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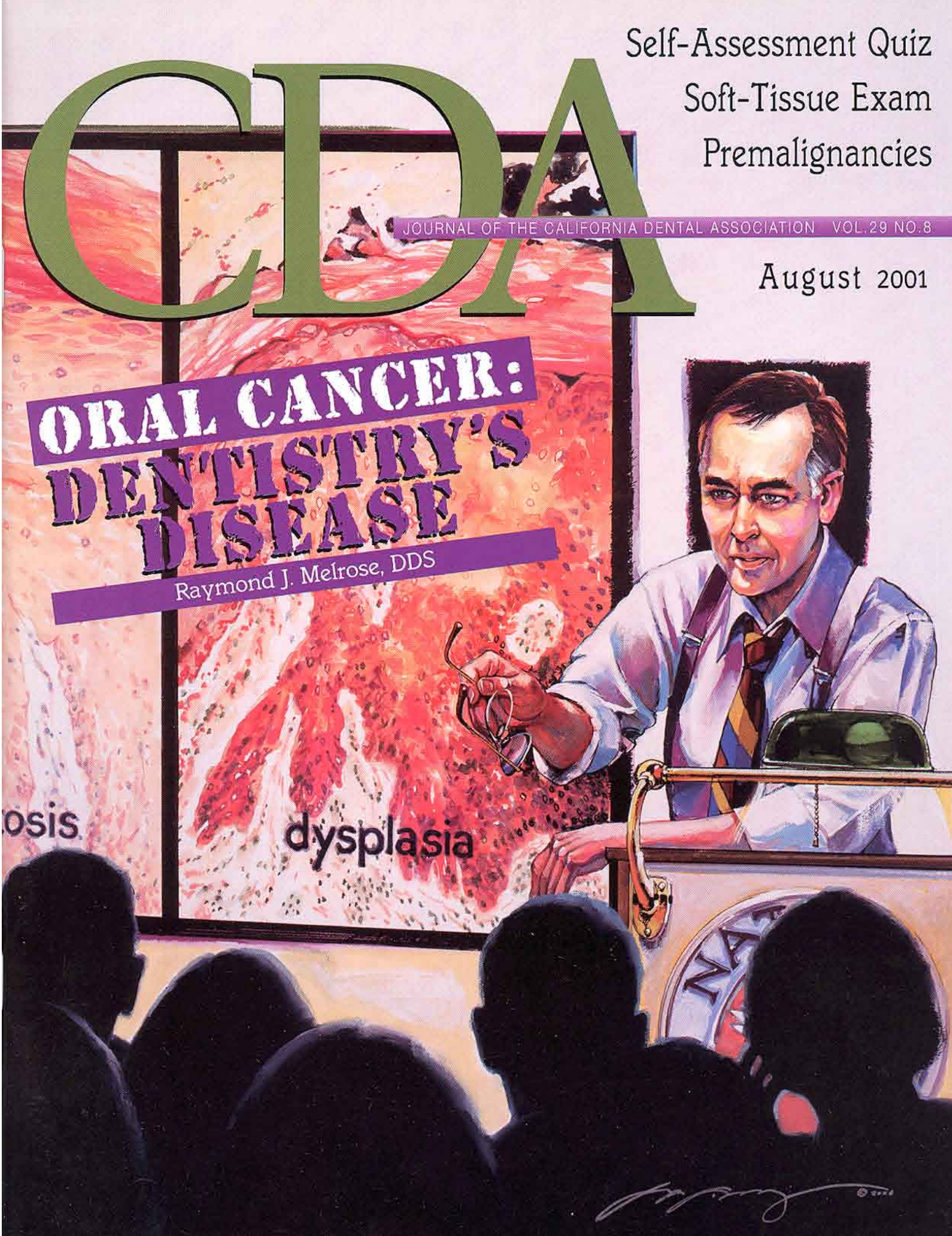
ORAL CANCER: DENTISTRY'S DISEASE

Raymond J. Melrose, DDS



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DEPARTMENTS

FEATURES

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The Cost of the Amalgam Issue

Jack F. Conley, DDS

As we move through the second half of the year 2001, we find the dental profession in California at the center of two controversies regarding the health and safety of the public. The safety of mercury in dental amalgam is pivotal to both.

At this point, we have no idea of what the final compromises, decisions, or agreements will be. To us, it is not just a matter of whether dentistry wins or loses, or whether other groups claiming to represent the best health interests of the public prevail. Our analysis suggests that the only real winners will be the legal interests who are driving the public controversy over mercury and other materials used in dentistry that have been alleged to be hazardous to health.

We are concerned about the debates that have consumed more than their share of organized dentistry's attention in the first half of 2001. If the private enforcer activity implementing Proposition 65 warnings in the dental office through fines has not been a large enough thorn in dentistry's side, then the class-action lawsuit filed in June accusing the American Dental Association and the California Dental Association of unlawfully deceiving patients about the presence of mercury in dental amalgam certainly will be. The headline in the *Los Angeles Times* went even further when it said, "Suit Seeks to End Use of Mercury in Dentistry."

In the former case, an organization called As You Sow has been at the center, while several groups and individuals including Consumers for Dental Choice and Kids Against Pollution are behind the recent activity to eliminate the use of dental amalgam and to seek "restitution" for payments that the ADA allegedly received to endorse amalgam products. The suit, labeled by both ADA and CDA as "without merit," also included a notice of intent to sue the ADA under Proposition 65. It would seem that all of these well-funded groups have determined that the time is right to remove amalgam from the dental landscape.

Dentistry has successfully defended the science that supports the conclusion that there is no link between amalgam fillings and systemic diseases or chronic illness. The U.S. Public Health Service has concluded that "there is no persuasive reason to believe that avoiding amalgams or having existing amalgams replaced will have a beneficial effect on health." Armed with science and scientific opinion on its side, dentistry has been able to fend off the controversies that individuals and small groups brought into media prominence. We well remember the ill-defined "60 Minute" effort that challenged dentistry to defend the safety of amalgam in the early 1990s. Despite a very negative national media event, the defense of amalgam was successful. But that was THEN, and we are sensing a more formidable threat NOW. Legal maneuvers and the court system are now being used to attack the scientific information and opinion that has been supporting dentistry's position.

For good reason, we believe that the outcome of the current debates will be costly and not in the best interests of the public or its health. The reason is simple. In the matter of Proposition 65, as of this writing, many costly hours of CDA staff and volunteer time have already gone into the efforts to achieve an acceptable compromise on the appropriate wording of warning signs to be posted in the dental office.

While the length and breadth of the legal battle in the amalgam litigation is not easy to determine at this early stage, one prediction is easy to make. Organized dentistry, in the words of ADA President

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Robert Anderton, "will mount a vigorous defense." That defense will undoubtedly have a significant price attached.

If dentistry were to lose in the litigation, it could forever compromise the ability of the association to effectively inform and educate the public on scientific opinion based upon valid scientific evidence. But even if dentistry prevails this time, it cannot be considered a victory because of the high anticipated cost.

A reality underlying the debates is that research has been unable over many years to develop a new material that has the advantages of amalgam, but not the controversy of the safety questions that have long plagued this reliable material. It seems unfortunate that the significant funds that will be expended on both sides of these two closely related matters could not be channeled directly toward scientific investigation that might result in development of a safe, long-term restorative material.

These contemporary controversies illustrate our rather unfortunate conclusion that those who seek changes in the interest of public safety, as well-meaning as their efforts might be, often only contribute to higher-cost public health solutions. It is a shame that dollars that could benefit research progress end up being spent on emotional causes that do not directly contribute to the health or the safety of the public.

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National Campaign Will Promote Oral Cancer Awareness

By Debra Belt

Oral cancer doesn't register high on the scale of health concerns in the minds of the general public. However, ADA is gearing up to help change that with a nationwide public awareness campaign scheduled to begin in September.

The message that "early detection of oral cancer is possible and painless" will be delivered via billboards in 10 cities and supplemented by taxi top, bus shelter, and subway signs. Kicking off in San Francisco and Chicago and working its way across the country, the campaign will continue until mid-February in Seattle-Tacoma, Denver, Houston, Kansas City, Miami, New York, Philadelphia, and Boston. Since the campaign will use outdoor advertising as the primary medium of communication, necessity dictates that the message about oral cancer be simple and direct.

"The message is powerful and concise," said Clay Mickel, associate executive director of ADA's Division of Communications. Early detection is the key, and the campaign urges people to talk to their dentist for more information."

Experts agree that public awareness is essential in helping to prevent oral cancer, a disease that claims about 8,000 lives annually in the United States.

"Public awareness is key to improving the dismal statistics for oral cancer," said Raymond J. Melrose, DDS, chair of the Department of Oral and Maxillofacial Pathology at the University of Southern California School of Dentistry and president-elect of the California Division of the American Cancer Society. "The public really is not informed or knowledgeable about oral cancer because it has not been the principal interest or thrust of cancer awareness programs."

Melrose points out that many people associate oral disease with tobacco and spit-tobacco use and don't understand other independent risk factors such as alcohol.

"Smoking and drinking substantially increase the risk of oral cancer, although people who neither smoke nor drink are still at risk," Melrose explained. "Other factors come into play, although at this point, we don't know what those factors are."

Melrose adds that three things need to happen for oral cancer survival rates to increase. First, the public needs to know to see a dentist for an annual oral exam. Second, people need to know if they are getting a proper oral exam. Third, the public needs to demand oral exams if they are not routinely receiving them.

"The best person to conduct an oral exam is a dentist or trained hygienist supervised by a dentist," Melrose said. "An oral exam must include a thorough and systematic evaluation of the soft tissue of the entire oral cavity. The tongue should be pulled out and examined; and the floor of the mouth, the hard and soft palate, and the cheeks should all be looked at. The sites of major salivary glands should also be palpated."

In preparing dentists nationwide for the public awareness campaign, the ADA will mail a letter from President Robert M. Anderton, DDS, to all association members.

"I hope you are as excited as I am about the good this campaign can do for the public and the profession," Anderton writes in the letter. "During the campaign," he continues, "you may find patients asking about oral cancer diagnosis after seeing advertisements or media coverage."

Mickel said that member outreach is an important part of the campaign.

"We will be providing dentists with tools to help them communicate with patients," he said.

ADA will publish a news insert in the ADA News in August and will establish a repository of oral cancer information on its Web site, www.ada.org.

Melrose suggests the following guidelines to dentists who wish to advance the fight against oral cancer:

- Do a thorough oral cancer exam on every patient and look for signs of oral cancer and early abnormalities.
- During an exam, tell the patient what you are doing and why so he or she is aware of proper exam techniques.
- Assess the patient's risk for oral cancer. Ask if they smoke or drink and how much. If a patient has quit smoking, find out when.
- Encourage patients to stop smoking and using tobacco products. Refer them to a smoking cessation clinic or to the American Cancer Society hot line, (800) 227-2345.
- Take advantage of continuing education classes on early detection, diagnosis, and treatment of oral cancer.
- Don't fail to refer patients for a biopsy of any suspicious lesion. Biopsy remains the gold standard for early diagnosis.

By actively working to detect oral cancer in its early stages, dentists respond to a duty that is uniquely suited to their profession, Melrose said.

"Other than CPR," he said, "early detection of oral cancer is a dentist's best opportunity to save a human life."

For more information on the ADA's public awareness campaign on oral cancer, please e-mail Clay Mickel: mickelc@ada.org

Perio Bacterium Genome Sequenced

Scientists have sequenced the genome of Porphyromonas gingivalis, the bacterium believed to play a major role in adult periodontitis. It is the first oral disease-causing microbe to be completely sequenced.

The sequencing project, supported by the National Institute of Dental and Craniofacial Research, was carried out by scientists at the Institute for Genomic Research in Rockville, Md., in collaboration with the Forsyth Institute in Boston.

"P. gingivalis is one of the most intensely studied dental pathogens," says Dennis Mangan, PhD, chief of NIDCR's Infectious Diseases and Immunity Branch. "There is a large cadre of researchers out there ready to use the sequence data to identify the genetic mechanisms for the organism's virulence and to develop better approaches for preventing or eradicating periodontitis."

With the genetic blueprint for P. gingivalis in hand, dental researchers will be able to identify potential targets for periodontal vaccines and drug therapies.

The P. gingivalis sequence also provides the scientific community with information on an organism from a major group of bacteria not previously sequenced: the bacteroides group of gram-negative anaerobes. The sequence, which contains 2.3 million DNA base pairs, will be valuable for comparative genomics and for advancing researchers' understanding of bacterial diversity. It will also enhance scientists' ability to find new gene targets for antibiotics that work on gram-negative anaerobes.

These bacteria are naturally resistant to some antibiotics, and are acquiring resistance to many others.

- The P. gingivalis genome is available on the Comprehensive Microbial Resource Web site at http://www.tigr.org/tigr-scripts/CMR2/CMRHomePage.spl.
- Additional information on the P. gingivalis genome project can be found at http://www.pgingivalis.org.

AIDS: 20 Years and Half a Million Dead

Twenty years of AIDS has had a tremendous toll in the United States. Since the first case was identified in 1981, 774,467 AIDS cases have been reported, and approximately 450,000 Americans have died, according to the Centers for Disease Control and Prevention.

"The greatest impact of the epidemic is among [gay men] and among racial/ethnic minorities," CDC researchers write in the June 1 issue of the CDC's Morbidity and Mortality Weekly Report, an issue commemorating the 20-year anniversary of the epidemic's beginnings.

"AIDS continues to have a tragic impact, not only on those who have died or are living with HIV infection, but also on the many friends, families, and entire communities that have been forever changed by the epidemic," said CDC Director Jeffrey P. Koplan, MD, MPH.

Today, an estimated 500,000 to 600,000 people in the United States are living with HIV infection, and another 320,000 people are living with AIDS. New infections, which peaked at more than 150,000 in the mid-1980s, were reduced to an estimated 40,000 a year in the early 1990s. Since the beginning of the epidemic, well more than 1 million Americans have been infected.

The first suspected cases of AIDS were reported in the June 5, 1981, issue of MMWR.

The CDC does note, however, that there have been some public health achievements during the AIDS epidemic: Fewer than one in 450,000 to 660,000 screened blood donations are contaminated with HIV. In addition, from 1985 to 1999, AIDS cases among children declined 81 percent due to Public Health Service guidelines released in 1994 and 1995, suggesting that routine counseling and voluntary HIV testing be offered to pregnant women, and that AZT be offered to infected women and their infants.

People With Arthritis Have More Perio Disease

Swollen joints and missing teeth often go hand in hand, according to a new study in the Journal of Periodontology.

In the Australian study of 130 people, the 65 people who had rheumatoid arthritis were more than twice as likely to have periodontal disease with moderate to severe jawbone loss as the control subjects. In addition, they averaged 11.6 missing teeth, compared with 6.7 in the control group.

"Periodontal disease and rheumatoid arthritis have very similar pathologies," said Robert Genco, DDS, PhD, editor of the Journal of Periodontology. "Damage caused by the immune system and chronic inflammation are central to both diseases. A better understanding of the biological processes common to these diseases may help us find new ways to treat them with medications that modify the body's response to inflammation."

At this point, researchers are not saying the relationship between the two diseases is causal. However, some scientists think a bacterial infection may trigger the disease process in some of the estimated 2.1 million people with rheumatoid arthritis.

Poll Finds Low Consumer Confidence In Managed Care

Consumer perceptions of the service provided by managed health care companies continues to be poor, according to a recent poll, and is expected to erode even further.

The 2001 poll by Harris Interactive shows than only 29 percent of adults surveyed believe that managed care companies are doing a good job serving their customers. While that figure is consistent with last year's, the number has plummeted in the five-year life of the poll. Managed care companies have lost 22 points in the survey since 1997.

"The forces that have damaged public perception of [managed care companies] are still in place and are, we believe, likely to inflict more damage over the next

few years," writes Humphrey Taylor, chairman of the Harris Poll, and Robert Leitman, group president of Health Care, Education and Public Policy.

"On balance, it seems more likely that the numbers will get worse before they get better," they predict.

Sleep Apnea Linked to Alzheimer's Gene

A gene linked to Alzheimer's and cardiovascular disease also has an association with sleep apnea, according to a report in the June 13 issue of the Journal of the American Medical Association.

Sleep apnea is marked by short interruptions in a person's breathing during sleep that are often accompanied by snoring. As a result of the frequent interruptions in deep sleep, sufferers are often intensely tired throughout the day. Sleep apnea is estimated to affect 10 percent of the population.

In their study, Dr. Emmanuel Mignot of the Stanford University School of Medicine and his colleagues monitored 791 patients at a sleep disorders clinic. Each study participant had blood samples taken and analyzed for the presence of the Apolipoprotein E-4 gene variant. ApoE codes for a cholesterol-carrying molecule. Individuals have two ApoE genes, one from each parent.

Participants who carried the ApoE-4 gene were twice as likely to suffer from sleep apnea compared with those who did not. Those with two copies of the gene had an even higher risk of sleep apnea.

"Our results indicate that ApoE-4 is associated with sleep apnea," the researchers write.

The study is the first to link ApoE-4 to sleep apnea. That same gene also predisposes people to high cholesterol and cardiovascular problems. Because sleep apnea is a major predisposing factor for high blood pressure, stroke, and other cardiovascular problems, the findings may have important health implications for general population.

Greedy Brain Circuits Isolated

Using money as an incentive, researchers from Massachusetts General Hospital and two other institutions found that human neural responses accompanying the anticipation and experience of winning and losing in a laboratory gaming situation were similar to those noted in animals responding to tactile or gustatory stimuli or to euphoria-inducing drugs.

This suggests that the same neural circuitry is involved in the highs and lows of winning money, abusing drugs, or anticipating a gastronomical goodie.

The findings were published in the May 24 issue of Neuron.

The investigators found that the same regions of the brain respond to the prospects of winning and losing money while gambling as have been reported to respond to an infusion of cocaine in subjects addicted to that drug, and to low doses of morphine in drug-free individuals.

These common patterns of response support the view that dysfunction of neural mechanisms and psychological processes crucial to decision-making and behavior may contribute to a broad range of impulse disorders such as drug abuse and compulsive gambling.

Data analysis from the study revealed the following:

- Money, an incentive unique to humans, produced cerebral blood flow changes similar to those seen previously in response to other types of rewards, such as euphoria-producing drugs;
- Changes in the cerebral blood flow in the sublenticular extended amygdala and the orbitofrontal cortex tracked the expected monetary values, and as the expected monetary value increased so did responses in the nucleus accumbens, sublenticular extended amygdala, and hypothalamus;
- The blood flow responses in three areas of the brain rich in dopamine receptors roughly paralleled previously observed findings in monkeys during anticipation and experience of reward.

To have a meeting included on this list, please send the information to Upcoming Meetings, CDA Journal, P.O. Box 13749, Sacramento, CA 95853 or fax the information to (916) 443-2943.

Honors

John S. Greenspan, BDS, PhD, has been named dean of research at the University of California at San Francisco School of Dentistry. The position was created to reflect the continuing need for the school to oversee and promote its research enterprise. Greenspan assumed the position July 1, 2001.

No-Hee Park, DMD, PhD, has been named the 2001 recipient of the Oral Medicine and Pathology Research Award, conferred by the International Association for Dental Research. Park, dean of the University of California at Los Angeles School of Dentistry, received the award in recognition of his fundamental contributions to the understanding of oral carcinogenesis.

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Oral Cancer Is Dentistry's Disease, But We Are Losing the Battle

Raymond J. Melrose, DDS

AUTHOR

Raymond J. Melrose, DDS, is a professor in and the chairman of the Department of Oral and Maxillofacial Pathology at the University of Southern California School of Dentistry. He is also president-elect of the California Division of the American Cancer Society.

Oral cancer is dentistry's disease because ours is the only profession whose scope of training and clinical practice specifically encompass preservation of the health and function of the oral cavity. No group of professionals is more familiar with the normal appearance of oral tissue and is specifically educated in professional school about oral cancer. Accreditation standards for dental education include specific references to education about oral cancer.

For the most part, our profession has taken vigorous actions to protect and to improve the oral health of our patients. Fluoridation, children's dental health, and research in periodontal diseases are but a few examples that have positively affected oral health. What about oral cancer? Oral cancer remains a disease whose victims, on average, have a 54 percent five-year survival, a figure that has not improved in 20 years. Whereas, the five-year survival rates for patients with "hidden" cancers such as those of the breast, prostate gland, and colon have all substantially improved in that period.1 Further, oral cancer is a far more prevalent disease than is appreciated by most. The American Cancer Society estimates that 30,100 new oral cancer cases will be diagnosed nationally in 2001.1 Similar data for California predict 3,370 new cases.2 Oral cancer, then, will be the ninth-most-common cancer to occur nationally and the eighth-most-common in California. Clearly, something is seriously wrong when a common disease occurring in a site readily accessible for examination by skilled health professionals is not being diagnosed early enough to effect improved survival.

