CDA

GI Disease
Chronic Lesions
Lip Cancer

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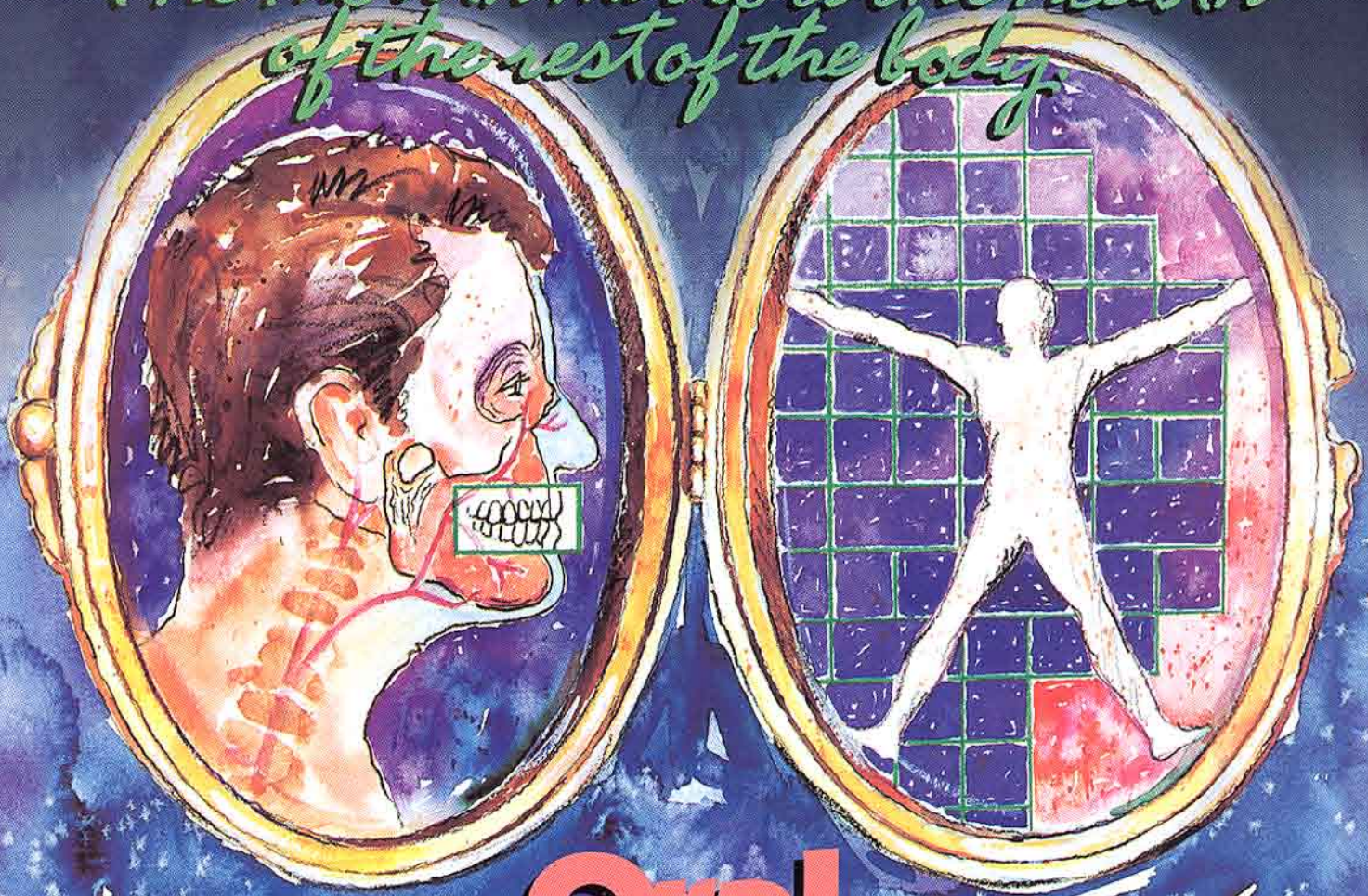
The mouth mirrors the health of the rest of the body.



Oral Pathology

Raymond J. Melrose, DDS

OF THE CALIFORNIA DENTAL ASSOCIATION
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DEPARTMENTS

FEATURES

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Our Day in Court

Jack F. Conley, DDS

Jan. 13, 1999, was a rather significant day in the history of the dental profession. On that day, dentistry found itself center stage on two matters with national reach. While the outcome in both cases is yet to be written, at this point we can be reasonably optimistic that the negative outcomes we often expect when something about dentistry reaches the public sector will not be realized in either of these situations.

One of those matters, the "60 Minutes II" report discussed in this space last month, has yet to raise significant discussion or inquiry. The considerable efforts by the California and American dental associations to prepare potential spokespeople to answer questions of concern were probably helpful in diffusing the negative fallout that frequently follows an emotionally charged report such as this one, which centered on the death during dental procedures of children under anesthesia.

But a more significant event occurred earlier that same day. The time was 11 in the morning, and the place was the chamber of the U.S. Supreme Court in Washington, D.C. The event was the hearing of oral arguments in the case of the California Dental Association vs. the Federal Trade Commission. At the time of this writing, the court's decision had not been announced, the expectation being that it would take from 60 days to six months for a ruling to be made. Significant in this long-standing dispute is the fact that the Supreme Court selected the matter for hearing. That, in a sense, was a victory for the profession in light of a long series of legal setbacks in this case dating back to the early 1980s.

A favorable decision would have great importance to CDA members for two major reasons. The first is the broad issue of whether the FTC has authority over nonprofit professional associations as it clearly has over for-profit corporations. Also, the FTC has continued to contend that CDA guidelines on advertising restrictions violate antitrust laws despite an administrative law decision that CDA didn't do anything anticompetitive. Despite the string of defeats on the antitrust issue, there is guarded optimism that the Supreme Court could come forward with a ruling on the broad issue that would give nonprofit professional associations some relief from an FTC that has appeared to venture beyond the authority granted it in the original legislation creating the commission.

Many longtime CDA members have been of the belief that some of the "negative" changes in the profession over the past few decades have come about as a result of regulations and decisions by outside agencies, such as the FTC. A positive decision would be a welcome relief from what many believe has been an all too familiar trend. Certainly, other professional nonprofit associations would also benefit from a decision that is favorable to CDA and organized dentistry.

The second reason a favorable decision would be of great importance to CDA members is a matter that has not been as frequent a topic for discussion as it was two decades ago. We refer to the responsibilities of self governance of the profession, articulated by standards established in codes of ethics and other professional guidelines. Since the early 1980s, members or potential members of organized dentistry have instead been regularly reminded of the benefits and services available through membership.

The actions of an entity such as the FTC on advertising standards have seemed to discourage pursuit of professional standards development or enforcement at previous levels of activity. We have seen membership become benefits-driven. The dentist facing increasing costs of operation who is not particularly interested in insurance or other benefits offered by the association often makes a decision on continuing membership without considering support for the profession and its efforts on behalf of the members and the public.

Interestingly, a generally strong public image of the profession, enhanced by initiatives in the public interest such as fluoridation, may well be key to showing the court the difference between organized dentistry and trade associations that come under the jurisdiction of the FTC, leading to a favorable decision in the FTC matter. It is important that members recognize that public relations and self-governance efforts by our professional organizations are ongoing, and that despite their seeming invisibility, they do have a very important and direct effect on dentists and their continuing ability to conduct a successful business enterprise and valuable service to the public.

If our day in court results in a favorable decision, maybe we will see the need for professional standards embraced with renewed energy. It is a new era -- almost a new millennium -- and many things have changed. We cannot go back to where the profession has been, but we can strengthen where we are to prepare for the future. Dentistry would not be the fine profession it is today without the standards put in place by many who preceded us. A favorable court decision could fuel a proactive attitude that moves the profession to deal with pending issues such as continuing competency before others, who are already at work developing guidelines, prevail.

No longer should the refrain "What has CDA or ADA done for me lately" be heard at membership renewal time. Our professional organization is continuously at work supporting our best interests, a prime example being this 14-year, often invisible, legal effort.

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Internet Becomes Part of Supplying's New Order

By David G. Jones

Some technical-savvy California dentists are riding a burgeoning wave of electronic commerce that is changing the way they and their staffs order dental supplies.

The Internet, already a major player in international commerce, is breaking new ground in connecting buyers and sellers of dental supplies. It is saving time and money for people willing to participate in a world of electronic commerce that has become part of big business.

Last year, the United States alone generated $12.5 billion, or 79 percent of total worldwide business-to-business (B2B) e-commerce revenues, according to the recently released "e-Commerce: B2B Report." While the dental and medical supply ordering segment is small by comparison, its use is increasing, according to industry analysts.

"The players, consisting of health care information technology and emerging companies, provide solutions to connect the various health care participants, including providers, payers and suppliers," say industry analysts Stephen M. Fitzgibbons and Richard Lee in their recent report titled Health.net. "E-commerce will generate hundreds of billions of dollars in health and medical supplies and product sales."

Providing counterpoint is a recent study commissioned by the two principle American dental supply industry associations, Dental Manufacturers of America and the American Dental Trade Association. Responses to a survey sent to 3,500 dentists nationwide indicate that despite the advent of computers and the Internet, most offices still place their bi-weekly orders by telephone. However, the Internet is playing an ever-increasing part in helping dental manufacturers sell their products directly to dentists.

"Last year we did in the neighborhood of 10 percent of total sales electronically, both through the Internet and other electronic means," says Bob Lamb, vice president of Information Systems for Henry Schein, Inc., the country's largest provider of Internet dental product ordering. "We've been in the electronic world for the last few years and were the first to get into Internet ordering about 18 months ago. That's been the fastest-growing part of our electronic business."

Some California dentists are logging on to take advantage of Internet ordering. A dentist practicing in Campbell in the heart of Northern California's Silicon Valley started using the Internet to order supplies about two years ago almost by happenstance.

"I started when I knew one of my staff was planning to be on maternity leave. I wanted a system I could use to order real quickly at home, and not have to train the new person we hired temporarily," says Walter G. Weber, DDS, immediate past president of the Santa Clara County Dental Society. "I right away liked the fact I don't have to call at a certain time and I could do it at home or in the office, even on the weekend. And it's kind of fun to order with the computer rather than writing up order slips or placing phone calls and pushing a lot of buttons."

He says that using his computer to order supplies and instruments is convenient because the program keeps track of everything he or his staff orders.

"I just ordered some bleaching supplies today, and I simply went into my previous order area and just clicked on it, and ordered it again," Weber says. "That's a real convenience factor that saves time in ordering. Of course, if you have new staff that comes in, you don't have to reinvent the wheel, because they can easily see what was ordered in the past, so that's another time saver."

Using the Internet to order supplies also saves money.

"Prices are a little less on the Internet than in the catalog," Weber says. "And some companies also give special discounts for ordering online, or put items on special sales available only online."

Weber says that virtually everything available in a regular printed catalog -- from burs to medications -- is available online.

"And if I order by noon I get it the next day," he says. "Delivery charges are the same as we were paying before, so there's no difference there."

While Weber is actively using the Internet to order supplies, another Internet-savvy dentist isn't quite there yet, admitting he's from the old school.

"I'm old-fashioned but want to get more into cyberspace," says Steven Hook, DDS, who practices in Marina Del Rey. Hook contributes to a Los Angeles-area web page that offers answers to web surfers' questions about health care issues.

"For years I was loyal to a full-service dental company. But I believe (Internet shopping) is something we'll have to get into," he says. "We've got 5-year-olds that can go all over the place on this. It's silly to not use the Internet to its multitude of advantages."

The advantages of ordering supplies via the Internet led Weber to prognosticate.

"It's a time saver, and it will also be a way to reduce costs, making it a more efficient and logical way to order supplies, so this is what's going to push this forward," Weber says. "If someone is computer literate, this is the best way for them to go."

Health Care Spending Follows HMOs' Lead

The more people in a given area served by managed care organizations, the lower the average expenditures for the care of patients in traditional Medicare fee-for-service plans, according to an article in the Feb. 3 issue of the Journal of the American Medical Association.

Laurence C. Baker, PhD, of Stanford University studied the association between the increasing market penetration by managed care organizations, specifically HMOs, and the payments made by Medicare for patients who were paying physicians per visit and per service (fee-for-service).

The author found that the percentage of fee-for-service expenditures paid by Medicare Part A (hospital care) and Medicare Part B (ambulatory care

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procedures and consultation that do not require an overnight stay at the hospital, such as regular doctor's visits and outpatient surgery) decreased as the market share of managed care organizations increased. The data was for the years 1990 to 1994, when the average HMO enrollment increased nationally from 15 percent to 21 percent.

"Lower expenditures in areas with high HMO market shares may indicate that traditional Medicare beneficiaries in areas with high market shares received fewer or less intensive services than traditional Medicare beneficiaries in other areas," according to the author.

Some reasons for the decrease in expenditures may be:

- The number of services used (e.g., the cost of two office visits versus the cost of just one office visit).
- The intensity or type of services used (e.g., the cost of diagnostic tests versus the cost of a simple office visit).
- The actual prices charged.

The author speculates that changes in number and intensity of services used, not necessarily changes in prices, are most likely to have the greatest overall effect on expenditures.

"Because it is relatively easy for managed care to affect expenditures by changing utilization but relatively difficult for managed care to affect expenditures by changing prices, perhaps the most straightforward explanation for the results seen here is that managed care contributed to reductions in the number or intensity of services received by patients covered by traditional Medicare," Baker says. He also notes that if managed care reduces the number or intensity of the services performed, then it is important to assess whether that will compromise the quality and results of the health care received.

Reach Out and Thank Someone

By Dell Richards

Washington wags used to say that former President George Bush got where he did by virtue of one thing and one thing only: thank-you notes.

Bush supposedly wrote 10 thank-you notes every day. While that story may be an exaggeration, in this alienated age a hand-written "thank you" touches people in a way that few other gestures do. It's an act of kindness that sets you apart and keeps you in a person's mind -- a good place to be when his or her tooth suddenly aches.

Dentists usually send notes to new patients, but that practice can be extended. Take time during the day to think of three people who did something for you -- from someone who went above and beyond the call of duty to someone who was just doing the job. It can be anyone from a hygienist or a dental supply representative to the department store salesperson or your dry cleaner.

To come across as genuine thanks, the notes must be hand-written. No matter what the size, use good quality paper or card stock. Postcard-size cards, third-cut cards that fit into No. 10 envelopes, and half sheets of stationery all work well. Always put them in an envelope.

A traditional thank-you note is a 5 -inch wide by 8 1/2-inch long half sheet of stationery, printed with your name and logo at the top. You could also have your name and logo printed on half of one side to create a card. If you use the greeting card format, write only on the inside bottom or right half. You may include "Sincerely" or not, depending on the familiarity of the relationship. Attach your degree after the signature if you feel so inclined or need it for recognition.

Even though it may seem like a lot of work to a busy professional, all you have to write is two or three sentences that mention a specific detail about the product, service or gesture and why it was appreciated. After a few weeks, you'll be amazed at the response.

Dell Richards is the owner of Dell Richards Publicity in Sacramento.

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Timing May Change in Children's Orthodontics

A recent study shows that adolescents are reaching dental maturation earlier, reports George L. Nadler, DDS, in The Angle Orthodontist, Vol. 68, No. 6.

From the 1970s to 1990s, the age for dental maturity decreased by 1.21 years for males and 1.52 years for females, with a combined average reduction of 1.40 years. This trend may lead to earlier treatment of these patients.

According to a prior study, anticipating the timing of future growth spurts is essential to ensuring a successful outcome of orthodontic therapy. The calcification of the lower canine as a maturational indicator is especially valid for Caucasians. In this study, patient selection was limited to the following:

- Age range 8.5 years to 14.5 years of age.
- Caucasian children only.
- Middle socioeconomic group.
- Negative past and current medical history.

The focus of the study was to compare the dental ages at which specific tooth calcification occurs in two groups of patients whose treatments were separated by approximately 20 years, using the calcification of teeth as maturational indicators. The indicator for this determination was the lower right canine (tooth 43, FDI system). The percentage of tooth calcification was rated according to a method in which the states of tooth calcification are divided into eight segments, A to H. In this study only stages E to H were used. Maturational stages are defined when the following characteristics are discernible:

- Stage E: Root length remains shorter than crown height.
- Stage F: The walls of the pulp chamber form an isosceles triangle, and root length is equal to or greater than crown height.
- Stage G: The walls of the root canal are now parallel, but the apical end is partially closed.
- Stage H: Root apex is completely closed. The periodontal ligament surrounding the root and apex is uniform in width throughout.

Only the F and G stages were used for comparison data. (The elimination of the E- and H-stage patients reduced the sample size by about 50 percent.) According to the study, the average ages at stages F and G were as follows:

Average Age of Patients in Study	
Stage F (boys):	10.78 years 10.52 years
Stage F (girls):	10.18. years 9.86 years
Stage G (boys):	12.23 years 11.02 years
Stage G (girls):	11.72 years 10.20 years

Handbook Offers Lowdown on State Dental Boards

The American Association of Dental Examiners has recently published the 10th edition of Composite, a handbook detailing the structure, licensing and disciplinary activities of all state dental boards.

Completed in 1998, the publication contains more than 25 charts describing state dental board structure and operations, licensee population within each state, 1997 board disciplinary activity and complaint statistics, and state licensing requirements. These charts, the result of surveys completed by the licensing jurisdictions, include general requirements, the use of clinical and didactic examinations, continuing education renewal requirements, and the methods used to conduct application background checks. Also included is a listing of licensure and disciplinary board contacts.

Charts are included on specialty licensure and nonaccredited graduates. Copies are available for $20 to AADE members and $35 for nonmembers (shipping costs included). All orders must be prepaid with check or money order payable to the American Association of Dental Examiners. Please print or type full name and mailing address, specify the number of copies you wish to purchase and send orders to: Composite, American Association of Dental Examiners, 211 East Chicago Avenue No. 760, Chicago, IL 60611.

For more information, contact Molly Nadler, AADE executive director, at (800) 621-8099 or (312) 440-7464.

Facial Plastic Surgery Is 'Archives' Subject

The American Medical Association has debuted a new journal -- the Archives of Facial Plastic Surgery.

The peer-reviewed journal offers original research from an international perspective for the medical specialties performing cosmetic and reconstructive surgery of the face which include: facial plastic surgery, otolaryngology-head and neck surgery, dermatology, and plastic surgery. The Archives of Facial Plastic Surgery is the 10th specialty journal in the AMA's Archive series.

The Archives of Facial Plastic Surgery is a complementary journal to the Archives of Otolaryngology -- Head & Neck Surgery, with the editorial boards working in cooperation. In addition to facial plastic surgeons, the editorial board of the Archives of Facial Plastic Surgery includes dermatologists, oculoplastic surgeons and maxillofacial surgeons. It is the official journal of the American Academy of Facial Plastic and Reconstructive Surgery and the International Federation of Facial Plastic Surgery Societies.

In addition to clinical studies, laboratory research and socioeconomic studies, the journal will also publish the following special sections: The Craft of Facial Plastic Surgery (presents innovative techniques); New on the Market (describes the results of using certain products with photographic illustrations); Beauty (a forum for visual or literary arts of interest to physicians); and Ethics and Public Policy (a section for essays on issues relevant to physicians and patients).

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Dental Treatment and Bacterial Endocarditis

Thomas J. Pallasch, DDS, MS

Editor's note: Many readers may have seen a recent study indicating that dental treatment is not a significant risk for bacterial endocarditis. To determine implications of the study on the use of antibiotic prophylaxis in certain patients, we contacted Dr. Thomas Pallasch, a co-author of the 1997 Endocarditis Prevention Recommendations, and asked him to clarify the issue.

AUTHOR

Dr. Pallasch is a member of the American Heart Association Commmittee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. This article is not an official publication of the American Heart Association.

Considerable interest has been expressed in the recent study by Strom and colleagues in the Annals of Internal Medicine[1] indicating that dental treatment procedures may not pose a significant risk for the development of bacterial endocarditis. The authors studied 273 adults who had a definite, probable or possible diagnosis of infective endocarditis with a matched group of control individuals without the disease. Both groups had approximately the same exposure to dental treatment over the three months prior to the diagnosis of endocarditis in the case-control group, from which the authors then concluded that dental treatment was not a factor in the acquisition of endocarditis. Dental extractions were performed in six patients with endocarditis and none of the controls, but the extractions were not included in the study protocol. Interestingly, any endocarditis attributable to viridans streptococci, alpha-hemolytic streptococci (not Group D), anaerobes, and HACEK organisms (Haemophilus influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens and Kingella kingae) was considered to have originated from the oral cavity, even though most of these organisms also reside elsewhere in the body. The authors did detect a strong relationship between cardiac valvular defects and the development of endocarditis.

