in the foreseeable future.

4. OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography, OCT, is an optical imaging method first used to visualize human tissue in 1991. It has been since refined and accepted as an imaging modality in ophthalmology. Several systems have been cleared by FDA for such use; one OCT system (Imalux) currently has FDA 510(k) clearance for nonophthalmalogic medical use.

OCT is a high-resolution optical technique that permits noninvasive imaging of surface and subsurface tissues. It has been compared to ultrasound scanning conceptually. Both ultrasound and OCT provide real-time structural imaging, but unlike ultrasound, OCT is based on low-coherence interferometry, using broadband light to provide cross-sectional, high-resolution subsurface tissue images (**FIGURE 5**). With a tissue penetration depth of 1 mm to 2 mm, the imaging range of OCT technology is suitable for the oral mucosa.[53-56] Previous studies using OCT have demonstrated the ability to evaluate macroscopic characteristics of epithelial, subepithelial, and basement membrane structures and show the potential for near histopathological-level resolution and close correlation with histologic appearance.[57]

In one of the authors' recent studies of 50 patients with oral dysplastic and malignant lesions, intra- and interobserver agreement between diagnoses based on histopathology and imaging data was excellent, with kappa values of 0.844-0.896.[58] For detecting carcinoma in situ or squamous cell carcinoma, SCC, versus noncancer, sensitivity and specificity were 0.931; for detecting SCC versus all other pathologies, sensitivity was 0.931 and specificity was 0.973. These data demonstrate the excellent capability of in vivo OCT for screening high-risk patients, monitoring existing lesions, and detecting, diagnosing oral premalignancy and malignancy in human subjects. This study showed that the in vivo OCT image of a dysplastic lesion (**FIGURE 6B**) parallels histolopathological status (**FIGURE 6C**), showing epithelial thickening, loss of stratification in lower epithelial strata, epithelial downgrowth, and loss of epithelial stratification as compared to healthy oral mucosa (**FIGURE 6D**).

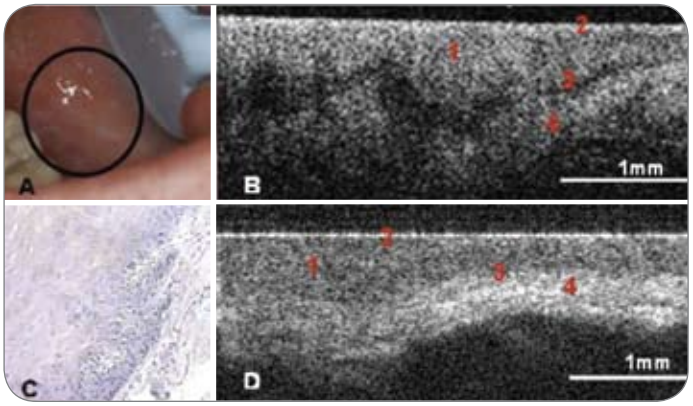

FIGURE 6. Dysplastic and normal buccal mucosa. **(A)** Photograph, **(B)** in vivo OCT image, and **(C)** H&E (10x) of dysplastic buccal mucosa. **(D)** In vivo OCT image of normal buccal mucosa. Key: 1-stratified squamous epithelium, 2-keratinized epithelial surface layer, 3-basement membrane 4-submucosa.

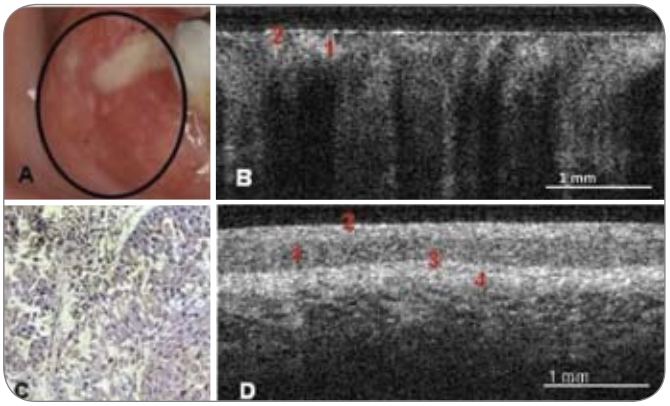

FIGURE 7. Squamous cell carcinoma of the buccal mucosa. **(A)** Photograph, **(B)** in vivo OCT image and **(C)** H&E (10x) of buccal mucosa with squamous cell carcinoma. **(D)** In vivo OCT image of normal buccal mucosa. Key: 1-stratified squamous epithelium, 2-keratinized epithelial surface layer, 3-basement membrane, 4-submucosa.

For oral cancer, **FIGURES 7A AND 7C** show clinical appearance and histopathology, respectively of an area of SCC on the buccal mucosa. In the OCT image (**FIGURE 7B**), the epithelium is highly variable in thickness, with areas of erosion and extensive downgrowth and invasion into the subepithelial layers. The basement membrane is not visible as a coherent landmark.[58]

As the technology and techniques evolve, this modality should progressively reduce the need for biopsy, define surgical margins, and provide a direct evaluation of the effectiveness of complete lesion removal.

Saliva as a Diagnostic Tool

Salivary diagnostics has come to the forefront of biomedical research. The ability to use salivary biomarkers (i.e., DNA, RNA, and proteins) as a predictive measure for systemic disease has generated much interest among dental researchers in the United States and Europe. Laboratory-based methodologies, which allow the rapid identification of proteins, RNA and DNA have afforded scientists the ability to examine and quantify complex salivary profiles. At the University of California, Los Angeles, School of Dentistry, Dr. David Wong and collaborators are developing research platforms toward the global identification of disease signatures in saliva.

The premise of their approach is that serum contents, such as disease biomarkers, are largely present in saliva, thus rendering oral fluid a logical source to harness disease biomarkers.[59] They employ both a proteome-wide as well as a genome-wide approach toward the identification of disease biomarkers and signatures. Dr. Wong's goal is to develop and utilize novel patient-oriented genome-wide molecular tools that may identify oral cancer specific molecular markers.

Early work by Wong and his coworkers identified interleukin 6 and 8 as predictive biomarkers for oral cancer.[60-63] They are now validating these findings and have expanded this work to breast and pancreatic cancer. Oral fluid–based tests presently exist or are being developed to detect a variety of infectious diseases (including HIV, parvovirus, acute hepatitis, dengue fever, and malaria), as well as to detect alcohol and drug use and steroid hormone levels.[64]

Other body fluids such as serum could possibly also be helpful in identifying common genetic mutations, promoter hypermethylation, and LOH.[65,66]

The UCLA group is at the final stage of developing an oral fluid nanosensor test device that could be used in the dental office. This portable, point-of-care, chairside device is to be used for saliva diagnostics, not only for oral cancer but other diseases such as diabetes, Sjögren's syndrome, and breast and prostate cancer (**FIGURE 8**).

Collectively, technology platform advancement and the identification and validation of robust and discriminatory suites of salivary biomarkers for disease diagnostics represent the necessary marriage to propel saliva diagnostics into a clinical and commercial reality. At the same time, they are building the scientific foundation toward the use of saliva as a diagnostic fluid. This is a perfect example of translational research in reverse, based on a highly relevant clinical observation that saliva contains proteomic and genomic biomarkers for oral cancer detection, and building a scientific foundation toward the mechanistic background, thereby enabling better exploitation of the full clinical potential of saliva diagnostics.[67-69]

Oral Cancer Chemoprevention

Many epidemiologic studies have consistently linked the abundant consumption of foods of plant origin, such as fruit, vegetables, whole grains, legumes, nuts, seeds, and tea, with a decreased risk of developing various types of cancers.[70,71] Chemoprevention is the use of pharmacologic or natural agents that inhibit the development of invasive cancer. These work either by blocking the DNA damage that initiates

FIGURE 8. The UCLA oral fluid nansosensor test (OFNASET): Showing two chips, one for oral cancer screening and one for Sjögren syndrome screening (*courtesy of Dr. David Wong*).

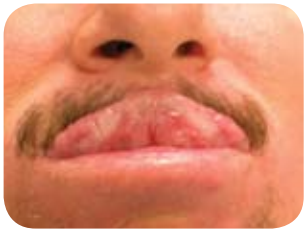

FIGURE 9A. A patient with proliferating verrucous leukolplkia (PVL) of ventral surface of tongue.

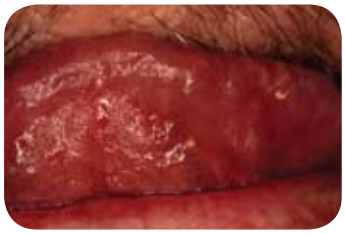

FIGURE 9B. Regression of the PVL lesion after six months of BBIC treatment.

carcinogenesis, or by arresting or reversing the progression of premalignant cells in which such damage has already occurred.

Recent advances in understanding the causes of cancer and the consequent ability to provide a genetic diagnosis of susceptibility necessitate the identification of agents that can effectively reverse, halt, or at least delay the carcinogenic process. It is important that any agents selected on the basis of trials in premalignant lesions have minimal or no toxicity since a large number of subjects whose lesions are unlikely to progress to cancer will necessarily be exposed to the product. Therefore, the development of new agents or the use of old agents at nontoxic doses is important.[72]

As in all cancers, the most effective way of approaching oral cancer prevention is to identify individuals who are at a high risk to develop such cancers (e.g., individuals with oral premalignant lesions) and to treat them with agents that can suppress the development of additional premalignant lesions and inhibit the development of oral cancer in existing lesions.

Oral carcinogenesis is a multistep process, which is characterized by genetic, epigenetic, and phenotypic changes. Many of these changes involve the activation of signaling or metabolic pathways that give the cells favorable growth and survival characteristics. Therefore, chemopreventive agents that can inhibit or reverse these changes by targeting specific molecular pathways have received increased attention as novel candidates for cancer prevention and therapy.[73]

A wide range of compounds has been investigated as possible chemopreventive therapies for potential oral cancer, such as vitamins and minerals, including vitamin A and other retinoids, beta carotene, vitamin E, vitamin C, folates, and selenium, and has been studied. Herbal treatments have generated interest recently. Molecularly targeted approaches have included cyclooxygenase-2 (COX-2) inhibitors, EGFR inhibitors, and adenovirus vectors.[74] Several promising new compounds are currently in clinical chemoprevention trials in head and neck cancer. These include curcumin analogs, green tea extracts (GTEs), selenium, polyphenols of pomegranate juice, Bowman-Birk inhibitor (BBI) from soybeans and others.[75]

The authors and other collaborators from multiple institutes are involved in a multicentric phase II NCI-sponsored study to examine the effect of the protease inhibitor Bowman-Birk Inhibitor concentrate (BBIC), on oral leukoplakia patients (**FIGURES 9A** and **9B**). This compound had previously been tested in patients with benign prostatic hypertrophy, ulcerative colitis, and those studies suggested clinical activity without toxicity being noted.[76] BBIC effect in the oral cavity is still not well established, but preliminary results are promising.[77]

Because of their easy accessibility to topical treatment and visual clinical examination, oral premalignant lesions provide an excellent model to study the effects of various chemopreventive agents on epithelial solid tumors. In case of oral premalignancy, the primary (clinical) endpoints are determined by clinical measurement of the lesion and confirmed by histologic examination of oral biopsy. Both are feasible in the oral cavity. Secondary (biomarkers) endpoints are usually biochemical and molecular markers found on tissues or buccal cells which are easily obtained from the oral cavity.