Dentists are well-aware of oral cancer, know the risk factors, and know how to examine patients for the disease. They learn this material thoroughly in dental school. But something seems to happen in the day-to-day activities of practice. Motivation to perform routine oral soft tissue examination on all patients declines.3,4 Is it from lack of time? Is there a loss of confidence in skill? Poor compensation? Is there a fear of finding

something? No one knows for certain, but the end result is very tragically clear. Patients suffer and die needlessly from a disease that is eminently curable when diagnosed early or, better still, when in its premalignant phase.

Our colleagues in medicine do not have the luxury of training or experience in oral cancer or in the technique of oral examination. For the most part, their examinations of oral tissue are cursory at best. The oral cavity is not their area of responsibility and, compounding the problem of late diagnosis, physicians tend to see the high-risk patients for oral cancer more frequently than dentists because these people are older and often have significant medical problems.3 A study assessing physicians' and dentists' oral cancer knowledge, opinions, and practices disclosed what is related above but also revealed that 37 percent of physicians and 34 percent of dentists responding to a questionnaire did not know the importance of early detection in preventing mortality, something that would seem to be intuitive.3 A later survey of dentists alone concluded that dentists are not as knowledgeable about oral cancer prevention as they could be but were interested in continuing education on the subject.4 These are very worrisome facts, but they can be addressed through professional education.

A far more difficult problem and one whose solution could be pivotal in changing the behaviors of dentists and the outcomes for oral cancer patients is the lack of an informed public. A survey of U.S. adult knowledge of risk factors and signs of oral cancers conducted in 1990 concluded that there is extensive misinformation and a general lack of knowledge on the topic.6 Nothing has been done in the interim to change this. It is very clear to me that paramount among the reasons for success in improving the survival rates for common cancers like those of the breast, colon, prostate gland, and cervix is a public informed of the risk factors, the diagnostic methods, and the relationship between early diagnosis and improved survival. Ordinary people have clamored for and gotten attention to the problems of these cancers in terms of research, better diagnostic and treatment methods, insurance coverage, and a host of other features important to quality of life. The American Cancer Society has made important measurable reductions in incidence and mortality of the major cancers the centerpiece of its goals for the year 2015. Unfortunately, oral cancer is not one of these and will not be the beneficiary of American Cancer Society national efforts.

If the major national volunteer organization dedicated to the reduction of the burden of cancer in our population is not going to act directly to reduce the incidence and prognosis of oral cancer, who should? I firmly believe that since oral cancer is dentistry's disease that dentistry must take it upon itself to mount comprehensive national public information programs. After the impressive national conference on oral cancer hosted by the American Dental Association in August 1996 reached the same conclusion regarding the necessity for widespread public information, it was hoped that action would follow. None did. Dr. Lawrence Meskin, the editor of the Journal of the American Dental Association, wrote that dentistry should "Do It, or Lose It," meaning that dentistry should step up to the plate and take responsibility for oral cancer.7

Following the lead of Dr. Meskin's editorial, and acting as then president of the American Academy of Oral and Maxillofacial Pathology, I wrote to the president of the ADA formally proposing that the association consider developing an annual oral cancer awareness program for professional and lay populations. I noted that the idea had received support from oral pathologists in the United States and Europe after it had been mentioned on the Internet. The idea was referred to a council that declined support for financial reasons citing that the ADA already had a national public and professional awareness program in National Children's Dental Health Month.8

It seems to me that our profession is too shortsighted in this battle to save lives from oral cancer. Does a high-profile celebrity have to develop advanced disease while under the care of a dentist and then have his or her story related on "60 Minutes" or "Nightline," which will delight in implying that dentistry doesn't seem to know or to care about the only disease in its purview that is likely to kill its victims? This really isn't the case, but it would be made to seem that way; and the cost to repair the damage, if it could ever be repaired, might be more than the cost to mount an effective program first. What if a consortium of state dental associations working together with the ADA and interested groups like the Centers for Disease Control and Prevention, Oral Health America, the Academy of General Dentistry, and others were to form to develop and test even one demonstration project for patient oral cancer awareness? This might be a difficult project to pull off; but if no one is willing to take the first step, our patients and our profession will surely suffer the consequences.

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The Best Cosmetic Service Our Profession Can Provide

TERAN J. GALL, DDS

AUTHOR

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Dentistry is riding a wave of public interest in pursuing a healthy smile. Cosmetic dentistry procedures and services are promoted widely in numerous magazine articles, on the radio and in TV infomercials. Many of us promote quite boldly our ability to perform cosmetic dental procedures. Specialized clinics for one-time bleaching are even spotting the landscape. All of this activity has obviously been quite beneficial for our profession.

However, there is a cosmetic procedure that many of us may not be providing as part of our daily practice routines. An annual oral cancer exam should be the most important cosmetic evaluation we provide. Why? Oral cancer accounts for 2 percent to 4 percent of all cancers in the United States.1 Every year, this accounts for more than 30,000 cases diagnosed with a resultant 8,000 deaths. It has a greater incidence than cervical cancer. The five-year survival rate for people with oral cancer is 81 percent for those with localized disease, 42 percent for patients with regional disease, and 17 percent for those with distant metastases. 2 Clearly, early detection is a critical intervention in the management of this disease.

I would venture to say that all of us in this profession have seen the ravages of oral cancer. Although our experiences may not be direct, we have certainly seen the results of ablative surgery in journals and textbooks throughout our careers. I had direct experience in the management of head and neck cancer patients during my tenure as a hospital dentist at the University of California in San Diego Medical Center. UCSDMC is a Regional Cancer Center. It was there that I followed the diagnosis, treatment, and post-treatment trials and tribulations of these unfortunate patients. I witnessed not only the physical ravages of oral cancer but the psychosocial and financial ravages as well.

Ablative surgical procedures and/or head and neck radiation drastically influence quality of life and place significant financial burdens on those who have such treatment. Postoperative sequelae include xerostomia, dysphagia, social isolation, depression, unemployment, financial hardships, and eventually premature death. This is yet another reason early detection is such a tremendous benefit not only to the patient but also to the treatment team and all of us who finance health care.

Oral cancer is not the only disease state one may identify when conducting such an exam. Diseases such as lymphoma (both Hodgkins and non-Hodgkins type); pathologies of the salivary glands, pharynx, tonsils, larynx, and mucosa; and even oral signs of systemic disease can all be detected by dentists. Although definitive diagnosis of such diseases may not always be made by the dentist, we can certainly initiate timely referrals to rule out

pathology or obtain a definitive diagnosis.

Given this scenario, it is imperative that we as oral health professionals rise to the challenge and responsibility to educate our patients about risk factors for oral cancer as well as provide annual screenings to detect early signs of this devastating disease. Consider this issue of the *Journal of the California Dental Association* to be an important reminder of our role and responsibility as oral health professionals in preventing, diagnosing, and/or treating all oral diseases and particularly oral cancer. We have a tremendous opportunity as dentists to reduce the incidence of late-stage oral cancer by conducting routine oral cancer screenings and educating those at risk about the consequences of their actions or behaviors.

In the summer of 1996, the Oral Cancer Strategic Planning Conference was held in Chicago. One of the recommendations from this meeting was to establish an Oral Cancer Working Group.

This recommendation came from the fact that a concerted effort in controlling oral cancer was lacking. The following is taken from the proceedings of this Working Group as reported in the *Morbidity and Mortality Weekly Report*:[2]

The Oral Cancer Working Group, a multidisciplinary group that attended the 1996 Oral Cancer Strategic Planning Conference, met in the fall of 1997 to identify 10 strategies from the 1996 meeting recommendations to receive immediate attention and implementation by the agencies they represented. The Oral Cancer Working Group considered political and scientific changes that had occurred after the 1996 conference (e.g., the Food and Drug Administration had been given regulatory authority over tobacco, legal cases involving tobacco had been settled in several states, national tobacco legislation had been proposed, and four comprehensive oral cancer research centers had been funded by National Institute of Dental Research) and selected strategies the group could effect (as opposed to strategies already under way as a result of the leadership and support of other groups). Leadership at the 1997 meeting was shared by representatives of the American Dental Association, the American Association of Dental Research, the Association of State and Territorial Dental Directors, the Centers for Disease Control and Prevention, the International Society of Oral Oncology, NIDR, and Oral Health America. The 10 priority strategies are as follows.

Advocacy, Collaboration, and Coalition Building

- Establish a mechanism to implement and monitor progress made regarding the recommended strategies developed during the 1996 national conference.
- Urge oral health professionals to become more actively involved in community health concerns.

Public Health Policy

- Require instruction in preventing and controlling tobacco and alcohol use at all levels of training in dental, medical, nursing, and related health-care disciplines.
- Encourage Medicaid, Medicare, traditional insurance plans, and managed-care entities to make oral cancer examinations an integral part of comprehensive physical and oral examinations.
- Designate federal funding for a national program of oral cancer prevention, early detection, and control.

Public Education

- After assessing local needs, develop, implement, and evaluate statewide models to educate all relevant groups.
- Develop and conduct a national campaign to raise public awareness of oral cancer and its link to tobacco use and heavy alcohol consumption.

Professional Education and Practice

- Develop health-care curricula that require competency in prevention, diagnosis, and multidisciplinary management of oral cancer.
- Sponsor and promote continuing education for health-care professionals on the multidisciplinary management of all phases of oral cancer and its sequelae.

Data Collection, Evaluation, and Research

Strengthen organizational approaches to reducing oral cancer by developing cooperative and collaborative arrangements, funding formal centers, and involving commercial firms.

This strategic plan should serve as a tremendous opportunity for CDA and California dentists to assume their roles in turning the tide on oral cancer. This issue of the CDA Journal should also serve as a call to action for our profession through our state association to embark on a formal and concerted effort to educate oral health professionals, the public, and policy makers about the ravages of oral cancer and its risk factors. It is both timely and necessary that the dental profession take a leadership role in promoting and performing oral cancer screenings as well as providing preventive education to the public. This can be best accomplished in conjunction with state and federal health agencies, our dental schools, and health promotion advocacy groups such as the American Cancer Society.

For now, we should provide the greatest cosmetic service we can provide for our patients -- conduct a thorough annual head and neck exam and provide education about known risk factors for oral cancer.

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To request a printed copy of this article, please contact/ Teran J. Gall, DDS, 25556 Meadowview Circle, Salinas, CA 93908-9393.

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Oral Cancer in the Molecular Age

Joseph A. Regezi, DDS, MS, and Richard C. K. Jordan DDS, PhD

ABSTRACT Oral cancer represents an accumulation of defects in the genes that encode key proteins associated with growth and development. Dysregulation of these proteins is central to malignant conversion. This appears to involve three major changes in cell function: 1. altered cell growth, death and longevity; 2. unencumbered cell movement; and 3. development of a new blood supply (angiogenesis). Specific genes, such as p53, p27, p16, and cyclin D-1, are altered in oral cancer through mutation, amplification, or deactivation. These genes are also frequently altered in many other malignancies. In oral mucosa, etiologic agents -- especially tobacco and alcohol, and possibly some viruses -- are known to induce alterations in the genes and gene functions associated with cell cycle regulation, contributing to the development of squamous cell carcinoma and epithelial dysplasias. Identification of the specific genes/proteins and the sequence in which they appear in the transformation of a normal cell to a malignant cell is necessary for the formulation of new treatment strategies, the development of early detection methods, and the prediction of patient outcome.

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Oral cancer, like most other malignancies, represents an accumulation of molecular lesions in genes that encode for proteins that control cell cycle, cell survival, cell motility, and angiogenesis. These complex changes give the tumor cells an independent growth advantage, leading to the ability to invade and metastasize to distant sites.1,2 Understanding how oral cancers develop at the molecular level will be necessary for the development of new cancer control methods. The purposes of this paper are to briefly review the causes of oral cancer, and the molecular mechanisms that are important in oral cancer pathogenesis.

Causes of Oral Cancer

Generally, the most important cause of oral cancer is tobacco.3 The use of tobacco, including smokeless forms, is known to increase the risk of oral cancer and is directly dependent upon the amount and duration of the habit. Alcohol, either alone or with tobacco, can also lead to oral cancer. The genes that have been shown to be altered in oral cancers by tobacco carcinogens are p53 and ras genes (see below). Human papilloma viruses (particularly subtypes 16 and 18) have been associated with some oral cancers, especially verrucous forms. HPV-encoded proteins, E6 and E7, are known to block the cell cycle inhibitory effects of p53 and

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retinoblastoma proteins, respectively.4,5 In the herpes virus group, Epstein-Barr virus has been closely linked to carcinoma of the nasopharynx and some lymphomas. Herpes simplex -- which commonly affects perioral skin, vermilion, palate, and gingiva -- has not been convincingly linked to the etiology of oral or lip cancers.6

How the various etiologic factors (e.g., tobacco carcinogens) operate at the molecular level is under investigation and is only partially understood. They are, however, believed to effect changes in the genome. Critical growth-related genes may become mutated, amplified, or deactivated by these agents, and the encoded proteins may be dysfunctional, overexpressed, or underexpressed.

Altered Gene Expression

No two oral cancers are exactly alike. The heterogeneous nature of oral cancers is evident at all levels, from molecular to clinical. Marked differences can be seen in clinical appearances (e.g., leukoplakia, erythroplakia, verrucous), histologic patterns (e.g., good to poor differentiation, inflammatory response, invasive architecture), and biologic behaviors (e.g., prolonged precancerous state, rapidity of invasion, metastatic potential). Likewise, the molecular (genetic) alterations are variable in type and, to some degree, in the sequence in which they occur. While oral cancers do not all exhibit the same genetic patterns or profiles, certain genes are apparently more commonly affected than others. Some of the genes known to be involved in oral carcinogenesis are discussed below.

Oral cancers progress through two important biologic stages. The first stage is loss of control of cell cycle through increased proliferation and reduced apoptosis. Clinically, this is most obvious in patients with in situ carcinomas where a higher number of dividing cells are evident in all levels of the epithelium (Figures 1 and 2). The second stage is increased tumor cell motility leading to invasion and metastasis (Figures 3 and 4). Here, neoplastic

Glossary

Adhesion molecules — Molecules that are involved in the adherence of cells to each other or to extracellular matrix proteins.

Allele — Alternate form of a gene that is found at the same locus of a chromosome

Angiogenesis — The formation of new blood vessels

Apoptosis — Physiologic or programmed cell death

Bcl-2 — A family of genes/proteins associated with the control (both induction and inhibition) of apoptosis

Cell cycle — The complex sequence of events associated with cell replication/proliferation

Chromosome — A structure in the nucleus that is made up of linear strands of DNA associated with nuclear proteins and RNA

Cyclin-dependent kinase — A cell cycle-related enzyme that, when combined with cyclin, assists in cell proliferation

Cyclin-dependent kinase inhibitor — A protein that inhibits cell proliferation through its effects on cyclin-dependent kinase

Gene — A region of DNA that codes for a single protein

Gene amplification — An abnormal cellular event that results in a cell having a greater number of copies of a gene than normally present

Gene expression — The process by which the information encoded by a gene is converted into a protein

Gene mutation -- A change in the genetic material. It can include all genetic alterations from single nucleotide substitutions to whole chromosome translocations.

Gene overexpression — Excessive protein production due to alterations in the gene that encodes it

Gene underexpression — Reduced protein production due to alterations in the gene that encodes it

Loss of heterozygosity — In cancer, loss of a second allele of a gene when the first allele is already altered or lost

Matrix metalloproteinases — A group of related proteins that promote degradation of connective tissue matrix and enhanced cell movement

Oncogene — A mutant gene, usually related to cell cycle, that contributes to cancer development

Proto-oncogene — A normal gene that encodes a protein usually related to cell cycle. When mutated, this gene is known as an oncogene.

Growth factor — Extracellular peptide that signals a cell to proliferate

Growth factor receptor — A protein on the cell surface receiving a growth factor molecule that starts a signaling cascade eventuating in proliferation

Signal transduction — The process by which a cell transmits an external stimulus (signal) to the nucleus for a response

Telomerase — A nuclear enzyme that is responsible for the extension and, therefore, maintenance of DNA sequences found at the end of chromosomes known as telomeres

Telomere — DNA sequences found at the end of chromosomes that are necessary to prevent chromosome shortening and degradation

Tumor suppressor gene — A gene whose protein product suppresses the cell cycle. It is often a target in cancer and requiring inactivation of both alleles to effect a loss of function.

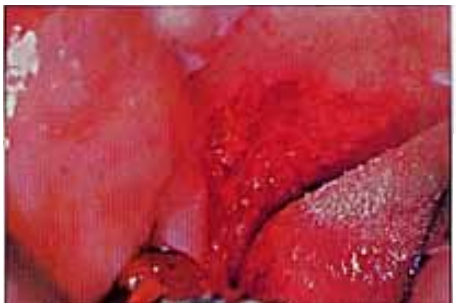

FIGURE 1. Erythroplakia of the soft palate with biopsy diagnosis of carcinoma in situ.

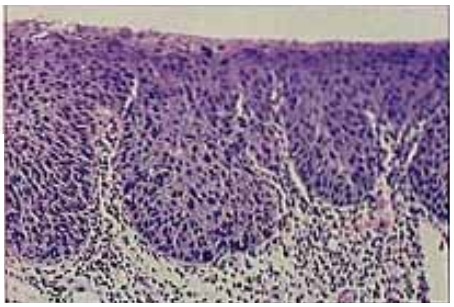

FIGURE 2. Carcinoma in situ. The abnormal epithelial changes represent hyperproliferation related to genetic alterations that led to abnormal expression of cell cycle-related proteins. It can be surmised that the cells have not acquired, as yet, the requisite genetic lesions that would facilitate basement membrane penetration and invasion.

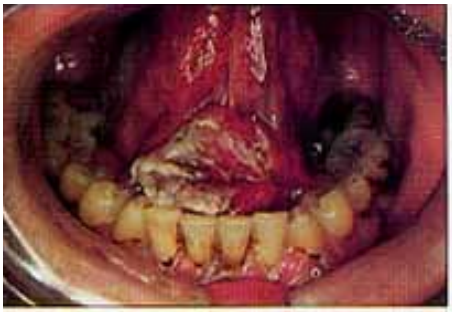

FIGURE 3. Invasive squamous cell carcinoma of the floor of the mouth.

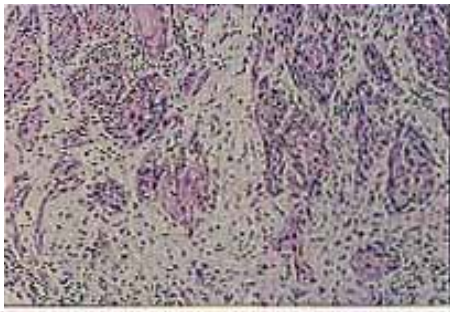

FIGURE 4. Invasive squamous cell carcinoma. Malignant keratinocytes have acquired the ability to degrade and move through connective tissue. Laboratory studies would show evidence (genetic lesions and altered protein expression) of impaired cell cycle, plus expression of matrix-degrading enzymes and an abnormal profile of adhesion molecules in the invading tumor cells.

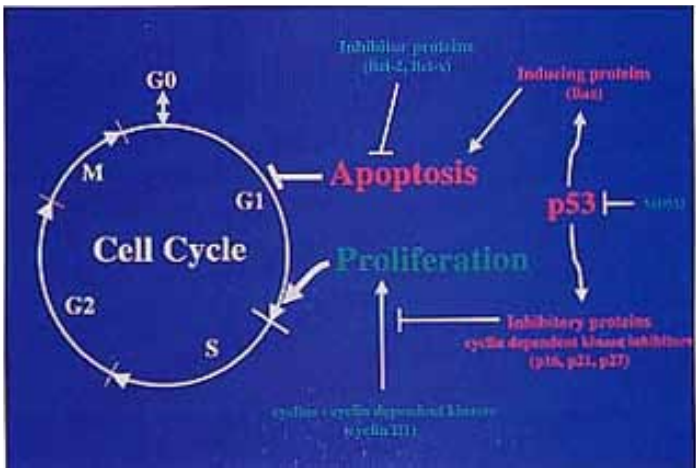

FIGURE 5. Illustration of the cell cycle and how some critical proteins, known to be dysregulated in oral cancers, influence or control proliferation and apoptosis. Proteins that accelerate the cell cycle are in green, and proteins that retard or block proliferation are in red.

epithelial cells are able to penetrate the basement membrane and invade underlying tissues, and eventually travel to regional lymph nodes. The associated genetic changes are related to the activation or up-regulation of oncogenes, and the inactivation or down-regulation of tumor-suppressor genes (anti-oncogenes).

Oncogenes, or proto-oncogenes under normal circumstances, encode proteins that positively regulate critical cell growth functions, such as proliferation, apoptosis, cell motility, internal cell signaling, and angiogenesis. If genes in this group become altered through one of several mechanisms (e.g., mutation), protein overexpression occurs, giving rise to a clone of cells with a growth/motility advantage.

Tumor-suppressor genes encode proteins that negatively regulate or suppress proliferation and are believed to play a more important role in oral cancer development than oncogenes.7,8 Alteration of the genes in this group essentially "releases the brake" on proliferation for a clone of cells. To have a phenotypic effect, differences in or loss of both maternal and paternal gene copies (alleles) are required. This inactivation of a tumor-suppressor gene occurs in a two-step process. First, there is alteration of one allele, followed second by alteration of the other allele leading to loss of the normal maternal-paternal heterozygotic allelic combination (loss of heterozygosity).