This study can now be added to other clinical studies,[2,3] analyses[4,5] and commentaries[6-11] that also either found

a low or no correlation between dental treatment and endocarditis or questioned the mass unqualified use of antibiotic prophylaxis in an attempt to prevent endocarditis in dental patients. These studies, analyses and commentaries were considered in preparing the 1997 American Heart Association (AHA) endocarditis prevention guidelines (as was this study by Strom, which was referenced as an abstract). They were also considered in the recommendation for a reduction in dental procedures requiring prophylaxis, as reflected in the following statement: "The vast majority of endocarditis due to oral organisms is not related to dental treatment procedures."[12]

In an accompanying editorial analyzing the Strom study and the previous analyses and commentaries cited above, David Durack has proposed that future AHA endocarditis prevention guidelines be primarily limited to patients with very high risk medical conditions (cardiac prosthetic valves, previous endocarditis) who undergo any of only three dental procedures (extractions, gingival surgery and/or implants).[13] The Strom study did not include children, and it is likely that complex cyanotic congenital heart disease would also be included for prophylaxis. Durack made it clear that "The concept of prophylaxis is valid and should be retained, but in a restricted and better-focused form."

The AHA has prepared the following statement:

"The American Heart Association Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease reviewed 'Dental and Cardiac Risk Factors of Infective Endocarditis,' published in the Nov. 15 issue of the Annals of Internal Medicine, with great interest and appreciation for the extensive clinical data collection that it represents. The committee's ongoing mission is to refine the criteria for endocarditis prophylaxis to maximize benefit and minimize risk. The committee believes that the AHA's published guidelines, which are described in the AHA Medical/Scientific Statement titled 'Prevention of Bacterial Endocarditis' remain valid in the face of these results and does not recommend changes in practice or patient education at this time. This study and others will be assessed in conjunction with previously available data in future discussions regarding prophylaxis guidelines."

Simply put, things remain as they are. Future AHA guidelines may, as they have in the past, be suitably revised as new documented data dictates. Until then, dentists should continue to follow the current 1997 AHA guidelines for the prevention of bacterial endocarditis.[12]

Dr. Pallasch is a member of the American Heart Association Commmittee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. This article is not an official publication of the American Heart Association.

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Snapshots in Oral Pathology

RAYMOND J. MELROSE, DDS

The full range of practice for which oral and maxillofacial pathologists are trained includes four principal areas: microscopic and laboratory diagnosis, clinical evaluation and management of patients, teaching, and research. Just as general dentists perform a variety of procedures on a daily basis, oral pathologists perform some or all of their prescribed functions daily. To capture a sense of this multiplicity, I have asked a select group of highly regarded oral pathologists to contribute papers of their choosing that embody one or more of the four cornerstones of an oral pathologist's practice. The result is an eclectic mix of subjects I call "Snapshots in Oral Pathology."

Dr. Joseph Regezi, of the University of California at San Francisco, has accumulated a number of cases that masqueraded as garden-variety periapical inflammatory disease but, upon biopsy, proved to be anything but routine periapical disease. His paper resoundingly makes the point that everything is not always what it appears to be.

Recently, an editor in a major journal was critical of oral pathologists' contention that pathologic periapical tissues removed as a component of surgical treatment ought to be sent for microscopic examination. The man's reasoning was based upon cost-effectiveness. In other words, is it worth it to have confirmed microscopically that you were indeed treating the disease you thought you were? If each of us were always correct in our clinical diagnoses, the answer would be no. As Dr. Regezi's paper makes clear, a host of both innocent and dangerous conditions can mimic periapical inflammatory processes. It might be merely embarrassing but it could be tragic to have to face a patient after treatment failure had finally necessitated a biopsy and disclose that diagnostic tissue had been discarded in favor of some supposed economy.

In the same general vein, Dr. Mark Bernstein, of the University of Louisville, presents eminently useful information on a range of inflammatory mucosal lesions that result from tissue reactions to restorative materials, medications, or food. His paper provides both information and sound advice on the approach to diagnosis based upon his clinical experience and research.

Dr. Robert Greer, of the University of Colorado, discusses his experiences in diagnosis, management, and follow-up of two patients with proliferative verrucous leukoplakia. This serious, enigmatic disease is becoming more widely recognized, but its etiology and means of effective treatment continue to elude us.

Dr. Janice Handlers, of the University of Southern California, presents clinically relevant information on the oral manifestations of certain diseases of the gastrointestinal system. For centuries, astute physicians have recognized that the mouth mirrors the health of the rest of the body. Dr. Handlers describes, for example, how two diverse, common diseases such as peptic ulcers and colon polyps can share anemia as a side effect and that this, in turn, has significant oral manifestations. She points out that patients with certain types of inflammatory bowel disease can develop oral lesions that, when biopsied, may cause an oral pathologist to predict the systemic problem.

Finally, Dr. George Kaugars and his associates, of the Medical College of Virginia, offer a most practical and informative discussion of ultraviolet radiation -- its types and effects on the skin and vermilion border of the lip. Their discussion of the types and mechanisms of action of common sunscreen agents is very practical for dentists in California since many are often queried by patients about this topic.

Although there is not a unifying theme among the papers that constitute the bulk of this month's issue of the *Journal of the California Dental Association*, it is my sincere hope that readers, and by extension their patients, will benefit from the information offered by this group of noted oral and maxillofacial pathologists. If readers have one or more specific topics they would like to have addressed in future issues of the Journal that may be devoted to topics in oral and maxillofacial pathology, I would be pleased to hear from them directly or by in writing in care of the Journal.

Contributing Editor / 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.

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Periapical Diseases: Spectrum and Differentiating Features

Joseph A. Regezi, DDS, MS

ABSTRACT There are a variety of lesions besides the typical granulomas and cysts that can appear at the apices of teeth. These other lesions must receive consideration in the diagnosis of periapical disease because of their potential impact on patient treatment and outcome. This paper will review the spectrum of diseases that may present in periapical tissues, the pathogenesis of periapical inflammatory disease, and the signs and symptoms that separate periapical inflammatory disease from neoplastic disease.

AUTHOR

Joseph A. Regezi, DDS, MS, is a professor of oral pathology in the Division of Oral Medicine, Pathology, and Radiology at the University of California at San Francisco School of Dentistry.

In addition to the commonly encountered periapical granulomas and cysts of the jaws, there are many other lesions that may appear at the apices of teeth. These other lesions, which range from nonodontogenic cysts to malignancies, must receive due consideration in the diagnosis of periapical disease because of their potential impact on patient treatment and outcome. In distinguishing between periapical inflammatory disease and periapical neoplastic disease, a definitive diagnosis based on clinical and radiographic parameters can never be absolute because of the many overlapping signs and symptoms. This makes differential diagnosis for a periapical lesion as important as it is for any other lesion of bone or soft tissue. Unless the clinician is thinking in broad rather than narrow terms, serious conditions may go undiagnosed and untreated for an inappropriate period of time.

The purpose of this paper is to review:

- The spectrum of diseases that may present in periapical tissues;
- The pathogenesis of periapical inflammatory disease; and
- The signs and symptoms that may be useful in separating periapical inflammatory disease from neoplastic disease.

Diseases That Appear as Periapical Radiolucencies

Inflammatory tooth-associated diseases, non-odontogenic cysts, dysplastic bone disease, benign neoplasms, and malignancies can all appear as

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radiolucencies at the apices of teeth (**Figures 1 through 4**). In **Table 1**, periapical diseases are classified according to biologic behavior. This is not an exhaustive list, but it is representative of the more commonly reported diseases found in periapical tissues of the jaws.[1-5] Only 10 percent of periapical lesions turn out to be something other than a granuloma or cyst.

TABLE 1.

Periapical Diseases Classified According to Biologic Behavior[1-5]

Inflammatory
Periapical Granuloma and/or scar
Periapical cyst
Periapical Abscess
Actinomycosis
Benign
Traumatic bone cyst
Nasopalatine duct cyst (incisive canal cyst)
Langerhans cell disease
Adenomatoid odontogenic tumor*
Periapical cemento-osseous dysplasia*
Ossifying/cementifying fibroma*
Vascular malformation
Benign Aggressive
Odontogenic Keratocyst
Central giant cell granuloma
Myxoma
Ameloblastoma
Calcifying odontogenic cyst*
Calcifying epithelial odontogenic tumor*
Malignant
Metastatic disease
Lymphoma/leukemia
Multiple myeloma
Other

*may also present with mixed lucent-opaque pattern

Pathogenesis of Periapical Inflammatory Disease

All periapical inflammatory conditions have a common etiology and represent variations of the inflammation-repair theme. All are associated with nonvital teeth whose necrotic pulps stimulate an inflammatory response in the periodontal ligament and bone at the tooth apex. Chemical mediators of inflammation (cytokines and chemokines) released from the dead and dying tissue affect the recruitment of white blood cells into the area. Here they phagocytose necrotic tissue and release additional mediators to sustain the inflammatory response and initiate the repair process. Specific diagnosis is dependent upon the stage of the inflammatory process, i.e., whether the process is acute, chronic, or chronic with acute exacerbation. Once the inflammatory stimulus is removed (through tooth extraction or endodontic filling), the repair process continues, ultimately resulting in healing with regenerated bone in the area.

A periapical abscess is an acute phenomenon characterized by rapid focal fluid exudation and neutrophil emigration from resident vessels, resulting in pus formation and intense pain. A periapical or dental granuloma represents a focus of granulation tissue and inflammatory cells that have replaced apical bone. Periapical granuloma is not the same as granulomatous inflammation, which is defined as a type of chronic inflammation that features a predominance of macrophages (e.g., tuberculosis, sarcoidosis). A periapical granuloma may develop from low-grade sustained chronic inflammation or from an abscess left untreated. Variable amounts of scarring are seen in periapical granulomas, and they represent advanced repair. Occasionally, when there is cortical perforation by the inflammatory process, osteogenesis may not occur, and the lesion remains as a fibrous scar even in the presence of an adequate root canal filling. Also, if there is open communication between the tooth apex and oral cavity (e.g., through a carious lesion), the microaerophilic bacterium actinomyces, found in the oral flora, can colonize in the inflamed periapical tissues (**Figure 5**). This variation of periapical granuloma can result in an actinomycotic infection of the jaw. Diagnosis of these various inflammatory conditions is usually obvious microscopically; but because chronic abscess, periapical granuloma, and periapical scar share many microscopic features, separation can be somewhat subjective.

A periapical cyst can be defined simply as a pathologic space lined by epithelium at the apex of a nonvital tooth. The epithelium, derived from the ubiquitous epithelial rests of Malassez in the apical periodontal ligament, proliferates due to inflammatory stimulation in a pre-existing periapical granuloma. The epithelial proliferation can be regarded as a defense mechanism that protects surrounding bone from the irritants of the necrotic dental pulp. Microscopic examination of this dynamic process shows a variable picture ranging from partial to complete epithelization of the periapex. Again, diagnosis is subjective and dependent upon when in this process the lesion is biopsied and how the pathologist defines periapical cyst. The subjectivity associated with microscopic diagnosis in all likelihood accounts for the wide range of periapical cyst incidences (10 percent to 50 percent) reported in the literature.[6]

It is generally agreed that once a periapical granuloma becomes well-epithelialized, complete bony healing is unlikely with root canal therapy alone. Whether a partially epithelialized periapical granuloma can heal following root canal

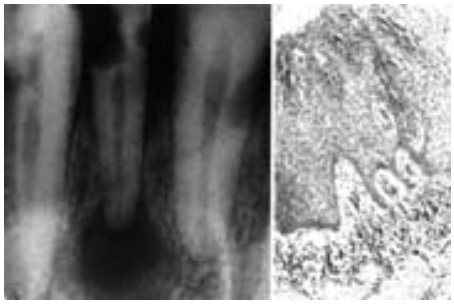

Figure 1. A periapical cyst showing radiographic continuity with the periodontal ligament space. The biopsy specimen (right) shows nonspecific hyperplastic epithelium supported by inflamed connective tissue. A cyst lumen is evident, top left.

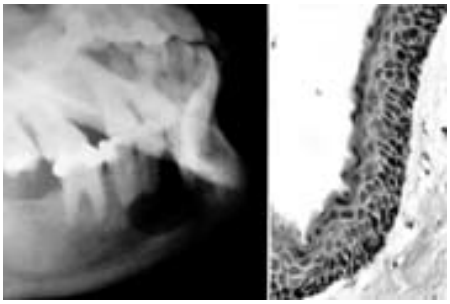

Figure 2. lateral jaw radiogram showing lucency at apices of vital canine and premolar teeth. The biopsy specimen (right) is a classic odontogenic keratocyst.

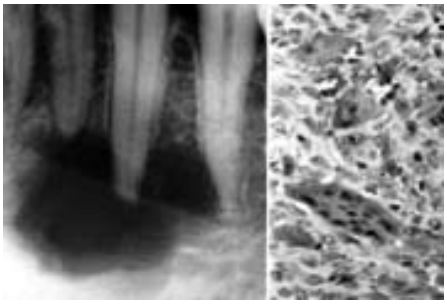

Figure 3. A periapical radiolucency at the apex of a mandibular canine with equivocal vitality. The biopsy specimen (right) shows fibroblasts and multinucleated giant cells, which are characteristic of central giant cell granuloma.

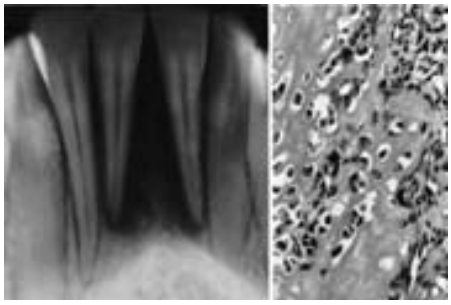

Figure 4. Periapical radiolucencies associated with mandibular incisors. Note that the lucency extends coronally along lateral periodontal ligament spaces and that the lamina dura is ill-defined. The biopsy (right), which shows atypical cells making tumor bone, was diagnosed as osteosarcoma.

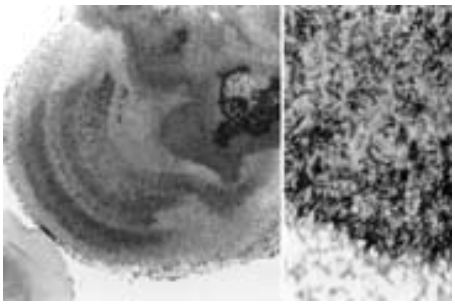

Figure 5. The microscopic appearance of a biopsy of a periapical lucency associated with a nonvital tooth shows a colony of actinomycosis. A gram stain (right) of tissue section shows characteristic gram-positive filamentous structures at the colony periphery.

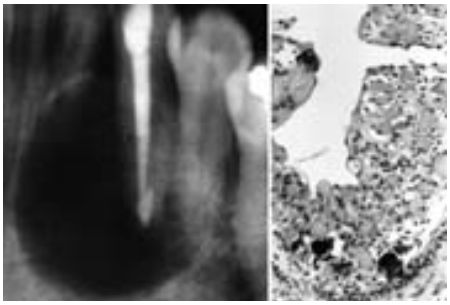

Figure 6. A persistent periapical radiolucency that upon biopsy (right) proved to be a calcifying odontogenic cyst. Note the typical keratinization (light globules) and calcification (dar globules) in the epithelial lining (courtesty of Dr. Timothy A. Wong, Sacramento, Calif.).

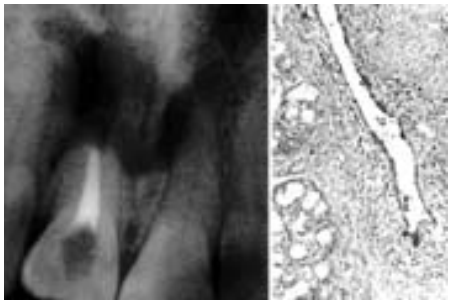

Figure 7. A persistent periapical radiolucency that upon biopsy (right) was found to be a nasopalatine duct cyst. Lobules of anterior palatal salivary gland can be seen to the left of the cystic lesion.

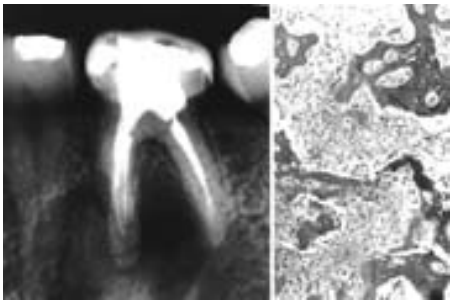

Figure 8. A persistent periapical radiolucency that was diagnosed as periapical cemento-osseous dysplasia after biopsy (right).

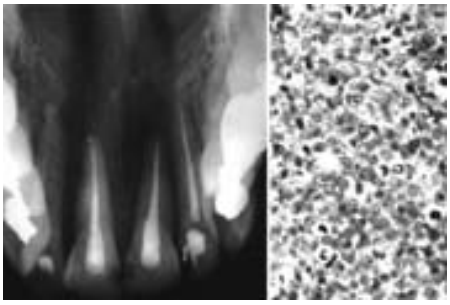

Figure 9. Poorly defined persistent periapical radiolucencies associate with apices of maillary incisors. The biopsy (right) was diagnosed as lymphoma.

therapy is still unknown, although it is likely that some can. Probably most of the endodontically treated teeth in which the periapical lesions persist (approximately 10 percent to 20 percent of cases) will be related to cystic change of a periapical granuloma. Also, persistent lesions may be associated with incompletely filled canals and/or apical foreign material.[7] Although large lesions are more likely to be cysts, there is no way to distinguish radiographically a periapical granuloma from a periapical cyst.

A small but important number of persistent periapical lucencies will be noninflammatory (**Figures 6 through 9**). These lesions, which range from dysplastic to malignant, should be considered whenever a periapical radiolucency is unusual or refractory to endodontic therapy. The benign aggressive and

malignant lesions are of particular importance because of their prognostic implications. Delayed diagnosis of one of these lesions could have profound consequences for the patient. Occasionally, signs and symptoms can give some early signals that the lesion in question is not inflammatory. It should be remembered that these other lesions not only can mimic chronic inflammatory periapical disease, but also can occur concomitantly with an inflammatory lesion. The reader is referred to a current oral pathology text for the clinical-pathologic details of these other lesions.[8]

In the vast majority of cases, it is neither practical nor desirable before performing root canal therapy to biopsy all periapical lesions to eliminate the risk of overlooking a malignancy or a benign aggressive condition. While a biopsy ensures the certainty of a diagnosis, it is invasive and may have some associated morbidity. When there are no inexplicable signs or symptoms associated with the lesion in question, it is most likely a periapical granuloma or cyst. This rationale would support endodontic therapy without microscopic diagnosis. If, however, a presenting sign or symptom suggests that malignancy or benign aggressive disease should be included in the differential diagnosis, a tissue biopsy would be well-advised. Also, if after "conservative" endodontic therapy, the lesion does not heal as expected or the patient continues to have symptoms, then a biopsy of the periapical region is warranted.

Following are the signs and symptoms that suggest the possibility of noninflammatory periapical disease:

- Paresthesia or atypical pain;
- A lesion that appears to have no radiographic relationship to the apical periodontal ligament and lamina dura;
- Large lesions and lesions with ill-defined margins; and
- A lesion-associated tooth that is intact and of positive or equivocal vitality.

If paresthesia is present, malignancy should be given serious consideration and placed at the top of the differential listing. Approximately half of the patients presenting with a numb lip have an intrabony malignancy. Because acute inflammation can also cause paresthesia, abscess should be placed high in the differential diagnosis. In the absence of paresthesia and in the presence of a long history of intermittent low-grade pain, an inflammatory process would receive top consideration. If the associated tooth also tests nonvital, the lesion is most likely a periapical granuloma/cyst/chronic abscess.

Focal widening of the periodontal ligament space and relative thinning of the lamina dura may be helpful in separating inflammatory lesions from others. The spatial relationship of "true" periapical inflammatory disease to tooth apex may be different than with other nondental lesions. Superimposition of a neoplasm on the tooth apex (so-called false periapical lucencies) can sometimes be detected by changing the radiograph angulation, thereby causing a shift of the pathologic image.

Generally, the larger the lesion, the greater the likelihood that it is a periapical cyst rather than a granuloma.[9] Other cysts and neoplasms will likewise be more likely. Because age and location are highly characteristic of many of the noninflammatory lesions, these two factors will have considerable influence on the differential ranking of these lesions. Slow-growing lesions such as periapical granulomas and cysts will typically be well-defined and surrounded by reactive sclerotic bone. These signs are not often associated with faster growing benign aggressive and malignant lesions.

If the tooth in question is deemed nonvital after pulp testing with one or, preferably, two vitality tests, inflammatory periapical disease should be strongly favored. The well-known vagaries of vitality testing and the occasional association of neoplasms with nonvitality deem it necessary, however, to be inclusive in building a differential diagnosis.[10] Further, a patient could have two lesions: a neoplasm superimposed upon a periapical granuloma/cyst.