Current clinical trials that use clinical and biomarker endpoints will identify useful agents for oral cancer prevention and provide a better understanding of the carcinogenesis process by investigating the specific targeted cellular proteins and dependent cell signaling pathways modulated by these agents. Such insights will not only shed a light on the mechanism of cancer progression but will also guide future drug development and ultimately improve therapy.[78] ■■■■

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Craniofacial Tissue Regeneration: Where Are We?

ARCHANA BHATT, BDS, AND ANH D. LE, DDS, PHD

ABSTRACT This paper provides a brief review of adult stem cells and their potential clinical applications, specifically in craniofacial regeneration. The initial discovery of stem cells from a variety of tissues has infused tremendous research, and, in conjunction with bioengineering technologies, has potential to transform clinical dentistry.

AUTHORS

Archana Bhatt, BDS, is with the Center for Craniofacial Molecular Biology, University of Southern California School of Dentistry.

Anh D. Le, DDS, PHD, is an associate professor, Division of Surgical, Therapeutic, and Bioengineering Sciences, Center for Craniofacial Molecular Biology, University of Southern California School of Dentistry.

Since the discovery of stem cells and their potential impact in revolutionizing current standard treatment in medicine and dentistry, patients are becoming increasingly aware that stem cells may benefit them or their loved ones. This review will highlight major postnatal dental stem cells, their biological properties, and differentiation capabilities relevant to clinical applications in craniofacial tissue regeneration. A scheme of clinical applications of dental stem cells is outlined in **FIGURE 1**.

Postnatal or adult stem cells, also known as somatic stem cells, are defined by two properties: self-renewal and multipotency.[1] Self-renewal is defined as the ability of the cell to undergo cell division. One daughter cell remains a stem cell while the other becomes a committed progenitor cell. This is a very important property for successful use of stem cells in therapy. Multipotency is a unique property of the cell to form multiple cell types. The stem cells, under suitable conditions, have a wide differentiation potential with the capability to develop into almost any cell in the body. For example, the neural stem cells from the mouse brain can differentiate into various blood cell types in addition to cells of the nervous system.[2] In the 1960s, researchers discovered that the bone marrow contains two kinds of stem cells, the hematopoietic stem cells that form all types of blood cells, and the bone marrow stromal cells, also known as mesenchymal stem cells, MSC, that generate bone, cartilage, fat, and fibrous connective tissue.

Hematopoietic stem cells are relatively easy to obtain and were the first stem cells to be used successfully in therapies to treat leukemia and other blood disorders.[3] First described by Friedenstein et al., bone marrow stromal cells, BMSC, are capable of high self-renewal capacity and can differentiate into mesodermal lineages forming cartilage, bone, adipose tissue, and skeletal muscle.[4-6] They are negative for hematopoietic stem cell markers. MSC have been

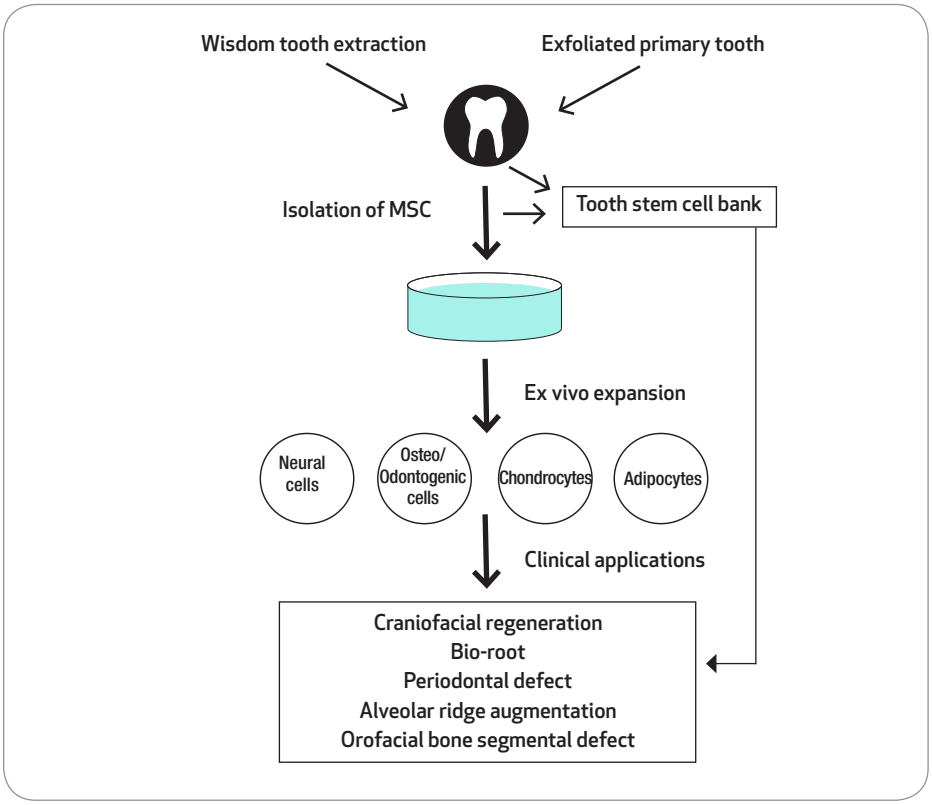

FIGURE 1. Clinical applications of dental stem cells.

reported to produce growth factors and cytokines that may prove useful for repair and regeneration of a variety of mesenchymal tissues, such as bone, cartilage, muscle, and the cells. BMSC have been researched extensively and appear promising in therapies for a number of skeletal diseases, nervous system disorders, cardiomyopathies, and hematologic disorders.[7]

Adult Stem Cells Derived From Dental Tissues

In the last decade, MSC have been isolated from several structural components of the tooth, including the dental pulp of adult and deciduous teeth, periodontal ligament, apical papilla, and dental follicle. Dental pulp stem cells, DPSC, possess a self-renewal capability and multilineage differentiation into odontoblasts, chondrocytes, adipocytes, and neurons under appropriate environmental condition.[8-10] DPSC can form mineralized nodules with a dentin-like structure in vitro under osteoinductive conditions and reparative dentin-like tissue on the surface of human dentin in vivo.[11-13] In vivo, they produce dentin/pulp-like complex, a dentin-like structure lined with human odontoblast-like cells surrounded by pulp-like interstitial tissue in conjunction with hydroxyapatite/tricalcium phosphate as a carrier.[14,15] Collection of the dental pulp may be obtained when young adults undergo extraction of the bicuspids prior to orthodontic treatment or during routine wisdom tooth extraction if there is no pulpal infection.

An exfoliated deciduous tooth contains a living pulp remnant containing stem cell known as stem cells from exfoliated deciduous tooth, SHED. They remain alive inside the tooth for a very short time after it exfoliates, during which it can be harvested for research. This exciting unexpected discovery in 2003 has important implications in the field of stem cell research. These stem cells are derived from the human deciduous teeth that are exfoliated in childhood with little or no morbidity to the patient. Stem cells isolated from the pulp tissue from exfoliated deciduous teeth are capable of differentiating into a variety of cells including neural cells, osteoblasts, chondrocytes, and adipocytes.[16,17]

SHED isolated from exfoliated deciduous incisors forms adherent clusters and showed a higher rate of proliferation as compared to BMSSC and DPSC and express a number of markers.[16,17] After transplantation into immunocompromised mice, they formed ectopic-like dentin-like tissue but were unable to regenerate the dentin pulp-like complex.[17,18] These results suggested that SHED can differentiate into odontoblasts in vivo. SHED are also capable of repairing critical-size parietal defects in immunocompromised mice; however, the bone lacks hematopoietic marrow elements.[19] Thus, SHED is capable of forming bone and small amounts of dentin in vivo as compared to DPSC that form dentin/pulp complex.

The periodontal ligament is a specialized connective tissue that anchors the tooth by connecting the cementum to the alveolar bone. Various studies have shown that periodontal ligament stem cells, PDLSC, can differentiate into adipocytes, chondrocytes, and osteocytes.[20] PDLSC obtained from extracted wisdom teeth are capable of forming adherent clonogenic clusters of fibroblast-like cells. PDLSC were found to express high levels of scleraxis as compared to BMSC and DPSC, in addition to a broad array of cementoblastic and osteoblastic markers.[20] They form mineralized nodules indicating calcium accumulation in vitro, though nodule formation was lower as compared to DPSC.[20] In vivo, PDLSC can form cementum/PDL-like structure with a thin layer of cementum, collagen fibers with cells. These collagen fibers connected

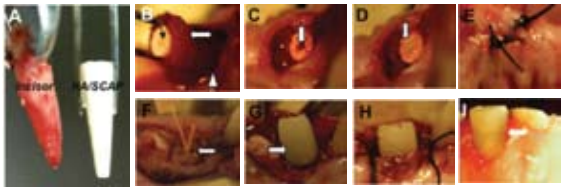

FIGURE 2. Regeneration of bio-root from SCAP/PDLSC in mini-pig model. Specialized scaffold loaded with SCAP and PDLSC in the shape of lower incisor root was implanted into extracted lower incisor socket, and subsequently restored with a porcelain crown. Bio-root integration was observed at 12 weeks postimplantation. *Adapted from Sonoyama, PLoS ONE 1:e79, 2006.*

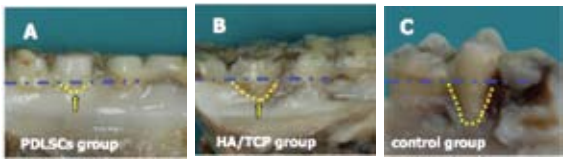

FIGURE 3. Regeneration of periodontal defects by PDLSC in mini-pig model. Transplantation of PDLSC with HA/TCP carrier **(A)** into intra-osseous defects restored buccal bone height as compared to control HA/TCP scaffold **(B)**, or untreated group **(C)**. *Adapted from AlphaMed Press, Stem Cells 26:1065-73, 2008. Liu Y, Zheng Y, et al, Periodontal ligament stem cell-mediated treatment for periodontitis in miniature swine. Stem Cells 26(4):1065-73, April 2008; e-pub Jan. 31, 2008. Used with permission from John Wiley & Sons, Inc.*

to the newly formed cementum, similar to the attachment of Sharpey's fibers.

When human PDLSC were transplanted into surgically created defects in periodontal areas in mandibular molars in immunocompromised mice, the cells integrated into the PDL and attached to alveolar bone and cementum surface.

Very recently, another type of MSC in the apical papilla of human immature permanent teeth termed stem cells from the apical papilla, SCAP, was discovered.[21] SCAP exhibits osteo/dentinogenic, neurogenic, and adipogenic differentiation capabilities.[21,22] Recently, several cases have reported apexogenesis in an infected immature tooth with periradicular periodontitis or abscess, and this may be triggered by the stem cells from the apical papilla that may have induced root formation. SCAP expressed similar but lesser osteo/dentinogenic markers and growth factor receptors as compared to DPSC.[21] In vivo, it forms a dentin-like structure on the surface of HA/TCP, along with connective tissue, and, in combination with PDLSC, is capable of generating a root/periodontal complex.[22]

The dental follicle is a mesenchymal tissue that surrounds the developing tooth germ. It contains stem cells that can differentiate into the periodontal ligament. In fact, stem cells derived from the dental follicle can differentiate into osteoblasts/cementoblasts and adipocytes when grown in appropriate osteogenic or adipogenic medium.[23,24] They provide an easy source of stem cells as they can be obtained during impacted molar surgeries.