Alterations of genes that control cell cycle seem to be of utmost importance in the malignant transition process. In fact, it has been suggested that cancer can be considered a disease of the cell cycle.9 Normally, the cell division process is divided into four phases, gap 1, DNA synthesis, gap 2, and mitosis. One of the most important events in this cycle is the progression from the gap 1 to the DNA synthesis phase. Genetic lesions, if left unrepaired in the gap 1 phase and carried into the DNA synthesis phase, can be perpetuated in subsequent cell divisions. The gap 1-DNA synthesis "checkpoint" is regulated by a complex system of proteins

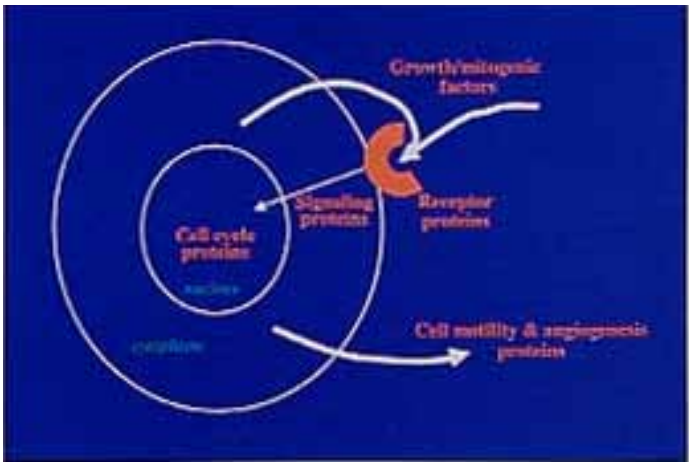

FIGURE 6. Diagram showing the cellular location of the protein groups that can be genetically altered or defective in oral cancer.

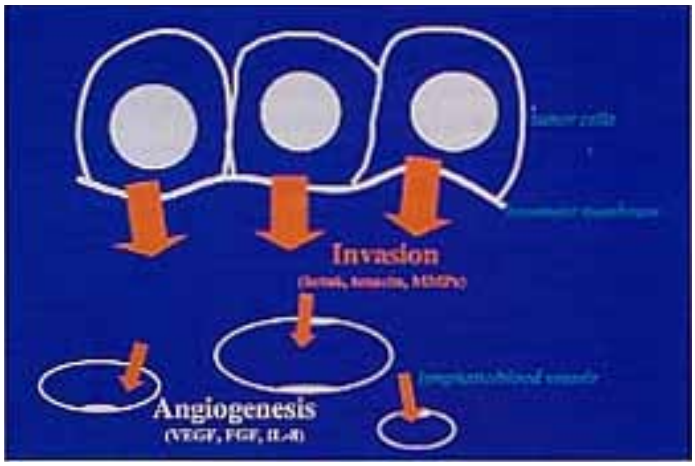

FIGURE 7. Diagram showing invasion and angiogenesis-related proteins that can be overexpressed in oral cancer due to genetic alterations.

whose balance is critical to normal cell division (**FIGURE 5**). Overexpression of oncogenic proteins or underexpression of anti-oncogenic proteins can tip the balance in favor of proliferation and neoplastic transformation. Two important groups of intrinsic cell cycle proteins that accelerate proliferation are cyclins and their activation binding enzymes, the cyclin-dependent kinases. They are counteracted by proteins known as cyclin-dependent kinase inhibitors.

The accumulation of a number of adverse genetic lesions in oncogenes/tumor-suppressor genes may give the cell an independent growth advantage leading to a malignant phenotype. In the case of oral cancer, this series of changes would occur in a keratinocyte, ultimately creating a single clone of cells with uncontrolled proliferation and motility.

Alteration of Specific Genes/Proteins

Cell Cycle-Associated Genes and Proteins

Dysregulation of the cell cycle is a frequent finding in the development of oral cancer (Figures 6 and 7). The cell cycle-associated oncogenes cyclin D-1 and MDM-2, and the tumor-suppressor genes p53, p16, and p27 are prominent among the genes that have been confirmed as being abnormally expressed in oral cancers.10-14

p53, normally is a tumor-suppressor gene and a key negative-regulator at gap 1/DNA synthesis of the cell cycle. In about 50 percent of oral cancers, p53 is mutated; and its encoded protein is nonfunctional. Defective p53 protein allows cells to proceed into the DNA synthesis phase of the cell cycle before DNA can be repaired. The result is an accumulation of deleterious genetic defects that contribute to malignant transformation. This key protein may be dysregulated in oral precancer as well and may serve as an indicator of high-risk lesions.15-21 MDM2, which blocks the effects of p53, is also overexpressed in some oral cancers. Overexpression of cyclin D-1 appears in many oral cancers, leading to increased proliferation rate and premature transition through the gap 1-DNA synthesis checkpoint. Underexpression of the cyclin-dependent kinase inhibitors, p16 and p27, is also another important feature of oral cancer and relates to loss of control of cell cycle because of an inability to inhibit the effects of cyclins and cyclin-dependent kinases.

The antithesis of proliferation is apoptosis (genetically determined cell death). If cells live longer through the effects of anti-apoptotic proteins, they have an advantage that favors neoplasia. Some of the genes that control apoptosis, especially the Bcl-2 family, are altered in many cancers. In some oral cancers, the anti-apoptotic proteins Bcl-X and Bcl-2, are overexpressed.22,23 Moreover, expression of the proapoptotic protein, Bax, also has been positively correlated with increased sensitivity to chemotherapeutic agents in head and neck cancers.24

Cell Growth and Signaling Genes

Several other oncogenes that function in the regulation of cell growth and for the transport of signals from the cell membrane to the nucleus are also frequently altered in many oral cancers. These include genes that code for growth factors such as int-2 and hst-1 (fibroblast growth factor); growth factor receptors such as erbB1 and erbB2 (epidermal growth factor receptors); proteins involved in signal transduction such as ras (GTP binding proteins); and nuclear regulatory proteins such as myc (transcriptional activator proteins). Correlations have now been identified between growth receptor overexpression and patient outcome.25-33

Genes Associated With Cell Motility and Invasion

Many oral cancers pass through a premalignant phase (dysplasia or in situ carcinoma), while others appear to arise de novo without clinical or microscopic

evidence of a pre-existing lesion. Invasive carcinomas have developed the ability to penetrate basement membrane and connective tissue, as well as enter the vascular system. These tumors are believed to have developed this invasive advantage through molecular lesions in genes and proteins associated with cell movement and extracellular matrix degradation. Changes in the phenotype of cell adhesion molecules (cadherins and integrins) release cells from their normal environment and give them the ability to move. This coupled with the enzymatic degradation of basement membrane and connective tissue provides the necessary components for invasion of the proliferating tumor.

Critical cell adhesions proteins are altered in invasive oral cancer. These proteins include intercellular adhesion molecule, e-cadherin, and the neoexpression of beta-6 integrin, a protein that assists keratinocyte motility. Matrix-related proteins produced by tumor cells and possibly by connective tissue cells (e.g., fibroblasts, macrophages) contribute to the breakdown of basement membrane and extracellular matrix proteins. Tenacin, an anti-adhesion molecule not evident in normal mucosa, is detectable in oral squamous cell carcinomas.34 Matrix metalloproteinases (MMPs 1, 2, 9, and 13) have also been demonstrated in invasive carcinomas and are believed to play a significant role in matrix degradation.35 In particular, MMP 3 and 13 are associated with advanced head and neck carcinomas.36,37 Controlling these proteins/enzymes through inhibitors or binding proteins has potential future therapeutic implications.

Genes Related to Angiogenesis

For tumors to grow much greater than 1 mm in size, a new blood supply is required (angiogenesis). This occurs through a tumor-associated process by way of induction or overexpression of angiogenic proteins (e.g., vascular endothelial growth factor [VEGF], basic fibroblastic growth factor [FGF]), and/or through the suppression of proteins that inhibit angiogenesis. VEGF, FGF, and IL-8 (proinflammatory cytokine) have been identified in head and neck cancers and are believed to be responsible, at least in part, for the angiogenesis associated with the progression of these tumors.38,39 The genetic alterations leading to the overexpression of these proteins has not been determined, but it likely involves interactions with other critical oncogenes and immunosuppressor genes. Nonetheless, identification of these abnormally expressed proteins marks another potential target for treatment of oral cancers (anti-angiogenesis).

Telomerase-Associated Tumor Cell Immortality

Another area of investigation, relative to gene-associated abnormalities in cancer, centers around telomere integrity. Telomeres are DNA-protein complexes found at the end of chromosomes and are required for chromosome stability. Normal cells have a finite life span related to telomere shortening that occurs with successive cell divisions. When a critical telomere reduction is reached, the chromosome and subsequently the cell are subject to degradation. Cancer cells may develop a mechanism that maintains telomere length and chromosome integrity and, thus, long-term viability. This mechanism is associated with the production of telomerase, an intranuclear enzyme that is not present in normal adult cells but is found in cancer cells. Most head and neck carcinomas have telomerase activity through neoexpression of this enzyme, giving the neoplastic cell extended life.40,41 This enzyme is another potential therapeutic target. Its detection in premalignant mucosal lesions (leukoplakia) may also serve as a biomarker for high-risk lesions.

Summary

Oral cancer has a complex molecular pathogenesis that is only partially understood. The cell cycle, when dysregulated, is believed to be central to malignant conversion, and with cell movement, when abnormally altered, can lead to invasion and metastasis. Angiogenesis and telomere integrity represent other facets that can contribute to cancer pathogenesis. Accumulation of defects in the genes that encode the proteins that regulate growth and development can lead to neoplastic change. In oral mucosa, etiologic agents -- especially tobacco and alcohol, and possibly some viruses -- can induce alterations in the DNA of these genes and contribute to the development of squamous cell carcinomas and dysplasias.

Further elucidation of the molecular mechanisms associated with the transition of a normal cell to a malignant cell is a vital step in oral cancer control. This new molecular era ushers in new opportunities for the development of early detection methods, novel therapeutic strategies, and outcome prediction.

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Soft-Tissue Examination in the Dental Office

Russell E. Christensen, DDS, MS

ABSTRACT This article describes in detail all features of the head and neck soft-tissue examination as performed routinely in a dental office. The ongoing thought process while performing the exam is described, and examples of findings are given.

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The head and neck soft-tissue examination given routinely in the dental office provides general information on the health of the patient, screens for potential or overt malignancies, and detects other conditions that may require dental or medical attention. The term "cancer screening" is limited, potentially misleading, and should be avoided except when included as one item in a description of a comprehensive examination or in advertising for a health fair. An appropriate medical history is usually obtained or updated prior to beginning the examination. Prompt attention to the patient's chief complaint is, of course, important, so the soft-tissue examination may take place at any time during the appointment. After the routine examination, supplementary examinations may be warranted, such as a cranial nerve exam or detailed examination of the temporomandibular joint and masticatory muscles.

The Examination Process

Step One: General Assessment

Step one in every patient examination begins the moment the patient is seen. Whether the patient is first encountered as he or she is walking into the treatment area or once already seated in the dental chair, a broad array of data can be collected instantly with practiced observation. General information such as sex; approximate age; general body type; gait; asymmetries; swollen ankles; large facial or skin lesions; and whether the patient

is well-groomed or disheveled, confident or frightened, or using walking aids, glasses, hearing aids, etc. is easily obtained in one head-to-toe glance. A moment of reflection on these observations can lead to other findings. This is particularly the case if there has been a change since the previous appointment. Weight loss could be from successful dieting or from malignancy, depression, hyperthyroidism, or other illness. Grooming may also reflect health status. Untied or loosely tied shoes could indicate edema; unkempt appearance may indicate depression; a copper bracelet might indicate arthritis; overly warm clothing could be a clue to the cold intolerance of hypothyroidism. Distinctive facial findings include the elongated head and bony prominence of the forehead in acromegaly, the moon face of Cushing syndrome, the mask-like face of Parkinson's or systemic sclerosis, and parotid enlargement from a wide variety of etiologic factors. Facial expressions may reveal pain, anxiety, anger, or depression. Use of accessory breathing muscles, exhaling through pursed lips, or too many sighs may be a clue to lung disease or hyperventilation. Patients who appear older than their stated ages may be intentionally misreporting their ages or perhaps have prolonged histories of cigarette smoking or sun exposure; others might be suffering from a chronic illness such as malignancy or widespread arterial disease.1 A younger appearance is less likely from misreporting of age and may be due to cosmetic surgery. Any of these findings could significantly influence treatment planning. Vital signs, if taken at this appointment, may also yield important information.

Step Two: Examination of the Skin

Step two in most cases is an inspection of the facial skin. The patient should be informed that an examination is about to begin. The dentist might say, "Let's begin with an examination of your mouth. First on the outside " Then, a few seconds, the dentist later might say, "Now on the inside ..." as a cue for the patient to open his or her mouth. The examination of the facial skin in the dental office is done to distinguish lesions of potential significance that need referral from a background of minor blemishes with no medical importance. The dental office is a particularly good environment for such an examination because of the good lighting and ready access to magnification. Inspection is the only necessary technique in the dental screening; palpation may help a more experienced clinician. A basic array of common skin disorders is included in dental school curricula, and dentists can find numerous sources to update their knowledge of common skin conditions.2,3 Habitually looking up skin lesions in an illustrated dermatology text can rapidly improve one's skills in screening them.

The skin examination began in step one; now deliberate attention is given to the facial skin. Color, moisture, temperature, and lesions can be assessed simultaneously when the examination is limited to the face. The eyes are a good place to start. Although the conjunctiva is not particularly good for assessing cyanosis, examination of this area may reveal jaundice. Before inspection of the eyes is finished, ptosis, exophthalmos, ectropion, xanthelasma, corneal arcus, pinguecula, pterygium, cataracts and other lesions of eyes and adjacent tissues may be seen. Routine, organized observation increases the knowledge and experience of the clinician. Although some of these conditions (e.g. pinguecula) are probably irrelevant to dental treatment planning, others reflect potentially serious conditions that require medical attention. Corneal arcus in a young patient or xanthelasma is suggestive of hyperlipidemia; jaundice and exophthalmos should be investigated promptly.

Lesions of the facial skin are discovered by a swift scalp-to-neck examination that also includes inspection from the sides. Depending on the age of the patient, an array of lesions will be present, ranging from normal to innocuous to concerning to obviously serious alterations. Nevi, seborrheic keratoses, dermatosis papulosa nigra, comedones, angiomas, melasma (mask of pregnancy), and other common lesions are often seen on a daily basis in a dental practice. Routine examinations provide the practitioner with experience to know the range of appearance of these completely benign conditions.

Actinic keratosis is also very common but often ignored by patients who do not realize that these lesions are a precursor to squamous cell carcinoma. Referral to the patient's physician can prevent serious trouble later. Basal cell carcinoma may have a variety of clinical presentations, but the classic presentation of a raised, rolled border with a depressed, often ulcerated center is easily identified in a dental examination. Any lesion suspicious for basal cell carcinoma requires referral to a dermatologist for evaluation. Basal cell carcinoma may be the most frequently discovered malignancy in the dental office. Pigmented lesions should be checked for the A, B, C, D characteristics: Asymmetry, Border irregularities, Color variation, and Diameter enlargement. These findings can be suggestive of malignancy in a pigmented lesion of the skin. Early, "thin" melanomas have an excellent prognosis compared with more advanced lesions. This is a classic example of a life-saving early detection.

Step Three: The Intraoral Examination

Step three begins when the patient opens his or her mouth. When the skin examination is completed, the patient might appreciate an opportunity to remove lipstick if this has not been done previously. The "Now on the inside " cue informs the patient that the intraoral examination is beginning. Dentures, retainers, or any other appliances should be removed at this time. During the examination, the dentist should keep risk factors in mind and pay particular attention to the "horseshoe area" of lateral tongue and floor of mouth in patients who have a history of smoking. However,

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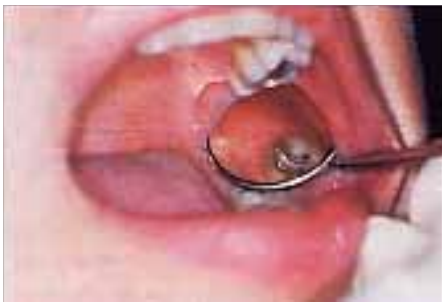

FIGURE 1. Mirror examination in #16 area.

FIGURE 2. Inspection and palpation of the tongue.

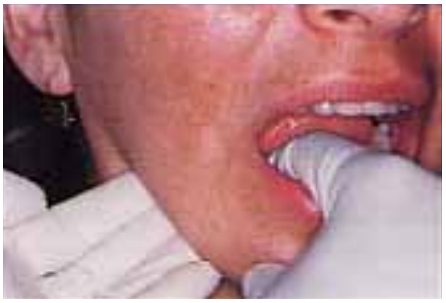

FIGURE 3. Bimanual palpation of floor of mouth and submandibular region.

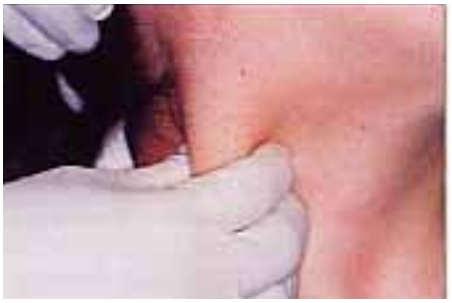

FIGURE 4. Palpation of deep cervical nodes.

all areas must be inspected regardless of risk factors.

The intraoral soft-tissue examination should be done in the same order and in the same way on every patient.

The sequence of examination is a matter of individual preference. The author proceeds in the following order:

- The dentist begins in the buccal vestibule near tooth #1 and inspects the buccal gingivae, vestibular mucosa, and inner surface of the lip following the maxillary teeth across to the left side, using a mouth mirror as necessary (**FIGURE 1**).
- The dentist then similarly inspects the lower vestibule, buccal mucosae, buccal gingivae, and lip. The coloration of oral tissues may be the first observable finding. Lack of oxyhemoglobin is best reflected in a bluish coloration of the lips, tongue, and buccal mucosa. Cyanosis may indicate anemia, congenital heart disease, and advanced lung disease among others.
- Next, the dentist inspects the palate and palatal gingivae. The patient is allowed to briefly close and swallow.
- When the patient opens, the tonsils, peritonsilar areas, and posterior pharynx can be inspected. If the tongue obscures these structures, the patient can be asked to "pant like a puppy." Alternatively, with a mirror or tongue blade placed in the mid-tongue area, not so far back as to cause gagging, the patient is asked to yawn or say "aah." The dentist should note the symmetry of the rising soft palate; asymmetry may indicate a 10th nerve defect. The patient is allowed to close and swallow once again while the dentist obtains a gauze.
- The dentist requests that the patient protrude his or her tongue and notes size, coloration, and whether the protrusion is symmetrical (asymmetry may indicate malignancy or a 12th nerve defect).
- The dentist then gently grasps the tip of the tongue and inspects the dorsum and reflects the tongue to one side, carefully inspecting the lateral and ventral surfaces, particularly the base. Then the dentist palpates the extended surface with the other hand (**FIGURE 2**), switches hands and repeats on the other side. If the dentist plans to lift the soft palate to better inspect the pharynx or perform indirect laryngoscopy, it can be done at this time. Having the patient tip his or her head slightly backward while the dentist gently grasps the tongue may allow better visualization. The patient should then swallow again.
- Upon opening again, the dentist should dry the parotid duct orifices and express saliva from the ducts by stroking the skin from the parotid area toward the cheek opposite the duct. Then, the dentist should dry the submandibular gland orifices and, if necessary, stroke the skin of the chin from the area posterior to the submandibular gland forward. After stimulation from the examination, the saliva should be clear and copious.
- The next focus is palpation. The dentist begins by gently placing one finger under the ventral tongue along the floor of the mouth; the dentist may have to pause just a moment to get the patient more relaxed. Then, with the other hand under the chin, the dentist bimanually palpates the floor of the mouth for masses or tenderness (**FIGURE 3**) and repeats on the contralateral side. With the floor of mouth depressed and the soft tissues of the chin moved laterally, submandibular nodes can often be palpated against the inferior border of the mandible as the skin and subcutaneous tissues of the chin are allowed to return to place. Palpation is then continued in an organized manner including buccal mucosae, lips, vestibules, alveolar mucosa, then hard and soft palate. Dryness as well as lumps or tenderness should be noted.
- The dentist should recall any lesions

he or she has encountered and return to these for a closer examination, if necessary, before leaving the oral cavity. Step four may be momentarily postponed and step five completed at this time if the dentist is performing this examination.