When reviewing the health history of a patient with a periapical lesion, any previous treatment for a jaw tumor would be significant, as recurrence could potentially appear near the apices of teeth. Also, a history of a previously treated malignancy of another organ, including lymphoma and multiple myeloma, would be important.[11] Of particular importance would be a history of breast, lung, gastrointestinal, thyroid, or kidney cancer, as these commonly metastasize to the jaws, especially the mandible.[12] It should be remembered that with adenocarcinoma of the breast, metastatic disease may occur as late as 10 to 15 years after treatment of the primary lesion. Paresthesia and pain are typically associated with jaw metastases.

Summary

The diseases that may present as periapical radiolucencies have been listed and some examples have been illustrated. Signs and symptoms that should be considered when evaluating a periapical lesion have also been discussed. The following points were emphasized:

- Neoplasms, while infrequently encountered, can clinically and radiographically mimic periapical granulomas and cysts.
- Atypical lesions (especially those associated with paresthesia) and large periapical lesions should be biopsied.
- If, following endodontic therapy, there is no relief of symptoms and/or the periapical lesion does not resolve, a biopsy should be considered.
- Definitive microscopic diagnosis should be made for all excised periapical lesions.

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The Diagnosis and Management of Chronic Nonspecific Mucosal Leasions

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The practicing clinical oral pathologist is often referred patients with oral lesions that present diagnostic and management challenges. Among the most frequent of these is a group referred to as "chronic nonspecific mucosal lesions." These disorders represent low-grade physical or chemical injuries or delayed hypersensitivity reactions that share a common clinical presentation as persistent, nonspecific focal white or mixed red and white lesions. These conditions can cause considerable morbidity; and they defy diagnosis and resist therapy, making them a chronic problem for the patients who live with them and the dentists who treat them.

Clinical Presentation

Chronic nonspecific mucosal lesions first come to a dentist's attention during a routine oral exam or in response to a patient complaint of roughness, a burning sensation, or pain. Clinically, they appear as localized or multifocal white or mixed red and white (speckled) lesions that range from flat to plaquelike and may be granular and partly erythematous. Such lesions are nondescript and not recognizable as a specific disease, thus meriting the clinical term leukoplakia or erythroleukoplakia. Others with striations, ulceration, or atrophy resemble the many forms of lichen planus and are referred to as lichenoid. The designation "lichenoid" is also a microscopic term describing the band-like subepithelial lymphocytic infiltrate typical of lichen planus but also seen in other conditions.

A clinician will be compelled to investigate these lesions because of their chronicity, symptomatology, or perceived risk of malignancy. What often happens next is that the uncertainty of diagnosis will prompt a biopsy to provide a solution. Regretfully, the histopathology of reactive or allergic lesions is often nonspecific, showing only chronic inflammation with epithelial changes of hyperkeratosis, atrophy, hyperplasia, and superficial erosion. A microscopic diagnosis of nonspecific inflammation or lichenoid mucositis is then made. Although this diagnosis rules out malignancy, it does little to direct treatment. Consequently, the lesion persists, and the patient is relegated to symptomatic treatment that offers only temporary relief. This chronicle of events is unfortunate because many of these lesions have a specific cause that if

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approached properly can be identified and removed to effect a permanent cure.

It is the objective of this article to call attention to some recognized etiologic agents and correlate them with subtle lesional patterns that suggest a precise diagnosis that can be pursued through additional history and testing.

Etiology

When any clinical white or speckled lesion is encountered, most knowledgeable clinicians will take a thorough history, asking about topical irritants; habits, including tobacco and alcohol use; medical conditions; and presence of skin lesions. Additionally, they will look for obvious local factors conducive to lesion formation. This information, combined with lesional patterns and locations, will allow a tenable clinical diagnosis of such distinctive conditions as nicotine stomatitis, snuff dipper's keratosis, leukoedema, cheek biting, geographic tongue, and classic lichen planus. The focus of this article is the remaining wastebasket of clinically and histologically undefined lesions for which a specific cause cannot be ascribed.

Table 1 lists the causes of clinically nondescript white and speckled lesions. One might wonder, if these lesions have determinate etiologies, why can't they be more easily characterized. The reason a causative agent cannot be attributed to a particular lesion is eightfold:

1. The etiologic agent is often ubiquitous and trivial and is not elicited nor considered during history taking.

2. Most of the agents act in an idiosyncratic fashion: They are encountered by a majority of the population but affect only a few people.

3. There may be no apparent temporal relationship between cause and effect: Lesions can appear years after exposure to a previously tolerated agent.

Table 1

Drugs Commonly Associated With Causes of Chronic Nonspecific White and Speckled Red-and-White Mucosal Lesions

Low-grade physical irritation
Medications
Dental materials (amalgam)
Flavoring agents (cinnamon)
Oral health care products (toothpastes, mouthwash)
Candida
Immunologic diseases (lichen planus, lupus erythematosus, graft-v.-host disease, chronic ulcerative stomatitis)
Dysplasia/squamous cell carcinoma

4. Identification of a particular agent among the many possibilities is empirical, achieved only by laborious trial and error that may be undesirable (withdrawal of a needed medication) or expensive (replacement of dental restorations).

5. Lesions are chronic and tend to wax and wane, not always in response to a suspected agent.

6. Many cases are "lichenoid" and resemble idiopathic lichen planus so convincingly that lichen planus becomes the scapegoat diagnosis, depriving the patient of a search for an etiology that can be eliminated.

7. Many lichenoid lesions are, in fact, atypical examples of lichen planus that cannot be better characterized. In such cases, a search for an etiology is futile. This erodes the confidence of the clinicians who seek causes of lichenoid lesions.

8. Many lichenoid lesions require months or years to remit even if the correct etiologic agent is eliminated.

Over the years, investigators have extracted from the wastebasket of lichenoid and leukoplakic lesions several distinct entities that -- by virtue of subtle clinical, histologic, and historic data -- facilitate a more precise diagnosis.

Lichenoid Drug Eruption

Certain medications are known to cause generalized or localized oral lesions that can be indistinguishable from lichen planus clinically and microscopically (**Figure 1**).

The medications are thought to alter the antigenicity of epithelial cells, rendering them targets for sensitized T-lymphocytes. In effect, the reactions can be thought of as lichen planus induced by drugs. The essential difference is that LDE remits when the drug is withdrawn. **Table 2** lists groups of medications associated with oral lichenoid lesions. In practice, any drug taken by a patient should be investigated. Lichenoid drug eruptions show a latent period averaging one year, with a full range of one month to three years, before development of lesions. The latent period depends on the drug, its dosage, drug interactions, and a patient's individual susceptibility. In all patients diagnosed with symptomatic oral lichen planus, suspect medications antedating the lesions should be discontinued or substituted, if possible, after consultation with the prescribing doctor. It might require from two weeks to two years for lesions to disappear. Resolution can be accelerated with topical steroids. It must also be realized that both lichen planus and the use of drugs producing LDE are common in older adults, but LDE itself is infrequent. Thus, in many cases the medication is unrelated -- a fact that may require months to determine when the lesions fail to remit after cessation of the drug.

Oral contraceptives

Others (penicillamine, levamisole, lithium, dapsone, allopurinol, cyanamide, propranolol, lorazepam, carbamazepine)

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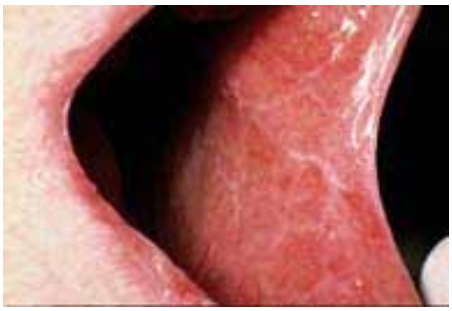
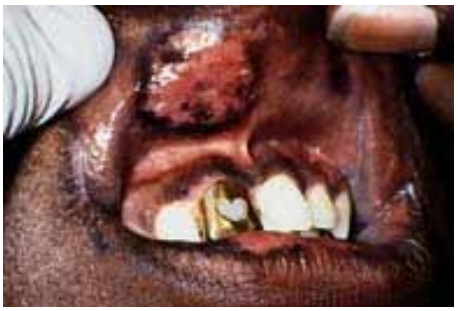


Figure 1. Diffuse network of white striae in buccal mucosa bilaterally of a woman treated for hypertension with methyldopa.



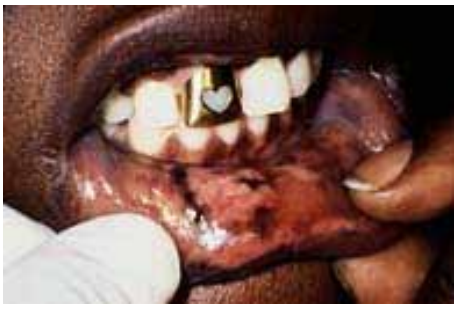


Figure 2a and b. Localized red and pigmented lesions in intimate contact with a shell crown. The lesions, present several months, were associated with swelling and pain. Histology showed epithelial thickening, melanosis and sever chronic inflammation with eosinophils — characteristic of an allergic response. Melanin pigmentation often accompanies chronic ulceroinflammatory lesions.

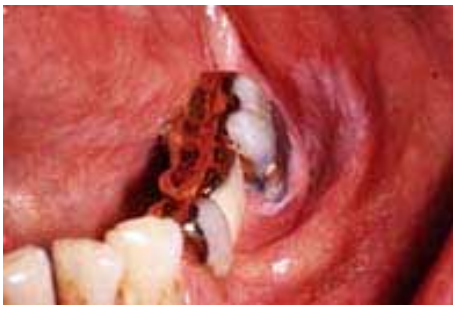


Figure 3. Leukoplakia confined to an area of contact with a large amalgam restoration proximate to gold. In this case, alvanism might contribute by accelerating corrosion. Replacement of the amalgam filling is indicated.

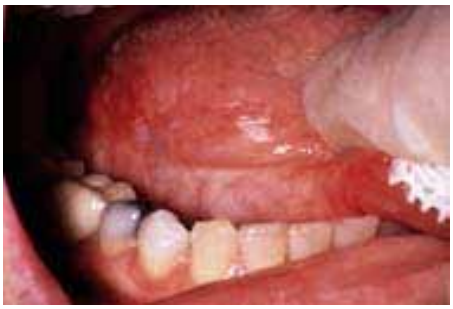


Figure 4a and b. Erythroleukoplakia of the lateral tongue. Improvement of the erythroleukoplakia shown in 4a following replacement of both the amalgam filling in No. 30 and the gold crown No. 31 with two porcelain-surface crowns.

Contact Lichenoid Reaction to Dental Materials

Lichenoid, leukoplakic, or erythroleukoplakic lesions are occasionally noted adjacent to dental restorations or prosthetic appliances. They are typically located unilaterally on the buccal mucosa, lateral tongue, or gingiva where they are localized to an area in contact with the material or may extend beyond the contact area (Figures 2 a and b). There are often symptoms of discomfort or burning. The clinical differentiation between idiopathic lichen planus or dysplasia and a lichenoid lesion induced by a restoration cannot be made with confidence. Restorative dentistry is prevalent in older adults where its coexistence with lichen planus or dysplasia might be fortuitous. Since lichen planus and dysplasia are clearly more common than a contact reaction, replacement of restorations based on a mere concordance of lesion and dental material is impractical. Yet, a growing number of studies indicate that lichenoid reactions to dental material do occur and that lesions resolve following removal of the contacting agent. How then does one determine when removal of dental work is justifiable?

Common Sensitizers in Dental Materials

In a study of 275 patients having skin or oral allergic lesions, the most frequent sensitizers were mercury (53 percent); followed by chromium, nickel, cobalt, and tin (35 percent to 32 percent); and platinum, iridium, palladium, cadmium, zinc, molybdenum, and gold (19 percent to 13 percent). Amalgam, with its content of silver, mercury, tin, copper, and traces of palladium and zinc is the most likely offender (**Figure 3**). Partial denture frameworks contain chromium and cobalt, and cast crowns may contain, in addition to gold and platinum, nickel, palladium, iridium, cadmium, and molybdenum. Even high noble alloys can include trace metals and impurities. Acrylic (denture baseplates and retainers), nickel (orthodontic wire), composite restorations, and BIS-GMA have been cited as mucosal irritants or allergens. Typically, the metal salts rather than the elemental metal incite the reaction, which is why the inert nonionizing metals are less likely to induce sensitivity.

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The Role of Galvanism

The experience of acute galvanic shock is familiar to patients when new amalgam fillings contact old restorations or metal foil. The shock sensation is due to a transfer of electrons between metals of different electromotive potential in an electrolyte (saliva). Chronic, asymptomatic, low-grade galvanism, occurring where dissimilar metals contact each other, has been implicated as a cause of lichenoid lesions, leukoplakia, and oral cancer; but proof is lacking. Oral electric currents cannot be recorded easily, and it is difficult to separate the influences of galvanism from primary metal reactions. Galvanism may contribute to lesion development by accelerating the rate of corrosion that forms the metal salts responsible for hypersensitivity (**Figure 3**).

Patient/Lesion Assessment

The decision to remove or replace a dental material adjacent to a lesion must include an assessment of the risk-to-benefit ratio, factoring in the likelihood of causation, cost, complexity, symptoms, patient stress, and concern about malignancy. Removable prostheses or isolated corroded/defective restorations are more conducive to removal than fixed bridgework. Lesions confined to the area of contact are more likely to respond to elimination of a material than lesions that extend beyond the confines of the material. If the composition of the material is known, each component can be evaluated with patch testing. Two percent to 5 percent of the general population is allergic to mercury, while 16 percent to 62 percent of individuals with adjacent lichenoid lesions are found to be allergic to the metal. Test results must be interpreted with caution. Dermal allergy testing can give false negative results if the oral lesion represents an irritation by the restoration rather than a hypersensitivity. False positive results can also occur for two reasons: skin is more sensitive than mucosa; and metal salts are usually used in patch tests, which is irrelevant if the oral metal does not ionize in vivo. When the constituents of a restorative material are not known, they can often be determined by name brand. If the brand name is not known, a small sample can be recovered with a handpiece and submitted for elemental analysis using energy dispersive X-ray microanalysis. This service is available from institutions that have a scanning electron microscope. Such sophisticated techniques are advocated for patients with extensive fixed dental appliances.

Upon removal of a causative material, resolution of the lesion can be expected in one to 12 months with relief of symptoms within three months (Figures 4a and b). However, this is too long a wait if the lesion is located in a high-risk area for oral cancer such as the lateral tongue, in which case a biopsy is recommended before replacement of the dental restoration.

Table 2

Drugs Commonly Associated With Lichenoid Reactions

Antimalarials (quinacrine, quinine, quinidine, hydroxychloroquine)
Diuretics (thiazides, furosemide)
Antihypertensives (B adrenergic blocking agents [methyldopa]; ACE inhibitors [captopril]; reserpine)
NSAIDS (indomethacin, azulfidine, phenylbutazone, naproxen)
Antimicrobials (tetracycline, penicillin, sulfonamides, nitrofurantoin, isoniazid, PAS, streptomycin, ketoconazole, griseofulvin)
Heavy metals (gold, bismuth, arsenicals, mercurials)
Sulfonylurea hypoglycemics

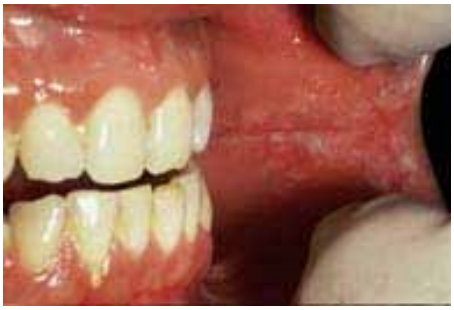
Contact Reactions to Foods and Oral Health Care Products

Toothpastes and mouthwashes contain a multitude of agents recognized as allergens. Additionally, ingredients such as pyrophosphate and zinc citrate (tartar control) and sodium lauryl sulfate (surfactant) are contact irritants that have been implicated in mucosal sloughing and aphthaeform ulcers, respectively. Up to 2 percent of toothpaste users report problems.

Cinnamon-Induced Lesions

The most notorious sensitizing agent in food and oral health care products is cinnamon flavoring, which causes contact mucositis in an untold number of patients. The lesions vary in appearance and location, corresponding to patient habits. Cinnamon-flavored chewing gum is most often implicated, and lesions form adjacent to the contact area, along the occlusal line of the buccal mucosa with or without corresponding "kissing" lateral tongue lesions (Figures 5a and b). They may be unilateral or bilateral. Some are lichenoid, whereas others are eroded and granular. Clinically, they may mimic lichen planus, cheek biting, snuff dipper's keratosis, candidiasis, hairy leukoplakia, or dysplasia. A directed inquiry of patient habits may identify the offending agent; but too often, patients are unaware of cinnamon use, not realizing that the brand of gum they chew is cinnamon-flavored or not knowing that foods they ingest contain cinnamon (e.g., sweet vermouth, chili). Often, the gum habit is a recently instituted substitute for smoking. Other vehicles such as candy or even dental floss might deliver cinnamon, resulting in different lesional patterns. The lesions may cause months of discomfort, burning, pain, or a rough feeling.

When biopsied, a characteristic histologic finding virtually identifies the



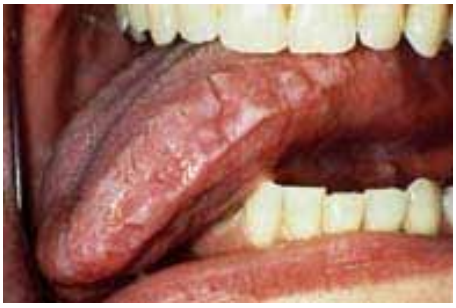
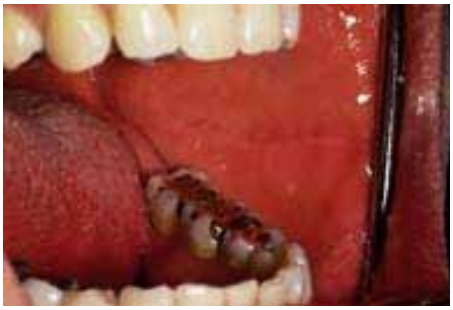


Figure 5a and b. "Kissing" granular leukoplakias of the buccal mucosa and tongue in a 54-year-old cinnamon-gum chewer.



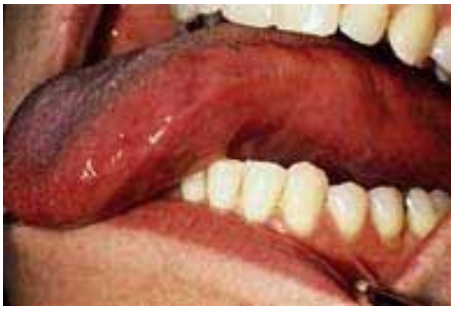
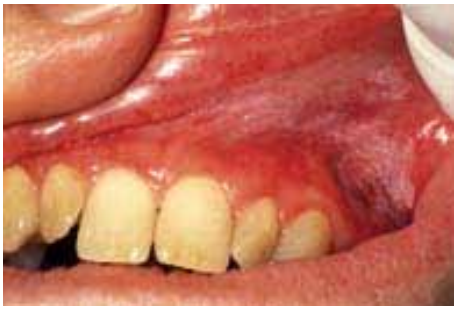


Figure 5c and d. Full resolution of the case in 5a and b within two weeks of discontinuance of the cinnamon-gum chewing.



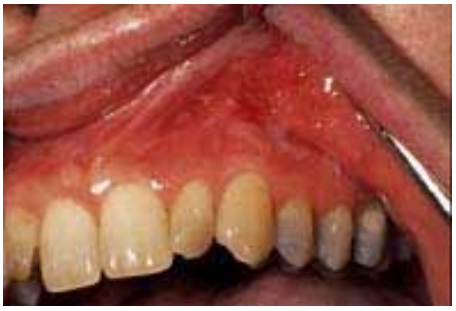


Figure 6a and b. Asymptomatic, irregular, extensive leukoplakia of the anterior maxillary vistibule, mucolabial fold and alveolar mucosa extending from the right canine to the left molar. The histology showed mild dysplasia. The patient, a 54-year-old-woman, used Viadent mouthwash and toothpaste for seven years. Partial improvement after 10 months.

lesion as a cinnamon reaction. These lesions are characterized by a pronounced perivascular chronic inflammatory infiltrate below a lichenoid surface change. Based on the predictive histology alone, patients have been contacted following biopsy and "accused" of a cinnamon habit. The patients are incredulous but grateful when the lesions remit within two weeks of cinnamon cessation (Figures 5c and d).

Sanguinaria-Related Lesions

Damm reported on 88 patients who developed a peculiar white mucosal patch extending across the maxillary labial mucosa, vestibule and alveolar mucosa. Histologically, these lesions showed hyperkeratosis, chronic mucositis, and mild dysplasia. These lesions were further investigated because of the unusual location of the dysplasia, which did not correspond to that seen with tobacco use. Upon further history, nearly 85 percent of these patients used sanguinaria-containing Viadent mouthwash and/or toothpaste for varying amounts of time.