Since the tooth results from epithelial mesenchymal interactions, dental-derived epithelial stem cells, EpSC, that give rise to ameloblasts may also be a potential source of stem cells. Although mesenchymal stem cells from different origins have been extensively studied, not much research has been done on EpSC. EpSC isolated from the porcine third-molar tooth buds were studied in association with MSC from the same tooth that showed enamel-dentin-like complex structures in vivo.[25] However, the clinical application of EpSC may be limited as ameloblasts and their precursors are eliminated immediately after tooth eruption, and the cells with potential role in the regeneration the human adult tooth are no longer available.

Stem Cell Banking Company Provides Storage of Dental Stem Cells

Several dental stem cell banks have offered to harvest and store stem cells that may potentially enable the use of the stem cells for therapy in the future for treatment of disease and regenerative therapy. Dental pulp stem cells can be collected and isolated from patients at any age, though preferably from young adults, during a routine visit to the dentist and stored in dental pulp stem cell banks such as the National Dental Pulp Laboratory.[26] The Bioeden Tooth Cell Bank, a European company that is FDA-registered, is the world's first company to harvest and store stem cells from baby teeth.[27] The company provides a kit in which the exfoliated deciduous tooth is stored and sent to the company where the stem cells are isolated and cryopreserved for future uses.

Potential Role of Adult Stem Cells in Craniofacial Regeneration

Despite all enthusiasms about the initial discovery of stem cells and potential clinical applications, currently, there are no human trials using the dental postnatal cells and no clinical applications available. However, a great deal of progress has been made in a relatively short duration in several translational studies using animal models. For dental and craniofacial reconstruction, researchers have combined ex vivo expanded stem cells with different scaffolds and carriers to develop appropriate preclinical animal models. Knowledge of dental stem cell biology allows a systematic approach to optimize conditions for ex vivo stem cell expansion, scaffolds, and carriers, in the regeneration of the craniofacial tissues.

Regeneration of Tooth and Bio-Root

Current management of tooth loss has been relied on conventional prosthodontic restoration or replaced with dental implants. Success of implants relies on the ability of bone to interface with metal. This interface would be improved with the development of a layer of cementum on the implant surface, along with the establishment of the PDL. The regeneration of a functional tooth or bio-root with normal cementum lining at the root surface will allow better bone-tooth integration and provide an optimal biological approach to replace the missing or damaged tooth.

Recent studies reported that stem cells isolated from unerupted tooth buds are capable to reorganize into "mini-teeth"

or tooth bud-like structures.[28,29] Using a mini-pig model, researchers transplanted dental stem cells, SCAP, and PDLSC using a specialized scaffold shaped as a lower incisor root structure to generate a root/periodontal complex capable of supporting a porcelain crown, resulting in normal tooth function (**FIGURE 2**). This novel approach utilizing stem cell-mediated tissue regeneration, bioengineered materials for scaffold and tooth framework, and conventional prosthodontic restoration, allows the generation of a functional bio-root in animal model.

Regeneration of the Craniofacial Bones

Reconstruction of the orofacial bones from the small intraosseous defect of the periodontal pocket to the large segmental defect is routinely performed to regenerate bone loss from trauma, disease, and developmental abnormalities. These procedures depend on autologous, allogeneic, or alloplastic grafting sources with variable clinical outcomes and morbidities. The long-term clinical outcome of orofacial reconstruction relies on the ability to drive local cells, stem cells or committed progenitor cells, to completely regenerate the defect, which would not repair on its own.

Using a mini-pig model of surgically created periodontal defect, researchers were capable in regenerating the periodontal tissues using PDLSC, leading to restoration of alveolar bone height, suggesting feasibility for stem cell-mediated tissue engineering to treat periodontal diseases[30] (**FIGURE 3**). In animal models, researchers have rebuilt alveolar bone height to augment the ridge using BMSC in conjunction with HA/TCP.[31] Using BMSC, researchers were able to repair critical-size defects in the cranium of dogs and mice, and reconstruct the mandibular defect.[19,32,33] Recently, researchers were able to regenerate bone to repair critical size mandibular defects using stem cells derived from miniature pig deciduous teeth.[34] This preclinical study using a large animal model, specifically swine, allows testing of stem cells/scaffold construct in the restoration of the orofacial skeletal defect and provides rapid translation of stem cell-based therapy in the orofacial reconstruction in human clinical trials.

Challenges and Future Directions

A number of drawbacks are associated with stem cell-based therapy. First, it is a challenged task to obtain sufficient number of cells for the treatment without incurring major morbidities to the harvesting site. Second, the transplanted cells tend to migrate or die, resulting in a small percentage of donor cells actually engrafted at the recipient site. Third, the lineage-specific stem cells, which have undergone multiple cell divisions for ex vivo expansion, may not be capable to maintain long-term viability or differentiation capacities necessary for the success of tissue regeneration. Fourth, there is uncertainty in the short- and long-term effect of graft versus host disease. And lastly, the unknown potential of chromosome instability and tumorigenicity observed in MSC after multiple cell division and exposure to different growth microenvironment.

Although the full possibilities of tissue regeneration in humans using tooth-derived stem cells are not well-known, these cells potentially play an essential component of the armamentarium for regenerative medicine, specifically in the reconstruction of the craniofacial region. Future directions to solve these technical challenges and further understanding of adult stem cell biology will facilitate translation of these advances in stem cell research into clinical practice. ■■■■

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Treating the Older Adult Dental Patient: What Are the Issues of Concern?

ROSEANN MULLIGAN, DDS, MS, AND MICHELE ALEXIS VANDERLINDE, MS, PHD

ABSTRACT Just as aging successfully requires a multifaceted approach that includes full engagement in life, maintenance of high physical and cognitive function, and avoidance of disease and related disability, so does the care of adult patients. This geriatric treatment model suggests that understanding the psychosocial, behavioral, and medical presentation of the older patient may prove to be the key to the ultimate success of the dental/oral treatment arrived at collaboratively by the dentist and the older patient.

AUTHORS

Roseann Mulligan, DDS, MS, is the Charles M. Goldstein Professor of Community Dentistry, associate dean for Community Health Programs at the University of Southern California School of Dentistry, and professor of gerontology at the University of Southern California Leonard Davis School of Gerontology.

Michele Alexis Vanderlinde, MS, PHD, is an assistant clinical professor, community liaison, at the University of Southern California School of Dentistry.

Understanding the differences between "normal aging" and "pathological conditions seen more frequently with aging" help us better appreciate a older adult's needs that may impact treatment. While a patient may readily mark-up a medical history questionnaire with his/her medical conditions of hypertension or diabetes, there are no overt red flags of that person's decreasing pharmacokinetic capabilities that occur even in the absence of disease due to declining kidney function with age. As a result how an older person metabolizes and excretes the medications prescribed by the dentist should always be foremost in the prescribing practitioner's mind and geriatric dosing recommendations followed.

Variations from physiologic standards, even in those patients who indicate no appreciable medical conditions, need to be considered. One of the four vital signs, body temperature is a great example of this, for in the elderly, rarely achieved is a normal temperature of 98.2 degrees Fahrenheit, which is now considered normal for adults, with typical fluctuations in temperature throughout the day.[1] Rather, a mean body temperature of 97.4 to 97.8 degrees Fahrenheit is more acceptable as a normal temperature reading in older adults with no diurnal rise evident for the very old who are also typically the coldest.[2] This means that a fever in an older adult is likely to occur at a much lower level than in middle aged and younger adults and not be appreciated.

Furthermore, alterations to disease presentations (e.g., silent MIs) and response to therapy (e.g., syncope from medications) further defines the exceptional vulnerability to diseases and their complications seen in older

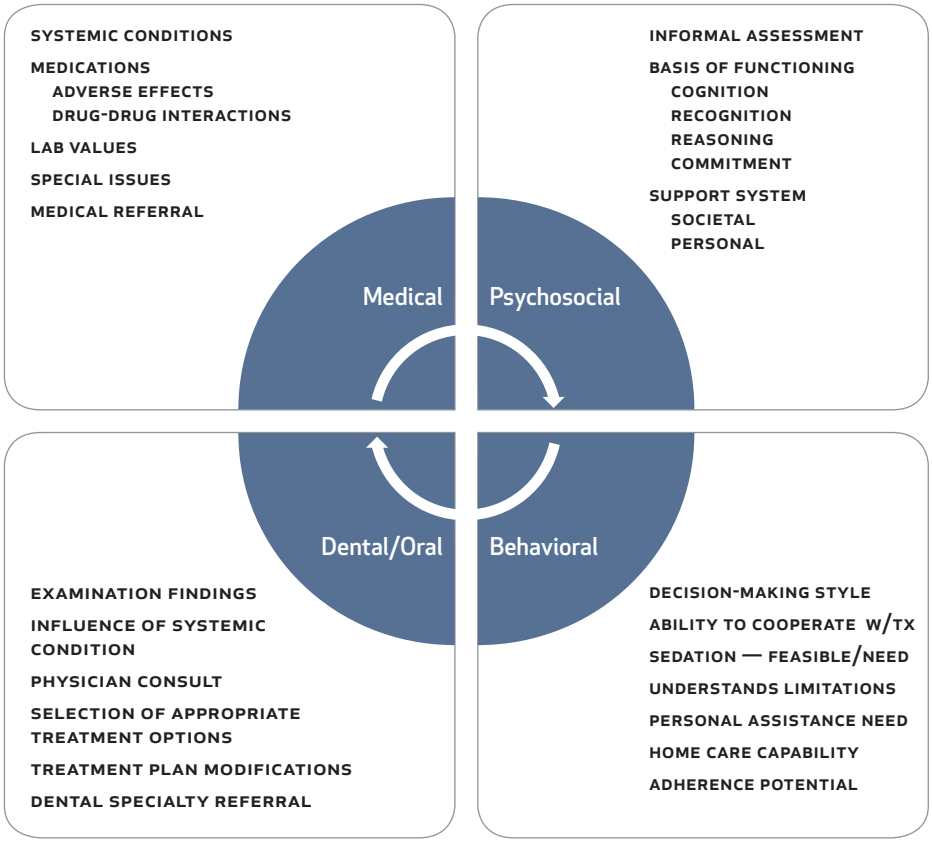

FIGURE 1. Geriatric dental care model: factors for consideration. The four factors of the framework: medical, psychosocial, behavioral, and dental/oral health reflect the unique interrelated components in a personal case history. Each specific factor is considered in the case study and how it will influence and determine the appropriate diagnostic plan. The model illustrates the process utilized for the practitioner's oral health assessment and treatment planning regarding the particular needs for the older adult patient.

adults. Clearly, dentistry for geriatric patients presents unique management challenges that, per a recent ADA survey, a large percentage of dentists are beginning to appreciate and feel they need to know more about, especially in the areas of managing patients with complex medical histories (68.5 percent), xerostomia (63.6 percent), manifesting dementia (49.1 percent), or having caries (48.7 percent).[3]

With certainty it is known that health and physical function decline over time. However, the rate of decline varies widely across individuals and systems with some organ systems actually demonstrating little to no decreases in capacity and biologic activity during function.[4] The impact of some aging changes can in some cases be fully or partially modifiable (e.g., eyeglasses and hearing aids), while other aging changes may not need any compensatory modifications (e.g., hair loss).