Step Four: Examination of the Neck

- The dentist begins with an examination of lymph nodes. He or she palpates pre-auricular and posterior auricular nodes along with the parotid region. Occipital nodes are at the base of the skull posteriorly. The posterior cervical chain lies along the anterior margin of the trapezius muscle. The superficial cervical nodes are superficial to the sternocleidomastoid. The deep cervical nodes require grasping around the muscle with thumb and fingers (**FIGURE 4**). If the patient turns to the opposite side, the muscle may be grasped more easily and then isolated as the patient returns to a forward gaze. This should be continued to the supraclavicular nodes found deep in the angle formed by the back of the sternocleidomastoid and the clavicle. The dentist palpates the region of the tonsillar nodes at the angle of the mandible then forward to submandibular and submental nodes. The hyoid bone lies high in the neck and should not be mistaken for a pathologic condition. Lymph nodes generally will be moveable to some degree in all directions. Blood vessels and muscles will not move up and down. With practice and experience, both sides may be examined at once.
- Finally, the dentist inspects the midline neck. The patient should tilt his or her head slightly backward. The trachea should be in the midline. The dentist then notes scars and obvious masses, particularly below the cricoid cartilage in the area of the thyroid gland. The patient is then asked to swallow; a sip of water may be necessary. Swallowing will cause the thyroid gland, along with the cricoid and thyroid cartilage, to rise and fall. Masses that rise with swallowing are likely to be thyroid in origin; bulky neck tissue that fails to rise with swallowing is usually fat and muscle. Palpation of the thyroid gland requires practice; usually the thyroid is not palpable in adults. Palpation of the thyroid is not a necessary part of the dental head and neck examination and is not covered here. Textbooks of physical diagnosis have a complete description of this procedure. 4

Steps one through four should generally be completed within two minutes.

Step Five: Generate a Differential Diagnosis

Step five begins with a re-examination by the dentist of any lesions or abnormalities discovered. Many aspects of the first four steps can be adequately performed by the hygienist during visits for scaling and prophylaxis. However, a complete examination by the dentist should be performed at least once per year on every patient and more often in high-risk patients or patients with lesions that are being "watched." When lesions are discovered, treatment planning, and even simple referral, requires a differential diagnosis by the dentist. Generating a differential diagnosis requires the clinician to categorize the lesion, in other words to ask, "Basically, what sort of lesion is this?" Categorization as a white lesion, papillary lesion, red lesion, pigmented lesion, mass, ulcer, or vesiculobullous lesion comes first. Then some subcategorization will help.

Lumps in particular locations carry their own set of common conditions. Lateral neck masses most commonly arise in lymph nodes. Therefore, infections, lymphomas, metastatic carcinomas, and branchial cleft cysts are of primary consideration. Midline neck lumps are often thyroid-related. Generalized gingival hyperplasias may result from medications, metabolic conditions, leukemia, and even heritable syndromes. Localized gingival masses are often pyogenic granulomas and related reactive lesions. Lumps of the lips and buccal mucosae can arise from any normal tissue present in that location, particularly salivary glands. Long-term ulcers are usually due to chronic trauma, major aphthae, squamous cell carcinomas, or specific infections. Papillary lesions are often warts, but may be verrucous carcinomas or papillary squamous cell carcinomas. White lesions that rub off may be materia alba or chemical burns, etc. The dentist should be well-aware of the typical presentations of a wide variety of oral lesions so that an appropriate differential diagnosis can be generated. No differential is ever "complete"; there is always something that is rare or presenting in an unusual way that could be added to the list. Narrowing the list of possibilities too swiftly can result in a grievous oversight. On the other hand, generation of a huge list of conditions may be good as an academic exercise, but a more compact list over a broad variety of etiologic factors is a more efficient way to "cover the bases." See **TABLE 1** for an example.

A differential diagnosis that includes a spectrum of specific conditions allows the clinician to ask appropriate, specific follow-up questions, to seek specific information from the medical history, or to perform specific supplemental examinations such as inspection of exposed skin. This process allows conditions in a differential diagnosis to be emphasized, diminished in likelihood, or eliminated from consideration while the dentist forms a concise working diagnosis. The differential diagnosis makes treatment planning much easier; if the patient is to be referred for a second opinion or biopsy, it provides clear information to the referral doctor who may see the lesion differently on a different day. Perhaps the most important reason for a differential diagnosis becomes apparent when the patient returns to the general practice for follow-up. The general practitioner's assessment of whether the pathologic diagnosis rendered matches her or his own findings is more critical than

TABLE 1. Differential for a White Lesion That Does Not Rub Off

Disease categories	Selected examples
Hereditary	White sponge nevus, other genokeratosis
Infectious	Hyperplastic candidiasis, hairy leukoplakia
Metabolic	None appropriate
Neoplastic/preneoplastic	Leukoplakia, submucous fibrosis, squamous cell carcinoma
Autoimmune/allergic	Lichen planus
Physical or chemical injury	Frictional keratosis, surgical scars

usually realized. This is the last and best protection for the patient. Occasionally, the biopsy was not taken at a representative site, or the pathology may even be misinterpreted, particularly by a pathologist unfamiliar with oral lesions. The general practitioner may have the last chance to notice a discrepancy before a tragic delay in diagnosis. Without an appropriate differential in mind, the practitioner may miss this critical opportunity. Many, if not most, medicolegal cases in soft-tissue diagnosis occur in this way rather than as a failure to detect the lesion in the first place.

Adjunctive techniques marketed to assist "screening" are no substitute for the techniques of inspection, palpation, and differential diagnosis.

Step Six: Documentation in the Dental Record

Step six is the recording of all places inspected and/or palpated, whether normal or not, along with a description of abnormal findings. Should a lesion arise in the future on any head or neck site, records of previous negative findings are not only helpful diagnostically, but they conform to accepted clinical guidelines.5 One simple method is a checklist that can be part of a separate sheet in the chart or stamped onto the progress notes. Simple drawings of lesions with measured dimensions and brief descriptions can be invaluable in recalling lesions from one visit to another. Documentation with intraoral cameras is extremely helpful. Surgeons and pathologists will appreciate a photograph of any lesion as it appeared upon discovery.

Step Seven: Treatment Planning

Step seven is the treatment planning phase. A differential diagnosis for the lesion has been generated; specific examinations or questioning have eliminated some possibilities and strengthened others. Choices for treatment or additional diagnostic procedures depend upon the working diagnosis. A decision to "watch" a particular lesion should result in re-evaluation at specific times and with particular features in mind.

Step Eight: Informing the Patient

The dentist should inform the patient of the extent of the examination. For example: "a soft-tissue examination including a screening for oral cancer." Then the dentist must summarize his or her findings, describe any recommended diagnostic procedures, and possibly discuss treatment options. When the dentist has a specific working diagnosis in mind, the appropriate level of concern is communicated; and the patient is more likely to feel confident of the dentist's recommendations.

Step Nine: Examination of the Teeth and Periodontium

Step nine comprises the examination of teeth and periodontium. Sometimes this may have begun earlier when focusing on the patient's chief complaint. This evaluation usually requires correlation with radiographs and is beyond the scope of this paper. Dental and radiographic findings also require differential diagnosis and treatment planning. Clear documentation of those findings is obviously important.

Conclusions

- The protection of patients necessitates a routine periodic head and neck soft-tissue examination performed by the dentist as part of standard comprehensive care.
- A sequence for the intraoral exam must be followed consistently on every patient.
- Areas examined will always include:
- Inspection of general features of the patient, facial skin, and midline neck and
- Inspection and palpation of the major salivary glands, lips, buccal mucosa, palate, tongue, floor of mouth, and regional nodes.
- Documentation of the examination must include normal findings as well as notation of lesions and abnormal findings.
- Development of an appropriate differential diagnosis is essential for treatment planning or proper referral.
- The patient must be informed of the examination itself and about any specific findings.

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Premalignant Oral Mucosal Diseases

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ABSTRACT A premalignant phase in the development of oral cancer is predicted by the classic model of experimental epithelial carcinogenesis. Virtually all oral squamous cell carcinomas arise from a premalignant precursor, but it is difficult to specifically define the term premalignant. Oral pathologists use the term epithelial dysplasia to indicate microscopic features in a biopsy specimen that are associated with a risk of malignant change and then assign a grade of severity. There is good correlation between higher grades of dysplasia and increasing risk of cancer but less so with the lower grades. The clinical appearances manifested by oral epithelial dysplasia and early oral cancer include leukoplakia, erythroplakia. and speckled leukoplakia. This paper discusses and illustrates these clinical lesions, their associated risk factors, their relationship to epithelial dysplasia, and the associated risk of evolution into oral cancer.

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The clinical concept of oral mucosal premalignancy is now more than 150 years old. Sir James Paget is credited with the first description of an association between an oral lesion (which he termed "ichthyosis") and subsequent development of tongue carcinoma.1 In fact, Paget had recognized 19 years earlier that oral mucosal white patches in pipe smokers bore a risk of transforming into cancer. Seven years after Paget's report, Schwimmer described white lesions of the tongue (which he termed "leukoplakia") that developed into cancer in patients with tertiary syphilis.2 Thus, the term "leukoplakia" and its association with oral mucosal premalignant disease has been extant in the literature for 128 years.

Similarly, a red lesion of the glans penis in a syphilitic man that evolved into cancer was designated "erythroplasia" by Queyrat.2 Darier, in 1924, was the first to describe an oral mucosal red lesion with the potential to turn into cancer and designated this the "erythroplasia of Queyrat."2

The biological basis for the concept of oral premalignancy has been established by studies of epithelial carcinogenesis. From the earliest studies in mouse and hamster models through today's elegant molecular and gene research has come confirmation that human epithelial cancer is not the result of a single random event. Instead, it has been established that epithelial carcinogenesis requires multiple "hits" over time that result in accumulated changes allowing now abnormal cells to proliferate while resisting both programmed cell death (apoptosis) and

the body's own immune surveillance.

The pathologic process of carcinogenesis takes time as well as an appropriate environment in order to produce a clinically perceptible result. That both time and a proper environment are required in most instances explains why the people at greatest risk of oral cancer are older adults who habitually use products such as tobacco and alcohol that contain carcinogens or that act as co-carcinogens.

Based upon years of clinical observations and buttressed by increasingly sophisticated research, it can be fairly stated that virtually all oral squamous carcinomas evolve out of an existing premalignant lesion. But, do all premalignant lesions develop into squamous carcinomas? How does one define what a premalignant lesion is? There is no completely agreed upon answer to either question. What have evolved are attempts to assess the risk or the likelihood of progression into cancer.

Clinicians have developed complex schemes of varied clinical appearances that attempt to correlate surface features such as color and texture with anticipated histologic appearance and a corresponding degree of epithelial dysplasia or carcinoma.3,4 For example, smooth, homogenous leukoplakia is assessed as having virtually no potential to harbor dysplasia; granular or verruciform leukoplakia is assessed as likely to show moderate to severe dysplasia on biopsy; and speckled leukoplakias are predicted to harbor severe dysplasia or carcinoma in situ. Such attempts at clinical pathologic correlation have merit but are flawed based upon observer bias and experience. Further, such schemes may result in all homogeneous leukoplakias being dismissed as "clinically benign" regardless of other important clinical considerations and thus not biopsied for confirmation of the clinical diagnosis.

Oral pathologists look at patterns of cell growth, maturation, and nuclear characteristics in biopsy specimens and assign grades of severity to dysplastic changes observed. A problem extant in this method is subjectivity and lack of clear, uniformly applied criteria for the diagnosis of dysplasias. Consistent reproducibility in the microscopic interpretation of dysplasias even by experienced oral pathologists has been an unachievable goal.

A further and significant problem with assessing the potential for the real risk of a premalignant lesion evolving into a squamous carcinoma is the lack of an agreed upon, comprehensive staging system for oral premalignancy. Such a system has been proposed but has not yet been adopted.

A number of clinical studies of leukoplakias and their malignant transformation rates (the percent of patients with leukoplakias developing an associated cancer per year) have been reported.4 These data show a mean transformation rate of 8.1 percent with a variance from 3.6 percent to 19.8 percent. The wide variance between rates in reported studies is testimony to the inherent risk associated with applying such data to any one clinical situation.

Thankfully, researchers today are measuring detectable levels of tumor-suppressor genes such as p53, oncogenes and their protein products, epidermal growth factors, tumor cell angiogenesis, and a myriad of others in attempts to find objective, reproducible criteria. So far, no reliable predictor has appeared, but there is great promise in research attempting to elucidate a sequence or cascade of molecular changes that will correspond to rates of malignant change as they evolve in patients.

Even when reliable molecular markers of an evolving oral cancer are available, they will be useless without the clinician who first suspects a patient is at risk and who is looking for clinical alterations from normal. No universal screening test for oral cancer is on the horizon. Molecular techniques do require some form of a specimen as substrate. The test specimen might be as small as a few cells or may still require a biopsy. But either obtaining a few cells or selecting a biopsy site implies that the clinician is seeing the abnormality. Thus, despite remarkable advances that portend sophisticated ability to reliably differentiate dangerous lesions from those that are less dangerous, the bottom line today is that dentists are not relieved of the obligation to assess every patient's risk for oral cancer, to look carefully for suspicious lesions, and to have these diagnosed as soon as possible after discovery.

Clinical Features

Oral mucosal premalignant lesions may manifest clinically in three principal forms: leukoplakia, erythroplakia, and speckled leukoplakia. Each of these will be discussed and illustrated.

Leukoplakia

Leukoplakia is defined as a "white patch that cannot be wiped off and for which no more-specific diagnosis can be given on clinical grounds." For example, neither mucosal candidiasis, which can be wiped off, nor reticular lichen planus, which has a specific clinical appearance, fits the definition.

Oral leukoplakias are common, most frequently innocuous, and related to low-grade local irritation that induces hyperkeratosis. Irritants most commonly associated with leukoplakias include mastication/parafunctional habits, removable prostheses, alcohol-containing products and beverages, and tobacco products. In assessing a given leukoplakia then, its relationship to local factors should be evaluated; and these should be eliminated to as great a degree as possible. Any leukoplakia for which there is no reasonable local cause, which fails to resolve with removal of presumed local irritants, or which is present in a high-risk site should be biopsied.

In a study of 3,360 biopsied leukoplakias, Shafer and Waldron found that 19.8 percent (670) were either mucosal dysplasia (premalignant) or squamous carcinoma.5 These authors also

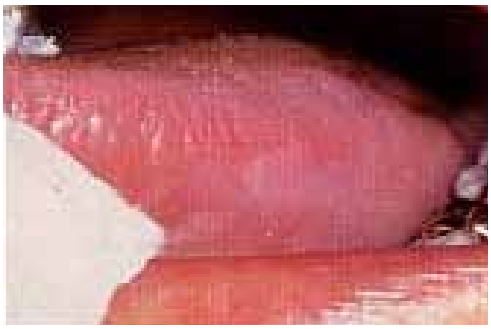

FIGURE 1. A thin, homogenous leukoplakia of the lateral tongue in a 42-year-old male cigarette smoker. A biopsy showed moderate epithelial dysplasia. Criteria other than clinical appearance must be used to assess such lesions.

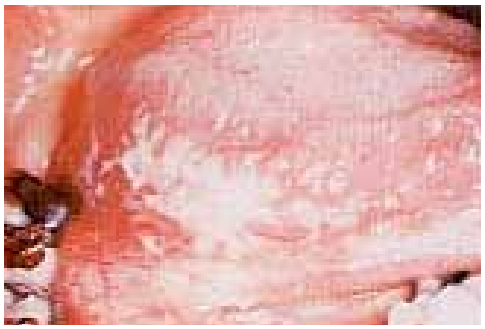

FIGURE 2. A thick leukoplakia. A biopsy showed moderate epithelial dysplasia.

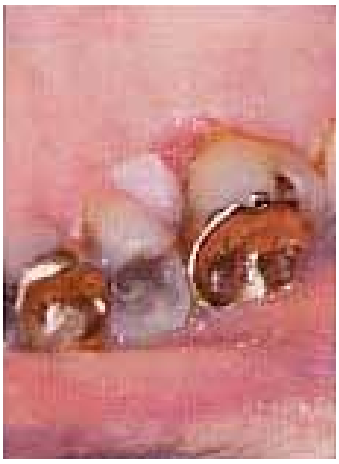

FIGURE 3. A rough leukoplakia of the maxillary gingiva. There were no risk factors and no discernable local irritants. A biopsy showed benign verrucous keratosis, but the lesion continued to enlarge. Several years later, another biopsy revealed moderate epithelial dysplasia confirming that that this is a case of proliferative verrucous leukoplakia.

found that the floor of the mouth (42.9 percent), lateral tongue (24.2 percent), and soft palate (18.8 percent) had the highest rates of serious disease among leukoplakias. Therefore, in addition to a relationship to local irritants, the site of a leukoplakia is highly significant in a decision to biopsy.

Oral squamous carcinoma is uncommon before age 40, but the risk for this disease increases greatly after age 40. Since premalignant change precedes development of squamous carcinoma, it stands to reason that one should be even more suspicious of leukoplakias seen in patients older than 40.

The clinical appearances of leukoplakias vary. Those that are thin, homogeneous, and smooth (**FIGURE 1**) tend to be less worrisome, for example, than those that are thick and/or fissured (**FIGURE 2**). But, one should not rely on surface features as much as location, risk factors, and age in making the decision to biopsy.

Although leukoplakia is a nonspecific clinical descriptor and requires a biopsy to determine its nature, several specific conditions have been reported in recent years whose names include "leukoplakia." These are proliferative verrucous leukoplakia, oral hairy leukoplakia, and Viadent leukoplakia. Oral hairy leukoplakia is a disease induced by Epstein-Barr virus infection of epithelium in people with compromised immune systems such as in HIV infection.6 This condition is not premalignant and will not be discussed. Viadent leukoplakia is a unique condition in which keratosis develops in the anterior maxillary vestibule or attached mucosa presumably as a result of the sanguinaria incorporated into the product. Slight mucosal dysplasia has been reported in a few of these cases, but it is not known if these lesions have any malignant potential so they cannot be considered in a discussion of premalignant lesions at this time.7 Proliferative verrucous leukoplakia, on the other hand, is well-established as a premalignant process.8

Proliferative Verrucous Leukoplakia

Proliferative verrucous leukoplakia is an enigmatic condition first described by Hansen and colleagues in 1985. It cannot be diagnosed on the basis of a single biopsy. Instead, patients who will develop it present first with an idiopathic leukoplakia that, upon biopsy, is a benign keratosis or verrucous keratosis. These patients are usually older adults who have no risk factors for carcinoma. The gingiva is a commonly affected site along with the buccal mucosa and tongue (**FIGURE 3**). The biopsied lesion will recur and/or increase in size slowly over time. Often it will thicken and appear leathery or verrucous. Additional sites may appear as well. Repeat biopsies begin to show dysplasia; and this feature, in concert with the clinical appearance, results in a diagnosis of proliferative verrucous leukoplakia. In most instances, it will inexorably progress into frank squamous carcinoma or verrucous carcinoma (**FIGURE 4**). To date, no completely effective treatment has been found to eliminate proliferative verrucous leukoplakia. Reports of human papilloma virus strains in proliferative verrucous leukoplakia have been published; but antiviral therapy has not been effective, and it is not proved that it is a virus-induced disease. Topical chemotherapy as with Bleomycin has been attempted along with wide (nonradical) excision, but neither modality has been reliably effective. Use of a carbon dioxide laser for ablation has produced the longest disease-free intervals but still no documented cure.

Spit Tobacco Leukoplakia

A type of leukoplakia that has a specific etiology is that which arises secondary to chronic use of spit tobacco products, including chewing tobacco, moist snuff,

FIGURE 4. Extensive proliferative verrucous leukoplakia of the mandibular gingiva. The process had been evolving for years, and ultimately the patient developed verrucous carcinoma in the area.

FIGURE 5. Wrinkled and fissured leukoplakia lines a pocket" into which spit tobacco is packed.

FIGURE 6. Squamous carcinoma of the maxillary alveolar mucosa and vestibule has developed in this area where spit tobacco has been placed for years.

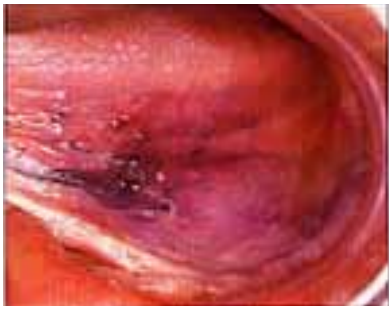

FIGURE 7. Positive toluidine blue staining of an extensive ventral tongue lesion in a patient successfully treated for squamous carcinoma of the soft palate 12 months prior. The patient continues to smoke. He was referred for a new denture by his radiation oncologist.

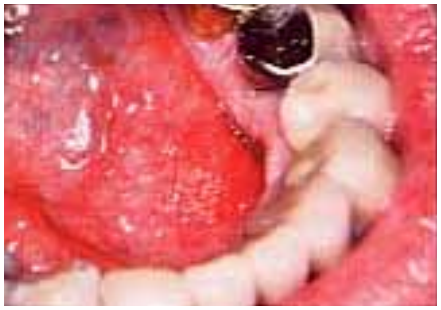

FIGURE 8. Erythroplakia of the oral floor in a patient at high risk for squamous carcinoma. A biopsy revealed severe epithelial dysplasia.