Once formed, these kinds of lesions are slow to resolve (Figures 6a and b). The histologic finding of dysplasia is worrisome, although sanguinaria-related lesions do not show a preneoplastic profile biochemically, according to Eversole and colleagues. The clinical lesion is so unusual that it should prompt questioning about the patient's dentifrice and mouthwash habits.

Atypical Lichen Planus

Ironically, lichen planus is included in the differential diagnosis of lichenoid lesions. Lichen planus is an idiopathic, chronic, recalcitrant disorder of the skin and mucous membranes thought to represent a Type IV hypersensitivity to an exogenous agent that alters keratinocytes. It is mediated by activated cytotoxic T-lymphocytes that damage basal keratinocytes and the basement membrane. Up to 2 percent of the population is affected, particularly women older than 40.

When lichen planus shows classic white striae arborizing throughout the buccal mucosa bilaterally in a patient who is not taking medications known to cause lichenoid reactions, the diagnosis is straightforward. But many cases are atypical. Atrophic or erosive forms present as fissured white plaques on the dorsal tongue, as a desquamative gingivitis, or as erythroleukoplakia with or without well-delineated yellow-tan ulcers. These are difficult to diagnose clinically, and so reliance is placed on a biopsy.

On the skin, the application of fastidious histologic criteria can establish the diagnosis of idiopathic lichen planus in 90 percent of cases. Oral lichen

planus does not necessarily exhibit these pathognomonic features. The microscopic features of oral lichen planus may be altered because of factors including superimposed inflammation or candidiasis, attempts at therapy, varied histology of oral tissues, and poor selection of biopsy site. Biopsies from the gingiva and areas of ulceration are frequently nondiagnostic. Neither histology nor clinical appearance are dependable as a gold standard to firmly establish the diagnosis of lichen planus in the oral mucosa. Consequently, idiopathic oral lichen planus may fall into the group of undistinguished lesions simply designated as lichenoid mucositis.

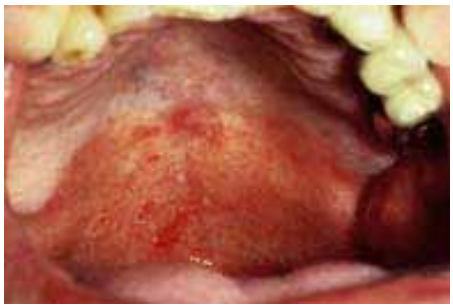


Figure 7. Red-and-white lichenoid lesion with cytologic evidence of candida. Complete resolution followed antifungal therapy.

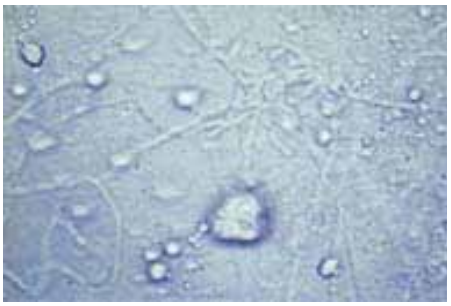


Figure 8. Unstained candidal pseudohyphae and spores as seem in a KOH prep, original magnification, 400x.

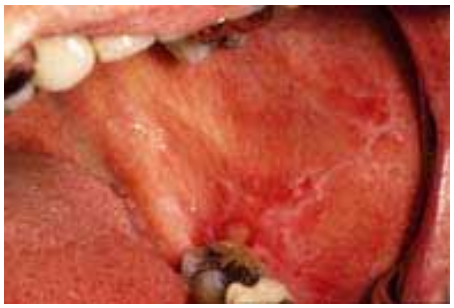


Figure 9a and b. Lichen planus in a 66-year-old woman with no contributory contacting materials or medications. Following a negative smear for candida, Temovate and Orabase B was applied topically for a period of three weeks. Resolution was complete.

Candidiasis

The consideration of candidiasis in the differential diagnosis of white and speckled lesions is relevant for three reasons. First, chronic atrophic or hyperplastic candidiasis may present as a lichenoid lesion (**Figure 7**). Second, candida may be superimposed on other lesions in this group and alter the lesional appearance and confound diagnosis. Third, steroid therapy, which is commonly used to treat chronic mucositis, is contraindicated if candida is present. For these reasons, cytologic testing for candida is recommended. A positive result indicates that candida is present but not necessarily the cause of the lesion. Antifungals should be prescribed. If the lesion completely resolves, it can be attributed to candida; and the patient should be evaluated for local and systemic factors that favor this opportunistic infection. Failure to respond to antifungal therapy should lead the clinician to pursue other causative factors, thus facilitating appropriate diagnosis and treatment.

Other Conditions in the Differential Diagnosis

There are several uncommon or rare causes of localized lichenoid lesions that are included for completeness. Most can be ruled out by history. Lupus erythematosus will produce painful, localized ulcers and atrophic, striated red and white lesions that resemble lichen planus clinically and histologically. Patients usually have a history of a facial rash; solar sensitivity; and, in the case of systemic lupus erythematosus, generalized symptoms. Graft-versus-host disease produces lichenoid oral lesions. This is not surprising because graft lymphocytes reacting against antigenically dissimilar host epithelium simulates the pathogenesis of lichen planus. A history of a bone marrow allograft establishes the diagnosis. Chronic ulcerative stomatitis is a rare and recently recognized disease that is responsible for widespread oral ulcers and desquamative gingivitis mimicking lichen planus clinically and histologically. It is most frequent in women older than 40. If it is considered in the differential diagnosis, immunofluorescent findings are diagnostic. Direct and indirect immunofluorescence is strongly positive for stratified epithelium-specific antinuclear antibody. The direct method also shows fluorescence of epithelial nuclei with anti-IgG. The disease is resistant to steroids but responds to therapy with hydroxychloroquine (Plaquenil), 200 mg. BID.

Patient Management

Chronic nonspecific reactive mucosal lesions are caused by so many disparate agents that no single management protocol can be applied to all cases. However, it is useful to be guided by a decision tree that reaches an appropriate end point expediently without placing the patient at unnecessary medical or financial risk. A logical progression should include:

1. Taking a complete history and physical exam;
2. Removing proximate agents that are likely to effect resolution of the lesion;

3. Ruling out candida;

4. Ruling out dysplasia/cancer or other diseases that can be diagnosed by biopsy; and

5. Investigating putative agents that are costly, risky, or may require many months to evaluate.

Initial Exam

A patient history and oral examination are the most immediate sources of diagnostic information and supply the foundation for further decision making:

- If the lesion is located in a high-risk area for oral cancer without obvious cause, a biopsy should be performed.
- If the lesion is localized and confined to intimate contact with an amalgam restoration, the restoration may be replaced.
- If "kissing" lesions of the buccal mucosa and lateral tongue are observed in a habitual cinnamon gum chewer, withholding cinnamon for several weeks should pre-empt other tests.
- If leukoplakia is detected on the maxillary alveolar mucosa in a user of a sanguinaria-containing product, a biopsy should be obtained, and the product discontinued.

Empirical Steroid Treatment

It is unwise to treat an undiagnosed lesion with a trial of steroids for several reasons:

- If candida is present, steroids will aggravate the lesion.
- Steroids alter the histologic appearance of inflammatory lesions, rendering them potentially nondiagnostic if a biopsy is subsequently performed.
- Steroid therapy may become a long-term proposition if the cause of the lesion is not discovered and eliminated.
- Steroid therapy may delay a diagnosis of dysplasia or cancer. Steroid use should be delayed until the cause of the lesion has been eliminated or a biopsy performed.

Ruling Out Candida

Ruling out candida involves a simple office screening test that should be routinely performed with white, red, and speckled lesions. If the clinician owns a microscope, a potassium hydroxide (KOH) prep can be examined within minutes. A smear of the lesional surface is applied to a slide onto which is placed a drop of aqueous 10 percent KOH. The slide is coverslipped, gently heated over a Bunsen burner to hydrolyse the epithelial cells and examined microscopically for evidence of yeast (**Figure 8**). If a microscope is not available, or if there is not a visible amount of material on the slide, the smear should be sprayed with a cytology fixative and sent to an oral pathology laboratory with instructions to evaluate for candidiasis using a periodic acid Schiff (PAS) stain.

Obtain a Tissue Diagnosis

After the elimination of candida and any easily correctable causes of the lesion, it is time to consider more speculative etiologies such as medications and contact reactions. Some of these reactions require several months to resolve, even if the cause is eliminated. This is an unacceptable waiting period if a histologic diagnosis has not been determined. If a biopsy has not yet been performed, it is now indicated. If a diagnosis of nonspecific or lichenoid mucositis is returned and the lesion is symptomatic, it is appropriate to eliminate suspect drugs, oral health care products, foods, and dental restorations and materials. This may require the support of allergy testing, as deemed necessary and within reason. Ultimately, removal of extensive serviceable restorations or discontinuance of a necessary medication may exceed the risk-to-benefit ratio and is simply not acceptable, particularly if the causation is in doubt. This is one area in the management of mucosal lesions where the interplay of options calls for judgment. Some decisions, like ruling out malignancy in a high-risk location, are compelling. Others, such as replacing a medication or costly dental work, are discretionary and largely the decision of the patient after a full disclosure has been made and informed consent obtained.

Recalcitrant Cases

If a symptomatic, biopsy-proven chronic inflammatory lesion persists despite a comprehensive diagnostic workup and reasonable elimination of suspect reactants, either the cause was not discovered, the lesion is idiopathic, or it has not been given adequate time to resolve. Topical steroids may be used if there are no medical contraindications. Triamcinolone acetonide 0.1 percent in Orabase B is a low-strength steroid preparation. Higher potency steroids such as fluocinonide 0.05 percent or clobetasol 0.05 percent gel mixed 1:1 with Orabase B can be used as well. A small amount is smeared across the lesion, TID, after meals and before bedtime for two to three weeks and then as needed if symptoms recur (Figures 9a and b).

Systemic steroids are reserved for extensive, debilitating lesions that do not respond to topical application. After an initial burst of 30 to 45 mg of prednisone, the dose is adjusted to the lowest amount needed to prevent recurrence. For long-term treatment, alternate day therapy is useful; and adjunctive treatment with agents such as azathioprine or levamisole can be added to decrease side effects. If at any time during the course of seemingly successful steroid treatment symptoms worsen, the patient should be clinically re-evaluated and checked for candida. Treatment with steroids and immunomodulating agents may require consultation with the patient's physician.

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Proliferative Verrucous Leukoplakia: Report of Two Cases and a Discussion of Clinicopathology

Robert O. Greer, DDS, ScD; John D. McDowell, DDS, MS; and George Hoernig, HT

ABSTRACT Proliferative verrucous leukoplakia (PVL) is a recently delineated but poorly recognized form of multifocal leukoplakia that is premalignant and of unproven origin. PVL generally presents as a simple benign form of hyperkeratosis that tends to spread and become diffuse. Although slow-growing, the disease is persistent and irreversible. Clinically, PVL often presents as an exophytic wart-like form of leukoplakia that appears to be resistant to nearly all forms of therapy. PVL of the oral cavity is best-defined as a continuum of oral epithelial disease with hyperkeratosis at one end of a clinical and microscopic spectrum and verrucous carcinoma or squamous cell carcinoma at the other. The microscopic findings associated with PVL are dependent on the stage of the disease and the adequacy of the biopsy. Microscopic findings can be markedly variable. PVL is a clinicopathologic disorder that includes the microscopic entity known as verrucous hyperplasia as a component of its histopathologic progression. This article reports on two cases of PVL, describes the clinicopathology of the disease process, and presents therapeutic and etiologic considerations.

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First described in 1985 by Hansen and colleagues,[1] proliferative verrucous leukoplakia (PVL) is recognized as a precancerous form of multifocal progressive leukoplakia with a strong potential for malignant transformation. The World Health Organization Collaborating Center for Oral Precancerous Lesions maintained at that time that leukoplakia should continue to be defined as a white patch of the oral mucosa that cannot be characterized clinically or pathologically as any other disease entity.[2] Hansen and colleagues, however, were able to demonstrate that the disease is indeed an idiopathic form of precancerous leukoplakia that fails to mimic the WHO pattern of disease and that it can present as a solitary homogeneous plaque-like oral lesion, an aggressive form of dysplasia, verrucous carcinoma, or squamous cell carcinoma. The vast majority of the lesions described by Hansen and colleagues were of unknown origin and exhibited a strong tendency to develop areas of carcinoma over time.[1] The disease is slow-growing, persistent, and irreversible; and over time it becomes exophytic, wart-like, and resistant to most forms of clinical therapy. Recurrence is common at all stages.

PVL is most commonly identified in elderly women and seems to occur in a

unique group of patients who do not give a history of tobacco use or alcohol abuse. The 30 patients that Hansen and colleagues identified were followed for from one to 20 years. Thirteen died of or with their disease, 14 were alive with PVL at the time of the study, and three were alive without PVL at last follow-up, up to 21 years later.[1]

Hansen and colleagues1 documented that 63 percent of their PVL patients harbored Candida albicans in the superficial layers of their biopsies. In studies in the laboratory at the University of Colorado, the authors of this article identified Candida albicans in 18 of 21 patients with PVL followed over a 10-year period. Marx[3] has recently reported that he was able to identify Candida albicans in 75 percent of biopsy specimens from patients with PVL in a series at the University of Miami Medical School.

All reports in the literature suggest that PVL is a single disease entity that demonstrates a unique spectrum of clinical and histopathologic expression that may terminate in squamous cell carcinoma (**Figure 1**).

During the past 10 years, the authors have had the opportunity to evaluate 21 cases of PVL at the University of Colorado School of Dentistry. The purpose of this study is to discuss the nature of two cases that have had benefit of long-term follow-up, discuss the clinicopathologic aspects of the disease, delineate differential diagnostic guidelines, and propose etiologic considerations and management modalities.

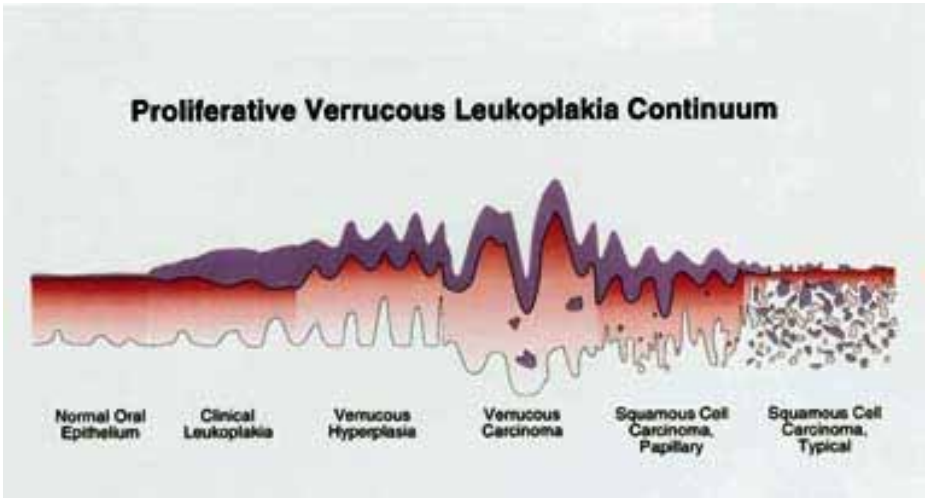

Figure 1. Proliferative verruccous leukoplakia continuum. From Greer RO, Hoernig G, McDowell JD, Proliferative verrucous leukoplakia: a clinical and histopathologic disease. Pathology Case Reviews, 4:3-7, 1999.

Case Reports

Case 1

A 56-year-old white male was seen in the Sands House Oral Cancer Clinic at the University of Colorado School of Dentistry for evaluation of multifocal white lesions affecting the maxillary gingival mucosa. The lesions were plaque-like, cobbled, and corrugated (**Figure 2**). The lesions were not painful, and the patient gave no history of ulceration, hemorrhage, or numbness. The patient was not a tobacco user and admitted to using alcohol only rarely. He was on no medications and indicated that until his dentist brought the lesions to his attention, he was unaware of their presence.

The patient's referring dentist reported that the lesions had been present for less than a year. The lesions were biopsied and described microscopically as verrucous hyperplasia with focal areas of moderate dysplasia. Tissue sections were stained with periodic acid Schiff (PAS) stains and shown to harbor Candida albicans. All lesions were excised completely, and the patient was lost to follow-up.

Two years later, the patient returned with a new exophytic lesion affecting the ventral tongue (**Figure 3**). The new lesion was approximately 2 cm in diameter, nodular, and focally hemorrhagic. The lesion was biopsied, diagnosed as verrucous carcinoma, and treated by a wide surgical excision. Once again, PAS stains were positive for Candida albicans. The patient has now been followed an additional eight years. Since that time, he has presented with an additional white reticular lesion affecting the right buccal mucosa. That lesion was biopsied six months prior to this report and found to demonstrate mild dysplasia. That lesion was totally excised. PAS stains for Candida albicans were negative. The patient continues to be monitored closely and has not developed any additional lesions.

Case 2

A 39-year-old white female who gave a history of never using tobacco products or alcohol presented to the Sands House Oral Cancer Clinic at the University of Colorado School of Dentistry as a referral from a southern California dentist who requested that she be evaluated for an oral lesion by the School of Dentistry's Oral and Maxillofacial Diagnostic Clinic upon moving to Colorado.

The patient indicated that a white lesion affecting the buccal mucosa had been excised approximately four years earlier and diagnosed as benign hyperkeratosis. At the time of her initial presentation to the clinic, she had a white plaque-like lesion affecting the left ventral surface of the tongue (**Figure 4**). The lesion was not painful, and the patient gave no

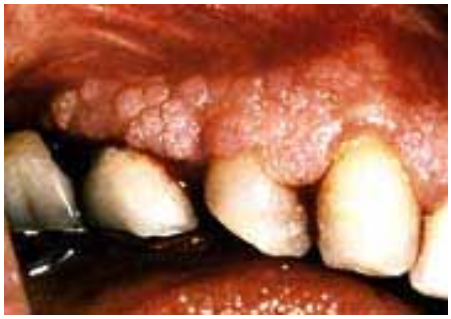

Figure 2. Case 1 — PVL of the maillary gingiva. Note cobbled character of lesions and their linear distribution.

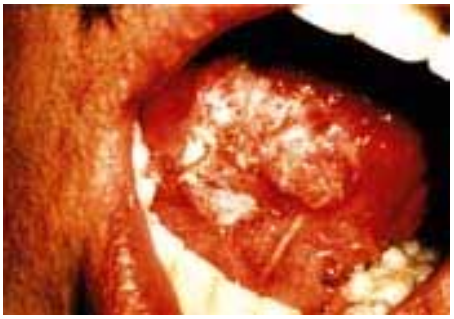

Figure 3. Case 1 — PVL transition to verrucous carcinoma of the ventral tongue. The lesion is exophytic, nodular and ulcerated.

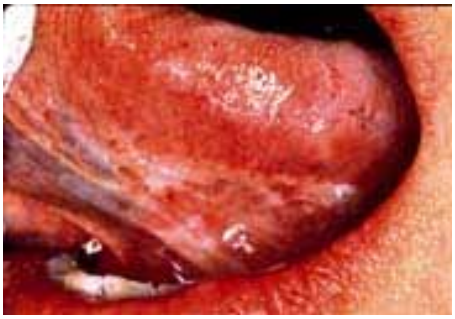

Figure 4. Case 2 — PVL, ventral surface of tongue. Note the white streaklike, somewhat lichenoid character of the lesion.

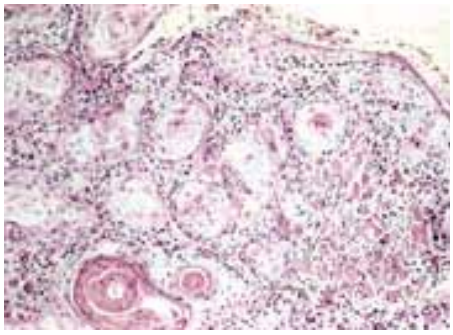

Figure 5. Focus of squamous cell carcinoma arising in the earlier PVL seen in Figure 4. This well-differentiated cancer demonstrates muscular invasion and significant keratin pearl formation.

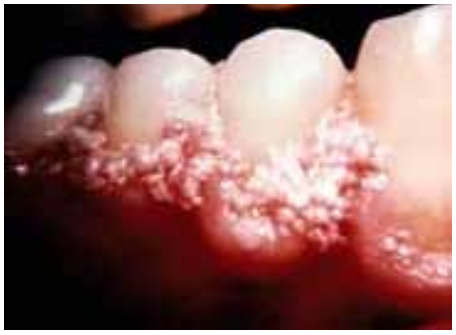

Figure 6. Case 2 — PVL, gingiva. Note the papillary character of the lesion.

history of trauma or injury to the area. The lesion was incisionally biopsied, and a diagnosis of severe epithelial dysplasia was rendered. The patient was rescheduled for surgery to have the tongue lesion removed.

At the time of definitive surgery, a diagnosis of squamous cell carcinoma was rendered (**Figure 5**). The first biopsy was retrospectively subjected to PAS staining for Candida albicans. The stains were negative; however, the definitive surgical specimen did show evidence of Candida albicans with PAS staining.