When functional declines are seen they are frequently due to one or more factors including physical health and/or medications, mental health including decreased cognition, feelings of fear/anxiety, or sensory deprivation. Given this complicated milieu it should be expected that aging successfully will require a multifaceted approach to care that considers not only the avoidance of disease but includes factors such as the individual's engagement with life, the maintenance of high physical and cognitive function, and the avoidance of disease related disability.[5]

Describing the Model

FIGURE 1 displays a model that lays out the various factors needing to be considered during the interaction between the dentist and older adult patient. This model depicts characteristics related to the medical, dental/oral, psychosocial, and behavioral considerations that may impact successful care delivery regardless of the setting. It is important to recognize that the model does not stop at the medical and dental/oral findings but must include the psychosocial and behavioral environment in which the patient is functioning, for factors in these areas are equally as important to successful treatment as are the physical findings. It also should be noted that although the factors are divided into discrete areas, there are many interactions between the various components, thus, the arrows in the central part of the figure are circled to call attention to how each area influences the others.

Medical

As might be anticipated the medical section includes any systemic health issues already diagnosed or undiagnosed conditions displaying signs or symptoms that may have been observed in the dental office. All medications (whether prescribed, over-the-counter or borrowed from friends, neighbors, family) are documented as is the potential for adverse reactions and interactions of those substances to new medications to be delivered, prescribed, or recommended by the dentist. This section includes the patient's lab values and referrals to other health care providers as any signs or symptoms observed during dental care may necessitate.

Finally, in this section are special considerations that might be needed such as prophylactic antibiotics, adjustment

to steroid therapy, or precautions due to bleeding risks as a result of a medical condition or current therapy. Given the high rate of chronic disease in those age 65 years and older, with 75 percent having one chronic condition and 50 percent having at least two such conditions, it is important that the treatment model consider all of the patients diagnosed, as well as covert medical problems.[6]

A medical history questionnaire with no positive findings should result in a high index of suspicion from the dentist and prompt a referral to a physician or a phone call or written consultation when there is already a physician of record (see the dental/oral section of the case model for actual comments regarding the physician consult). With 80 percent of older adults taking at least one prescription medication and nearly half taking three or more, the potential for side effects and adverse reactions due to medications is quite real.[7] Therefore, acquiring a thorough medication history and especially one that includes a listing of the 1.8 typical over-the-counter drugs likely to be taken daily by individuals 65 and over is critical.[8]

Psychosocial

While interacting with the patient to confirm and explore the specifics of each medical history finding and during the exam and assessment of the oral health status another activity is taking place: the informal assessment of the patient's psychological state, social variables and behavioral capability. To all appearances this information is obtained casually by the practitioner and oftentimes not documented in the chart; yet, the information acquired from the older adult in this manner may prove to be the key to the ultimate success of the chosen treatment. Through this interactive dialogue the practitioner forms an impression of whether the patient is operating from a basis grounded in reality.[9]

The patient's cognitive ability to follow a line of reasoning, to recognize and prioritize information provided, to understand the consequences of agreeing to or withholding consent, and the ability to commit to a plan of professional visits, regular home care, and long-term follow through, as well as the financial obligations that will accrue as a result of such acceptance become clear as the practitioner and patient interact.

A MEDICAL HISTORY questionnaire with no positive findings should result in a high index of suspicion from the dentist and prompt a referral to a physician.

A critical component of the psychosocial factors relates to the support system of the patient. Societal supports include ready availability of transportation and easy access to health care, housing and in-home health aides to name a few of the most sought-after services. In spite of the difficulty obtaining many of these supports, most elderly continue to live in traditional housing in the community throughout their older adult lifespan, with 93 percent living in such an arrangement through age 84, while a full 76 percent of individuals age 85 are still in their homes. When given the choice, aging in place is the desire of most older adults (89 percent).[10]

Successful aging in place though requires that the individual is able to maintain a home not only conducive to ongoing decreases in physical capabilities and motor skills, but that a personal support system is available with family, friends, neighbors, and spiritual advisers supplementing the community support systems that provide home maintenance and repair, shopping and meal preparation, socialization opportunities, financial counseling, grooming and bathing assistance, mental and spiritual counseling, and opportunities for employment and learning.[11,12]

Medicare enrollee records from 2005 demonstrate that 65 percent of U.S. adults 65 years or older have some difficulty in accomplishing activities of daily living, ADL, in one or more of the following areas: bathing, dressing, eating, getting in and out of chairs, walking or using the toilet, needing either equipment, or personal help to accomplish the task.[13] Learning about each patient's use of such supports better helps the practitioner understand the patient's strengths, limitations, and depth of resources.

Visits to the dental office or clinic by older adults will continue to be the usual model followed by most seeking oral health services. Long-term care or nursing home settings actually are the residences of very few older adults (1 percent at age 65-74) until the age of 85, whereupon the proportion jumps to 14 percent.[14] Given that nearly half of individuals who are currently 65 years old will live to age 85, it is likely that more practices will be challenged to provide dental care to skilled nursing home residents who are brought to them or need to be seen at their facilities.[15]

Behavioral

Older adults' decision-making styles may range from handing off decision-making to a practitioner who demonstrates a

paternal approach, to a desire for autonomy in all aspects of their care. It is important to understand their expectations and operational behavior and encourage the patient's family member to assist in making decisions when the patient is unable to do so himself/herself. Many of the findings in the medical and psychosocial sections previously described have an influence on the behavioral variables.

For example, an individual with advanced dementia would likely have difficulty in cooperating with dental care. One who cannot cooperate may be an appropriate candidate for one of the many sedative modalities, as long as the benefits outweigh the risks of the intervention.

Not all older adults understand their limitations or are willing to accept help when unable to perform tasks at the level of proficiency needed to adequately support their personal health and hygiene. This is when properly coached family and friends may help in providing personal care without infantilizing the individual. The ability to predict adherence to proposed treatment regimens is another area that needs assessment based in reality. Often times it is up to the dental practitioner to convey a realistic estimation of the effort needed for home care and debunk unrealistic assumptions (e.g., fixed prosthesis and the mistaken assumption that because they stay in the mouth and are porcelain or metal they will be easier to clean and less susceptible to disease).

Dental/Oral

The dental/oral section begins with the examination findings but also considers the influence of any systemic condition on the oral cavity. It includes a physician consult as needed to discover information about previously diagnosed systemic diseases, lab values, and more information about any additional signs or symptoms of ill-health as noted during the dental visit. Development of a treatment plan that results in a maintainable outcome must then consider the findings of the medical, psychosocial, and behavioral elements. This treatment plan would thus give consideration not only to the patient's medical problems and the progressiveness of a diagnosed condition, but also consider any declines, disabilities, or diminishing resources in the elements that contribute to the psychosocial and behavioral fields.

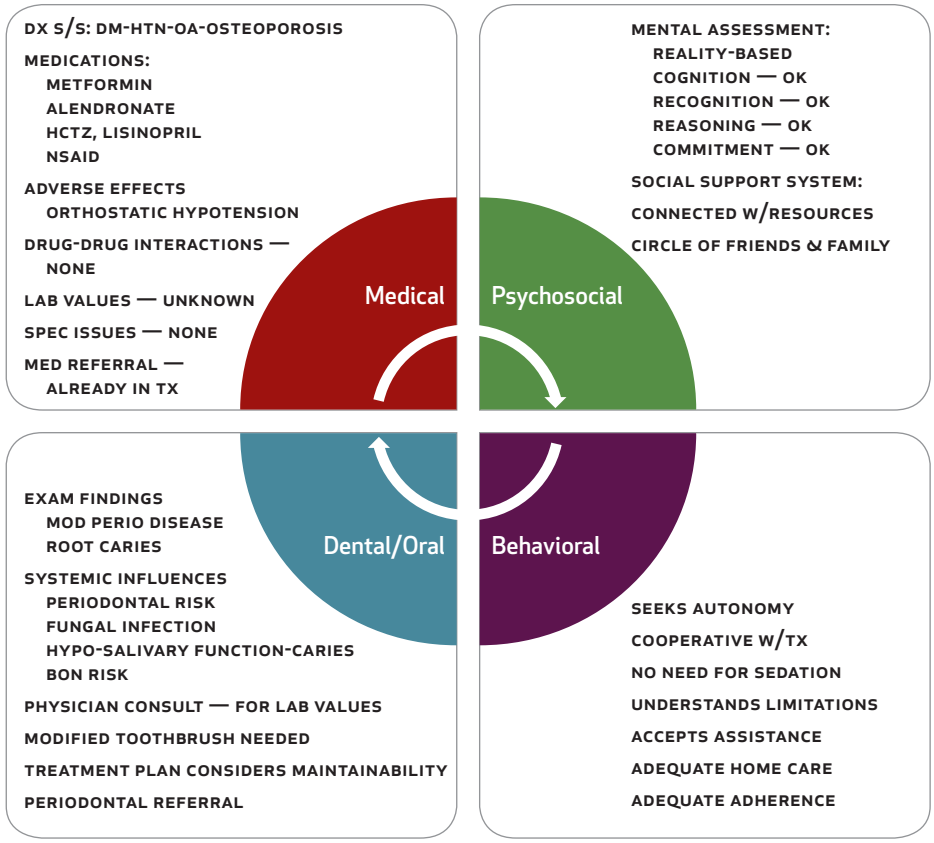

FIGURE 2. Geriatric dental care model: case study of MG: factors for consideration. The four factors of the framework: medical, psychosocial, behavioral, and dental/oral health reflect the unique interrelated components in MG's case history. Each specific factor is considered in MG's case study and how it will influence and determine the appropriate diagnostic plan. The model illustrates the process utilized for the practitioner's oral health assessment and treatment planning regarding the particular needs for MG's unique treatment plan.

Applying the Model to a Patient Case

FIGURE 2 displays the model with the results of patient MG who presents to your dental office for care. She is 92 years old and she arrived unescorted for her 10 a.m. appointment. She is wearing a very nice three-piece suit, shoes, and a matching purse complete her ensemble. When you ask if you can take a picture of her she immediately consents and strikes the pose of a photographer's model.

Medical

Using the systematic framework to investigate factors as previously described, it is learned about MG's diagnosis of diabetes (type 2), for which she is taking metformin; her hypertension is being controlled by hydocholothiazide (HCTZ) and lisinopril; she is self-medicating her osteoarthritis with over-the-counter NSAIDS; and her osteoporosis is being treated with the bisphosphonate, alendronate.

A review of the adverse effects of each drug indicates that orthostatic hypotension could be an outcome for individuals on anti-hypertensives. Therefore, cautioning the patient to stay seated in the dental chair after it is returned upright before allowing her to stand is important to allow adequate brain perfusion and eliminate the potential for fainting. By running the interaction feature of an online drug program you observe that none of the medications that this patient is presently taking are expected to interact with medications that are typically prescribed and delivered in the dental office (e.g., local anesthetics and antibiotics).