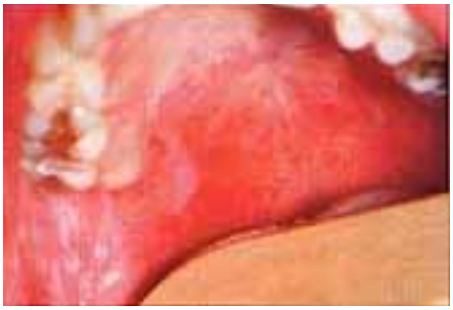

FIGURE 9. Erythroplakia of the soft palate in a patient at high risk for squamous carcinoma. A biopsy of this case also revealed severe epithelial dysplasia.

and dry snuff. These leukoplakias, which may be thin or thick, arise at the site of placement of the product. Therefore, the buccal mucosa, mandibular vestibule, and buccal/facial gingiva are the sites most frequently affected. In some patients, the leukoplakia may develop within a few months after initiation of use, but it is more common for several years to pass before change is apparent. Often, the mucosal surface is wrinkled or fissured as well as white. This is because of a "pocket" that forms at the site where the quid of the product is placed. With the quid in place, the wrinkles disappear, leaving a greater absorptive surface for the nicotine and other products including carcinogens (FIGURE 5).

Those who habitually keep the quid in the same site have an increased risk of leukoplakia development compared with those who move the material from site to site. Snuff is said to be more likely to induce leukoplakias than chewing tobacco. Other factors that relate to increased incidence of leukoplakia are daily contact hours and the amount of product used daily. Spit tobacco leukoplakias tend to regress or to disappear with cessation. Cessation is difficult to achieve with an established habit because a "typical" pinch of spit tobacco contains approximately the same amount of nicotine as three cigarettes.

The risk of carcinoma or premalignant change in spit tobacco leukoplakias is not known. However, tobacco itself has been estimated to carry a four times greater risk of oral carcinoma development than that to be expected in populations not using tobacco.

A few dysplasias have been seen in biopsies of spit tobacco leukoplakias, but there are unquestionable cases of squamous carcinoma and verrucous carcinoma related to spit tobacco use (FIGURE 6). Therefore, in the assessment of a spit tobacco leukoplakia, biopsy should always be performed to establish a definitive diagnosis of the lesion at that point in time. If no dysplasia is found, then elimination of the habit and follow-up should suffice. If a patient cannot or will not give up the habit, then close follow-up and re-biopsy should be performed when progressive change such as thickening is seen or if evolution of a red component is found.

Leukoplakias of oral mucosa are common and readily recognized. Most leukoplakias represent benign keratosis, but these cannot be distinguished on clinical

grounds from those that are premalignant. Only biopsy can make that determination reliably. Clinicians must develop criteria to use to determine which leukoplakias must be biopsied. Among the most important of these are anatomic site, patient age, risk factors, relationship to a probable irritant, and lesion response to removal of the suspected irritant. More frequent use of biopsies to assess leukoplakias will result in earlier diagnosis of oral cancer and, even more importantly, prevent oral cancer by virtue of intercepting lesions in their premalignant state.

Erythroplakia

The term erythroplakia is derived from erythroplasia. While erythroplasia has a diagnostic connotation in dermatology, erythroplakia as used in oral pathology is a clinical descriptor only. Erythroplakia may be defined as "a persistent, velvety red patch that cannot be identified as any other specific red lesion such as inflammatory erythemas or those produced by blood vessel anomalies or infection."9

Erythroplakias are less commonly seen than leukoplakias, but they are more ominous when identified. For example, Waldron and Shafer studied 58 cases and found that 51 percent were early invasive carcinoma and 41 percent were either carcinoma in situ or severe dysplasia.10 Similarly, Mashberg and colleagues described erythroplakia as the earliest sign of asymptomatic oral cancer.11

As mentioned previously, Waldron and Shafer found that of the 3,360 leukoplakias in their study, 670 were either dysplasia or carcinoma. The majority of those (413) represented at most mild or moderate degrees of dysplasia microscopically. Subsequently, the same authors studied erythroplakias and found that 92 percent were either early carcinoma or severe forms of dysplasia. Why the difference in severity between white and red lesions? The answer lies in the fact that leukoplakias are white principally due to hyperkeratosis. In the process of dysplasia, the epithelial cells tend to progressively lose differentiation, including their ability to keratinize. Also, as the cells become progressively more atypical, the body may mount an inflammatory reaction against the threat that the progress of the dysplasia represents, increasing the red component. Thus, erythroplakias tend to be composed of cells that are less mature, more atypical, and of a higher microscopic degree of dysplasia than leukoplakias. The loss of keratinization and increase in DNA content per unit area that accompanies increasing degrees of dysplasia and carcinoma is also the reason erythroplakias and carcinomas stain deeply with toluidine blue whereas leukoplakias do not (**FIGURE 7**).

The risk factors for erythroplakia are the same as those for oral carcinoma: tobacco use, alcohol abuse, and age older than 40 years. The oral sites where erythroplakias are most likely to occur are the oral floor, soft palate, tonsillar pillar, and lateral/ventral tongue (**FIGURES 8 AND 9**).

There are relatively few considerations in the clinical differential diagnosis of erythroplakias. Burns will have an appropriate history and are usually painful. Inflammatory processes such as erythematous candidiasis will have an associated cause that can be removed, modified, or treated. In these situations, clinical improvement is to be expected within two weeks. Vascular abnormalities will generally be of long duration and tend to fade or blanch with pressure. Something virtually unique in the clinical appearance of an erythroplakia, but which may be difficult to appreciate without good light and a dry field, is a distinctly velvety surface texture (**FIGURE 10**).

High-risk patients for oral cancer should receive the most critical examination that looks for even tiny lesions that fit the criteria for erythroplakia. When observed, these should be biopsied without delay.

Speckled Leukoplakia

Speckled leukoplakia, also known as erythroleukoplakia, is a clinical hybrid lesion. Most authors describe it as a leukoplakia with interspersed red areas (**Figure 11**). Conversely, it may be an

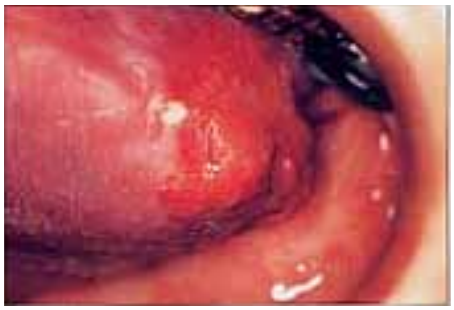

FIGURE 10. This erythroplakia of the lateral tongue shows a distinct margin between normal smooth texture and the velvety appearance often seen in erythroplakia. A biopsy showed carcinoma in situ, the most severe degree of dysplasia.

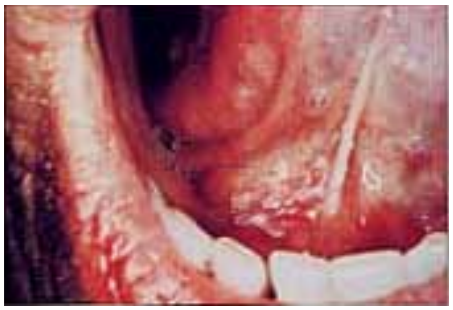

FIGURE 11. Speckled leukoplakia may seem to be leukoplakia with a red component. A biopsy of this lesion revealed severe epithelial dysplasia.

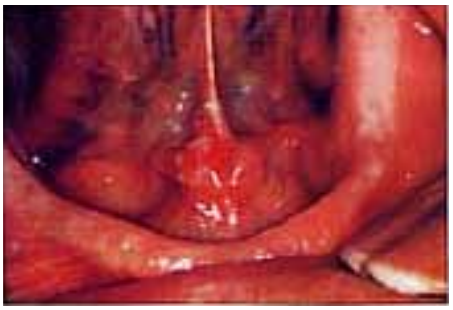

FIGURE 12. Speckled leukoplakia may also seem to be a red lesion with white foci. A biopsy of this lesion also revealed severe epithelial dysplasia.

FIGURE 13. Actinic keratosis with dysplasia was found in a biopsy of the crusted area. Note the thick, puffy contour, vertical fissuring and loss of definition of the skin/vermilion junction.

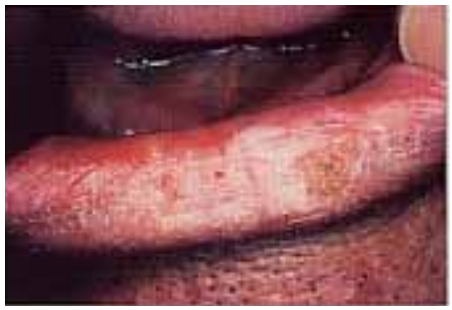

FIGURE 14. Pre-operative photo of an older man with biopsy-proved actinic epithelial dysplasia.

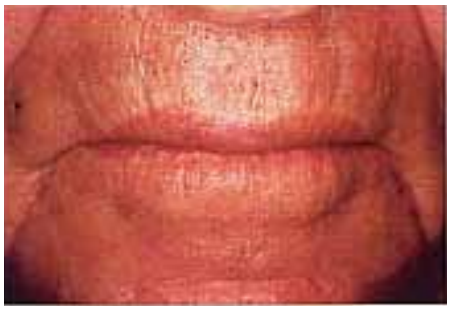

FIGURE 15. Postoperative photo after treatment by vermilionectomy. Note the reduction of contour and excellent cosmetic result.

erythroplakia with a few white spots that do not wipe off (**Figure 12**). In truth, both descriptions are apt. Speckled leukoplakias are as dangerous as erythroplakias in terms of the tendency to represent more serious dysplasia or cancer on biopsy. It is of clinical relevance then that when selecting a site for an incisional biopsy in a leukoplakia, any red component should be included in the sample.

Actinic Keratosis

Squamous carcinoma of sun-exposed skin is a common disease and is second in incidence only to basal cell carcinoma. Actinic radiation is a potent carcinogen. The process by which carcinogenesis occurs in sun-exposed skin is comparable in most respects to that in oral mucosa. The cutaneous process includes a premalignant phase often termed actinic keratosis by dermatologists.

The vermilion border of the lips is a transition site between skin and mucosa but is somewhat more closely related to skin. Both the upper and lower vermilion borders are exposed to sunlight, but the lower vermilion receives substantially greater doses of actinic radiation. Therefore, it is the lower vermilion border that is at greatest risk for sun-induced cancer and for its premalignant counterpart, actinic keratosis.

People at greatest risk of developing labial actinic keratosis are older men with a fair complexion who spend considerable time out of doors. Women, presumably because of the protective effect of cosmetics, have less risk.

Along with the carcinogenic effect of ultraviolet radiation is a tendency for this radiation to cause damage to elastic fibers and to produce collagen degeneration. The result of the former is to induce vertical wrinkling or fissuring from the vermilion surface into adjacent skin. The result of the latter is to produce a thickened, puffy, and less pliable lip.

Typically, a person with labial actinic keratosis will present with one or more chronic crusting, keratotic patches on the lip, in addition to the above-described wrinkling and thickening (**Figure 13**). The patient will relate no symptoms but will often say the crusts can be peeled off but always return. Occasionally, a patient will have been told by a health care practitioner that the problem is "chronic herpes" and may have been prescribed an antiviral medication that has no beneficial effect. Typically, the crusts are not indurated. If induration is present, it is likely that carcinoma has developed.

The diagnosis of actinic keratosis can be made only by biopsy. The biopsy should include sufficient depth to allow the pathologist to be certain there is no invasion.

Treatment of labial actinic keratosis includes a minimum of complete excision of the lesion with a border of normal tissue and an admonition to protect the lip from sunlight, including use of a highly rated sunscreen. If the process is multicentric or if recurrence or a new lesion develops, then consideration should be given to vermilionectomy. The latter, if carried out as a plastic procedure to reduce the thickness of the sun-damaged collagen of the lip, results in a thinner lip whose new vermilion surface is composed of skin. The end result is usually very cosmetically and functionally acceptable (Figures 14 and 15).

Conclusion

The concept of oral premalignancy is well-established and clearly occupies the middle ground in the evolution of cancer from normal tissue. The process, as it involves the oral mucosa, is little different from that occurring in the bronchial tree, the uterine cervix, or the colon. What is significantly different is that the oral mucosa can be readily examined without special techniques or inconvenience to the patient.

The dentist is most familiar with the normal appearance of the oral mucosa, is best equipped to examine it, and is the individual with greatest opportunity to intercept premalignant oral disease.

Biopsy is the only method available to the profession that can unequivocally establish a definitive diagnosis of a clinical abnormality. When an abnormal lesion is found in a patient at risk for oral cancer, when an abnormality fails to respond to removal of a presumed local irritant, or

when no local factor is present to account for a lesion, the dentist should not hesitate to perform a biopsy or to promptly refer the patient to a dental specialist for biopsy.

It must be realized that the dentist who detects, diagnoses, and causes a premalignant lesion to be effectively treated has essentially prevented his or her patient from developing oral cancer and has likely contributed significantly to saving that patient's life.

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Diagnosis and Management of Oral Soft-tissue Lesions: The Use of Biopsy, Toluidine Blue Staining, and Brush Biopsy

Janice P. Handlers, DDS

ABSTRACT Upon discovery of a lesion after thorough oral soft-tissue examination, the dentist is confronted with the often-troublesome decision of how best to manage the patient. The management protocol must provide for early diagnosis in the case of oral cancer so as to reduce cancer morbidity and mortality. Options for management would include an observation period of some defined time, use of toluidine blue stain or oral brush biopsy to screen the lesion, or immediate biopsy and follow-up. This article reviews the assets and limitations of each and suggests a rational, science-based approach to diagnosis and management.

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Once a soft-tissue lesion has been discovered on clinical oral examination, how should the clinician proceed? The clinician, at this point has several options:

- Observe the lesion for a defined period and reassess;
- Screen the lesion before scalpel biopsy by the use of toluidine blue staining or computer-assisted oral brush biopsy analysis (OralCDx); or
- Perform a scalpel biopsy of the lesion.

Observation of Lesion

The decision to "watch" a lesion must be based on a clinical likelihood that the lesion is of reactive or inflammatory etiology. In the case of a white lesion, the presumed local irritating factors should be eliminated. In most instances, these lesions will resolve within two to four weeks. Ulcers and red lesions should heal within two weeks. Oral cancers do not disappear without definitive therapy and may take time to evolve to a more advanced stage that will be clinically obvious. Therefore, all lesions that fail to resolve in this period should have a biopsy performed.

Too often, early carcinoma appears as a painless lesion with minor local changes, and the clinician underestimates the clinical significance of the lesion. The patient is told to return only if there is any change in the lesion prior to the next regular recall examination, usually in six months. At this point, if the lesion has shown no change, the dentist feels validated in assuming that it

FIGURE 1A. Squamous cell carcinoma of the right lateral border of the tongue and the floor of the mouth – unstained.

FIGURE 1B. Positive royal blue staining of squamous cell carcinoma by toluidine blue.

is entirely innocuous and is comfortable in continuing the observation period, only to be surprised when sometime in the future the lesion does change and is finally diagnosed as squamous carcinoma. Sometimes, it changes in the six-month period and is diagnosed, but not until six months after the initial presentation.

There is sufficient evidence that visual inspection alone is not adequate to differentiate early oral cancer from benign lesions regardless of the expertise of the clinician. Sandler1 found that approximately 25 percent of 207 early stage oral cancers lacked any clinical features of malignancy. Dentists specializing in oral and maxillofacial pathology, oral medicine, and oral surgery clinically characterized 647 lesions as benign in a study by Sciubba and colleagues. 2 At least 29 of these were diagnosed malignant or dysplastic upon scalpel biopsy.

A professional delay is defined as the period from the patient's first consultation with a health care professional to his or her first consultation with the treating specialist.3 Such professional delays in diagnosis result in increased risk for local extension and spread to distant sites.3-7 The prognosis of the patient relates directly to the stage at which the cancer is diagnosed. The five-year survival rate in the United States for a localized oral squamous carcinoma is 81 percent, 44 percent for patients with nodal metastases, and 21 percent for patients with distant spread.8 In addition, failure to pursue diagnosis of a suspicious lesion or improper delay in the initiation of the diagnostic process can be considered negligence, and the dentist can encounter legal difficulties. 9

Screening the Lesion

Screening procedures such as the use of toluidine blue staining and OralCDx are used to determine the significance of an oral lesion prior to scalpel biopsy. These tests supplement the clinical oral examination in the early detection of premalignant and malignant oral lesions, which are often quite innocuous in appearance.

Toluidine Blue Staining

Toluidine blue is a metachromatic dye that shows affinity for the perinuclear cisternae of DNA and RNA. Selective staining of malignant and dysplastic cells might be explained in that these cells contain quantitatively more nucleic acids than normal tissue. Toluidine blue staining, in vivo, by malignant and dysplastic cells might also be the result of the immediate binding by sulfated mucopolysaccharides, which are found in higher quantities in tissues that are actively growing, such as tumors and tissues that are healing.10

The staining technique involves applying a 1 percent aqueous toluidine blue dye to the suspicious lesion for approximately 30 seconds, followed by a tap water rinse. The lesion is then lightly blotted with 1 percent acetic acid to reduce the background level of staining. Only positive areas will retain stain after this decolorization process (Figures 1a and b).

The technique is highly efficient in detecting malignant disease with reported sensitivity of over 95 percent.11-14 It has significantly less usefulness in detecting premalignant lesions. Warnakulasuriya and colleagues14 found a false-negative rate for oral epithelial dysplasias of 22 percent. Martin and colleagues13 found false-negative staining rates for carcinoma in situ of 42 percent and 58 percent for moderate and severe dysplasia. False-positive results are quite common in ulcerated inflammatory or traumatic lesions.11-14

The data indicates that there is limited value in using toluidine blue stain to determine the significance of an oral lesion prior to biopsy. Positive staining may indicate either an inflammatory or malignant lesion. Negative staining may mislead the clinician into believing that the lesion is a benign process when it may indeed be a premalignant lesion; however, toluidine blue staining may be of use in helping the clinician in choosing incisional biopsy sites within suspicious lesions.

OralCDx Computer-Assisted Oral Brush Analysis Method

OralCDx (OralScan Laboratories, Suffern, N.Y.) is a computer-assisted method of analysis of the oral brush biopsy in the detection of precancerous and cancerous lesions of the oral mucosa. The kit consists of a glass slide, fixative, and an oral brush biopsy instrument that is used to obtain a transepithelial specimen. The collected sample is spread onto the glass slide and bathed with the liquid, ethanol-based fixative. The slide is sent to OralScan Laboratories where it is scanned by the OralCDx neural net computer system to detect potentially abnormal cells. The computer produces approximately 200 digitized images of the suspicious cells for review by specially trained pathologists. The test results are faxed to the referring doctor.

The seminal study by Sciubba and colleagues2 reports a high sensitivity and specificity for malignant and dysplastic lesions. In the study, 945 lesions were identified by dentists specializing in oral and maxillofacial pathology, oral medicine, and oral surgery and classified as Class I lesions, if clinically believed to be suspicious (298 lesions), and as Class II lesions, if clinically believed to be benign (647 lesions). A scalpel biopsy was performed for all the clinically suspicious lesions. The OralCDx brush biopsy did correctly classify all of the histologically confirmed malignant or dysplastic lesions as "positive" or "atypical" (131 cases). It also identified 29 clinically benign appearing lesions as "positive" or "atypical," which subsequently were histologically confirmed as malignant or dysplastic. The implication is that these patients may not have received a biopsy on initial examination, as these lesions were clinically perceived as benign.

The remaining 618 clinically benign appearing lesions, including 99 that were classified as "atypical" on OralCDx, were not confirmed with scalpel biopsy. It would be useful to know how many of these may have been histologically confirmed as premalignant or malignant since there remains a question as to whether the false-negative rate indicated in the paper is accurate. It should not be assumed that the 618 Class II lesions not subjected to biopsy would have produced results identical to those that were subjected to scalpel biopsy. In addition, the reasons given in the study for the lack of biopsy confirmation of the 99 lesions with "atypical" OralCDx results were that patients were lost to follow-up; and, in the majority of other instances, the investigator "determined clinically that the oral lesion was benign."2 The study itself confirms the difficulty that even specialty-trained clinicians have in clinically determining benignity, in that 29 lesions clinically perceived to be benign were actually premalignant or malignant. If these lesions did indeed clinically appear to represent pemphigus, lichen planus, or geographic tongue as indicated in the paper, perhaps OralCDx was not the appropriate initial test of choice.

This author's experience at Oral Pathology Associates, Inc., has been fairly limited. The pathology group has been in receipt of 16 biopsies with previous OralCDx "atypical" results. Fifteen of the 16 cases were confirmed histologically as benign. One case was diagnosed as pemphigus vulgaris, one as exogenous pigmentation, one as lichen planus, two as lichenoid mucositis, one as pyogenic granuloma and epithelial hyperplasia, one as migratory glossitis, one as inflammatory fibroepithelial hyperplasia, and eight as benign keratosis. Only one of the 16 cases was confirmed as dysplastic. Although far from conclusive, this might suggest a higher false-positive rate than previously reported. Of the two biopsies received on lesions with "negative" OralCDx results, one was histologically confirmed as chronic granulomatous inflammation and one as benign keratosis and chronic mucositis.