The patient was placed on long-term follow-up and followed for four years and six months with no evidence of residual disease. Four years and nine months into the follow-up, the patient presented with new areas of papillary hyperkeratosis affecting the mandibular gingiva (**Figure 6**).

On excisional biopsy, the lesions demonstrated mild epithelial dysplasia microscopically. PAS stains were negative for Candida albicans. Ten years after the initial biopsy, the patient continues to be monitored closely at three-month intervals, without evidence of new disease.

Discussion

PVL is considered by most authorities to be a persistent progressive preneoplastic process. The disease is thought to have a broad, continuous spectrum of clinical and histologic features with high potential for malignant transformation. The authors believe that the two cases of PVL presented here represent the full spectrum of PVL from benign hyperkeratosis to squamous cell carcinoma.

The most common sites for PVL have been reported to be the buccal mucosa and palate,[1,4] followed by the alveolar mucosa, tongue, floor of the mouth, gingiva, and lip. Hansen1 reports that in early PVL, clinical findings consist of multifocal white plaques of the type presented in the two cases reported here. As PVL progresses, solitary lesions spread and similar lesions appear elsewhere on the oral mucous membrane, often accompanied by diffuse papillary and erythematous changes. The authors' experience suggests that the natural progression of the disease almost always includes some verrucoid or papillary pattern. In late PVL, some areas become clinically indistinguishable from verrucous carcinoma or papillary squamous cell carcinoma.

One consistent feature documented in PVL is that a large percentage of cases demonstrate infection with the fungal organism Candida albicans.[1,3] Some investigators report that this association is the key to neoplastic transformation, suggesting that the endogenous production of nitrosamines by Candida organisms is the neoplastic stimulus in PVL,[3] while other investigators suggest that there is not enough evidence for a causal claim since Candida may be found in biopsies of normal mucosa.

One of the difficulties in diagnosing PVL has been the lack of clinicopathologic continuity associated with its microscopic diagnosis. The lesion can easily be misinterpreted as a form of simple hyperkeratosis microscopically, especially when its multifocal nature is not passed on to the pathologist.

Recently Murrah and Batsakis[5] have suggested that verrucous hyperplasia, a term first coined by Shear and Pindborg[6] and a well-recognized histologic precursor of verrucous carcinoma, is indeed no more than a late-stage and microscopically definable component of PVL.

In a review of 68 cases of verrucous hyperplasia, Pindborg and Shear reported that 40 percent of histologically definable verrucous hyperplasia cases underwent malignant transformation to either verrucous carcinoma or squamous cell carcinoma.6 Murrah and Batsakis[5] champion the fact that verrucous hyperplasia as a unique histologic component of PVL be restricted to lesions of the oral mucosa, sinonasal cavity, and laryngeal mucosa that meet the criteria of an atypical verrucoid growth with keratotic hyperplasia, mucosal clefting, keratotic clefts, parakeratin plugging, and irreversibility. These authors further suggest that verrucous hyperplasia can sometimes be indistinguishable from verrucous carcinoma and note that both disorders require initial aggressive surgical management.

The diagnosis of PVL remains, in large measure, a clinicopathologic one. However, there are unique and reproducible epidemiologic features that distinguish this unusual disorder. In contrast to many forms of oral epithelial dysplasia and leukoplakia, PVL tends to occur more frequently in women than men; and PVL has an affinity for the mucosa of patients with no history of tobacco use.[1,4,7]

Silverman and colleagues profiled patients such as these in an assessment of 257 leukoplakic patients followed for a mean period of 8.4 years. They noted that isolated cases initially thought to represent nothing more than simple hyperkeratoses tended to become PVL over time.[8]

Etiology

Considering the difficulty involved in establishing an early diagnosis of PVL, researchers have recently undertaken investigations that attempt to identify a molecular basis for the disease. Flow cytometric analysis has been used by Kahn and colleagues[4] to study four cases of PVL in an attempt to determine if flow cytometry might be useful in early diagnosis.

These investigators performed flow cytometry on 27 formalin-fixed and paraffin-embedded tissue samples and found DNA aneuploid cell lines in each of the PVL cases studied. A DNA index range of 1.1 to 2.6 was reported. In all four cases studied, the abnormal cell line DNA index appeared to be maintained throughout the sampling period. These results suggest that flow cytometric analysis may be useful in the early recognition of PVL and support the concept that flow cytometric analysis may serve to support aggressive intervention at an early stage in the disease. This is an important intervention since PVL can recur at a faster rate than non-PVL forms of leukoplakia.

Studies in the authors' laboratory over the past decade suggest that the histologic features seen in PVL – including its often verrucoid clinical appearance and its uniquely identifiable pathologic stages, including verrucous hyperplasia and verrucous carcinoma – favor a disease-associated infection by human papillomavirus (HPV).[9] A host of studies have identified HPV infection of oral lesions of all types including leukoplakias[9-11] over the past 10 years. The most compelling work in this arena related to PVL is perhaps that of Palefsky11 and Shroyer and colleagues[12,13] who have shown an association between HPV infection and PVL using molecular biological techniques. Shroyer and colleagues[12,13] evaluated 17 verrucous carcinoma cases seen at the neoplastic end of the PVL spectrum using biotin-labeled probes. These investigators found HPV 6 and 11 DNA in 41 percent of cases they studied by in situ hybridization. They also studied 22 cases of non-PVL-associated oral lesions, including 12 squamous cell carcinomas, and found HPV 16 in five of 12 cases.

To date, more than 80 distinct types of HPV have been identified. A host of studies involving cervical cancer support the premise that HPV 16 and 18 have an affinity for potentiating malignant disease in that site.[14,15] The characterization of HPV infection in PVL, however, has only recently begun. Studies have shown lesser amounts of HPV in oral squamous cell carcinomas than in cervical cancer. This finding may be related to the fact that oral neoplasms harbor low copy numbers of HPV or that oral tissues subjected to HPV DNA typing may have been inadequately sampled.

Finally, unidentified HPV subtypes unique to the oral cavity may remain undetected. Although HPV 16 and 18 appear to be the most commonly identified forms of HPV found in certain mucous membrane malignancies, HPV 6, 11, 16, and 18 remain the most consistently identified types, in precancerous lesions of the oral cavity, including PVL.[11-13]

In fact, Palefsky et al11 report that HPV 16 plays a fundamental role in the pathogenesis of PVL-associated oral epithelial dysplasia and possibly cancer. These findings are all the more compelling when one considers that these investigators found HPV in only a small fraction of the more common non-PVL-associated lesions they also studied.

The mechanism by which HPV infection contributes to the progression of PVL has not been fully appreciated,

but the process is likely related to a series of chromosomal mutations. Credence is given to this mutation theory when it is recognized that the E6 and E7 proteins of HPV 16 bind and inactivate two significant cell cycle regulators, the p53 and retinoblastoma proteins.[16-18] HPV E6 protein and p53 may in fact enhance the chromosomal instability that potentiates the PVL cascade.

Differential Diagnostic and Histopathologic Considerations

Verrucous Hyperplasia

Shear and Pindborg6 initially described two classic histologic patterns for a disorder termed verrucous hyperplasia, which is now recognized as a late-stage component of PVL. The first pattern, or "sharp variety," of verrucous hyperplasia features long, narrow, and heavily keratinized verrucous processes (**Figure 7**). These hyperplastic lesions may or may not present as multifocal homogenous areas of leukoplakia when identified clinically.

A second type, or "blunt variety," of verrucous hyperplasia consists of verrucous processes that are broader, flatter, and not as heavily keratinized as in the sharp variant (**Figure 8**).

Both histologic subtypes of verrucous hyperplasia can progress to verrucous carcinoma over time.

In their study of 68 verrucous hyperplasia cases, Shear and Pindborg[6] found that 37 cases were of the sharp variety and 24 were of the blunt type. In nearly all cases, a dense inflammatory infiltrate was seen in the supporting collagenous lamina propria. Dysplastic atypia was identified in 66 percent of cases. These authors emphasize that verrucous hyperplasia is best distinguished from verrucous carcinoma in biopsies taken at the margins of lesions. Verrucous hyperplasia demonstrates verrucous processes where the greater part of the hyperplastic epithelium remains superficial to adjacent normal epithelium. Verrucous carcinoma features verrucous processes that are also superficial, but the broad rete processes of that disease extend deeper than the abutting normal epithelium, often enveloping a margin of normal epithelium into the underlying connective tissue.

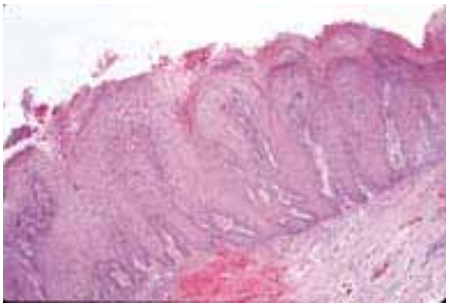

Figure 7. "Sharp variety" of PVL demonstrating narrow keratinized verrucous processes and makred epithelial acanthosis.

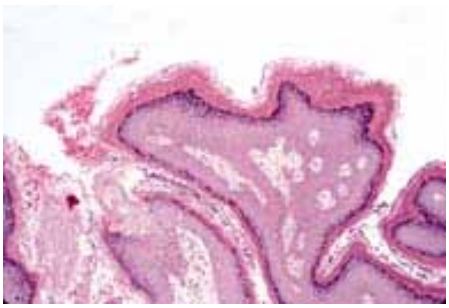

Figure 8. "Blunt" variety of PVL demonstrating broad, flat verrucous processes, and minimal keratin plugging between papillary fronds.

Non-PVL-Associated Leukoplakias

Leukoplakia is a term that continues to cause considerable consternation in the literature. The term leukoplakia simplex is most often used to define a localized homogenous form of white hyperkeratoses affecting the oral mucous membrane. The lesion is generally dense and can have a corrugated or smooth surface. In those instances when a solitary oral leukoplakic lesion is recognized in a patient, it may be difficult to determine if the lesion is early PVL without a characteristic history of clinical persistence, irreversibility, focal erythematous components, and an exophytic or wart-like pattern. For this reason, biopsy, long-term follow-up, and close scrutiny of such lesions is mandatory for proper patient management.

Nodular Leukoplakia

Nodular leukoplakia is a term that has been variously referred to in the literature as erosive leukoplakia or speckled leukoplakia. It is a form of leukoplakia that characteristically contains zones of redness or erythema. The lesions of nodular leukoplakia are rarely, if ever, long-standing; and they typically are not multifocal. Nodular leukoplakia generally presents histologically as some form of epithelial dysplasia, or maturational atypia, and from 5 percent to 25 percent of nodular leukoplakias are reported to be dysplastic.[19]

Viadent Hyperkeratosis

Viadent hyperkeratosis is a form of leukoplakia that develops in the oral cavity in association with the use of an oral antigingivitis rinse that contains an extract from the blood root plant, Sanguinaria canadensis L. This form of leukoplakic hyperkeratosis is typically identified in the buccal vestibule. In the authors' experience, women with Viadent hyperkeratosis far outnumber men. The authors have had the opportunity to evaluate 65 cases of this unusual form of leukoplakia, recording it most often in the maxillary buccal vestibule.

Damm and colleagues have documented their experience with 88 cases and report that 33 Viadent hyperkeratoses demonstrated basal layer hyperplasia and maturational atypia histologically consistent with dysplasia. The authors' experience, however, has been that none of the Viadent hyperkeratoses that they have identified clinically and examined histologically have shown any form of preneoplastic or dysplastic differentiation. Some lesions are reversible following biopsy, while others persist or recur.

Additional Papillary Lesions

Papillary oral lesions such as squamous papilloma, condyloma accuminatum, molluscum contagiosum, and verruca vulgaris may be difficult to distinguish from some of the phases of PVL. Generally, the diagnostic problems associated with such distinctions are related to the papillary quality of the lesions. Diagnostic problems may arise when the papillary lesions are evaluated by pathologists in the face of minimal or inadequate tissue for examination or insufficient clinical information, or when the tissue has been processed or embedded improperly. Thus, it is exceedingly important that the clinician provide the pathologist with as much information about the lesion as possible so that specific papillary lesions can be distinguished from certain clinical phases of PVL.

Management

Because of the neoplastic risk associated with it, any case suspected of being PVL must be extensively sampled during the evaluation. Medina and colleagues[21] reviewed 104 cases of verrucous carcinoma and found foci of conventional squamous cell carcinoma in 20 patients. These investigators suggest that such diagnostic errors relate to the problem of insufficient tissue sampling. The same can be said for PVL as it relates to clinical sampling. Lesions suspected of representing PVL should be sampled from several areas if they are multifocal, and several biopsies may have to be taken over time to determine if one is dealing with PVL. The pathologist has a responsibility to contact the clinician for clarification when problems related to clinical sampling arise.

In light of the fact that PVL is a multifocal residual and recurrent disease, many investigators have attempted to develop a standard protocol for management of PVL lesions. Marx has suggested[3] that all PVL cases be screened for Candida albicans infection since most investigators have indicated that Candida is present in close to 75 percent of cases.

He further suggests that multiple tissue samples be taken to prevent sampling errors, recommends a course of long-term follow-up, and favors total excision of PVL. Following excision, the patient is placed on a regimen of beta carotene, 30 mg, q.i.d.; Griseofulvin Microsize, 250 milligrams, t.i.d.; Nystatin Oral Suspension, 100,000 units per cc in a full teaspoon that is swished and expectorated, t.i.d.; or, Diflucan, 100 milligrams, p.o., q.d. Marx reports that this protocol has proven beneficial to his patients with PVL, but that long-term studies need to be completed to determine the protocol's ultimate success. Radiation therapy is contraindicated in the management of PVL, as is laser ablation therapy according to Marx, since radiation may pose a risk for a more rapid neoplastic transformation of the disease, and laser ablation carries with it the risk of masking clinical signs of the disease process as well as limiting proper pathologic scrutiny of the tissue.

Summary

PVL is a dynamic process representing a linear progression of oral hyperkeratosis from a clinically benign manifestation to, in some cases, invasive squamous cell carcinoma. The end stage of the progression of PVL is often manifested by clinical lesions that are verrucous or papillary.

This verrucoid or papillary character may ultimately be classified as verrucous hyperplasia, verrucous carcinoma, or papillary squamous cell carcinoma; but, regardless of terminology, papillary lesions tend to favor the neoplastic end of the PVL spectrum. Clinicians and pathologists must remain vigilant in their examination of the multiple molecular pathways by which this disease can develop, and pathologists must recognize its dynamic histopathology. Management of PVL is often frustrating for clinician, patient, and pathologist; and only as all three parties become more cognizant of the disorder will there be a fuller understanding of the disease.

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Oral Manifestations of Gastrointestinal Disease

Janice P. Handlers, DDS

ABSTRACT A variety of gastrointestinal diseases can be associated with lesions of the oral cavity. The lesions usually correlate to active intestinal disease, but they may present prior to any other evidence of the disease and even be used to initiate diagnosis and treatment. This paper reviews the more common oral manifestations of gastrointestinal disease and their dental management.

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It is not uncommon for a variety of systemic conditions to be associated with lesions of the oral cavity. This is particularly true of gastrointestinal diseases. The lesions usually correlate with active intestinal disease. On occasion, however, they may present prior to any evidence of gastrointestinal disease and initiate diagnosis and treatment of the underlying disease process. These lesions may cause severe discomfort to the patient. In some cases, they even cause extreme destruction to the teeth and periodontium, which results in premature loss of teeth. It is, therefore, important that the oral manifestations be recognized and managed appropriately.

This paper will review the more common oral manifestations of gastrointestinal diseases (**Table 1**) and the appropriate dental management.

Nutritional Deficiencies

Anorexia Nervosa and Bulimia

Anorexia nervosa and bulimia are psychological disorders that are generally seen in young to middle-aged females. These patients perceive themselves as fat and become obsessed with losing weight. Patients with anorexia nervosa often appear emaciated. They may stop eating or gorge themselves secretly and subsequently induce vomiting. Patients with bulimia tend to appear of normal weight and eat normally but engage in chronic self-induced vomiting. Both groups show oral signs of chronic regurgitation. There are varying degrees of chemical erosion of enamel and dentin, which is particularly noticeable on the palatal and occlusal surfaces of the maxillary teeth (**Figure 1**). The lower teeth are less severely affected, probably

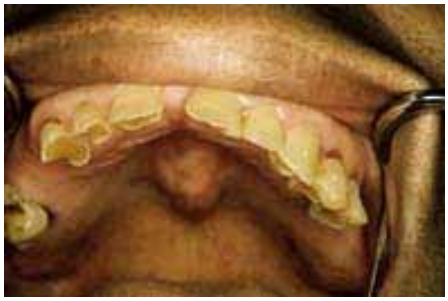

Figure 1. Bulimia — severe palatal and occlusal erosion of the maxillary teeth causing the incisal edges of the incisors to be thin and knife-edged. The occlusal surfaces have a flat to cupped-out appearance

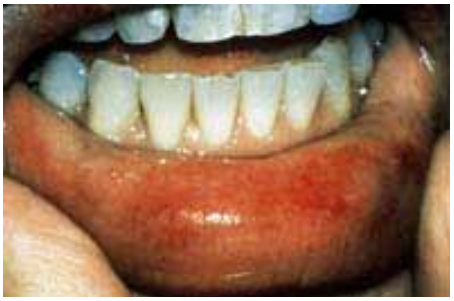

Figure 2. Pernicious anemia — patchy area of mucosal erythema (courtesy of Dr. Sadru Kabani).

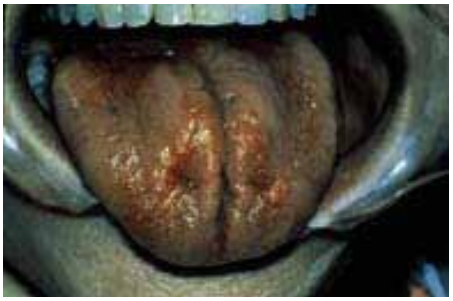

Figure 3. Pernicious anemia — Areas of papillary atrophy, erythema, and ulceration on the dorsal tongue (courtesy of Dr. Sadru Kabani).

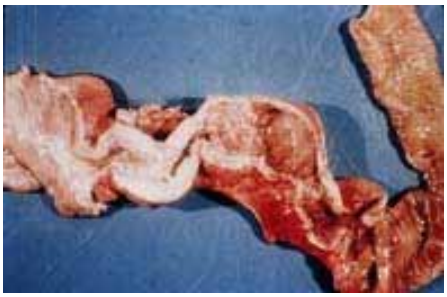

Figure 4. Crohn's disease — portion of small intestine showing multifocal areas of thickening of the wall and narrowing of the lumen.

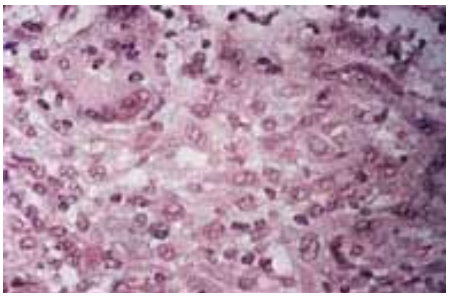

Figure 5. Crohn's disease — giant cells and epithelioid macrophages in granulomatous inflammation.

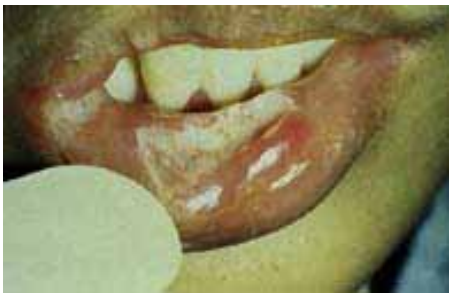

Figure 6. Crohn's disease — deep crateriform ulcer with rolled border and necrotic center as well as angular cheilitis.

due to the protection of the tongue during vomiting. These patients also show increased susceptibility to caries and gingivitis, although plaque accumulation is not a prominent feature. Restorations often fail as the erosion progresses and the teeth become sensitive to hot and cold. Xerostomia, which is sometimes painful, is also common. These patients often deny the problem, but anorexia nervosa or bulimia should be considered when these characteristic oral changes are present. Patients should be advised to immediately rinse the mouth with water, a fluoridated mouthrinse, or antacids after vomiting. They should not brush the teeth immediately after vomiting as this may increase the erosive process. Daily self-application of fluoride in custom trays is also helpful. In addition, these patients may be subject to nutritional deficiencies and may manifest oral lesions associated with those deficiencies.

Iron-Deficiency Anemia

Iron-deficiency is the most common cause of anemia, and it typically affects young women of childbearing age. The iron deficiency is caused by chronic iron loss associated with excessive blood loss during menstruation. However, 2 percent of adult men are iron-deficient because of chronic blood loss associated with gastrointestinal disease. Peptic ulcer disease, diverticulosis, hiatal hernia, and colon cancer are the most likely underlying problems.