Since the patient does not check her blood glucose levels at home and doesn't really know what her levels are when she has her blood drawn at her physician's office or her hemoglobin A1C values (blood work typically used to monitor a patient with diabetes), a medical consultation would be in order. It would be wise, however, to complete the dental exam first, noting the presence and extent of oral disease and to develop a possible plan of treatment so that the scope of treatment issues such as extent of any surgery, resulting bacteremia, physiological and psychological stress, and healing is able to be estimated and provided to the physician.

Psychosocial

MG lives in a beach house in an upscale community in southern California and also has her own apartment in Paris. She indicates that she was widowed some years ago but that she gets along fine and still has her male friends whom she enjoys entertaining and who often bring her groceries. She is visiting your office because her current prostheses are unsatisfactory and her appearance is very important to her. She also thinks she has cavities as she has seen some discolored areas.

During this discussion, MG has no flights of fancy, she clearly recognizes the issues associated with her treatment, responds appropriately to questions asked, and states that her resources are not unlimited. She engages in a rationale discussion about treatment costs in time, inconvenience, and money relative to the benefits of an enhanced appearance and improved function. She also indicated that on her way to this first appointment she was pulled over by a highway patrol officer who told her she was going too slow on the freeway and that she needed to stop using the freeway or risk being ticketed. Since there exists no public transportation between her home and the dental office, she subsequently arranges for a college student from the nearby university to serve as her driver in later visits. She enjoys living alone, has a housekeeper who comes in regularly and cleans and cooks for her, and has many friends who take her out and run errands.

A REVIEW OF the adverse effects of each drug indicates that orthostatic hypotension could be an outcome for individuals on anti-hypertensives.

Behavioral

In the dental office, MG demonstrates her desire for individual autonomy taking an active role in all decisions related to her care. She is highly cooperative and looks forward to her treatment without anxiety. She understands the limitations of the various treatment choices and her own physical limitations related to reduced oral hygiene capability as a result of her osteoarthritis. Although she typically disregards automated personal hygiene devices, she is willing to use an automatic toothbrush to compensate for her reduced grip strength so that she can clean her mouth more thoroughly. She displays a willingness to adhere to treatment recommendations and strategies, an assessment that over time is borne out as treatment progresses and is completed.

Dental/Oral

MG's exam findings include moderate generalized periodontal disease and multiple carious lesions on root surfaces. Her periodontal disease is not unexpected given the increased rate of periodontal disease in diabetics, especially those who are not in good control. Fungal infection consistent with a putative diagnosis of *Pseudomembranous candidiasis* is found and is likely an outcome of her diabetes. Palpation of her salivary glands demonstrates a diminished salivary flow that is a contributory factor in the etiology of root caries. Her history of bisphosphonate therapy puts her at risk for osteonecrosis and, therefore, nontraumatizing prostheses and appropriate preparations prior to extractions must be part of the treatment protocols.

Due to the patient's lack of information about her diabetes, a consultation would be prudent to determine the laboratory values once possible treatment options are determined. Her osteoarthritis has affected her grip strength and decreased the effectiveness of her oral hygiene efforts; an automated toothbrush or alternatively a tooth-

brush with a modified handle will be recommended for her daily oral hygiene efforts as will home fluoride. Once the physician input has been considered a final treatment plan is arrived at that considers all of the patient's capabilities to maintain a healthy oral environment.

Why Is There Need for a Model?

As the number of older adults increases in the 21st century, dental practitioners need to recognize and carefully modify care delivery based on age-related and age-associated changes, diseases, drugs, and individual determinants that characterize each geriatric patient. This case outlines many of the challenges in maintaining the oral health of older adults, assuring good home care, and regular professional visits.

Clinical decision making for the dental care of older patients is becoming extremely complex, especially as more older patients will be dentate and demanding care. Gone are the days when treatment for an older adult routinely meant providing complete dentures; the edentulous rate for those ages 75 and older having fallen to an all time low of 30 percent in 2007 (as compared to a 1957 rate of 61 percent).[16,17]

Instead, the challenges of caries, especially root caries and the contribution of hyposalivary function to caries and periodontal conditions, the oral sequelae of systemic diseases (e.g., diabetes) and the incidence and prevalence of mucosal lesions, oral cancers, and traumatic injuries to the intraoral and extraoral facial structures are all issues that must be paramount in the treatment of older adults who are seeking dental care in record numbers.[18-22]

In spite of little dental insurance coverage for most older adults, oral health care-seeking behavior as measured by annual dental visit rates has significantly increased from 37 percent of those 65 years and older in 1983 to 58 percent in 2006.[23] In many cases, the barriers between the older adult and good oral health care are not always financial. Instead, a host of human, societal, educational, and bureaucratic barriers may exist and negatively impact the receipt of proper oral health care and treatment.

Due to the multifaceted nature of the geriatric patient, guidance would be helpful to assist the practitioner in caring for the older adult. Although the American Dental Association has in place 34 practice parameters, none of them deal specifically with caring for the elderly, but speak more broadly to issues such as caries, oral lesions, TMJ disorders, and exam components.[24] Another national source for clinical practice guidelines, the National Guidelines Clearing House, an initiative of the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services provides clinical practice guidelines to a wide variety of health professionals and purchasers of health care systems.[25] Unfortunately, of the 251 summaries about dental topics available, this resource has no guidelines on geriatric dentistry.

GONE ARE the days when treatment for an older adult routinely meant providing complete dentures.

Reshaping the Dental Treatment Perspective

The rising demographic tide in the numbers of older adults seeking dental care presents a variety of additional challenges including ethical conundrums, resource limitation issues, and innumerable adaptations, and compromises that are part of the unique realities faced by these individuals. Associated life events and demands placed on older adults unmistakably permeate multiple aspects of their lives. Although we are more used to confronting the medical and dental/oral variables as we sort through the potential confounders of a treatment plan, there are frequently numerous psychosocial and behavioral variables that can equally impact the outcome of oral health care.

Focusing on the less familiar inquiry and acquisition of information about the psychosocial and behavioral components involves gathering sufficient information to form a behavior profile, state and gain consensus on specific goals, and customize objectives that matches the individual's unique circumstances and personality.[26] Of course, the considerably lengthened life spans of many with serious medical conditions who are undergoing high-tech treatments, and/or the use of investigative or recently released to the marketplace drugs, creates its own challenges for the practitioner who may have had little experience or training in understanding the downsides, adverse reactions, or interactions of such treatments.

Changing social norms relating to the definition and treatment of illness are further factors to consider. The practitioner treating an older adult may be faced with a veritable blizzard of potentially relevant clinical information. How does this care giver decide on the most salient facts and make the most efficient clinical decisions about the process of care?

Preliminary evidence suggests that there is a need for a dental/oral diagnostic treatment planning process for the older patient in the context of medical illness, disability, psychosocial, and behavioral impoverishment.[27] Armed with facts about the myths and realities of aging, knowledgeable about the problems older adults face, and being cognizant of how to assess and treat oral health in older persons, dentists can maximize their efforts to treat this large, diverse, and important segment of our society.

Conclusion

The geriatric oral health model presented offers a framework for diagnostic treatment planning. More geriatric oral health models need to be developed and tested that integrate interdisciplinary health and nonhealth-related activities into the dental consciousness so that timely and appropriately targeted interventions may be applied. Following the model presented with consideration given to the psychosocial, behavioral, and medical presentation of the older patient may prove to be the key to the ultimate success for adherence of the chosen dental treatment arrived at collaboratively between the dentist and the older patient. ■■■■

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TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT Roseann Mulligan, DDS, MS, University of Southern California, School of Dentistry, 925 W. 34th St., Los Angeles, Calif., 90089.

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Oral Health and HIV Infection: A Chronic Disease Model

FARIBA S. YOUNAI, DDS, AND CRAIG VINCENT-JONES, MHA

ABSTRACT HIV disease is now considered a chronic illness requiring continued management and monitoring. However, for those with poor access to anti-retroviral medications, the disease continues to be associated with higher morbidity and mortality. With the expansion of the HIV pandemic into vulnerable subpopulations, HIV care requires coordinated and integrated care for a complex mix of psychosocial and clinical services that must include oral health care.

AUTHORS

Fariba S. Younai, DDS, is a clinical professor of oral medicine and orofacial pain in the Division of Oral Biology and Medicine at the University of California, Los Angeles, School of Dentistry.

Craig Vincent-Jones, MHA, is executive director of the Los Angeles County Commission on HIV in Los Angeles.

The HIV pandemic remains the most serious infectious disease challenge to global public health. Worldwide, more than 6,800 people become infected with HIV every day and more than 5,700 individuals die from AIDS leading to an ever-growing number of individuals living with HIV.[1]

The incidence of HIV has decreased in many parts of the world including North America, Western Europe, and even in sub-Saharan Africa. However, in Latin America, Asia, and Eastern Europe, new patterns of the HIV epidemic have emerged.

Despite a decline in prevalence that has continued since the year 2000, sub-Saharan Africa remains the hardest-hit region in the world where the adult prevalence is estimated at 5 percent and HIV accounted for 76 percent of all deaths in 2007.[2] In Eastern Europe, the total number of people with HIV increased 150 percent between 2001 and 2007, and 90 percent of the new cases (about 150,000) occurred in the Russian Federation and Ukraine in 2007.[1] The estimated number of people living with HIV/AIDS is 7.4 million in Southeast Asia, 1.8 million in Latin America, and 1.6 million in Eastern Europe and Central Asia.[1] Globally, since 1990, almost half of the world's AIDS cases have been women.[1]

In the United States, cumulative data from 1981 to 2007 shows reports of more than 1,051,000 cases of AIDS and more than 560,000 AIDS-related deaths.[3] It is estimated that almost 1.2 million individuals are currently living with HIV in the United States, with more than 25 percent undiagnosed and unaware of their infection.[3] In August 2008, the Centers for Disease Control and Prevention reported the use of new epidemiologic methods that led to a significant

revision in the estimated number of new HIV infections in the United States.[4]

Based on extrapolations from the estimated number of new infections in 2006, the previous estimated incidence rate of 40,000 was adjusted to 56,300, a rate that it is believed has been relatively stable since the late 1990s. In California, there are more than 66,000 individuals living with HIV/AIDS.[5] In 2006, an estimated 935 new HIV cases were reported in San Francisco, an incidence rate that is most likely stable for this geographic area.[6] In Los Angeles, an accurate HIV incidence rate is not yet available. However, at the end of 2008, a total of 23,679 people were reported to be living with HIV/AIDS and another 18,124 people were reported to be living with HIV/no AIDS (unpublished data).[5]

Worldwide, the predominant HIV transmission mode is heterosexual, with two broad patterns identified. The first pattern is a generalized epidemic sustained in the general populations of many sub-Saharan African countries; the second is the epidemic most common in the rest of the world, primarily concentrated among populations most at risk.[1] The at-risk populations include men who have sex with men, injecting drug users, and sex workers and their sexual partners. The most common form of transmission in the United States HIV epidemic is men having sex with men, MSM. Of new HIV infections among males in 2006, 72 percent were MSM. Among MSM with new infections, 46 percent were white (67 percent of general population), 35 percent were black (13 percent of general population), and 19 percent were Hispanic/Latino (15 percent of general population).[7] Of all new infections among women in 2006, 73 percent of transmissions occurred as a result of high-risk heterosexual contact and 68 percent were in black women.[3]

Current State of HIV Disease Management

HIV disease is a spectrum ranging from an asymptomatic phase to severe immunosuppression manifested by many types of opportunistic infections and malignancies. The mechanisms involved in immunologic suppression comprise a variety of immunologic defects that include severe reduction in the CD4 positive T-lymphocytes, cytokine dysregulation, and defective innate immune responses.[8] It is now widely accepted that intervention with anti-retroviral (ARV) drugs and adherence to appropriate medications can prolong life and delay HIV disease progression.