It would seem that OralCDx might best be used in those instances where the lesion is thought clinically to be reactive or inflammatory (e.g., denture sore, ulcer, cheek-biting trauma). Rather than watch the lesion for two to four weeks, the clinician could use OralCDx immediately to help identify potentially harmful lesions. However, as recommended by the ADA Council on Scientific Affairs15 and by the manufacturer, all OralCDx "atypical" and "positive" results must be confirmed by incisional tissue biopsy followed by histologic examination to completely characterize the lesion. Persistent lesions, even with "negative" results, must receive adequate follow-up evaluation. At this point, scalpel biopsy should be performed to make a definitive diagnosis.

In cases where the lesion clinically appears suspicious, although OralCDx might be employed, it would seem that an immediate scalpel biopsy would be more definitive and therefore a better clinical choice. Certainly, if oral cancer is high on the list of differential diagnoses, a scalpel biopsy should immediately be pursued. As Dr. Sol Silverman, Jr., suggests, "There's no point in using the brush biopsy technique on lesions so advanced you can see them from across the room."16

In that OralCDx only tests the overlying epithelium, it is not appropriate for lesions situated in the submucosa and covered by apparently normal mucosa such as fibromas, salivary gland lesions, or pigmented lesions. It is not for use on the vermilion border of the lip. It is also not appropriate for generalized white or vesiculoerosive lesions such as pemphigus vulgaris, mucous membrane pemphigoid, or lichen planus (reticular and erosive forms). These generalized conditions rarely imitate premalignant or malignant conditions; and regardless of what results are obtained via OralCDx, scalpel biopsy is required for definitive diagnosis. In summary, a certain amount of clinical acumen seems to be necessary in knowing when to use the OralCDx brush biopsy.

Scalpel Biopsy

The reason to perform a scalpel biopsy on a clinical lesion is to establish a definitive diagnosis. It is not "a test for cancer." While it is generally true that a cancer diagnosis must be confirmed by biopsy before treatment can be given, it is not a diagnostic tool for cancer only. Biopsy can and should be used routinely to diagnose the hundreds of benign conditions that occur in the oral and paraoral regions. If a biopsy is performed on representative tissue, it is the most reliable test and serves as the gold standard against which all other tests are judged.

There are several things to keep in mind when performing an oral biopsy that will contribute to the success of the procedure.

- **Carefully select the biopsy site(s)** — The incisional biopsy should include the most representative portion(s) of the lesion (**Figure 2**). As indicated above, toluidine blue staining may be useful in determining the most suspicious area(s). There is little need to include a border of "normal" tissue.

FIGURE 2. Incisional biopsy of white lesion on buccal mucosa. It includes a good-sized portion of a representative area. No border of normal tissue is necessary.

The exception to this rule is when an incisional biopsy of an ulcer or desquamative condition is performed. In this case, it is important to include a margin of normal tissue and ensure that mucosal sloughing does not occur during the biopsy procedure itself or during transport of tissue to the laboratory. This can be accomplished by passing a length of suture through the sloughing portion into submucosa and then out through the "normal" mucosa. The suture should not be tied or knotted. The specimen should then be placed with the connective tissue side down on a dry piece of paper (e.g., sterile insert from scalpel blade). The connective tissue will adhere to the dry paper. Paper and specimen should be put into the specimen bottle containing 10 percent neutral buffered formalin. This will ensure that the specimen fixes flat, without twisting, and that the surface mucosa will not be traumatized during transport.

- **Remove sufficient tissue** — Generally, the larger the sample, the greater the chance of an accurate pathologic diagnosis. Fixation causes shrinkage, color changes and firming of the tissue. The greater size of the tissue biopsy allows for that shrinkage and permits the pathologist to better orient and cut the specimen, avoiding tangential sectioning, which can greatly hinder the definitive diagnosis.
- **Use sharp instruments (scalpel, dermatologic punch, scissors)** — This is especially critical when performing an incisional biopsy or excising a small lesion. Do not use electrosurgical knives or a carbon dioxide laser as these instruments cause heat damage and produce distortion and artifact that can seriously interfere with microscopic evaluation.
- **Handle tissues gently** — Crushing and squeezing the sample with forceps can interfere with diagnosis. Placing a suture through the specimen prior to removal will afford control and atraumatic handling. It will also make it less likely that the specimen will be dropped, sucked into an aspirator, or inadvertently swallowed.

Place specimen immediately into fixative solution — Fixation retards the normal enzymatic degradation and bacterial growth that occurs after tissue death. These biological processes will interfere with microscopic evaluation.

Management

Once the biopsy result has been received, the clinician determines the appropriate management of the patient based on the definitive diagnosis. The clinical scenario that seems to be the most problematic in developing a rational follow-up protocol is the white lesion that is diagnosed as "benign keratosis." Several studies have reported that these lesions do have a significant tendency to undergo malignant transformation, with rates varying from 0.13 percent to 15.7 percent.17-18 Risk factors that increase the likelihood of transformation include:

- The patient's being a nonsmoker;
- The patient's being female;
- The lesion's having an erythematous component;
- The lesion's having a clinical appearance of proliferative verrucous leukoplakia;
- Microscopic evidence of candidiasis;
- Location of the lesion on the tongue, floor of mouth, and soft palate; and
- The patient's having pain or discomfort. [18-21]

As it is not possible to distinguish clinically which lesion is undergoing malignant transformation, management of the patient will revolve around elimination of the lesion. The first step should be the elimination of any local irritating factors, including, but not limited to, the use of tobacco or alcohol, candida, and sources of trauma. If the lesion persists in spite of this conservative approach, surgical removal (excisional biopsy) with microscopic evaluation of the lesion is the most effective treatment. If the lesion is large, surgical removal may have to be accomplished in stages, or ablation with a carbon dioxide laser may be performed. For recurrent lesions, biopsy should be re-performed. Although chemoprevention has been used experimentally, its long-term effectiveness has not been established.17

Any lesion that is microscopically diagnosed as "dysplasia," must be removed in its entirety as these are considered premalignant lesions. Lumerman and colleagues22 retrospectively evaluated 44 of 308 cases of oral epithelial dysplasia diagnosed by their biopsy service. Thirty-four percent of patients (15) had a recurrence of the dysplasia and 16 percent (7) developed oral carcinomas seven to 78 months later (mean of 34 months). Silverman and colleagues18 reviewed follow-up data for 22 patients with oral leukoplakia and microscopic dysplasia reported in a prospective study of 257 oral leukoplakia patients. These patients were followed for a mean time of 8.1 years. Eight of the patients (36.4 percent) with epithelial dysplasia developed oral carcinomas.

Ideally, surgical excision should be performed with microscopic evaluation of margins. For large lesions, ablation with a carbon dioxide laser is effective; but, again, a biopsy should be performed on any recurrent lesions to rule out invasion. Any lesion microscopically diagnosed as malignant must be referred immediately for definitive therapy.

Conclusion

Biopsy remains the gold standard in the diagnosis of oral lesions. "Watch and wait" is only appropriate for lesions that are thought to be inflammatory (e.g., denture sores ulcers or cheek-biting trauma). The waiting period should be no longer than four weeks before definitive diagnosis by biopsy. An alternative to the observation period would be to immediately perform an OralCDx brush biopsy on the lesion and potentially identify lesions that require immediate biopsy ("atypical" or "positive" results). All persistent lesions that are diagnosed as "negative" on OralCDx should be definitively diagnosed by biopsy. Any lesion that is not thought to be inflammatory or is obviously suspicious for cancer should have an immediate biopsy. Toluidine blue staining may have value in helping the clinician to select the most representative areas for biopsy.

Early detection of oral cancer and removal of potentially malignant lesions are two weapons in the cancer control program. Early detection results in increased survival and reduced morbidity. Removal of lesions that may have malignant potential may prevent the occurrence of cancer.

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Oral Cancer: A Self-Assessment Quiz

Sol Silverman, Jr., MA, DDS, and Raymond J. Melrose, DDS

ABSTRACT This article consists of a quiz on oral cancer knowledge. The goals of the quiz are to reinforce known cancer information and present new information. Photographs are used to bring a sense of the practical problems that clinical pathology presents. Also, a number of real-life case situations are presented with their corresponding illustrations so that the readers may use their clinical judgment and experience in choosing an answer.

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The authors have developed a new and updated iteration of the "Oral Cancer Quiz" that was published in this journal in March 1982 and rewritten and published again in this journal in October 1991. This version is shorter, more profusely illustrated, and divided into five key sections.

The goals of the oral cancer quiz remain the same as those of the earlier versions. The authors wish to reinforce known cancer information and present new information in an intellectually stimulating way. The photographs from the collection of the primary author are used to visually enhance the material and bring a sense of the "real life" practical problems that clinical pathology presents. Also, a number of real-life case situations are presented with their corresponding illustrations so that the readers may use their clinical judgment and experience in choosing an answer. The answers to the quiz are published elsewhere in this issue. It is suggested that readers take the quiz in small increments over several days rather than try to digest the quantity of material in one sitting.

Oral cancer remains a hugely significant problem not just in California, but also worldwide. Dentists are the principal health care practitioners responsible for educating patients about risk factors for oral cancer; for routinely conducting oral cancer detection examinations on their patients; for detecting abnormalities; for taking appropriate, timely actions to obtain a diagnosis of abnormalities detected; and for assisting in the management of patients who have been treated for oral cancer or other malignancies involving the head and neck region. No profession is better-trained for the assumption of these responsibilities, and only dentistry will be held publicly accountable if it fails as a profession to fulfill them.

The quiz is divided into sections:

Sections

A: Epidemiology/Biology
B: Etiology/Prevention
C: Precancer
D: Early Detection/Diagnosis
E: Treatment/Complications

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Section A: Epidemiology/Biology

1. The leading causes of death of adults in the United States may be ranked in order as follows:
   a. Cancer, heart disease, accidents.
   b. Heart disease, accidents, cancer.
   c. Heart disease, cancer, accidents.
   d. Alcoholism, heart disease, cancer.

2. Which of the following sites is at the highest risk for developing cancer?
   a. Tongue
   b. Floor of mouth
   c. Soft palate
   d. Lip

3. The most common form of oral cancer is:
   a. Lymphoma.
   b. Squamous cell carcinoma.
   c. Basal cell carcinoma.
   d. Adenocarcinoma.

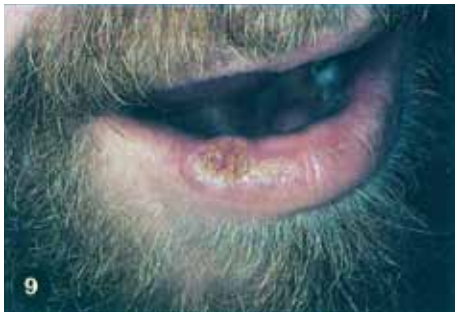
4. Data on racial characteristics and occurrence of oral cancer indicate that:
   a. Environment and habits play a small role in etiology.
   b. Inheritance has been shown to play a major role.
   c. There are no ethnic differences.
   d. Familial tendencies are not apparent in oral cancer.

5. Once a pat ient has had one primary oral cancer:
   a. There is almost no risk of developing a second head and neck cancer.
   b. More than 15 percent of patients will develop a second head and neck cancer.
   c. Little can be learned about second oral cancers since about 50 percent of the patients die within five years of diagnosis/treatment.
   d. An immunity is developed against subsequent head and neck cancers.

6. Of all oral cancers, squamous cell carcinoma accounts for approximately:
   a. 20 percent.
   b. 50 percent.
   c. 70 percent.
   d. 90 percent.

7. Carcinoma and sarcoma are different by virtue of:
   a. Tissue of origin.
   b. Histologic grading.
   c. Growth rate.
   d. Signs and symptoms.

8. Current data on the relative frequency of oral cancer in men and women indicate that:
   a. Estrogen definitely offers tissue resistance or protection.
   b. Habits and environment may be the most important factors.
   c. In those over 40, men should be more closely examined for oral lesions than women.
   d. Inheritance is the most important factor.



9. Lip cancers:
   a. Are decreasing in incidence yearly.
   b. Are not related to sun exposure.
   c. Have a poorer prognosis than most oral cancers.
   d. Are related to herpes simplex virus infections.

10. The most common mode(s) of oral carcinoma spread is/are by:
   a. Blood vessel and direct invasion.
   b. Direct invasion and lymphatics.
   c. Lymphatics only.
   d. Blood vessels only.

11. Induration refers to:
   a. Redness.
   b. Hardness.
   c. Swelling.
   d. Painfulness.

12. Patient prognosis for oral squamous cell carcinoma appears to be most dependent upon:
   a. Tumor stage and early treatment.
   b. Combining radiation and surgery.
   c. The addition of chemotherapy to radiation and/or surgery.
   d. The patient's age and gender.

13. Most important for reducing morbidity and mortality from an oral cancer is:
   a. Combination treatment involving surgery, radiation, and chemotherapy.
   b. Optimal nutrition.
   c. Discontinuation of all tobacco habits.
   d. Early detection.

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Section B: Epidemiology/Prevention

14. This 22-year-old male patient has used snuff daily for four years. He was referred by his dentist. He is in good health and takes no medications.
   a. There is an extremely high risk for developing a carcinoma within 10 years.
   b. The primary carcinogen in smokeless tobacco consists of nitrosoamines.
   c. There are no sugars in smokeless tobacco, thus no risk for caries.
   d. There is so little nicotine in smokeless tobacco that habituation and/or addiction are unimportant factors.

15. Which of the following statements is true?
   a. Most oral cancer patients smoke cigars.
   b. Tobacco contains nicotine, which is the main carcinogen.
   c. The main carcinogen is carbon monoxide.
   d. Tobacco can induce abnormal epithelial cell changes.

16. Which forms of tobacco are associated with increased risk of oral cancer development?
   1. Filtered cigarettes
   2. Unfiltered cigarettes
   3. Cigars and pipes
   4. Snuff and chewing tobacco
   a. Only 2 and 3 are correct.
   b. Only 2 and 4 are correct.
   c. Only 1, 2, and 3 are correct.
   d. All are correct.

17. Which of the following demonstrates little or no association with oral cancer?
   a. Advancing age
   b. Dental prostheses
   c. Leukoplakia
   d. Diets low in fruits and vegetables

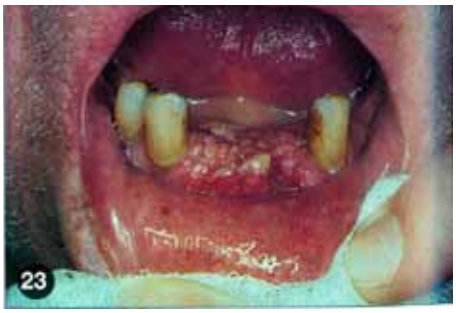
18. Which statement about the use of smokeless tobacco is correct?
   a. It is a safe alternative to smoking.
   b. It delivers a rapidly absorbed dose of nicotine.
   c. It is not habituating.
   d. Long-term use is not associated with an increased risk for oral cancer.

19. Which of the following smoking cessation techniques/methods has no validity?
   a. Transdermal nicotine patches to increase nicotine blood levels to help break tobacco smoking habituation/addiction
   b. Group psychology sessions to help break the smoking habit
   c. Hyperbaric oxygen treatments to reduce tobacco-related carbon monoxide blood levels
   d. Use of a chewing gum containing nicotine to reduce the urge to smoke

20. Human papillomaviruses can occur in oral epithelium. They are LEAST associated with:
   a. Geographic tongue (glossitis migrans).
   b. Oral condyloma (warts).
   c. Oral squamous cell carcinoma.
   d. Oral leukoplakia.

21. The main difference between severe dysplasia/carcinoma in situ and carcinoma is based on histologic evidence of:
   a. Invasion of connective tissue.
   b. Mitotic activity.
   c. Nuclear/cytoplasmic ratio.
   d. Degree of differentiation.

22. Epithelial dysplasia refers to:
   a. A discrepancy in cellular maturation with an increased risk for malignant transformation.
   b. An abnormality of keratin (dyskeratosis).
   c. Tissue changes with a certainty to transform to carcinoma.
   d. A well-defined clinical entity with rigid, well-described, and reproducible criteria.



23. Squamous carcinoma of the mandibular gingiva developed in a patient who has worn a partial denture for many years. A cause-and-effect relationship between removable dentures and oral cancer is not clear because:
   1. Denture materials are noncarcinogenic by accepted testing methods.
   2. Gingiva is an infrequent site of oral cancer, accounting for less than 6 percent of oral cancers.
   3. In epidemiologic studies, there have been no statistically significant correlations between prosthetic appliances and sites of oral cancer.
   4. Gingival cancers occur only in areas of denture irritation.
   a. Only 1, 2, and 3 are true.
   b. Only 2, 3, and 4 are true.
   d. Only 1, 3, and 4 are true.
   d. All are true.

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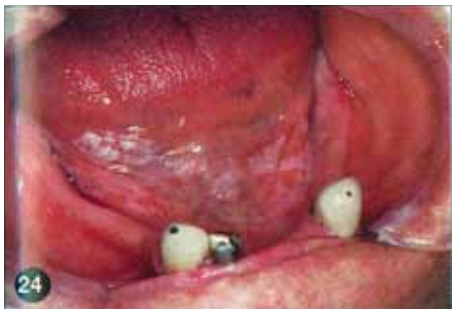
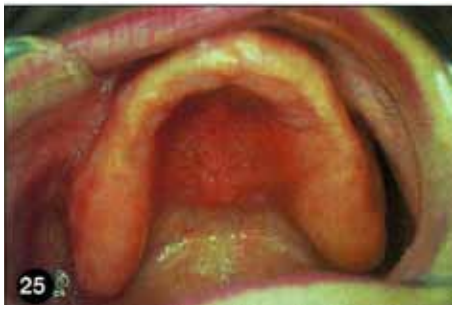
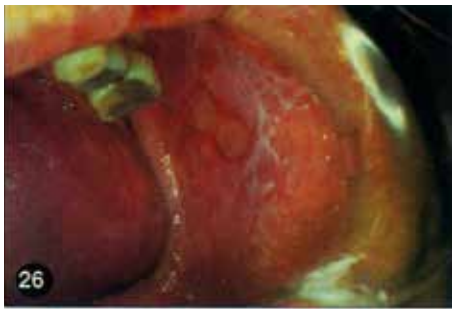
Section C: Precancer



24. This 40-year-old woman has smoked from one to two packs of cigarettes daily for about 15 years. She has mild hypertension and diet-controlled adult-onset diabetes. She takes birth-control pills and occasional Tylenol for headaches and "arthritis." The lesion was biopsied six months ago and signed out as a benign focal keratosis without evidence of cellular atypia or dysplasia. The patient's chief complaint at this visit was a recent slight discomfort/irritation at the lesion site that has persisted for about one month. There were no areas of induration or palpable lymph nodes. The next most appropriate step would be:
    a. To have the patient go on a three-month smoking-cessation program to see if the lesion disappears.
    b. To perform an incisional biopsy even though there was a negative biopsy six months ago.
    c. To have the patient return in four to six weeks to determine if there is a change in signs or symptoms.
    d. To check the patient's blood sugar, since poor glycemic control can aggravate leukoplakia.



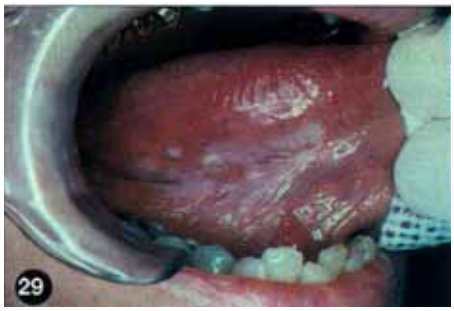
25. Palatal papillary hyperplasia:
    1. Is premalignant.
    2. Is not premalignant.
    3. Is generally considered to be an allergic reaction.
    4. May be biopsied and/or followed periodically.
    a. Only 1 and 4 are correct.
    b. Only 2 and 3 are correct.
    c. Only 2 and 4 are correct.
    d. Only 1 and 3 are correct.



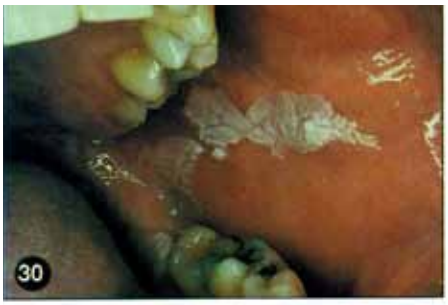
26. This patient has the erosive form of lichen planus. This lesion:
    a. Is premalignant with a high risk for malignant transformation.
    b. Appears to be associated with some increase in risk for oral cancer.
    c. Will often undergo spontaneous remission.
    d. Should be surgically removed.

27. The cause of lichen planus is:
    a. The human papillomavirus.
    b. Nutritional deficiency.
    c. Tobacco-induced.
    d. Probably immunopathic (i.e., autoimmune).