Oral manifestations include angular cheilitis, glossitis, and generalized mucosal atrophy, which may lead to ulceration. The dorsal surface of the tongue shows patchy or diffuse atrophy of the filiform papillae, and about 30 percent of patients will complain of soreness of the tongue or mouth.[1] The gingiva, soft palate, and tongue may be pale. Oral candidiasis is sometimes present.

Diagnosis is made by appropriate laboratory testing. Iron-deficiency anemia is characterized by microcytic, hypochromic red blood cells, decreased hemoglobin, decreased serum iron, and increased total iron-binding capacity. It is important that the cause of the deficiency be identified, especially in adult men and postmenopausal women. Treatment consists of dietary iron supplementation and antifungal agents when appropriate.

A severe form of iron-deficiency anemia associated with glossitis and dysphagia is known as Plummer-Vinson syndrome. On examination of the esophagus, postcricoid webs are present. The fingernails also have a spoon-shaped morphology (koilonychia). Oral changes include those described above, although they may be more severe. Patients often are unable to tolerate dentures.

This condition has special significance in that it has been associated with a

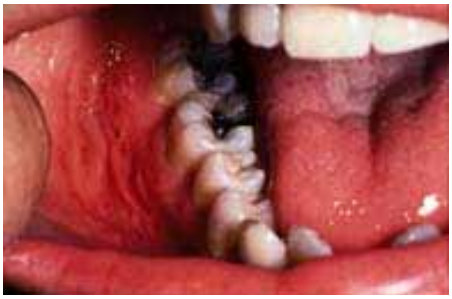

Figure 7. Crohn's disease — mucosal hyperplasia and fissuring with linear ulceration (courtesy of Dr. Mark Kernstein).

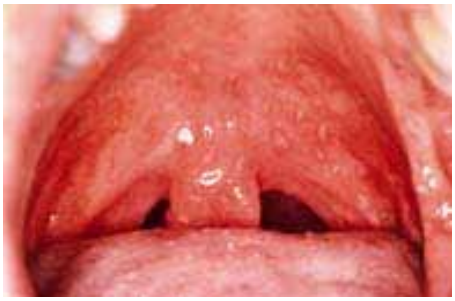

Figure 8. Crohn's disease — mucosal edema, aphthaform ulcers and military granulomas (Courtesy of Dr. Mark Bernstein).

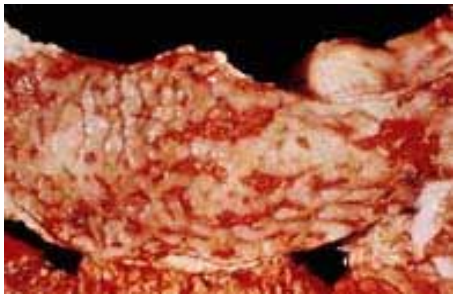

Figure 9A. Ulcerative colitis — a segment of colon showing superficial, hemorrhagic mucosal and submucosal ulceration.

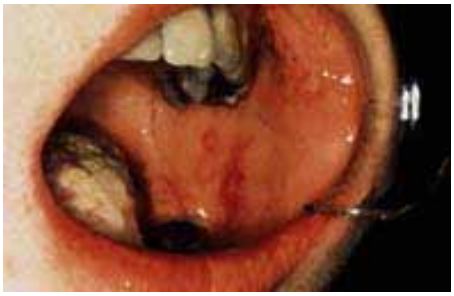

Figure 9B. Ulcerative colitis — similar appearing ulcers of the buccal mucosa (courtesy of University of Oklahoma School of Dentistry).

high frequency of oral squamous cell carcinoma. Therefore, in addition to correcting the underlying iron deficiency, clinicians should thoroughly evaluate these patients on a periodic basis for oral, pharyngeal, and esophageal cancer. Any suspicious lesions should be biopsied.

Pernicious Anemia

Pernicious anemia most often affects elderly patients of northern European descent and is caused by lack of intrinsic factor, which is produced by the parietal cells of the stomach. These cells also produce gastric hydrochloric acid. Parietal cells are probably destroyed by an autoimmune mechanism. Because intrinsic factor is necessary for the absorption of vitamin B-12 in the distal portion of the ileum, patients with pernicious anemia suffer from a vitamin B-12 deficiency even though their diet may be adequate. A similar condition has been reported following gastrointestinal bypass operations for weight control.[2]

Oral manifestations include generalized atrophy of the oral mucosa leading to ulceration and focal patchy areas of oral mucosal erythema (**Figure 2**). Many patients complain of a burning sensation of the tongue, lips, and buccal mucosae. Aphthous ulcers have also been reported. Fifty to 60 percent of patients have tongue changes including erythema and atrophy[3] (**Figure 3**). The tongue may also appear flabby because of loss of muscle tone.

Laboratory testing will reveal a macrocytic anemia and decreased levels of serum cobalamin (vitamin B-12). Treatment consists of monthly intramuscular injections of cyanocobalamin. The oral lesions respond rapidly, sometimes within five days. If not treated, pernicious anemia can lead to irreversible central nervous system damage because vitamin B-12 is necessary for myelin synthesis. Without vitamin B-12, demyelinization of the spinal cord will slowly occur over a period of years. The patients may experience ataxia, decreased vibratory sensation, and dysfunction of the urinary bladder.

Scurvy

Caused by a lack of vitamin C, scurvy is an uncommon disease in the United States. It is typically seen in young children whose diets often consist entirely of milk and in elderly edentulous men whose diet lacks fresh fruits and vegetables. Because of inadequate collagen synthesis, the vascular walls are quite weak and subject to injury. The oral manifestations include generalized gingival swelling with spontaneous hemorrhage. There may be rapid loss of supporting alveolar bone with loosening and loss of teeth. There is impaired wound-healing and an increased susceptibility to secondary infection.

Although this condition may appear clinically to represent a platelet problem, the platelet count and bleeding time values will be normal. The underlying vitamin C deficiency must be treated, or scurvy can lead to death.

Inflammatory Bowel Diseases

Crohn's Disease

Crohn's disease is an inflammatory condition of unknown etiology that primarily affects the distal portion of the small intestine, rectum, and proximal colon. It may, however, affect the entire gastrointestinal tract, including the oral cavity. The affected areas of the intestine show fissuring, fistulae, and thickening (**Figure 4**), which often results in narrowing of the intestinal lumen. There are often several noncontiguous areas involved. Histologically, the intestinal

lesions often show granulomatous inflammation (**Figure 5**). Extraintestinal symptoms may involve joints, skin, and eyes and are more common in patients with colonic involvement. Clinically, the gastrointestinal signs and symptoms include abdominal cramping, pain, nausea, and diarrhea.

The oral lesions are well-documented and typically involve the lips, gingiva, vestibules, and buccal mucosa. Less frequently, the tongue, palate, and pharynx may be involved. The lips often show edema, deep ulceration, and angular cheilitis (**Figure 6**). The gingiva often appears edematous and erythematous. A pattern of hyperplasia and fissuring (cobblestone appearance) may be seen. Deep linear ulcers are associated with the hyperplasia in the vestibular, buccal, and labial mucosa (**Figure 7**). Polypoid or papillary lesions are common in the vestibules, on the buccal mucosa, and on retromolar pad areas. Swelling and edema of the buccal mucosa and lips may lead to facial asymmetry. Occasionally, aphthaform ulceration has been reported (**Figure 8**). Additional lesions associated with Crohn's disease include metallic dysgeusia, erythema migrans, Melkersson-Rosenthal syndrome, and involvement of mandibular lymph nodes and salivary glands.

Oral lesions generally occur in the first three decades of life with 39 percent occurring to people younger than 16. In more than half the patients, the oral lesions recur. Histologically, the oral lesions have been reported to show noncaseating granulomas in 10 percent to 68 percent of cases.4,5 Some studies have shown that oral manifestations may precede intestinal symptoms in 37 percent to 60 percent of patients.[5,6] This is of significance to the dental practitioner as patients may present first to the dental office because of the oral lesions.

It has also been recommended that in any patient with orofacial granulomatosis or in patients with chronic or relapsing but undiagnosed oral lesions, a complete gastrointestinal evaluation by esophagogastroduodenoscopy, ileocolonoscopy, and small bowel radiography be performed, even in the absence of gastrointestinal symptoms. It is further recommended that if the results are negative, the potential diagnosis of Crohn's disease should not be ruled out, and evaluation should be repeated at a later date.[5]

Treatment of Crohn's disease generally includes systemic drug treatment with sulfasalazine or steroids and/or azathioprine as well as diet restriction. In severe cases, the complications of Crohn's disease such as fistulae and abscesses may necessitate surgical intervention. If a substantial portion of the distal ileum is removed or is severely involved by the disease, the patient may develop a vitamin B-12 deficiency anemia or vitamin

TABLE 1.
Summary of Oral Manifestations of Gastrointestinal Disease

Angular cheilitis
Iron-deficiency anemia
Plummer-Vinson syndrome

Hemorrhage
Pyostomatitis vegetans
Scurvy
Ulcerative colitis

Aphthous ulcers
Crohn's disease
Pernicious anemia
Ulcerative colitis

Intraoral burning
Iron-deficiency anemia
Pernicious anemia
Plummer-Vinson syndrome

Candidiasis
Crohn's disease (steriod therapy)
Iron-deficiency anemia
Pyostomatitis vegetans (steriod therapy)
Ulcerative colitis (steroid Therapy

Labial swelling
Crohn's disease
Osteomas of the jaws and facial bones
Gardner's syndrome

Erosion of enamel and dentin
Anorexia nervosa/bulimia

Odontomas, supernumerary teeth, impacted teeth
Gardner's syndrome
Gingivitis
Anorexia nervosa/bullimia
Crohn's disease
Scurvy

Pigmentation
Peutz-Jeghers syndrome
Glossitis
Crohn's disease
Iron-deficiency anemia
Pernicious anemia
Plummer-Vinson syndrome
Ulcerative colitis

Ulcerations and erosions
Crohn's disease
Iron-deficiency anemia
Pernicious anemia
Pyostomatitis vegetans
Ulcerative colitis

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K deficiency. Supplemental intramuscular injections of cyanocobalamin may be necessary. The possibility of vitamin K deficiency-associated coagulopathies should be considered and prothrombin time should be evaluated before invasive dental procedures are performed. These patients might also develop an iron-deficiency anemia because of malabsorption, limited diet, or the inhibitory effect of sulfasalazine on absorption of ingested folate. In these patients, oral manifestations of the nutritional deficiencies might also be present (see above descriptions).

Treatment of the oral lesions often consists of systemic and/or topical steroids in the forms of rinses, pastes, and ointments. The results have been variable in patients with orofacial granulomatosis. Approximately one-half of patients respond favorably with complete remission.[5] The other half do not fare well and suffer multiple exacerbations. Plauth and colleagues recommend the use of systemic steroids and/or azathioprine if topical therapy fails to control symptoms.[5] It should be kept in mind that the use of steroids may predispose the patient to the development of secondary infection with Candida. Treatment with antifungal agents may be necessary. In some cases, it may be necessary to alternate the use of different antifungal agents to avoid the development of resistant strains.[1]

Ulcerative Colitis

Ulcerative colitis is an inflammatory condition of the bowel that primarily involves the colon and rectum. The gastrointestinal lesions consist of contiguous broad areas of hemorrhagic ulceration and small abscesses. Lesions are superficial and limited to the mucosa and submucosa. They do not extend into the muscularis. Clinical manifestations include bloody diarrhea; weight loss; generalized fatigue; and, often, fever.

Oral lesions of ulcerative colitis include recurrent major or minor aphthous ulcers, ulcers similar to pyoderma gangrenosum of the skin, and hemorrhagic ulcers of the oral mucosa. Aphthous ulcers are common, affecting 4 percent to 20 percent of patients.[4] Their onset is usually sudden and, in many cases, coincides with exacerbations of the gastrointestinal symptoms.[1] The lesions of pyoderma gangrenosum are characterized by progressive necrosis with deep ulceration. These have been noted on the tongue in some patients.

The hemorrhagic ulcers seen in the mouth are quite similar to the lesions in the colon (Figures 9a and 9b). They are irregular in shape, superficial, and of varying size. Similar lesions are also seen on the skin of the cheeks, inner aspects of the thigh, buttocks, and lower abdomen. The lesions may start as a hemorrhagic blister and over one to three days burst and progress to ulceration.

Treatment of ulcerative colitis involves the use of sulfasalazine and /or systemic steroids. In severe cases, surgical resection may be necessary. Patients with ulcerative colitis also seem to have an increased risk of the development of colon cancer. Periodic thorough evaluation is essential for early detection. In addition, approximately 7 percent of patients have some liver abnormality ranging from abnormal laboratory values to sclerosing cholangitis and postnecrotic cirrhosis.[7] Therefore, regular monitoring of liver function is also recommended.

Oral complications of the medical management of ulcerative colitis are similar to those seen in Crohn's disease and include possible nutritional deficiencies and anemia, particularly iron-deficiency anemia. Iron deficiency may be due to chronic blood loss from the gastrointestinal lesions as well as malabsorption, limited diet, and the inhibitory effect of sulfasalazine on absorption of ingested folate. Secondary candidal infections are also common.

Successful treatment of the oral lesions has been variable and unpredictable. Topical and/or systemic steroids have been employed.

Pyostomatitis vegetans

Pyostomatitis vegetans is an unusual, but well-documented oral lesion that has been primarily associated with ulcerative colitis, but has been reported in a small number of cases of Crohn's disease.[8,9] It is considered a highly specific oral mucosal marker for inflammatory bowel disease.[10] Generally a disease of adults, it may also occur in children.

Pyostomatitis vegetans is characterized by the development of numerous 2-3 mm yellowish pustules as well as small vegetating or proliferating lesions on an erythematous mucosa that may undergo degeneration, ulceration, and suppuration (**Figure 10**). Necrotic lesions can be wiped off, leaving a hemorrhagic surface. The lesions often have a snail-track pattern.

Most areas of the mouth may be involved, including buccal mucosa, gingiva, hard and soft palate, and vestibule. The dorsal tongue, however, is rarely affected.[10] Symptoms are not usually severe. In most cases, the bowel disease precedes the onset of oral lesions and the severity of the disease tends to parallel the activity of the bowel disease.11 In some cases however, the gastrointestinal symptoms may be so mild as to remain undetected unless thorough inspection of the gastrointestinal tract is performed.[9,11]

The histopathologic features

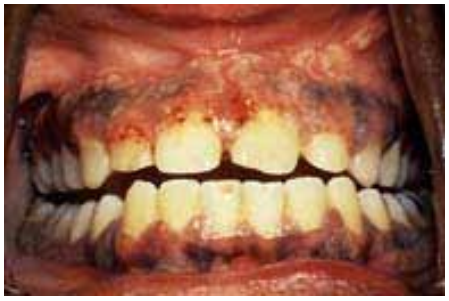

Figure 10. Pyostomatitis vegetans — yellowish, slightly elevated, linear pustules on the gingiva that have the so-called "snail-track" appearance (courtesty of Dr. Mark Bernstein).

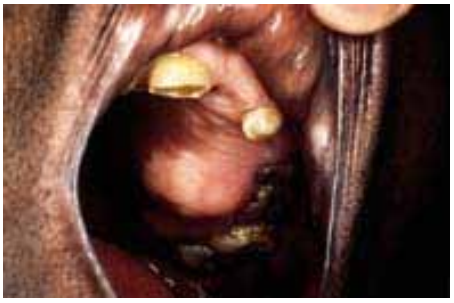

Figure 11. Gardner's syndrome — osteoma of the maxilla (courtesy of Dr. Mark Bernstein).

Figure 12. Gardner's syndrome — polyposis of the colon with multiple areas of adenocarcinoma (arrows).

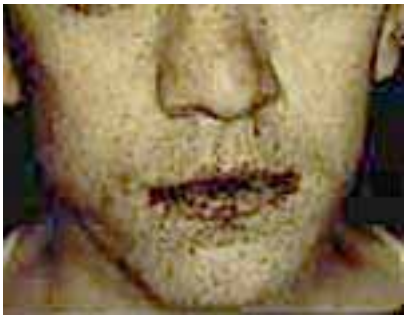

Figure 13. Peutz-Jeghers syndrome — cutaneous small, flat brown to gray pigmented lesions on the face with concentration in the perioral area.

of pyostomatitis vegetans are fairly consistent. The lesions show hyperkeratosis; acanthosis, which often results in a deep folding of the epithelium; and acantholysis. A dense cellular infiltrate of eosinophils and neutrophils is present throughout the epithelium and lamina propria. Small eosinophilic abscesses may be seen in the basilar portion of the epithelium and superficial lamina propria. A mixed infiltrate of polymorphonuclear neutrophil leukocytes, plasma cells, and lymphocytes is present in the connective tissue, often in a perivascular orientation. Direct and indirect immunofluorescence are usually negative.[12] Serum eosinophilia may also be present.

Recently, there have been reports of pyostomatitis vegetans presenting with primary sclerosing cholangitis and liver disease prior to any other manifestations of inflammatory bowel disease.[11,13] These cases may reflect a lack of long-term follow-up since the association of liver disease and inflammatory bowel disease is well-known, as is the association of pyostomatitis vegetans and inflammatory bowel disease. In either case, liver function monitoring should be pursued in every patient diagnosed with pyostomatitis vegetans.

Treatment of pyostomatitis vegetans has had variable success. Topical therapy has included the use of corticosteroid rinses, pastes, and ointments; tincture of iodine; and hydrogen peroxide. Systemic therapy has included corticosteroids, sulfasalazine, dapsone, and azathioprine. Interestingly, the oral lesions do not always regress when the colitis is controlled.[12]

Polyposis Syndromes

Gardner's Syndrome

Gardner's syndrome is inherited as an autosomal dominant trait. It is characterized by multiple adenomatous polyps of the colon and rectum, multiple osteomas, cutaneous epidermoid cysts, and fibromas. The osteomas most commonly occur within the jaws (**Figure 11**), particularly at the angle of the mandible, frontal bones, and within the frontal and ethmoid sinuses. They may cause facial deformities that necessitate removal. Supernumerary teeth, multiple odontomas, and impacted teeth have also been reported.

In most cases, the patient will have knowledge of the underlying condition; but, in some cases, the detection of the oral lesions initiates diagnosis. This is important because these patients have a high risk of colorectal carcinoma (**Figure 12**). Fifty percent of patients with Gardner's syndrome will develop colorectal carcinoma by age 30, and the risk approaches 100 percent in older patients.[14]

Diagnosis of an oral osteoma, particularly in the presence of a history of "skin tumors" or other oral findings, should elicit a suspicion of Gardner's syndrome and precipitate a thorough evaluation of the gastrointestinal tract for polyps. Genetic counseling would also be appropriate.

Peutz-Jeghers Syndrome

This is an autosomal-dominant condition, although a number of cases will have no family history. It

generally manifests in childhood and is characterized by benign polyps involving the entire intestinal tract in association with pigmented cutaneous and mucosal lesions. The pigmented lesions measure 1-5 mm and are often brown, although they may also be black or blue-gray. They are generally found in a perioral location (**Figure 13**) and on the dorsal surfaces of the fingers and toes. Intraorally, the lips, buccal mucosa, gingiva, and hard palate are most often involved. Skin lesions may fade with age but the oral lesions tend to become more prominent.[1]

The prognosis for this condition is much better than for Gardner's syndrome in that the intestinal polyps are not premalignant. They may, however, lead to intussusception, which can result in infarction and peritonitis.

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Prevention and Detection of Lip Cancer — The Dentist's Role

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ABSTRACT With their attention to the oral area, dentists are in an excellent position not only to diagnose lip cancer, but also to counsel patients in its prevention. Patients need to be educated on the dangers of ultraviolet radiation and the measures available to decrease exposure to it. This article discusses the circumstances that increase the chance of developing lip cancer, the variety of ways to decrease that chance, and the recognition and treatment of premalignant and malignant lip lesions.

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Evaluation of the lips should be a part of every oral examination. The purpose of this article is to discuss recommendations for the prevention of lip cancer, the clinical recognition and diagnosis of suspicious changes of the lip, and follow-up care for patients with a history of premalignant or malignant lip lesions.