WORLDWIDE, the predominant HIV transmission mode is heterosexual, with two broad patterns identified.

Since the discovery of the very first anti-HIV compound, Zidovudine (AZT), more than 21 years ago, great advances have been made in understanding the disease pathogenesis. The translation of that knowledge into practical therapeutics has led to the development of more than 30 individual drugs and combinations for treatment of HIV infection. Despite these advances, disease management remains challenged by toxicities, treatment maintenance and adherence, clinical manifestations of the disease and the drugs used to treat it, and the threat of drug resistance.[8] In recent years, newer formulations of ARVs have been developed that are more potent, produce durable results, and are less toxic.[8]

Current HIV/AIDS treatment guidelines recommend that anti-HIV treatment should be initiated for all symptomatic patients and asymptomatic individuals before the CD4 count goes below 350/mm^3.[8] Studies showed that if left untreated at this marker, the risk of the disease progressing to opportunistic infections and death within two years approximates 30 percent.[8] As even the CD4 counts higher than 350/mm^3 have been shown to be associated with increased mortality, malignancies (lymphomas, lung, anal, head and neck cancers), and major organ system dysfunction (cardiac, hepatic, renal), whenever possible, ARVs should be considered as early as possible.[9-16] A decision to begin ARV for higher CD4 counts depends on patient readiness, drug interactions, adherence challenges, toxicities, and costs of treatment, recognizing that treatment must be sustained.[8] Factors that call for earlier therapy include rapidly declining CD4 count, high viral load, the presence of comorbid conditions, and other clinical indications, such as chronic HBV infection and HIV-associated nephropathy.[8] In addition, risk factors for cardiovascular disease, such as hypertension, hyperlipidemia, diabetes, and tobacco use, should be aggressively managed in all patients.[8]

Mechanisms of Anti-Retroviral Treatment

Strategies in HIV disease treatment involve intervention at several junctures of HIV infection and replication. The HIV life cycle includes six main stages: entry, reverse transcription of RNA into DNA, integration of proviral DNA into host DNA, transcription back to mRNA, viral assembly, and host cell lysis. Currently,

there are 32 FDA-approved ARV agents and combinations that address several of these replicative stages. The classes of those ARVs include 1) nucleoside reverse transcriptase inhibitors (NRTI), 2) non-nucleoside reverse transcriptase inhibitors (NNRTI), 3) protease inhibitors (PI), 4) entry and fusion inhibitors, and 5) integrase inhibitors.[17]

The primary aim of anti-HIV treatment is to provide a durable suppression of HIV replication that is below detection limits of plasma HIV RNA assays.[18] Durable viral suppression results in fewer drug-resistant viral variants that occur through random mutations during the high rate of HIV replication and mostly because of poor patient adherence to medication regimen. The current ARV combination regimen for treatment-naïve patients is two NRTIs and either one NNRTI or two PIs (protease inhibitor-boosted regimen) (**TABLE 1**).

Baseline genotypic testing for resistance should be performed in all treatment-naïve patients to determine the best choice for the ARV regimen.[8] The other classes of drugs, fusion, and integrase inhibitors are used in treatment-experienced patients after other regimens have failed (salvage therapy). Combination formulations of two NRTIs (Combivir, Epzicom, Truvada), three NRTIs (Trizivir), two PIs (Kaletra), or multiclass combinations of two NRTIs and one NNRTI (tenofovir + emtricitabine + efavirenz or Atripla) have made medication adherence easier for many patients.

Long-term use of ARVs may be associated with a number of clinical sequelae, including metabolic complications, cardiovascular disease, musculoskeletal presentations, and certain types of cancers. Metabolic complications include hyperglycemia, insulin resistance, and hyperlipidemia (elevations in total cholesterol, LDL, and triglycerides) mostly caused by older formulations of PIs.[19] Lipoatrophy or peripheral fat-wasting occurs with NRTI use while visceral fat deposition is associated with hyperinsulinemia and dyslipidemia.[20,21]

Increased risk for coronary heart disease may be attributed to a number of factors, including metabolic alterations, changes in body composition (with loss of subcutaneous fat and/or accumulation of visceral fat), inflammation, the direct effects of the virus on the vasculature, and as a result of specific anti-retroviral drugs.[22] Specific guidelines for reducing the risk of these complications have been published.[23,24] Other consequences of ARV use include osteoporosis and avascular necrosis in bones, prostate neoplasia, and lethal solid tumors such as NHL associated mostly with NNRTIs.[25-27]

THE PRIMARY AIM of anti-HIV treatment is to provide a durable suppression of HIV replication that is below detection limits of plasma HIV RNA assays.

New Intervention Strategies

Current ARV drug development focuses on HIV entry into host cells and the specific regulatory mechanisms necessary for either successful viral replication or its release from the host cells. An entry inhibitor has already been marketed for clinical use, and new therapeutic agents targeting HIV regulatory gene products are in development. As reviewed by Greene et. al., some of the specific new therapeutic targets include the integrase enzyme cofactor LEDGF/p75; several innate immune factors, such as TRIM5α that restrict HIV integration; APOBEC 3G that interferes with viral DNA synthesis; and Tetherin that blocks viral release.[28]

Viral Entry

HIV attacks CD4 receptors on the surface of cells like lymphocytes and macrophages, and attaches to the receptor through gp120. There is evidence that there are additional receptors involved in the attachment process. The natural chemokine receptors, such as CCR5 and CXCR4, act as coreceptors for HIV anchorage and host cell entry[29] (**FIGURE 1**). The R5 strain of HIV has an affinity for the CCR5 receptor and is the predominant type of HIV in mucosal transmission — distinct from the X4 strain of HIV that is primarily transmitted through blood exposure and with the primary CXCR4 coreceptor.

Due to genetic variability, people who do not fully express these coreceptors on the HIV target cells are either immune to HIV infection or their HIV disease does not progress as rapidly compared to people with full coreceptor expression. One of the reported genetic mutations involves a 32-base pair deletion in CCR5 receptor (CCR5-Δ32 allele) that infers resistance in those who are homozygote for the mutation and slow progression for the heterozygotes.[30,31] The CCR5-Δ32 allele is mainly present in Europeans (10 percent on average); the allele frequency is highest (>15 percent) in the areas surrounding the Baltic and White seas, and in Central Russia.[32]

The mutation frequency gradually decreases in all directions across Europe and is found with the lowest frequency in the Mediterranean area, North Africa, Middle East, Central Asia, and is absent in sub-Saharan Africa, east and Southeast

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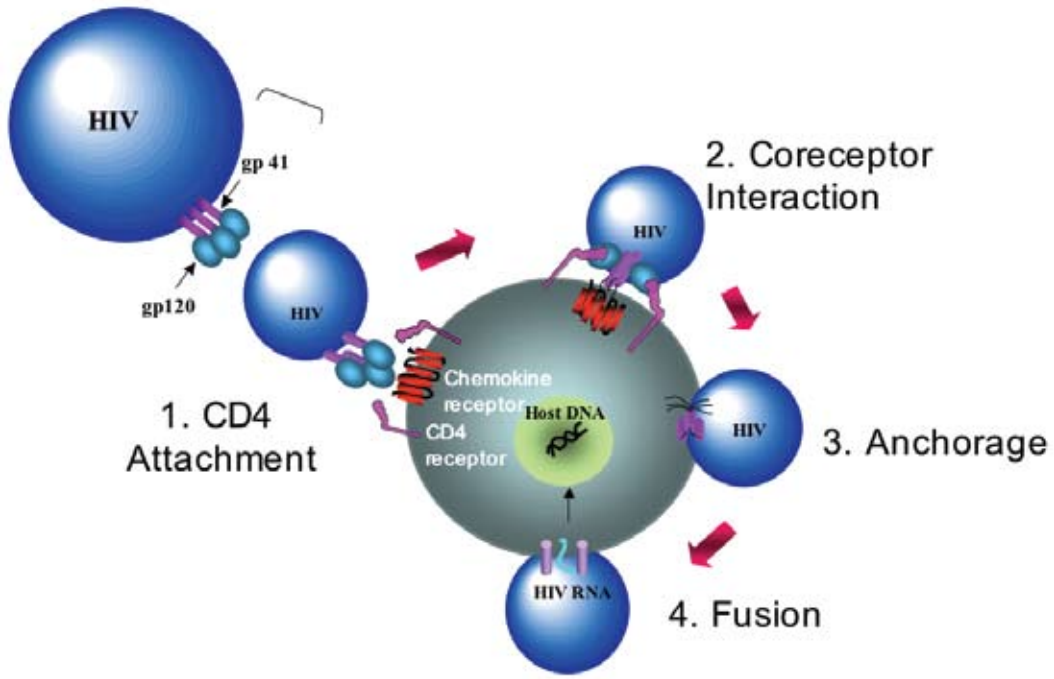
TABLE 1

Major FDA-Approved Anti-HIV Medications

Drug Class	NRTIs	NNRTIs	PIs	Integrase Inhibitors	Entry Inhibitors
Main formulations	AZT – zidovudine (Retrovir) ddI - didanosine (*Videx*) ddC - zalcitabine (*Hivid*) d4T- stavudine (*Zerit*) 3TC - lamivudine (*Epivir*) ABC - abacavir (*Ziagen*) TDF - tenofovir (*Viread*) FTC – emtricitabine (*Emtriva*) **Combinations** Zidovudine + lamivudine (*Combivir*) Abacavir + lamivudine (*Epzicom*) Abacavir + zidovudine + lamivudine (*Trizivir*) Tenofovir + emtricitabine (*Truvada*)	ETV – etravirine (*Intelence*) DLV – delaviridine (*Rescriptor*) EFV – efavirenz (*Sustiva*) NVP – nevirapine (*Viramune*)	APV - amprenavir (*Agenerase*) TPV - tipranavir (*Aptivus*) SQV – saquinavir (*Invirase*) IDV – indinavir (*Crixivan*) FPV - fosamprenavir (*Lexiva*) RTV – ritonavir (*Norvir*) DRV – darunavir (*Perzista*) ATZ – atazanavir (*Reyataz*) NFV – nelfinavir (*Viracept*) **Combination** Loprinavir + Ritonavir (*Kaletra*)	Raltegravir (*Isentress*)	ENF – enfuvirtide (*Fuzeon*) Maraviroc (*Selzentri*)
Advantages	• Easy dosing schedule • Little food effect • Dual NRT established as the backbone of combination therapy • Fewer drug interactions	• Low toxicity • Impressive long-term results • Less lipid abnormalities • Saves PIs for future use	• High genetic threshold	• Useful for treatment experienced patients with multiple drug resistance	• Useful for treatment experienced patients with multiple drug resistance
Disadvantages	• Some members lead to serious side effects	• Low genetic barrier for mutation • Cross-resistance • Potential for CYP450 drug interactions • Side effects	• Complex food requirements • Cross-resistance is common & have severe side effects • CYP3A4 inhibitors and substrate • Drug interaction • Side effects	• Effectiveness in treatment naïve patients still being studied	• Effectiveness in treatment naïve patients still being studied • Maraviroc only effective against R5 strain
Major side effects	• Peripheral neuropathy • Myopathy, cardiomyopathy & myositis • Lactic acidosis (lactate >2-5 mmol/dL plus symptoms) • Nausea, vomiting, abdominal pain, muscle weakness • Hepatic steatosis (adiposis) • Lipodystrophy • Pancreatitis • Bone marrow suppression Side effects worse w/ older formulations	• Rash • Drug-drug interactions **Nevirapine** • Hepatotoxicity • Stevens-Johnson syndrome **Efavirenz** • Neuropsychiatric effects • Teratogenic in primates (FDA Pregnancy Class D)	• Insulin resistance and relative insulin deficiency • Hyperlipidemia • Lipodystrophy • Elevated liver function tests/ hepatotoxicity • Osteonecrosis & osteoporosis (increased in corticosteroid tx, alcohol abuse) • Hyperlipidemia, • Possible increased bleeding risk in hemophiliacs • Drug-drug interactions Side effects worse w/ older formulations	• Depression • Suicidal tendencies • Diarrhea • Headaches • Stevens-Johnson syndrome	**Fuzeon** • Injection-site reactions • Hypersensitivity reaction • Increased risk of bacterial pneumonia • Risk of kidney dysfunction **Maraviroc** • Bladder irritation • Hepatitis • Hypercholestrolemia

Note: Table does not include multiclass combination drug Atripla (efavirenz [NNRTI] + tenofovir [NRTI] + emtricitabine [NRTI]).