28. Clinical leukoplakia is usually a manifestation of which histologic change?
    a. Hyperplasia
    b. Dysplasia
    c. Hyperkeratosis
    d. Atrophy



29. This patient manifests a clinical leukoplakia of the lateral tongue.
    a. This always represents an epithelial response to a well-defined irritant.
    b. This lesion could represent microscopic epithelial dysplasia.
    c. Surgical removal will prevent recurrence.
    d. Tobacco plays no role.



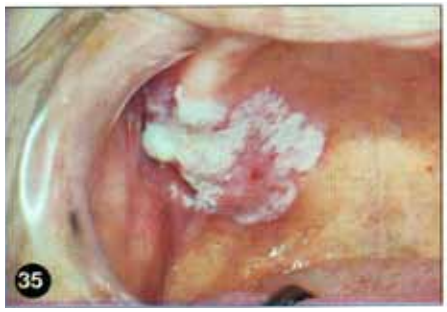
30. A clinical leukoplakia involving the buccal mucosa, gingiva and oropharynx persists despite removing all identifiable irritants. Brush biopsy, toluidine blue staining and several representative incisional biopsies show no evidence of dysplasia or malignancy. This leukoplakia then:
    a. Is not premalignant.
    b. Must still be considered to have a risk for malignant transformation.
    c. Need not be observed any further.
    d. Should be automatically biopsied every six months.

31. The above leukoplakia is best managed by:
    a. Avoiding laser vaporization because of the risk of inducing carcinogenesis.
    b. Excision and skin grafting.
    c. Intensive vitamin A therapy.
    d. Periodic follow-up with incisional rebiopsy if there is a change in signs and/or symptoms.

32. The prognosis for leukoplakia worsens if there is:
    1. Microscopic dysplasia.
    2. A red (erythematous) component.
    3. Evidence of proliferation and a verrucous appearance.
        a. Only 1 and 2 are correct.
        b. Only 1 and 3 are correct.
        c. Only 2 and 3 are correct.
        d. All the above are correct.

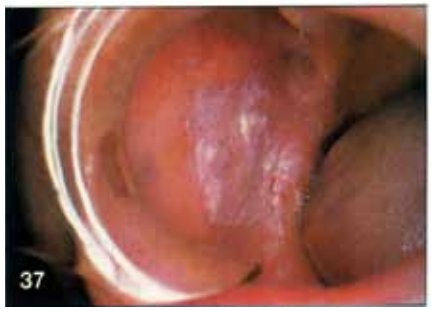
33. A red component (erythema) in a leukoplakic lesion indicates an increased risk for:
    a. Infection.
    b. Allergy or hypersensitivity.
    c. Dysplasia.
    d. Immune deficiency.

34. Oral hairy leukoplakia is:
    a. Associated with the human immunodeficiency virus (HIV).
    b. Usually caused by candidal overgrowth.
    c. A form of lichen planus.
    d. Associated with a premalignant risk.



35. This proliferative verrucous leukoplakia occurred in a female nonsmoker:
    a. It is not likely to transform into carcinoma because she is a nonsmoker.
    b. Chances are about 50 percent that it will eventually disappear.
    c. It is probably related to a herpes family virus.
    d. It could be associated with a type of human papillomavirus.

36. Vitamin A or its precursors (carotenoids):
    a. Are predictably effective as a means of controlling leukoplakia.
    b. Play an important role in epithelial keratinization, although the exact biochemical mechanism is unknown.
    c. Are not toxic to humans even in high dosages.
    d. Are effective pro-oxidants.



37. This 50-year-old woman has had an area of leukoplakia on the buccal mucosa for about a decade. It is asymptomatic and has not shown any changes since the original biopsy (patient and dentist observations). The patient has good hygiene and no other mucosal lesions. She has not smoked for more than 15 years, only drinks socially, is in good health, and takes no medications.
    a. This more than likely would show areas of moderate dysplasia upon biopsy because of the long duration.
    b. Even if a biopsy would show no dysplasia or carcinoma, there would be a need for periodic follow-up examinations.
    c. Since there is no red component, one would not find any epithelial dysplasia.
    d. The most effective management would be chemoprevention rather than laser removal.

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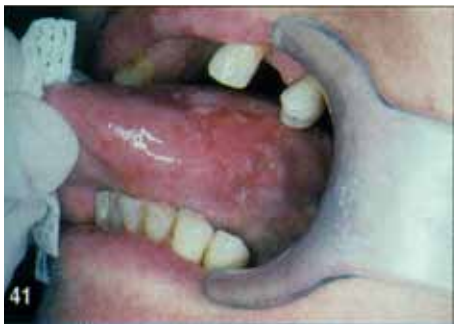
Section D: Early Detection/Diagnosis

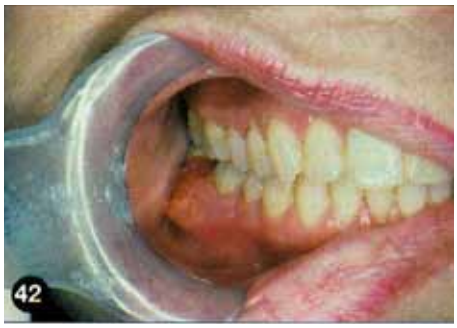
38. Staging of an oral cancer depends upon:
    a. Tumor differentiation.
    b. Size and spread.
    c. Location.
    d. Immune status.

39. A palpable neck (cervical) lymph node in a patient with an oral cancer:
    a. Indicates an advanced cancer.
    b. Has no relation to prognosis.
    c. Does not influence treatment.
    d. Indicates that an incisional biopsy should be done for evaluation.

40. A swelling in the head and neck thought to be associated with a lymph node should be evaluated initially by:
    a. Incisional biopsy
    b. Excisional biopsy
    c. Brush biopsy
    d. Fine-needle aspiration biopsy

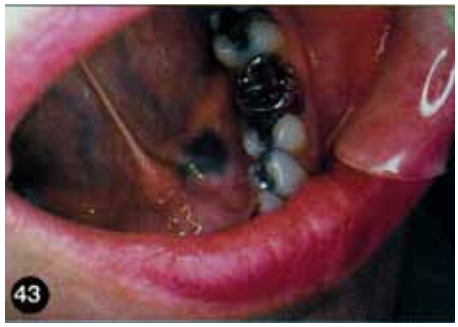


41. This 55-year-old woman has noticed this painful tongue lesion for more than three months. It does not seem to be getting any worse, but it is no better. She doesn't smoke or use alcohol. She has diet-controlled diabetes and mild hypertension. Outside of her tongue discomfort, she feels fine. The differential diagnosis includes carcinoma, dysplasia, infection, and vesiculoerosive disease.
    a. Most probably, her blood sugar is out of control; and she should be referred to her physician for a complete work-up.
    b. As the first step, she should immediately be put on a three-week course of antibiotic and anti-inflammatory drugs.
    c. An incisional biopsy should be performed, since this is an effective way to rule out dysplasia and carcinoma.
    d. A biopsy should definitely be delayed in order to first learn more about her medical status.

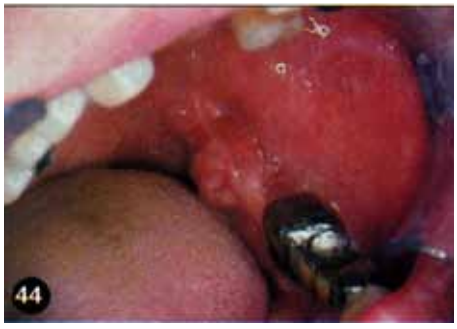


42. This 48-year-old woman has a rubbery-firm swelling of the #30 buccal gingival area. It is uncomfortable, and has been bothersome for about three weeks. A periapical X-ray shows an irregular loss of alveolar bone in that area. The oral hygiene is excellent, and a full mouth X-ray survey one year ago shows minimal evidence of periodontal disease. There has only been a minimal response to a 10-day course of antibiotics. Tooth #30 is moderately mobile. The next step should be:
    a. Extract #30
    b. Switch antibiotics and institute aggressive curettage
    c. Biopsy the swelling
    d. Start endodontic treatment on #30

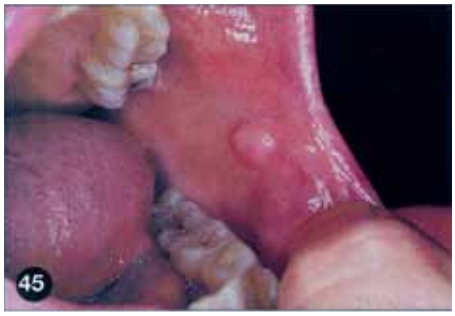
43. This patient has been referred because of concern regarding an asymptomatic discoloration in the left floor of mouth. While the duration is uncertain, it "seems to be getting a little darker in color." The area is soft, and there are no palpable lymph nodes. There are no other oral lesions. She takes thyroid and hormone supplements and an antacid for regurgitation. She smokes and drinks moderately.



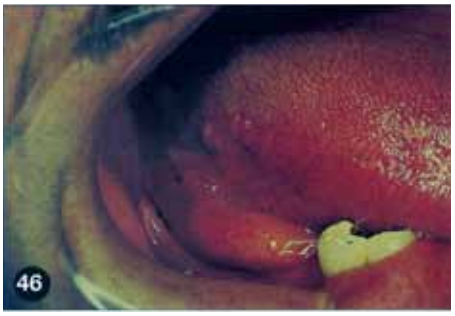
    a. Because of the dark color and uncertain history, this pigmentation almost certainly represents a malignant melanoma.
    b. An incisional biopsy would significantly spread malignant cells if this were a melanoma, as well as markedly worsen the prognosis.
    c. Racial melanosis is the most logical explanation.
    d. An incisional biopsy would be a better choice than periodic observations.



44. This lesion is thought to be either a benign or malignant tumor of minor salivary gland origin. The most appropriate diagnostic technique would be:
    a. Fine-needle aspiration biopsy.
    b. Incisional biopsy.
    c. Excisional biopsy.
    d. MRI or CT imaging.



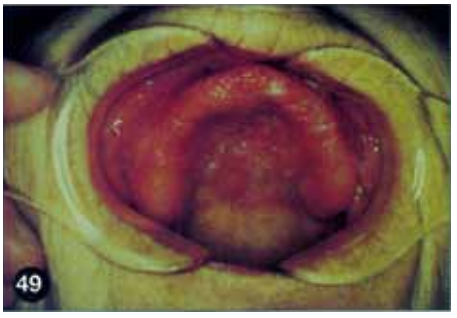
45. This soft, sessile, asymptomatic mass has been noticed for about one year. The patient bites it occasionally, and there has been a minimal increase in size. The most likely diagnosis is:
a. Fibroma.
b. Benign mixed tumor.
c. Squamous cell carcinoma.
d. Lymphoma.



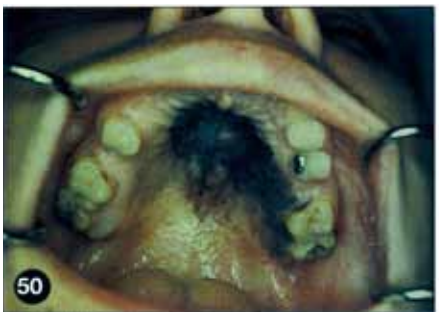
46. These asymptomatic tissue proliferations or lobules at the lateral border of the oral tongue represent:
a. Traumatic fibro-epithelial hyperplasia.
b. Premalignant mucosal changes.
c. Foliate papillae.
d. Fungiform papillae.

47. Purpura is a clinical manifestation of:
a. Bleeding.
b. Leukemic infiltrates.
c. Anemia.
d. Melanin deposition.

48. A complete blood count is LEAST useful in establishing a diagnosis or assessment of:
a. Leukemia.
b. Anemia.
c. Leukopenia.
d. Carcinoma.



49. The erythematous denture-bearing mucosa has been painful for one month. The 65-year-old patient has had these dentures for more than 10 years. She complains of a slight dryness but otherwise seems to be in good health. The most likely diagnosis of this condition is:
a. Epithelial dysplasia.
b. Candidiasis.
c. Nutritional deficiency.
d. Allergy to denture materials.



50. This patient is suspected as having a malignant melanoma.
a. Melanoma is a common oral cancer.
b. Oral melanomas are associated with smoking.
c. Oral melanoma has a poor prognosis, with less than 10 percent surviving five years.
d. Suspected oral melanomas should not be biopsied because of the risk of metastasis.

51. Fine-needle aspiration biopsy:
a. Is dangerous because it may spread tumor cells.
b. Cannot differentiate between benign and malignant cells.
c. Is useful in assessing potential malignancies of major salivary glands.
d. Is usually very painful and requires anesthesia.

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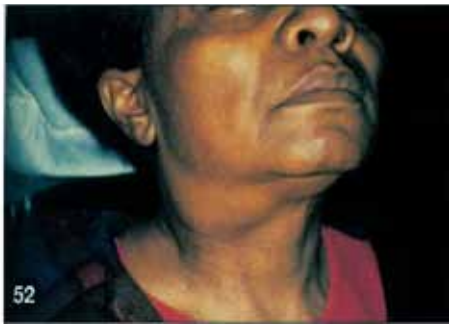
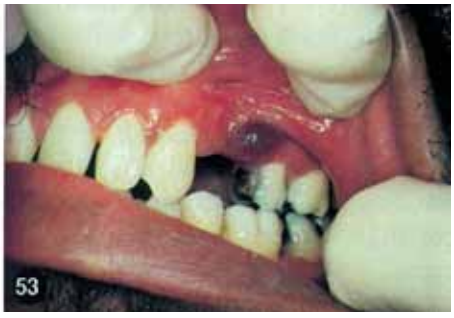
Section E: Treatment/Complications



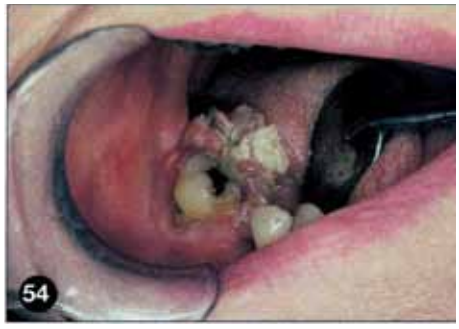
52. This patient presents complaining of a lump in the neck noticed for about four months. It is slightly uncomfortable and is slowly increasing in size. Which of the following statements is correct?

a. This may represent a metastatic tumor with an oral, oropharyngeal, or nasopharyngeal primary.
b. This most likely represents a dental infection.
c. A fine-needle aspiration biopsy would not yield any useful information.
d. An incision and drainage procedure should be attempted immediately.



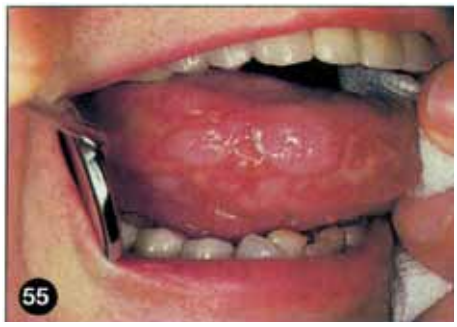
53. This HIV-positive patient has developed Kaposi's sarcoma of the gingiva. Which statement about Kaposi's sarcoma is INCORRECT?

a. The palate is the most frequent oral location.
b. Kaposi's sarcoma is vascular and should not be biopsied.
c. Although most commonly a disease of the facial skin, Kaposi's sarcoma can occur first in the mouth.
d. Kaposi's sarcoma is associated with the herpes simplex virus, type 8.



54. A 60-year-old woman is referred with complaints of a sore in her mouth that has been present for more than two months. The biopsy and history document that this is a rapidly growing exophytic, well-differentiated squamous cell carcinoma with no X-ray evidence of bone invasion. The tumor board recommends that external beam radiation therapy alone (approximately 7000 cGy in six to seven weeks) can control this cancer and that the prognosis is good. The patient is otherwise in good health.

a. The lower right molar should be extracted immediately, even though it might delay therapy about one week.
b. The patient should be maintained on antibiotics to avoid dental infection and start radiation immediately, since there is little risk for osteoradionecrosis.
c. Radiation therapy should be started immediately and the molar extracted immediately after radiation is completed.
d. An attempt to delay extraction of the molar for six months should be made, since extraction is much safer then.

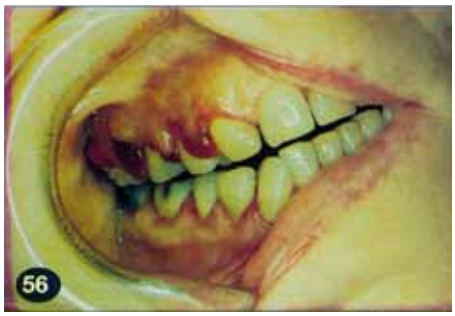


55. This patient with chronic leukemia has just finished a course of cytotoxic drugs as a monthly regimen of chemotherapy to control the blood dyscrasia. She has two complaints: a sore tongue and dental pain with swelling from a periapical abscess in a periodontally involved tooth.

1. The patient should be put on antibiotics immediately.
2. A molar extraction should be considered when the white blood cells are at or near normal levels.

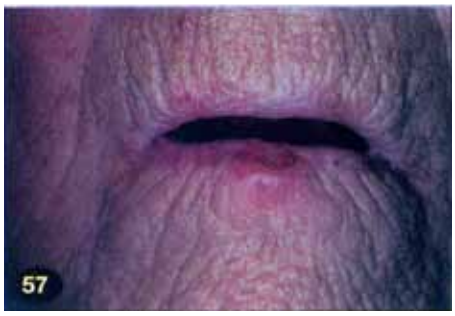
3. The tongue changes probably represent a mucositis secondary to the cytotoxic drugs.

a. Only 1 and 2 are correct.
b. Only 1 and 3 are correct.
c. Only 2 and 3 are correct.
d. All are correct.



56. This patient has persistent breast cancer. She has just completed an intensive seven-day conditioning regimen of cytotoxic drugs preliminary to a stem-cell transplant (the latter to reconstitute her destroyed white blood cells). The gingival findings are most likely a reflection of:

a. Leukopenia.
b. Thrombocytopenia.
c. Infection.
d. Metastatic cancer.



57. This 82-year-old woman has noticed this asymptomatic, indurated lesion on her lower lip for about five weeks. There are no palpable cervical lymph nodes. She doesn't smoke or drink and generally feels quite well. Her hypertension is under control with diet, diuretics, and mild exercise. She has a history of breast cancer treated by surgery four years ago without evidence of local recurrence.

a. This most likely is a metastasis from her breast cancer that was inadequately controlled by surgery.
b. This probably is a persistent herpes labialis that requires topical antiviral medications.
c. An incisional biopsy is the most appropriate next step.
d. Institute topical anti-inflammatory agents.

58. Hyperbaric oxygen treatments have been useful in some cancer patients for the management of osteoradionecrosis resulting from radiation effects on bone because:

a. High concentrations of oxygen kills cancer cells.
b. Hyperbaric oxygen stimulates the formation of blood vessels (angiogenesis).
c. Hyperbaric oxygen attracts white blood cells to necrotic areas by chemotaxis.
d. Hyperbaric oxygen doesn't require any surgery.

59. A patient with a non-Hodgkin's lymphoma is receiving monthly chemotherapy to control the disease. An extraction of a periodontally involved molar is planned. The patient might combat a post-extraction bacteremia poorly because of potential:

a. Leukopenia.
b. Thrombocytopenia.
c. Poikilocytosis.
d. Leukocytosis.

60. In oral cancer patients with healthy teeth and gingiva who are to be treated by radiation, the dentition should be managed by:

a. Extracting all teeth in the primary beam of radiation before therapy begins.
b. Restoring all teeth in the primary beam of radiation with crowns.
c. Instituting optimal hygiene, home care, and fluoride applications.
d. Replace all metal fillings with composites.

61. In patients who have completed radiation therapy for oral cancer:

a. Dentures can never be worn again because of the risk for developing osteoradionecrosis.
b. Dentures cannot be worn for six months.
c. Properly fitting dentures can usually be worn without a high risk for developing osteoradionecrosis.
d. Special soft liners must be used if dentures are to be worn.

62. The most critical variable influencing the lack of complications following tooth extraction in patients who have been irradiated for oral cancer is:

a. Stage of the primary tumor.
b. Total radiation dose to bone.
c. Post-treatment timing of the extraction.
d. Surgical technique.

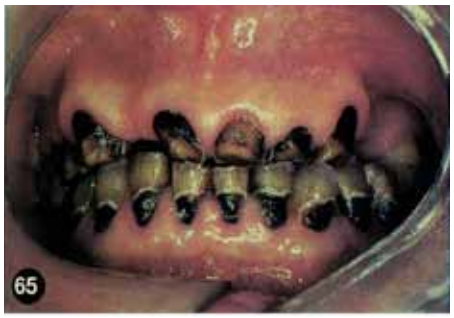
63. Post-radiation and post-surgical trismus are both best managed by:

a. Daily exercise of the muscles of mastication.
b. Immobilization.
c. Cortisone injections.
d. Surgical intervention.

64. Therapeutic radiation for oral cancer may directly and/or indirectly cause:

1. Hyposalivation and xerostomia.
2. Bone marrow fibrosis and avascularity.
3. Altered taste.
4. Dental caries.

a. Only 1, 2, and 3 are true.
b. Only 2, 3, and 4 are true.
c. Only 1, 3, and 4 are true.
d. All are true.