Lip cancer

The link between lip cancer and sunlight was first noted in 1923[1]; and exposure to sunlight, particularly in fair-skinned individuals, is widely accepted as the principal cause of lip cancer.[2] An overwhelming percentage of premalignant and malignant changes of the lips affect the lower lip because of its greater exposure to sunlight. An estimated 3,500 cases of lip cancer are diagnosed every year in the United States.[2] Lip cancers are generally painless, which explains the average time of patient delay of from five months to two years before seeking professional help.[3,4] One study noted that almost half of the patients with lip cancer had lesions greater than 1.5 cm in diameter at the time of their diagnosis.[3] The time needed for solar-induced changes of the lip to evolve into cancer is generally 20 to 30 years, but it can occur in less time.[5] The profile of a patient at high risk for lip cancer is a tobacco-using Caucasian male older than 40 with a fair complexion and a history of chronic exposure to the sun.[6]

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The Lip

The lip is clinically divided into "wet" and "dry" components. The wet lip, which extends from the oral mucosa to the contact line between the upper and lower lip, is rarely the site of malignant change. The dry lip or exposed portion, which is unique to humans, is the transition between the wet lip and the skin.[1,2] The dry lip contains some sebaceous glands but usually does not have hair follicles or sweat glands.[1] The dry lip appears reddish because the blood vessels are in a superficial location and the overlying epithelium is thin. The term "vermilion," which is often used for the dry part of the lip, simply means a reddish appearance.[7]

The epidermis of the skin provides some natural protection against the damaging effects of the sun. About 5 percent to 10 percent of ultraviolet (UV) radiation is reflected from the skin, and as much as 70 percent is absorbed.6 The thicker the epidermis and the higher the melanin content, the better the skin's ability to absorb UV radiation without damaging epithelial cells. The lip has less protection than the skin because the lip epithelium is thinner, has a thinner keratin covering, has less melanin, and has fewer secretions from sebaceous and sweat glands.[8]

The early clinical changes of a sun-damaged lip, usually referred to as actinic cheilitis, are subtle and not directly related to the histologic degree of either epithelial or connective tissue change. Generally, the sun-damaged lip has a white lesion of variable thickness with interspersed red foci, and it may be either well- or ill-defined (**Figure 1**). Although the lesions are usually unilateral, it is also common to see lesions that cross the lip almost from commissure to commissure. Actinic cheilitis is usually asymptomatic and will often have been present for months or years. Palpation is an important clinical test because actinic cheilitis feels like fine sandpaper as one slides a gloved finger across the lesion. Induration and a noticeable thickening are rarely present in the early stages of the lesion. Almost all cases of a sun-damaged lip will be noted on the lower lip; the upper lip is rarely involved. Histologically, the sun damage on the lip can be a reactive change called hyperkeratosis, premalignant changes ranging from mild epithelial dysplasia to carcinoma in situ, or even invasive carcinoma (**Figures 2 and 3**).

The decision as to whether a biopsy is necessary is difficult to make for an asymptomatic, subtle lesion of the lip because it is not possible to determine the degree of cellular damage based solely on clinical appearance.[5] To ask a patient to return in six months for re-evaluation carries the risk that the lesion may increase in histologic severity or even metastasize during that time. An incisional biopsy has the advantage of providing a definitive diagnosis and minimizing the amount of tissue removed. The biopsy can easily be done with a punch; and if the diameter is small enough, sutures may not even be necessary. Usually the lip heals quickly after a punch biopsy, and rarely do the patients need anything stronger than over-the-counter analgesics for a day or two afterward. The patient should be informed that it takes about a week to get the results of the biopsy and that after obtaining the histopathologic diagnosis, the appropriate follow-up care can be determined. If the diagnosis is hyperkeratosis, the patient should be monitored and additional incisional biopsies considered if the clinical appearance of the lesion changes or the patient becomes symptomatic. It is the authors' recommendation that if the diagnosis is either epithelial dysplasia (premalignant) or carcinoma that the lesion be removed entirely unless there are mitigating circumstances. The drawback to an incisional biopsy is that only a small area of the lesion is sampled, and other affected areas may have a greater degree of cellular damage. It is reasonable to assume that because the entire lip has been exposed to the same amount of sunlight, areas that appear clinically normal may also have histologic abnormalities. In spite of the disadvantages of an incisional biopsy, the authors' recommend one to rule out the possibility of malignant change and to reassure the patient.[9] Unfortunately, exfoliative cytology and toluidine blue staining are generally not useful in assessing these lip lesions because of the keratinization that is present.[4]

Table 1.

Radiation from Sunlight

Type	Wavelength	Effect
Infrared	760-1,800 um	Heat
Visible light	400-760 um	
Ultraviolet A	320-400 um	Aging of skin, probably some role in skin cancer
Ultraviolet B	290-320 um	Causes sunburns, significant factor for skin cancer
Ultraviolet C	200-290 um	Blocked by earth's atmosphere

Ultraviolet Radiation

Sunlight consists of radiation that varies in wavelength from 200 to 1,800 m (**Table 1**). The infrared spectrum is from 760 to 1,800 um and is responsible for the heat associated with sunlight. Visible light is from 400 to 760 um and UV rays are from 200 to 400 um.

UVA radiation makes up 90 percent of the UV radiation that reaches the earth's surface and is associated with connective tissue changes that accelerate aging of the skin. Initially, UVA radiation was thought to be harmless, but it now has been implicated in cellular DNA changes and probably participates with UVB radiation in the development of cancer. One widespread use of UVA radiation is in tanning salons. The radiation emitted by a tanning bed consists of 98 to 99.5 percent UVA rays, but chronic exposure carries with it an increased risk of developing either cutaneous basal cell carcinoma or melanoma.

UVB radiation causes sunburns and is the form of UV radiation responsible for lip and skin cancer. The atmosphere filters only some UVB rays, and the time of greatest UVB radiation exposure is from 11 a.m. to 2 p.m.[6] Clouds do little to block UVB rays,[6] and even being in the shade does not provide complete protection because the rays are scattered by the ground and water. For example, dry sand reflects 17 percent of UVB rays at 300 m and fresh snow reflects as much as 85 percent.[6]

UVC radiation has the shortest wavelength and the greatest potential to cause skin damage, but its rays are blocked by the ozone layer and the earth's atmosphere.

Sunscreen Products

There are two types of sunscreens: chemical and physical. Chemical sunscreens act by absorbing UV radiation, especially in the UVB range. Some chemical sunscreens contain either para-aminobenzoic acid (PABA) or one of its esters such as Padimate O.[10] Many sunscreens are now being sold that utilize other chemicals and advertise themselves as being PABA-free. Oxybenzone is a popular UVA sunscreen, but it blocks only 50 percent of the UVA rays.[11] Eusolex 8020 and Parsol 1789 are also used for UVA protection, but contact sensitivity is an occasional side effect.[11] Physical sunscreens reflect rather than absorb UV radiation, which provides maximum protection.[12] Zinc oxide and titanium dioxide are examples of physical sunscreens. The physical sunscreens have not been as popular as chemical ones because of their opaque white appearance. A good sunscreen should contain a combination of ingredients that will protect against both UVA and UVB radiation and have a sun protection factor of at least 15.

Some sunscreens are specifically designed for use on the lips because there is a need for the vehicle to be physically retained after exposure to fluids, to be cosmetically acceptable, and to not taste bad. Coppertone, Banana Boat, Hawaiian Tropic, ChapStick, and Panama Jack offer fruit-flavored lip balms that contain a waxy or petroleum-based ointment that aids in retaining moisture. Gel-based lip sunscreens provide the longest retention: More than 90 percent of the protection is still present three hours after application.6 Because of the large variety of lip sunscreens available, dentists should encourage patients to try more than one brand to find the one they would be most likely to use consistently. Cost, availability, cosmetic appearance, and taste will influence the patient's decision. Because of these personal variables, the authors do not recommend one specific lip sunscreen but instead encourage patients to find one with a minimum SPF of 15 that they like. Lip sunscreens should be applied at least 15 minutes before exposure to the sun and reapplied at hourly intervals while in the sun and right after swimming.[6,13] Lip sunscreens need to be applied more frequently than the ones for the skin because of removal by licking the lips and the need for greater protection for the lips.

Sun Protection Factor

The sun protection factor (SPF) is determined by taking the time needed to reach a minimum erythema dose (MED) in sunscreen-protected skin and dividing it by the time required to reach MED in unprotected skin.[6] These tests are usually done by exposing the skin on the backs of 10 to 20 subjects with laboratory light sources and then averaging the results.10,11 A sunscreen is given an SPF of 15 if it takes 15 times longer for the skin to turn red in the protected area than in unprotected areas. The SPFs determined with natural sunlight are generally lower than those done with artificial laboratory light.[10] A minimum SPF of 15 is recommended for most people. There is not a proportional increase in protection with greater SPFs. For example, an increase in SPF from 15 to 34 only increases the protection by 4 percent.10 The long-term benefit of using a sunscreen with an SPF of at least 15 is that there is a 78 percent lifetime reduction in the incidence of cutaneous basal cell and squamous cell carcinomas if there is regular application during the first 18 years of life.11 Although SPF is a popular way to compare sunscreens, it has been shown that suberythemal doses cause skin damage without any apparent reddening of the skin.[11]

The effective SPF of a sunscreen is reduced by incorrect application. Correct application of sunscreens in adults who have been diagnosed with skin cancer is remarkably low, with only 34 percent of these patients using sunscreens effectively.14 The true SPF of a sunscreen can be as little as 50 percent of the stated SPF if it is incorrectly applied.[11]

Lip sunscreens and balms usually have an SPF of at least 15 and even a few lipsticks have an SPF of that high.

Adverse Reactions to Sunscreens

Contact dermatitis can occur with

Figure 1. This fairly well-defined white lesion of the right lower lip was noted in this Caucasian male. The lesion was of variable thickness and demonstrates a number of fissures. This large lesion illustrates the difficulty in deciding which area should be biopsied to get a representative sample. The left side of the lower lip also shows subtle changes consistent with chronic sun exposure.

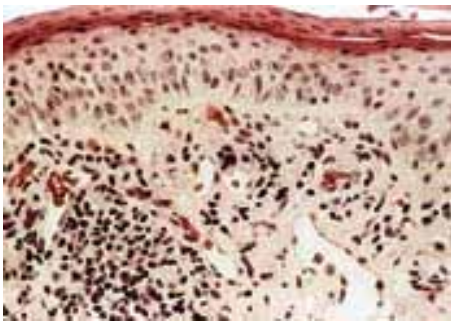

Figure 2. The epidermis in this photomicrograph is covered by a thin layer of parakeratin, which would correspond to a subtle white color found in many of these lesions. The abnormal maturation pattern and variation in cellular size indicate mild epithelial dysplasia within the epidermis. The underlying fibrous connective tissue contains enlarged vascular spaces and chronic inflammatory cells, which would cause erythematous foci to become clinically apparent. (Hematoxylin and eosin stain, 100x)

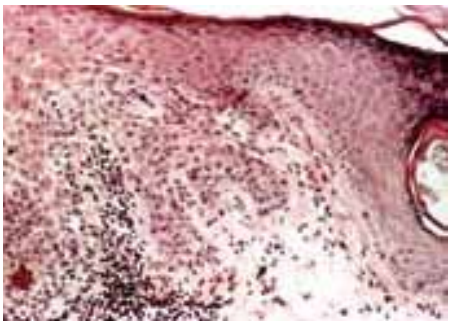

Figure 3. The right side of the photomicrograph shows normal epidermins with an abrupt change to epithelial dysplasia on the left side. It is typical to have a sharp transition from normal to affected epidermins in sun-damaged lips and to have several affected foci with interspersed areas of normal epidermis. (Hematoxylin and eosin stain, 100x)

chemical sunscreens and is usually due to one of the preservatives or fragrances used in the formulation rather than the active ingredient.[10] Clinically, it is difficult to distinguish redness of the skin caused by sun exposure from contact dermatitis, and allergic reactions are probably underdiagnosed for that reason. One other drawback to the use of sunscreens is that patients may spend more time in the sun because they feel protected. Some authors have discussed the possibility that sunscreen use might increase the risk for melanoma because carcinogenic compounds are produced when sunscreens are exposed to sunlight.[11] At present, an increased risk for melanoma because of sunscreen use is unproven, and a recommendation for the routine usage of sunscreens is prudent until evidence to the contrary becomes available.

Patient Education

It may be that skin cancer is perceived by many as being a minor nuisance because most basal cell and squamous cell carcinomas are effectively treated as an office procedure and have little impact on the patient's life. However, an estimated 41,600 new cases of melanoma will be diagnosed in 1998; and while the prognosis for melanoma has considerably improved, there are still unfortunate cases that cannot be successfully treated.[15] For prevention to be maximally effective, it must be directed toward preadolescents and adolescents, which is a group that may not readily accept the importance of a problem that may not appear for at least several decades.[14] Because a tan is associated with good looks and general health, it is difficult to persuade some patients to reduce their time in the sun and to use sunscreens. As health professionals, dentists should encourage their patients to use sunscreens to protect their lips as well as their skin. The physical sunscreens, zinc oxide and titanium dioxide, are the most effective because they reflect UV radiation. These should be recommended to patients with unavoidable chronic exposure to the sun, such as fishermen, farmers, and sailors.[12] If there is a cosmetic objection to the "whiteness" of zinc oxide, then one of the many lip balms should be recommended. The use on the lips of sunscreen intended for the skin is not as effective as true lip sunscreens because of the diminished physical retention.

One study showed that only 62 percent of patients with nonmelanoma skin cancer started using sunscreen after their diagnosis.[14] For patients with a history of a sun-damaged lesion of the lip, there must be an increased emphasis on prevention and education because of the possibility of developing another lesion. If sun exposure is unavoidable, a physical sunscreen should be recommended for daily use on the parts of the body that cannot be covered. If sun exposure is sporadic, then one of the chemical sunscreens that protects against both UVA and UVB radiation is acceptable. Patient education should stress the need for more frequent application of lip sunscreens as compared to the ones for the skin and the need to apply them even on cloudy days. Although people tend to think of sunscreen use only in the summer, patients must also understand the need for protection during the remainder of the year.

Conclusions

A dentist should examine the lips of every patient at every visit and periodically emphasize the use of sunscreens for both the skin and lips. The clinical signs of sun damage to the lip may be subtle, but a biopsy should be considered so that a diagnosis and appropriate follow-up care can be determined. Patients with a biopsy-proven premalignant or malignant change

of the lip must be educated about the need for eliminating sun exposure to the lips. They should be clinically monitored for any other changes of the lips and counseled on the possible need for future diagnostic biopsies. Consistent use of lip sunscreens beginning at an early age and early diagnosis of sun-damaged areas of the lips may help in reducing the number of lip cancers diagnosed each year in the United States.

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When the President Vanished

JOHN B. MOSES, MD, AND WILBUR CROSS

EDITOR'S NOTE: Following is a fascinating story involving oral cancer, presidential politics, and subterfuge. Few people know that President Grover Cleveland was diagnosed with oral cancer and was operated on to remove it while he was in office. The president, his advisers and his doctors when to great lengths to conceal his ailment and subsequent surgery. This version of the story first appeared as a chapter in the book "Presidential Courage" by John B. Moses, MD, and Wilbur Cross. We thought it would make an interesting adjunct to our issue on oral pathology. Our thanks to Dr. Aaron B. Koran, retired oral surgeon and anesthesiologist, for bringing the story to our attention.

A little before seven on the hot, humid morning of Saturday, May 27, 1893, President Grover Cleveland shuffled drowsily into his White House bathroom and began brushing his teeth. That commonplace act touched off a series of events that are recounted in very few history books or biographies -- events that were ingeniously camouflaged to prevent a public panic that would have jolted the entire American economy.

Running his tongue across the roof of his mouth, the 56-year-old president felt a rough spot that disturbed him. Later in the morning, after dressing and eating breakfast, he asked one of his aides to summon Dr. Robert M. O'Reilly, a physician assigned to the care of government officials. There was no White House doctor during that era. Nor was there any practitioner in the Washington region who was familiar with Mr. Cleveland and his medical history, which included, among other infirmities, hypertension, obesity, and susceptibility to frequent biliousness.

Not liking what he saw when he examined his heavy-jowled, bull-necked patient, Dr. O'Reilly, a major in the Army Medical Corps, asked the White House dentist to look at the president's gums and teeth. When O'Reilly was solemnly informed that this was no mere dental problem, he immediately contacted Dr. Joseph D. Bryant, a friend of the president and a prominent New York City surgeon whose specialty was the head and neck. Dr. Bryant lost no time in visiting the White House and within the next 10 days

he had examined the lesion several times, had taken small samples of tissue for biopsy review, and had proposed his plans for an operation.

The fears of the president's medical attendants were confirmed by Dr. William H. Welch, a noted pathologist at Johns Hopkins Medical School. After examining the tissues under the most powerful microscope available, he declared positively that the president had a cancer of the mouth and that it appeared to have spread to at least one side of his jaw. To be certain of this diagnosis, O'Reilly and Bryant sent the slides containing the specimens to the Army Medical Museum for examination by its staff of pathologists. The patient was not identified, but O'Reilly made it clear to his military colleagues that the matter was urgent, as well as confidential. The army specialists confirmed the findings of Dr. Welch.

From the start, all outsiders who examined slides or otherwise worked on the case were told to use the utmost diligence and skill, that the specimens were "the most important ever submitted for examination," and that the name of the patient could not be divulged for reasons of national security. All efforts -- sometimes devious or misleading -- were made to keep the secret not only from the press but from White House staff members, friends, and

even relatives.

When Grover Cleveland was finally informed that he had cancer, he showed less personal concern about the outcome than did the doctors who had to report the grim news. The president's greatest and most immediate fear was that the public might find out. "We cannot risk any leak that would touch off a panic," he confided to Bryant, "if a rumor gets around that I'm 'dying,' then the country is dead, too."

Cleveland had good reason to be apprehensive during the spring and early summer of 1893. Although he had displayed great optimism and confidence when he pressed a button opening the World Columbian Exposition in Chicago on May 1, he knew that the country was already in the grip of a spreading depression. The Philadelphia and Reading Railroad had recently gone bankrupt. The Atcheson, Topeka, and Santa Fe was shaky, following the revelation that its officers had defrauded the public of $7 million. And Wall Street was increasingly unstable, as experts tried to evaluate the impact of escalating unemployment and the failure of some 500 banks and 15,000 businesses. The country's financial footings had been left in a rickety state when Benjamin Harrison turned his office over to the new president, with the Treasury depleted by more than $100 million.

Faced with such adversities (later to be described by historian Charles Francis Adams as "the most deep-seated financial storm in the history of the country"), Cleveland was actually at his best -- a positive-thinking, active leader. He had already taken a firm stand in his adherence to the gold standard, despite continuing pressures from Western legislators who insisted on the free coinage of silver and the circulation of more money. Though winning that battle, he was fully aware that his control would be severed if his opponents sensed that he had a serious physical disability. He was concerned about his vice president, Adlai E. Stevenson of Illinois, assuming power. Stevenson was a free-silver man. To put it in the blunt phrases of the influential Commercial and Financial Chronicle, whose editors did not realize the import of their words, "Mr. Cleveland is about all that stands between this country and absolute disaster, and his death would be a great calamity."

Thus it was that Cleveland, rather than being unnerved by the diagnosis, looked upon the situation as a fateful challenge. After asking questions about the nature and extent of the facilities that would be needed to perform the operation, he appointed Dr. Bryant to take charge. At the outset, he made two points clear: First, he said, "I cannot leave here before the end of June under any circumstances. So I will say to you that I will be ready on the first day of July." Second, he ruled out hospitals as too risky from the standpoint of secrecy, even if he could be disguised and smuggled in after dark. The press would become suspicious about any unexplained absence from the White House, and there was always the chance that a nurse or orderly would leak the news, whether unintentionally or for personal gain.

They would all have to give the problem enough thought to come up with a foolproof alternative.

From that day on, all letters, memos, telegrams, and other communications referred to the president as "your friend" or "my patient" or "our guest." So jittery were the doctors that they might make a fatal slip that they took some measures which, in retrospect, seem too melodramatic to have taken place. Bryant, for example, decided that he would need the assistance of Dr. William Williams Keen, professor of surgery at Jefferson Medical College in Philadelphia, an outstanding surgeon and pioneer in neurosurgery. He wrote Keen a letter, requesting consultation "in a very important matter," and insisted on meeting one afternoon at 3:15 on the deserted deck of the Fall River Line boat on which Keen was to leave for Boston three hours later. Here, surrounded by empty deck chairs, gently slapping ropes, and clanking rail chains, they plotted a course of action.

O'Reilly, who had not intended to be present at the operation, became so involved in the conspiracy of silence that he feared his very nervousness and preoccupation would be a giveaway if he were to remain apart from the scene. So he elected to be present, but only after instructing his colleagues that henceforth he was to be referred to as "Major Mills," and in no way associated with his office of attending surgeon.

Now the big question was, where?

Gray Gables, Cleveland's summer home on Buzzard's Bay in Marion, Mass., was considered -- and quickly rejected. Although the excuse of a "brief vacation" sounded credible, there were too many reporters prowling about, certain to be curious about the arrival of unusual visitors or equipment, no matter how well disguised. The house would be a natural for the later period of recuperation. But the operation and the immediate postoperative care required a location that was beyond suspicion or access by outsiders.

UItimately, Cleveland himself came up with a solution. He would make arrangements with his good friend, the noted Commodore Elias C. Benedict, to spend a few days aboard the latter's 75-ton yacht, Oneida, on which he had already cruised upward of 40,000 miles enjoying respites from the demands of office during his first term, from 1885 to 1889. With the yacht floating at anchor in New York City's East River, members of the medical team could arrive by small boats, leaving, inconspicuously from any number of piers that lined the east side of Manhattan. Or the yacht could anchor in the Hudson River, with easy access from the New Jersey shore as well as from New York. Each could bring a share of the instruments and supplies in suitcases and handbags. Once under way, this floating operating room would be unassailable by either the press or the curious public.