Chemokine receptors: CCR5 found on macrophages & CSCR4 found on T-lymphocytes

FIGURE 1. HIV entry.

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Asia, and in indigenous populations of the Americas and Oceania.[32] Considering these observations, developing compounds capable of blocking the HIV-coreceptor interaction has been one of the main targets of anti-HIV drug development for years. With the creation of Maraviroc (Selzentri), a medication that causes a structural change in the CCR5 coreceptor, a new approach has become available in blocking HIV infection or progression.[17]

In addition, monoclonal antibodies (mAbs) against CCR5 have entered clinical testing as potential therapeutic agents in the near future.[33] A viral assay (Trofile Assay, Monogram Biosciences) has been developed to determine the proportion of the HIV viruses in an individual with the R5 strain. Using information obtained from this assay, Maraviroc may be used to block HIV entry in individuals infected with the R5 strain.

HIV Regulatory Genes

The very simple HIV genome consists of three structural and at least six regulatory genes. The structural genes include env encoding for the viral capsid proteins (gp 120 and gp 41, the main sites for interactions with CD4 receptors); gag encoding for the matrix and core proteins (p17 and p24); and pol encoding for the key viral enzymes (protease, reverse transciptase, and integrase). As described earlier, current anti-HIV drugs mainly target the key viral enzymes that are necessary for replication and assembly.

However, with greater understanding of the role of HIV regulatory genes, Tat, Rev, Nef, Vif, Vpr, Vpx, Vpu, novel approaches to treatment may be on the horizon. The HIV regulatory genes and their protein products interfere with a number of host immune mechanisms that help enhance viral RNA transcription and processing, lead to cytokine dysregulation, or induce host cell cycle arrest and apoptosis.[34-37]

Of all the regulatory genes, Vif has been shown to have great efficiency crippling an innate host defense molecule "Apolipoprotein B" or "APOBEC 3G," a polypeptide responsible for amino acid substitution on newly synthesized viral DNA that interrupts HIV replocation[38,39] (**FIGURE 2**). Viral Vpr gene appears to aid in this process as well.[40] Vpu is effective against another host defense molecule, "Tetherin," a membrane protein (CD317) with nonspecific anti-viral properties that blocks the envelope protein release[41] (**FIGURE 2**). Vif and Vpu function are among several prime targets for new classes of anti-HIV drugs.[28]

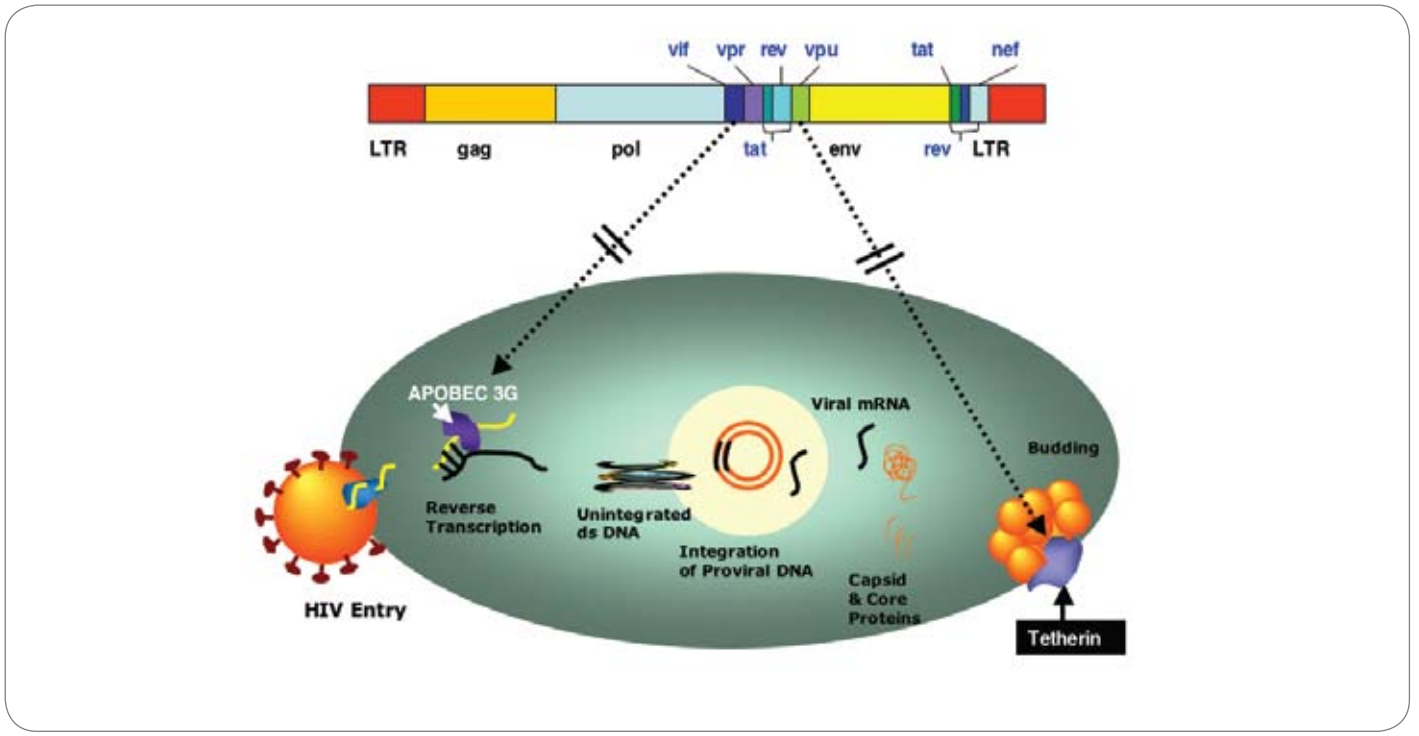

FIGURE 2. HIV genes and life cycle.

HIV Infection and Oral Health

Scientific discoveries in HIV medical management have transformed HIV infection from a rapidly progressive terminal disease to a chronic illness that can be compatible with a long and productive life for patients. The role of oral care providers in overall HIV management has evolved consistent with the changing face of the disease and its comorbid conditions. In patients who are receiving appropriate medical care, oral health care is focused on treating chronic oral diseases, restoring function, and improving a patient's quality of life. This is in stark contrast with the urgent oral care needs of individuals who are not receiving adequate or appropriate medical care, are failing ARV treatment, or are experiencing oral side effects of HIV-related or unrelated treatments.

Epidemiologic reports have indicated that with adequate ARV treatment, the incidence and prevalence of many HIV-related soft tissue pathologies have significantly decreased.[42-47] Clinical detection of oral soft tissue lesions is associated with a low CD4 count and high HIV viral load, inferring inadequate treatment, development of resistance, and therapeutic failure among those receiving ARVs.[48-55] However, with optimal ARV treatment, the decline in prevalence is not uniformly observed for all types of HIV-related head and neck manifestations. Among patients receiving ARVs, an increase in prevalence of human papilloma virus (HPV)-related lesions and salivary gland disease (HIVSGD) has been reported.[42,43,56-58] In addition, approximately 20 percent of patients who start ARV treatment experience specific clinical events associated with immune reconstitution inflammatory syndrome, IRIS.[59-63]

This phenomenon, reported among people who start treatment when their CD4 counts are very low and their viral loads are high, consists of clinical emergence of a prior subclinical infection or severe recurrence of an old condition.[63] Manifestations of IRIS have been reported to include mostly dermatologic lesions such as anogenital herpes, genital warts, molluscum contagiosum, and varicella zoster, as well as other conditions like mycobacterial infections, hepatitis B and Kaposi's sarcoma.[62,63]

Opportunistic oral infections and parotid enlargement have also been implicated in the clinical spectrum of IRIS.[64,65] In considering oral soft tissue lesion prevalence rates, another caveat is the pattern observed in the developing world, where the level of access to ARVs is extremely variable among different countries.[66-69] With less access to fewer ARVs, HIV-related oral manifestations continue to be reported in high prevalence rates in many regions of the world.[70-77] In a comprehensive review of HIV-related oral lesions worldwide, oral candidiasis was noted as the most common opportunistic infection reported in high rates among the adult and pediatric populations.[77]

HIV Disease Management Models of Care

The many medical advances in HIV disease management described in this paper have contributed to the evolution of HIV infection into a chronic disease where infected persons who can ac-

cess proper medical treatments can live longer, more normal lives. On the other hand, like other complex chronic diseases, HIV infection may be associated with a myriad of clinical presentations that occur at any point in the course of the disease that can lead to severe complications, morbid conditions, and major disabilities. As a result, preventive measures, early detection, timely intervention and long-term monitoring are key components of HIV care. Concurrently, ethnic minority populations, the poor, and people living with co-occurring illnesses, substance abuse and/or mental health diagnoses are increasingly more vulnerable to HIV exposure and infection. Overall, treatment of HIV seropositive patients and the affected, complicated subpopulations has become more challenging, requiring integrated and coordinated approaches to care.[78]

There are numerous models for managing patients' care and treatment, including integrated care, disease management, chronic care, and care coordination that may be considered for implementation in the HIV field as HIV is increasingly characterized as a chronic, rather than terminal, disease. *Integrated care* actively combines interventions in order to treat presenting disorders and the needs of the whole person more effectively.[79] *Disease management* emphasizes evidence-based interventions and outcome evaluation.[80] The *chronic care model* represents a shift from acute episode-based service delivery to a holistic approach that includes biological, psychosocial, social, and environmental needs of an individual.[81] *Care coordination* involves the development of a comprehensive assessment as the patient enters care, of all of their biological, psychological, and social needs so they can be addressed, as needed, concurrently.[82]

Incorporating Oral Health Care in the HIV Continuum of Care

Oral care providers must remain knowledgeable about HIV-related head and neck manifestations and their relationship with HIV disease status. The presence of oral opportunistic infections and malignancies not only correlates with the effectiveness of anti-HIV treatments and the degree of immunologic suppression or rebound described earlier, but also has new implications for oral health itself. For instance, the higher prevalence of HPV-related lesions may contribute to oral cancer development.[83] Similarly, the presence of xerostomia and its deleterious effects on dentition, periodontal structures, and oral mucosa must be considered when monitoring for caries, periodontal conditions, and oral mucosal diseases. For all people living with HIV/AIDS, PLWHA, vigilance in detection, prevention, and treatment of all oral diseases remains critical. Therefore, access to routine dental care, as well as referral to specialty clinics, must remain a priority in the overall spectrum of HIV care.