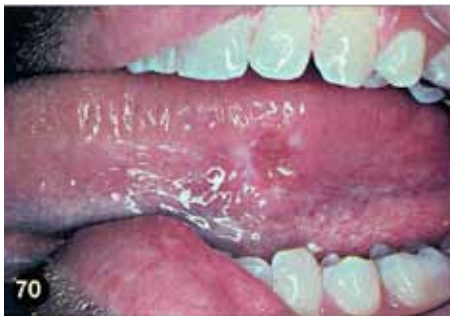
65. This patient received 7,200 cGy radiation for a carcinoma of the base of the tongue one year ago. He has had no dental care for the past five years. Aside from the carious teeth, full-mouth X-rays reveal a bone pattern that appears to be within normal limits. The bone in the primary beam of radiation:
    a. Is probably normal and at no risk for osteoradionecrosis.
    b. Is probably abnormal and at some risk for osteoradionecrosis.
    c. Can never support a prosthetic appliance if the teeth were extracted.
    d. Would not respond well to endodontia.

66. The development of osteoradionecrosis is most closely related to:
    a. Character of the oral bacterial flora.
    b. Xerostomia.
    c. Pre-radiation extractions.
    d. Radiation dose to bone.

67. The development of dental caries in post-irradiated oral cancer patients is most closely related to:
    a. Xerostomia.
    b. The direct effect of radiation dose to teeth.
    c. Altered vascular supply.
    d. Pulpal damage.

68. The greatest danger that invasive dental care presents to leukemic patients is:
    a. Infection.
    b. Hemorrhage.
    c. Severe pain.
    d. Blast crisis.

69. In the management of leukoplakia:
    a. The carbon dioxide laser has been effective.
    b. Most should be excised and skin grafted.
    c. It responds well to vitamin A.
    d. It responds well to corticosteroids.



70. This 30-year-old man is referred because of a slightly painful sore on the left lateral tongue that has been noticed for about four weeks. He does not smoke or drink alcohol, he has no other risk factors, takes no medicines, and is in good health. He has had occasional canker sores (recurrent aphthae) in the past. Because of some induration and the fact that the lesion has been present for about a month, the differential diagnosis includes dysplasia and squamous carcinoma.
    a. Best managed by observation and palliation since the patient has no risk factors for cancer
    b. Best managed with systemic or topical corticosteroids for unusual aphthous ulcer
    c. Best managed by an excisional biopsy
    d. Best managed by an incisional biopsy

Quiz Answer Key

Oral Cancer: A Self-Assessment Quiz Answer Key

Sol Silverman, Jr., MA, DDS, and Raymond J. Melrose, DDS

1. C
2. A
3. B
4. D
5. B
6. D
7. A
8. B
9. A
10. B
11. B
12. A
13. D
14. B
15. D
16. D
17. B
18. B
19. C
20. A
21. A
22. A
23. A
24. B
25. C
26. B
27. D
28. C
29. B
30. B
31. D
32. D
33. C
34. A
35. D
36. B
37. B
38. B
39. A
40. D
41. C
42. C
43. D
44. B
45. A
46. C
47. A
48. D
49. B
50. C
51. C
52. A
53. B
54. A
55. D
56. B
57. C
58. B
59. A
60. C
61. C
62. B
63. A
64. D
65. B
66. D
67. A
68. A
69. A
70. D

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Oral Management of the Patient With Cancer in the Head and Neck Region

Bruce F. Barker, DDS, and Gerry J. Barker, RDH, MA

ABSTRACT Cancer therapies -- including surgery, radiation, and chemotherapy -- may unfavorably affect the oral/dental health of patients. Existing dental problems can also result in serious complications that may be prevented by dental intervention prior to cancer therapy. This paper will be limited to a discussion of the detrimental effects of radiation therapy on the oral cavity and salivary glands and appropriate dental management.

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A patient calls a dental office for an appointment before beginning cancer therapy for a cancer in the head and neck region. The dentist may or may not receive a consultation from an oncologist. What are the questions the dentist needs to ask? What are the dental implications? What should the dentist recommend? Dentists who have not been confronted with these questions may be in the near future. The oral cavity can be affected by therapy for any cancer in the head and neck region, including cancers of the oral cavity, pharynx, larynx, thyroid, esophagus, and lymph nodes, including lymphomas and Hodgkin's disease. Radiation treatment for some types of brain cancer may affect the tissues of the mouth or salivary glands. While not related to the topic of this paper, it should be noted that chemotherapy or bone marrow/stem cell transplantation for other malignancies also requires dental consultation to prevent or ameliorate serious complications, especially systemic infection.1,2

Most head and neck cancers are treated with surgery and/or radiation therapy and sometimes adjuvant chemotherapy. The effects of surgical treatment are immediately obvious, but radiation therapy may result in both acute and long-term consequences to the oral mucosa, salivary glands, teeth, and bone. This discussion will be limited to the oral effects of radiation in the treatment of all head and neck malignancies.

It is critical that the dentist not delay a patient's requested dental appointment.

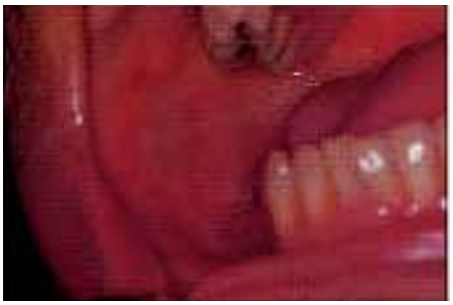

FIGURE 1. Severe oral mucositis with ulceration that developed in the third week of radiation therapy.

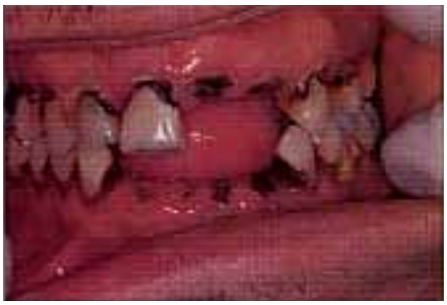

FIGURE 2. Radiation-type caries at the cervical margins. Several teeth exhibit circumferential caries that will lead to amputation of the tooth at the gingival.

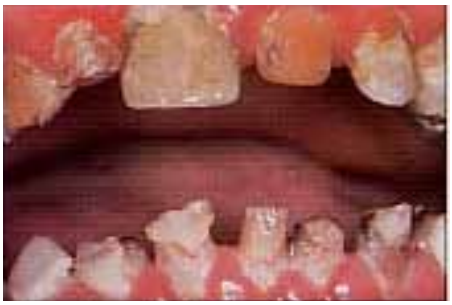

FIGURE 3. Severe demineralization and caries that developed within months of undergoing mantle field radiation therapy for Hodgkin's disease. The radiation therapy involved a portion of the salivary glands but not the teeth.

Radiation therapy should not be initiated until the dentist has completed a dental evaluation. Prior to seeing the patient, the dentist will want to contact the radiation oncologist and ask the following questions:

- What is the type of cancer, and where is it located?
- What is the proposed total dose of radiation, and what are the exact anatomic areas to be radiated?
- How much radiation will the jaws, teeth, and salivary glands receive?

A referral form requesting this information on a diagram of the head has been published.3 Most cancers receive from 4,000 to 7,200 cGy (centigrays: 1 cGy = 1 rad.) This radiation is typically delivered five days a week in doses ranging from 180 to 200 cGy per day. The dentist's concern is for any patient who receives more than 4,000 cGy to salivary glands and more than 5,500 cGy to maxillary and mandibular bone. These doses may result in serious side effects, some of which may be permanent.4,5

Oral and Dental Effects of Radiation Therapy to the Head and Neck

Within the first two weeks, the direct effect of radiation therapy on oral soft tissue results in mucositis, edema, erythema, ulceration, and pain (**FIGURE 1**). Tissue breakdown causes difficulty in eating and secondary infections. Mucositis persists throughout radiation therapy but resolves within weeks after completion of therapy.

Salivary glands that receive more than 4,000 cGy may be permanently destroyed.6 It is very important to find out which glands will be within the field of radiation. If the parotids, submandibular, sublingual, and minor glands are radiated, there will likely be severe salivary gland hypofunction. Even radiation to only a portion of the salivary gland tissue, such as that administered for thyroid and laryngeal cancer and lymphoma of the neck, may result in permanent salivary gland damage and severe adverse oral effects. Salivary flow does not improve after completion of therapy, and dysfunction may actually worsen with time.1,7,8,

The results of a change in the quantity and quality of saliva are numerous, including alteration of taste (dysgeusia), increased mucosal infections, difficulty in swallowing, decreased oral pH, enamel demineralization, and rampant radiation caries. While taste loss and infections diminish after therapy, the risk of demineralization/rampant caries persists throughout life. Typically, the teeth begin to break down at the cervical margins and incisal edges and progress rapidly (**FIGURES 2 AND 3**). An oral hygiene program that will be discussed later can prevent breakdown of the teeth. Recently, some pharmacological interventions have been introduced during radiation therapy in attempt to preserve the salivary gland function, including sialogogues such as Salagen and a radioprotective agent, amifostine. These drugs are effective and should be offered to the patient.

The direct effects of radiation on the muscles of mastication and the TMJ may result in fibrosis and trismus leading to limited mouth opening and future oral care problems. Simple exercises may reduce the severity of trismus.

For patients receiving more than 5,500 cGy to the jaws, the most serious and devastating complication is osteoradionecrosis. The risk increases as the dose of radiation increases. It was previously believed that osteoradionecrosis was an infection or osteomyelitis. Studies have established that it is due to the bone's inability to heal properly because of the effects of radiation on blood vessels, fibroblasts, and osteoblasts. This has been called the "triple H effect" or hypovascularity, hypoxia, and hypocellularity.9 As a result, the bone and connective tissue lose their capacity to heal or repair tissue damage. There is an increased risk of osteoradionecrosis in the mandible because it is less vascular than the maxilla and because its density results in a higher absorbed dose of radiation.5 Some cases are spontaneous, but most are the result of trauma such as tooth extraction and denture irritation after radiation therapy.

What are the implications of osteoradionecrosis to the dentist? A patient that reports radiation therapy of more than 5,500 cGy to tooth-bearing areas is at risk. Osteoradionecrosis caused by tooth extraction usually occurs within

TABLE 1. Strategies for Preradiation-Therapy Dental Evaluation

Radiographs, including panoramic and selective periapicals
Extra- and intraoral soft-tissue exam for surgical defects, compromised vascularity, infection, recurrent or additional cancer.
Periodontal evaluation for furcation involvement, mobility, or greater than 50 percent bone loss
Existing carious lesions and faulty restorations
Oral hygiene and previous dental compliance
Cariogenic/xerogenic diet and medication analysis
Tobacco and alcohol use
Psychosocial issues that may affect future compliance

three months to five years after completion of radiation therapy.4 The risk of osteoradionecrosis does not disappear with time and may occur years after radiation therapy.10

Preradiation-Therapy Dental Evaluation and Treatment

What can be done to reduce or eliminate some of the problems discussed? The most important is that every patient undergo a preradiation-therapy dental evaluation. A 1989 National Institutes of Health Consensus Conference recommended that all cancer patients have an oral exam before initiation of therapy.1

Table 1 lists the suggested strategies for a preradiation-therapy dental evaluation. Intra- and extraoral soft tissue exams, periodontal probing, caries evaluation, and radiographs with panoramic and selective periapical films should be done. Because the risk for osteoradionecrosis does not diminish with time, the dentist needs to predict what teeth might need to be extracted at any time during the patient's life. To avoid possible complications of osteoradionecrosis, all questionable teeth in the proposed radiation field should be extracted prior to radiation therapy. Teeth that exhibit advanced caries, periapical pathology, or advanced periodontal disease, including molar teeth with furcation involvement, should be extracted. Full bony impacted teeth do not need extraction; however, partially impacted teeth should be removed. Increased caution should be employed for patients who exhibit poor oral hygiene, poor compliance with prior dental recommendations, or greater than 50 percent periodontal bone loss. Prosthetic considerations such as undercuts and tori need to be addressed prior to radiation therapy. It is necessary to delay radiation therapy for 14 to 21 days after oral surgery to allow for healing.10 Inadequate healing time can result in a higher incidence of osteoradionecrosis. The radiation oncologist should be consulted prior to any invasive dental procedures.

Salivary flow and the normal constituents of saliva will be permanently changed following radiation. As a result, there is likely to be an increased incidence of dental caries, demineralization of enamel, and candidiasis. Patients should be cautioned that dental caries and demineralization might dramatically increase with the consumption of a highly cariogenic diet or beverages containing sugar, phosphoric acid, or citric acid. This includes most dietary soft drinks.

Custom fluoride carriers should be fabricated for all dentulous patients receiving more than 4,000 cGy to salivary glands. These vacuum-formed carriers are made from flexible vinyl mouthguard material and should cover the cervical margins of the teeth and have smooth edges that will not irritate adjacent gingival tissue. The authors recommend a 1.1 percent sodium fluoride gel that is spread in the carriers and applied to the teeth for five minutes a day. Following application of the gel, the carriers are removed and washed; but the patient should not rinse or eat for 30 minutes.3

If time permits, the patient should have dental prophylaxis before therapy begins. Oral hygiene instructions should be tailored to meet the needs of the patient, especially those patients who have had surgery and limited opening.

All patients should be evaluated for tobacco and alcohol use that may contribute to a recurrence of or new primary oral and pharyngeal cancer as well as worsen oral complications of radiation to the oral mucosa.11 Cessation counseling should be offered.

Oral Care During Radiation Therapy

Oral complications become more severe as the patient progresses through the weeks of therapy. Early management of mucositis and infection may alleviate pain and prevent the necessity of interruption of radiation therapy to allow for healing of mucosal lesions. Routine and consistent oral cleansing to reduce microbial burden, replacement of moisture, and use of topical anesthetics and analgesics are typically recommended.

Emphasis should be placed on the importance of keeping the mouth as clean and moist as possible throughout therapy.12-15 Regular tooth brushing and flossing should continue until the mouth is too ulcerated to tolerate the trauma of a toothbrush and the strong flavoring agents of toothpaste. An alternative is gentle cleansing of the teeth and oral tissues with gauze moistened with a baking soda water solution (1 teaspoon of baking soda to 1 pint of water.) This solution is mucolytic and may be used as a gentle rinse several times a day.

Many oncologists prefer the use of topical anesthetics such as viscous xylocaine, but the authors prefer other

agents that will not impair swallowing and lead to aspiration pneumonia. The authors' standard has been a 50/50 mixture of alcohol-free Benadryl and a coating agent such as Maalox or Mylanta. Patients can use this as needed, and they repeatedly acknowledge its effectiveness.

Evidence of mucositis outside of the radiation field or a significant increase in pain may indicate candidiasis, viral, or bacterial infection. Cultures are the gold standard for diagnosis. Antifungal rinses that are high in sucrose should be avoided due to the high cariogenic potential. Patient compliance with taking fluconazole 100 mg (2 tablets on day one, then one tablet for six to 13 days) is greater than with sucrose-rich nystatin suspension or clotrimazole troches, which are difficult to dissolve in the mouth.

Trismus is a late result of the direct effect of radiation to the muscles of mastication and possibly the temporomandibular joint. Limited mandibular opening may result, with reductions of 10 to 15 mm of opening. A simple regimen of exercising the muscles three times daily by opening and closing the mouth 20 times without pain may prevent or reduce the severity of trismus. If difficulties in opening do develop, dynamic bite openers are beneficial.4

Dental Management Following Radiation Therapy

At the end of therapy, complications will begin to improve but may linger for a month or two. Xerostomia, however, persists and generally will show little improvement with time because the salivary gland acini may be permanently destroyed. Therefore, maintenance of excellent oral hygiene and daily fluoride gel treatments using custom-fit carriers must continue throughout life. Dental recall should be frequent for early intervention in dental complications. Scaling and root planing can continue to prevent progression of periodontal disease. If caries develop despite daily fluoride treatments, the addition of a calcium-phosphate remineralizing gel such as Revive should be recommended. Additionally, a fluoride varnish should be applied to the entire dentition and a two-week course of chlorhexidine rinse recommended to suppress cariogenic bacteria.16 Patients must adhere to a noncariogenic diet for maintenance of a healthy dentition. Sialogogues, commercial saliva substitutes, and frequent sips of water may help alleviate the discomfort of xerostomia.

The greatest concern is osteoradionecrosis. While spontaneous osteoradionecrosis may occur with high doses of radiation, the most common cause is from the trauma of tooth extraction. Other invasive procedures or ulceration from a dental appliance may also precipitate osteoradionecrosis. Teeth can never be safely extracted from bone that has received more than 5,500 cGy without the risk of osteoradionecrosis. If oral surgery is necessary, the standard of care in the United States is referral to a physician for hyperbaric oxygen therapy prior to the surgery.5,10 Malpractice settlements have been awarded for failure to use hyperbaric oxygen therapy.17 Twenty such treatments of 100 percent oxygen under pressure are recommended prior to tooth extraction with 10 to 20 additional treatments following surgery. Treatments are costly and do not ensure prevention of osteoradionecrosis. If it does develop, additional hyperbaric oxygen may be necessary and/or resection of the involved bone.18 There appears to be a significant reduction in risk of osteoradionecrosis for single tooth extractions. An alternative to extraction for a single tooth is amputation of the crown and root canal therapy.4

Conclusion

Responding to the needs of dental patients receiving cancer therapy is critical. This manuscript discusses the effects of radiation therapy to the oral tissues and their management. The dentist's care must be immediate and appropriate to ameliorate acute oral complications and prevent serious long-term sequelae. Patients receiving chemotherapy or bone/stem cell transplantation may also have serious oral complications that are beyond the scope of this paper.

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2 + 2 = Who cares?

Robert E. Horseman, DDS

It is February of 1945, and I am lost in Texas. Well, not in Texas, but rather over Texas. Eight of us Navy aviation cadets flying North American SNJs are milling around hopelessly in the middle of nowhere like rats in a maze. Ashen-faced and numb with dread, we've come to the realization that all of Texas looks pretty much the same from 6,000 feet. Somewhere down there is NAS Corpus Christi; and we -- the hottest of the hot, the smartest of the smart -- haven't a clue as to where. With the whole country depending on us to win a war, we can't even find our home base, let alone Tokyo.

At this point in our flying careers, we have become proficient in algebra, geometry, trigonometry, and celestial navigation and can intelligently discuss the merits of domestic beer over imported. We are equipped with the knowledge of True North vs. Magnetic North and can manipulate the latest in navigational aids: the E6B plotter with its factors of wind direction and velocity, air speed, and altitude. And still we are lost.

Fast forward 56 years and plunk a 10-year-old kid down in that same middle-of-nowhere. This kid, who wears his hat backwards and thinks Adam Sandler is a hoot, can tell you within 6 feet exactly where he is. Why? Because he has in his grubby little hands a Global Positioning System device. Anybody can buy one; if I am ever unfortunate enough to be lost in Texas again, I will buy one and the only mathematics involved will be checking to see if my VISA is maxed out.

In my opinion, mathematics has never in the history of the world been less important to learn. We have calculators, computers, ATMs, and CPAs to take care of this. Yet this flies directly in the face of educators who are adamant in their insistence that every child know how to determine the area of a trapezoid and learn to call everything he doesn't know "X." In the dark recesses of our adult minds are the words logarithm, cosine, quadratic equations, and square roots. For about 15 minutes back in high school, we had a grip on this stuff and knew that πr^2 was so important we could never look at a circle again without reveling in the fact that we knew the secret to its area -- a secret that will go with me to my grave as far as I'm concerned.

When I braced my high school counselor with the announcement that I was going to seek fame and fortune in the field of dentistry, she said, "Then you must take integral and differential calculus." I said, "Why?" I considered "because" an inadequate response, signing up for a course in co-ed badminton instead.

The point is, everyone from the president on down (or up depending on your proclivities) declares our youngsters to be deficient in math skills. Perhaps they are. Lord knows they are deficient in a number of other areas, but that is what the

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teen years are all about, and the hope is that they will outgrow it, whatever "it" is.

Let us try to keep a positive spin on this. Although the dumbing down of America has been going on now for years, the present generation does excel at many things, notably skateboard tricks, finding new places to pierce and wailing away at whiny pop songs. But except for a handful of students who will go ahead to develop the technology for the rest of us, the vast majority needs only to master the multiplication tables, or better yet, learn to replace the batteries in their calculators when necessary.

One hundred thousand or so dentists have fruitlessly tried to put the sentence "The square of the length of the hypotenuse of a right triangle equals the sum of the squares of the lengths of the other two sides" out of their minds. Not once during a 40-year practice has this ever come up, either in a clinical or social setting. Pythagoras was not a dentist. He wouldn't know an onlay from a lingual torus, yet every dentist had to have the Pythagorean Theory drilled into him like it was the Final Answer.

Once you've learned that lending a person $10 for one week is not the same as lending him $1 for 10 weeks, you've pretty much got the problem of mathematics licked. For everything else, there is "X."