Bryant was in full accord. A vessel of this size, cruising in protected waters, would pose no problems for experienced surgeons, providing they had adequate lighting and suitable support for the overweight patient. The doctor's greatest concern was that the president, under even the best of conditions, might not be able to withstand the radical surgery proposed without serious complications. Although generally in good health, the man suffered from the side effects of his obesity, was afflicted with gout, and had punished himself physically in earlier years with excessive eating, drinking, and partying. Moreover, no one knew how fatigued Cleveland really was after four arduous months in office with the growing financial crisis.

To cap it all off, no matter how successful the operation turned out to be, would the patient's condition be such that he could be seen by the public within a week or 10 days without causing instant alarm? It is no wonder that Dr. Bryant later commented to Commodore Benedict, "If anything happens to the president, get your navigator to run us on the rocks and sink us all!"

There seemed to be no other alternative. As a final safeguard, Bryant called in yet another noted specialist, Dr. Edward Gamaliel Janeway, professor of medicine at Bellevue Hospital in New York City and a member of an esteemed medical family associated with the profession for many generations. Janeway knew as much about anaesthesia as any doctor then in practice. He also knew that he could make no mistakes, for the mortality rate from anaesthesia alone was 14 percent during simple operations and a great deal higher for more radical surgery, especially if complications set in or if the patient had to be anaesthetized for longer than anticipated.

Now Janeway's ingenuity was put to the test. He would have to arrange for the secret transfer of tanks of compressed gas and other seldom-moved equipment from hospital to ship without arousing suspicion or curiosity. He laid his plans with the adroitness of an undercover agent. At the same time, he also took one step that widened the circle of those who were in on the secret and thus increased the chances of exposure. To lessen the risk of an accident with anesthetics, which were in those days somewhat unstable and unpredictable, as well as inadequately researched, he enlisted the aid of Ferdinand Hasbrouck, a young dentist with experience in the use of the recently discovered nitrous oxide. Janeway felt that nitrous oxide (later to be popularly known as "laughing gas") would hold the president for the duration of the operation.

Hasbrouck, who would also start the operation by removing several teeth before the surgeon took over, did not share Janeway's optimism. In his opinion, laughing gas could only hold the patient for the first part of the ordeal -- the removal of the teeth and possibly the cutting away of soft tissue in the gums. But ether would then be required to knock out the corpulent Cleveland for the removal of those parts of the jaw bone and hard palate tissues that were thought to be cancerous. Ether was tricky, difficult to administer under the most well-controlled conditions, and sometimes ineffective when metered out in doses that were considered safe. Ether frequently brought on pneumonia and almost always triggered side effects. A further risk, as yet unknown to Janeway, was that a urinary exam would indicate the beginnings of chronic nephritis, a condition that Dr Keen recognized as being dangerously aggravated by the administration of ether.

The president, informed of the risks and the lack of emergency equipment and facilities on shipboard, was unwavering in his decision to use the Oneida. Thus it was that at 4:20 on the afternoon of June 30, he left Washington on a private Pennsylvania Railroad car (belonging to Frank Thompson, one of the company's vice presidents), attached to the New York Express. Few people knew of his departure and even fewer of his arrival in Newark, where he was hustled into a waiting carriage and hidden from public sight. The carriage then crossed by ferry to the lower tip of Manhattan, where it proceeded almost unobserved along Cortland Street and part of Broadway to Pier A. There a launch transported Cleveland to the Oneida, lying at anchor some distance from shore. The president was accompanied by only a handful of people, including Secretary of War Daniel S. Lamont, who functioned as a personal

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aide and press secretary. The Oneida then proceeded slowly down the bay and anchored in the Narrows off Bay Ridge for the night.

June 30 was a Friday, a perfectly logical time for a brief sojourn away from the heat and pressures of Washington. That morning, in a bright show of confidence, Cleveland had issued a call for a special session of Congress to meet on Aug. 7 for the purpose of repealing the Sherman Silver Purchase Act. To all outward appearances, he was in robust health and so soundly in control of executive affairs that he could absent himself from the White House long enough to relax and enjoy life, and such a statement was released to the press.

Why was he not accompanied by Mrs. Cleveland, the pretty young Frances Folsom who was just half his age and the most attractive First Lady yet to grace the White House? To any who might inquire, there was good reason: She was in her seventh month of pregnancy and naturally had to avoid the risks of travel. There was little likelihood that Frances would slip up and reveal her husband's dark secret -- she did not even know that he was sick.

That night, the president was in excellent spirits and able to sleep without sedatives. A medical examination the following morning found him fit enough to proceed with the plans. At 8:30 he drank a single cup of coffee, ate a slice of toast, and was reported to have "moved his bladder and bowels in a natural manner." In the meantime, the Oneida was proceeding slowly up the East River, headed for Long Island Sound. A major crisis seemed imminent when Dr. Bryant noted that the vessel was almost as far upriver as 26th Street, the location of Bellevue Hospital. Hastily, he ordered all doctors and members of the president's party to leave the deck and go into a cabin where they could not be seen and inadvertently recognized. (It was later reported that some interns had set up a telescope on the roof and were observing the yacht. Whether true or not, nothing ever came of the incident.)

Besides the captain of the yacht and Commodore Benedict, the only member of the ship's crew who was aware of the proceedings was a steward (described as "extremely loyal and faithful") who had been assigned the arduous task of fetching hot water, towels, and other supplies on demand. The steward, together with members of the crew, had been informed that the president was to have two badly ulcerated teeth extracted and that extra precautions were being taken to prevent any blood poisoning, which naturally would be disastrous because of his high position. The explanation sounded logical enough to stir up little or no curiosity.

At noon on Saturday, July 1, the president steeled himself for the ordeal. At 12:25, he undressed in his cabin and by 12:31 was seating himself in a large chair that had been lashed to the interior footing of the ship's mast so that it would not slide in case the vessel rolled or pitched unexpectedly. He was wedged in a sitting position for the expected two-hour ordeal, head slightly tilted back and held securely in position by pillows that had been tied in place. In attendance were Doctors Bryant, O'Reilly, Keen, and Janeway; Hasbrouck, the dentist; Bryant's young assistant, Dr. John F. Erdmann; and Secretary of War Daniel S. Lamont.

At 12:32, Hasbrouck began administering the nitrous oxide gas, which took effect so quickly that he was able to swab the President's mouth thoroughly with Thiersch's solution, a disinfectant, and begin the removal of teeth by 12:40. A few minutes later, with the bleeding under control, Dr. Bryant stepped in to perform the critical part of the operation. He carefully injected cocaine along the lines of his intended incisions, then called upon Hasbrouck to administer the ether under the direction of Janeway, who was keeping a close watch on the patient's breathing, pulse, and general condition.

Together, Bryant, Keen, and Erdmann dissected part of the inner cheek, arresting the bleeding by applications of hot water and pressure. Among the unusual instruments of the day that were called into play were a "cheek retractor," an ingenious instrument Keen had brought back from Paris, and a "white-hot electric knife." The former made it possible for the doctors to hold back the heavy jowls so often caricatured in cartoons of Cleveland, without having to leave any external scars. The latter device, deriving energy from two large storage batteries, instantly cauterized tissues that were beginning to bleed. The front of the jaw was then chiseled loose and part of the palate removed. Examination revealed that the disease had begun at the roots of the left molars and spread into the antrum, the hollow cavity of the upper jaw, in the form of a gelatinous mass which Keen described as a sarcoma, or malignant tumor.

Faced with this evidence, there was nothing the surgeons could do but remove all but a small portion of the President's left upper jaw. Bryant, as surgeon in charge, made the critical decision to cut back as far as the orbital cavity (which contains the eye socket), beyond which he could not go without endangering the President's sight. Fortunately, there was no evidence that the lower jaw had been affected yet, or that the malignancy had spread to other areas.

By 1:55 that afternoon, the operation was finished. Erdmann disinfected the cavity with further applications of Thiersch's solution and packed it firmly with gauze. Janeway observed that the patient's pulse was 80, that the president was perspiring moderately, and that his color was good. He estimated that, despite their preoperative fears of hemorrhaging, they had been able to limit the loss of blood to well under a pint. Within two hours from the time the president was brought into the makeshift operating room, he was back in his own stateroom in bed, further drugged by an injection of

morphine to kill the pain. At that time, no ill effects from the ether were noted.

A key decision on the part of the doctors, one largely motivated by Cleveland's insistence on secrecy, had been the agreement to perform the operation entirely through the mouth so there would be no external evidence that the chief executive had undergone anything but substantial dental work. It is doubtful that this could have been accomplished without Dr. Keen's "retractor," the newly invented cauterizing device, or the skill of the surgeons.

The president was described as "up and about" on July 3, following the removal of abscessed teeth. But the crisis was by no means over. As the doctors were well aware beforehand, the removal of such a large section of the jaw and palate would have a severe effect on the speech. However, when Bryant visited his patient, heard his pitiful attempts to communicate, and saw the anguish on his face, he was struck by a feeling of helplessness and dread. Had he cut away too much tissue? Would the President ever be able to talk again coherently? Everything would now depend upon the experience and skill of a New York dental surgeon, Dr. Kasson C. Gibson, who was at that very moment on his way to Cleveland's summer home, Gray Gables, on the Massachusetts shore. Gibson had been selected as the expert best suited to molding and fitting an artificial jaw.

By this time, the Oneida had cruised leisurely through Long Island Sound, eastward toward its destination, Buzzard's Bay. As it approached Plum Island, off the inner tip of Long Island, it veered suddenly northward toward New London, Conn. When Bryant inquired of the captain if anything were wrong, he was informed that Ferdinand Hasbrouck was being landed. Bryant knew that the president would be alarmed because of possible exposure to the prying eyes of the press. But Hasbrouck insisted so strongly that there seemed to be no alternative. He had already promised to be at New London a day earlier to administer nitrous oxide for a surgical operation at the hospital there. His unexplained delay and continued absence would arouse far more suspicion than any change in the vessel's course.

On the evening of Wednesday, July 5, the Oneida docked in Marion, Mass., and the president walked briskly from the shore to Gray Gables, unassisted and virtually unobserved. Thus far, he had avoided public notice.

Col. Lamont was experienced enough in communications to know that he could not press his luck too far. Therefore, he scheduled a "routine" press conference in a barn, some distance from Gray Gables on Friday of that week. How was the President? Well, he was feeling slightly better, following the extraction of a couple of teeth, but he was not going to try to get around for awhile because he had a lame knee and slight swelling of the foot. Nothing serious, but certainly more difficult for a man of Mr. Cleveland's size and weight than for the average citizen. In any case, he had spent the greater part of the previous day playing checkers with Mrs. Cleveland, who had arrived from Washington at the beginning of the week.

What about the rumor that the president had a malignant growth? A distorted account, engineered by his opponents who were trying to weaken his position on gold. One of the president's medical advisers was there and could confirm his health and general well-being. As a result of the press conference, the New York Times reassured the nation. "Dr. Bryant said the president is absolutely free from cancer or malignant growth of any description," reported the Times on July 8. "No operation has been performed except that a bad tooth was extracted."

Lamont, Bryant, and the others were able to put up a good front only because of the skill of Dr. Gibson, who had established a small dental laboratory in a back room at the cottage. He had fashioned an artificial jaw from vulcanized rubber and had already positioned it temporarily in place in the president's mouth. The effect was astonishing. Without this device, Cleveland's speech was described by Dr. Keen as being "wholly unintelligible, resembling the worst imaginable case of cleft palate." With it, however, Cleveland could speak in a manner that was easily understood, though his words sounded heavy and slow. Gibson confidently explained that it was now simply a matter of refining and refitting the prothesis and training his patient in its most effective use.

In mid-July, as Lamont was beginning to breathe more easily about the president's recuperation, he received a shock. Bryant had detected a suspicious-looking growth along the inner margin of the surgical wound. It would have to be removed immediately. Plans were quickly laid and announced for a short pleasure cruise around Martha's Vineyard and into Nantucket Sound. The president was gone for only two days, during which time the growth was surgically removed with no complications.

By Aug. 7, the scars of both operations had healed successfully enough, and the artificial jaw fit snugly enough, so that the president was able to entrain for Washington and address the special session of Congress which he had called for on June 30. His speech, though brief, was forceful enough to motivate the House to repeal the Sherman Act by a vote of more than two to one. Tired by the stress and tension of playing his role in public for the first time after his ordeal, Cleveland returned once more to his summer home.

The battle for secrecy was over. Or was it?

On Aug. 29, suddenly and unexpectedly, the Philadelphia Press published a disturbing letter from its investigative reporter in New York City, E.J. Edwards, who used the byline "Holland." The implications were sensational and alarming. Did Congress and the public know that the head

of the nation was critically ill with a malignancy that was possibly terminal? The death of the president would split the country in two and make it vulnerable to the "absolute disaster" that had been prophesied by the Commercial and Financial Chronicle should such a misfortune occur. According to Edwards, an operation of the most critical kind had been performed on the president, raising the question of whether he was fit for office and capable of leading the country. Edwards named the doctors in attendance and supplied details that seemed too factual to be discounted.

The press was divided. Some newspapers termed the story an irresponsible hoax. The editor of a rival paper, the Philadelphia Public Ledger, denied that it had been scooped, since the story was obviously just another "cancer fake." Cabinet members -- notably Daniel S. Lamont, who was the foremost spokesman for the White House -- indignantly denied everything. They conceded only that Mr. Cleveland had been subjected to painful tooth extractions that were slow in healing. As for the doctors, they avoided the press for the most part, or when cornered asserted that it was unethical for any practitioner to break the confidentiality of the doctor/patient relationship. As Dr. Erdmann later confessed, "I did more lying during this period than in all the rest of my life put together."

One fact is certain: Every other member of the medical team who had been present on the Oneida was disgusted with Ferdinand Hasbrouck. The finger was clearly pointed at the young dentist as the source of the leak. It was said that he had blabbed the full story to a Dr. Leander Jones of Greenwich, Conn., after being chided for arriving late for his anesthesia appointment in New London. Jones later told the story to reporter Edwards, who then confronted Hasbrouck and somehow pressured him into talking. Dr. Bryant was so upset by the dentist's breach of his confidence that he never again spoke or wrote to him. In fact, when he finally paid Hasbrouck the sum of $250 for his services, he sent the check by messenger, with no note or other comment.

President Cleveland faced the challenge head-on and with remarkable fortitude. He was his own best press agent, simply by undertaking his normal duties at the end of the summer as though nothing unusual had taken place. He neither shied away from public appearances nor sought refuge in seclusion. Those who heard him speak publicly could not help being convinced that the story in the Philadelphia Press was fictitious, for the president's voice was stronger and clearer than ever, providing little comfort to his enemies that he might be in weakening health.

On Sept. 5, he welcomed Congress with a voice that was described as "even clearer and more resonant" than when he had given his inaugural address six months earlier. According to the Times, his speech "removed every lingering doubt of his entire soundness of body." Cleveland's position was further enhanced when, on Sept. 9, his pretty young wife, Frances, gave birth to a second daughter -- the first child of a president to be born in the White House.

The strange secret of Grover Cleveland was kept for more than two decades. Finally, in 1917, long after Cleveland's death, the full story was told in The Saturday Evening Post. The author was William Williams Keen, MD, who, in addition to having participated in that historic operation, was a prolific writer during his later years. Keen was able to state, with justifiable pride, that the cancer operation had been a complete success for the patient and doctors alike. Cleveland not only survived his second term of office but continued a fairly active life, living with his family in Princeton, N.J. In his last years, he continued to be plagued by gout and suffered a number of heart and kidney diseases. On June 24, 1908, at the age of 71, he died of a heart condition, undoubtedly complicated by his obesity but in no way related to his historic cancer operation.

For many years, the case of President Cleveland was shrouded in mystery, a controversial issue that provoked some doctors to assert that he had never had a cancer after all and that the whole story had been embellished. The tumor that was removed was described variously as an epithelioma, a sarcoma, and a malignant growth by the doctors present. Although the remains of the tumor were sealed in a bottle of alcohol in the possession of the Mutter Museum of the College of Physicians in Philadelphia, which also has John Marshall's kidney stones and Florence Nightingale's sewing kit, the curator steadfastly refused to permit any analysis of the sample. Only recently was the question resolved when pathologists were finally given the sample for examination. They pronounced it to be a "verrucoid carcinoma," common in smokers and very malignant.

The medical dilemma of President Cleveland, while perhaps more dramatic than some presidential illnesses, was by no means unique. The public -- and even people close to the White House -- would be astonished, if not horrified, to learn about the infirmities, accidents, and mental disorders that have been hushed up from the time of George Washington down to the present. It is ironic to think that Cleveland, despite his medical history of obesity, hypertension, stomach trouble, and cancer, can be numbered among our healthier chief executives. It is doubtful that many of our leaders would have survived the ordeal that Cleveland experienced, under the circumstances that prevailed in 1893. It is certainly safe to assert that few of them would have emerged robust enough to convince a jittery public that they had never had any operation at all.

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Weirdos Need Not Apply

Robert E. Horseman, DDS

I've discovered that if you recline your lounge chair just right and make a "V" with your feet, you can see your TV screen perfectly. This will hold true for up to a 27-inch screen at a distance of 15 feet. If you have one of those monster 60-inchers and your viewing chamber is about the size of a room at a Motel 6, forget it -- you'll pop out your knees trying to accommodate.

Recently, I was in the above optimal viewing position when that Nice Lady from the dental referral service came on. I have always admired this person. She seems genuinely concerned about the plight of thousands of people whom she perceives as having no dentist of their own and wandering about willy-nilly, clueless about how to connect with a professional tooth person. What are these people to do, she worries, twin furrows appearing between her brows. She is not actually wringing her hands, but you can tell she's close to tears.

Before the impact of her agitation can upset viewers to the point of upping their dose of medication, she quickly beams the following message to unfortunates "out there" bereft of a DDS they can call their own: Why take a chance picking a strange dentist from the Yellow Pages? If you've flipped through the Yellow Pages recently, you can appreciate that the odds of getting a strange one are excellent. He could be buying his supplies from Earle's House of Toxic Materials or secretly using ordinary tap water for rinses, for all you know.

Would you choose a brain surgeon in this manner? Or a blind date, unless you're really, really hard up? What can you really KNOW about this person other than the fact that the bigger and more garish the ad, the more it's costing him a month -- a nut that's bound to be reflected in his fees, if you get my drift.

As far as asking for a recommendation from a neighbor who is insensitive enough to own a beagle who barks nonstop and to leave the emptied trash barrels out front for two days, forget it! Also, none of your friends' teeth, upon close inspection, look all that good anyway, so what could they know about dentists?

Well, stop worrying, she comforts those few who haven't developed an aversion to talking heads and clicked to another channel. We have carefully and thoroughly screened -- YES! screened thoroughly and carefully -- a select few dentists in your area that meet our rigorous criteria. We know everything about them from where they went to school to what, if any, their specialty is and whether they played any significant part in Paula Jones' makeover.

Watching this, I am devastated. Much as I would like to belong to this elite group of carefully screened dentists, I

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know I could never survive the investigation. That time I was caught sleeping in the pharmacology lecture during my junior year and that ugly episode with the spilled merthiolate in a patient's lap would certainly be unearthed in even the most superficial screening.

This referral message -- repeated nightly over the years -- has left me depressed, on the outside, looking in. I feel that my patients have found me quite by accident and at the first chance of learning details of a more qualified provider, will desert me in a heartbeat.

But wait! The tone of tonight's referral commercial has taken on a different imperative. The Nice Lady is visibly upset. Oh, she tries to hide it beneath some of the same references to the cream-of-the-crop professionals she has painstakingly researched, but no mistake, there's a new urgency to the message. It seems that some of you viewers -- you know who you are, she gently accuses -- have NOT called this 800 number we thoughtfully flash on the screen 50 times during this 30-second public announcement. There's no doubt she is hurt and disappointed. I feel terrible. I'm acutely aware of the fact that, because I could never pass the rigorous screening to achieve a position on this Alpha list, the Nice Lady doesn't know I exist, but that doesn't mean I don't have empathy for a person giving her all for the advancement of dentistry.

What's going to happen? She asked politely for us to call for a referral. Perhaps some of us called, but obviously not enough. These TV spots cost a bundle and the participating dentists grow restive without tangible results.

She chides us, giving us one more chance to do the right thing. There's a clear imputation that if we don't get to the phone forthwith, the gloves are coming off, and we are going to witness a hard sell the likes of which we haven't seen since Clinton tried to define some common terms as he sees them.

I've grown fond of the Nice Lady and don't want to see this happen. I want you and your friends to call that 800 number right now and get the name of a dentist. If you already have a dentist, get another one -- get two or three -- otherwise we may well be seeing the beginning of the end for public-spirited broadcasts such as this one, and the Nice Lady will have to go back to selling time shares in the Aleutians.