ORAL CARE PROVIDERS must remain knowledgeable about HIV-related head and neck manifestations and their relationship with HIV disease status.

Studies in the United States have consistently shown significant disparities in PLWHA accessing and utilizing oral health services; these disparities are primarily driven by an individual's socioeconomic characteristics.[83-89] Most recently, in a national survey of 1,802 respondents, dental care was identified as the highest unmet need for all participants.[90] These observations are reported while there are public dental insurance programs and funding under the Ryan White HIV/AIDS Treatment Modernization Act that support, in part, the provision of oral health services for PLWHA.[91,92] For many who depend on public programs, referral and utilization of dental services is mostly episodic and only for urgent-type care.[93] Therefore, in designing, funding, and implementing an HIV spectrum of care, in both private and public insurance systems, timely access to routine dental care and referral to specialty clinics must be considered a priority and oral health services should be included in the overall HIV care scheme.

The authors propose a model of care that was recently developed within the Ryan White Care system in Los Angeles County.[94,95] This model of care involves a system of care coordination where every patient entering care is assessed, comprehensively, for all their needs and is guided through collaborative service delivery to ensure optimal health outcomes.[96] The new care coordination model allows for a significantly enhanced prominence for oral health care — a long-identified unmet need of HIV patients in the region. Previously, oral health needs were only addressed when the patient requested them or a medical provider identified them during the medical exam. In the new continuum, oral health care is included in the medical cluster as part of core medical services and oral health examination and determination of a patient's need for oral health services are a part of the initial comprehensive patient assessment. Furthermore, in planning the medical care coordination model and the new comprehensive HIV continuum of care, outcomes-based evaluation and assessment methods for clinical

service delivery have emerged. Specific oral health measures are included as a part of the overall health outcomes targeted for this local HIV service delivery system.

Conclusion

Recent advances in HIV medical management have transformed HIV infection from a terminal disease into a chronic illness requiring continued management and careful monitoring. The improved general health observed in patients is also associated with lower prevalence rates for many HIV-related oral soft tissue lesions, while new oral health implications have emerged. In the current state of the HIV epidemic, the link between oral and systemic health is especially important because of the relationship between oral findings and HIV status, as well as the impact of oral health in a patient's functional state and quality of life. HIV care exceedingly requires coordinated care and oral health care must be viewed as a critical component of the overall HIV disease management. As many HIV/AIDS services programs around the country are developing and adopting chronic disease models of care, dental care providers must remain engaged in the process to ensure the integration of oral health services in the HIV continuum of care. ■■■■

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TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT

Fariba S. Younai, DDS, University of California, Los Angeles, School of Dentistry, 10833 Le Conte Ave., Los Angeles, Calif., 90095-1668.

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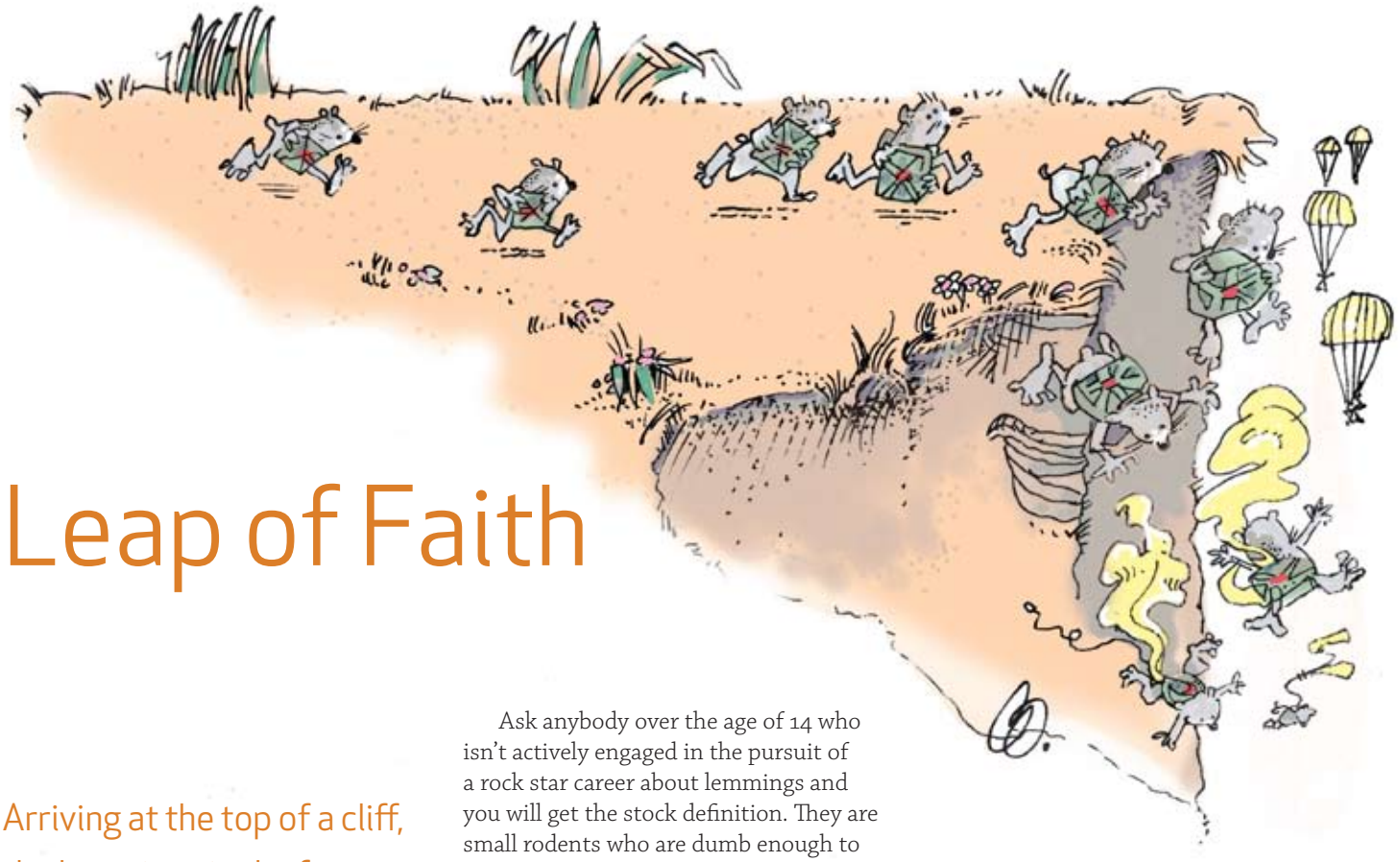

Leap of Faith

Arriving at the top of a cliff, the lemmings in the front row screech to a halt, peering cautiously over the edge to determine their next move.

Robert E. Horseman, DDS

ILLUSTRATION BY CHARLIE O. HAYWARD

Ask anybody over the age of 14 who isn't actively engaged in the pursuit of a rock star career about lemmings and you will get the stock definition. They are small rodents who are dumb enough to follow their leaders over cliffs thus satisfying an inherited "mass suicide" gene. This is a myth and a misconception. The fact is that lemmings breed like there is a government program subsidizing large families. Because of being equipped with continuously growing incisors that allow them to devour areas as large as Delaware in a single afternoon, they eventually have to move on like migrating caribou in search of food.

Arriving at the top of a cliff, the lemmings in the front row screech to a halt, peering cautiously over the edge to determine their next move. "Whoa!" they cry, frantically waving their little paws to alert the mob behind them. Obeying one of Newton's immutable Laws of Motion that states a mob in motion tends to remain in motion until hosed down by water cannons or police batons, the results are inevitable — they protest to the gathered media and the ACLU moves in swiftly. No, actually they all go over like base jumpers who have forgotten their chutes.

With that in mind, turn your attention to a state park in Montana some 23 miles south of Bozeman. This is the Madison Buffalo Jump State Park, a site featuring a limestone cliff where for 2,000 years buffalo used to hurl themselves off into space playing a fatal game of follow-the-leader. In this instance, the leader was an American Indian dressed up in a cheap buffalo suit. Behind the thundering herd were other native Indians waving wigwams and shouting, "Go, buffalo!" Picture a thousand Dumbos without ears. Consider a lot of American Indians without refrigerators coping with 200,000 pounds of buffalo steaks.

The result was inevitable because buffalo, individually and collectively, are

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no smarter than cows and would make the average lemming look like a Mensa candidate. Aerodynamically challenged, their remaining survivors hang around places like Yellowstone National Park and would probably still jump off a cliff if they could find one. Today, there are signs posted at the park prohibiting visitors from disguising themselves as American Bison and importuning the beasts to follow them to the nearest hazard. If a nostalgic buffalo, reviewing the glories of the old days, should launch himself off a cliff of his own volition, it simply means six more weeks of winter.

Stay with me here. The grizzly bear is an animal with plenty of smarts, as evidenced by its point-blank refusal to leap off cliffs. Lacking any ordnance beyond his claws and a set of teeth capable of devouring a Volkswagen, the grizzly nearly was hunted to extinction by people who should know better. They bought into the myth the bear's strength would be magically transferred to any daring sportsman who could dispatch the animal with a cardiac-piercing bullet safely beyond the reach of tooth and nail. Others wanted a taxidermist to stuff the 9-foot-behemoth to impress other like-minded morons.

Although the Adopt-a-Grizzly program never got off the ground, thanks to overprotective mothers, the Friends-of-Ursus Arctos Horribilis enthusiastically convinced the government to fund a $4.8 million dollar five-year study to determine if a committee could be formed to study the feasibility of creating a series of subcommittees that would put together a program dedicated to the environmental impact study of a Grizzly Awareness month. As a result, the U.S. Geological Survey recently announced the number of grizzly bears in Montana had now reached 765 individuals. They have rebounded! The bears, in turn, announced there would be no more help from them until the name "Horribilis" was removed from its Latinized designation. It sounded too much like Hagar the Horrible.

The point is, they rebounded, thus giving heart and encouragement to a group of old-fashioned dentists who are not comfortable with their view of where dentistry as a profession is going. It's one thing, the solo practitioners say, to see large clinics employing dozens of dentists embodying all the specialties and advertising their wares to the public in every media, but it's quite another to see restorative and preventive dentistry sharing seemingly unrelated amenities. Hand and foot massages, Botox injections and dental hygiene supplies for sale, they deplore, are more appropriate in an atmosphere commonly found at Costco and MiLadies Spa.

Take heart, you old timers, you solo operators in your 1,000-square-foot-kingdoms. Extinction is possible, of course, but so is rebounding. You don't have to jump off the cliff. ■■■■