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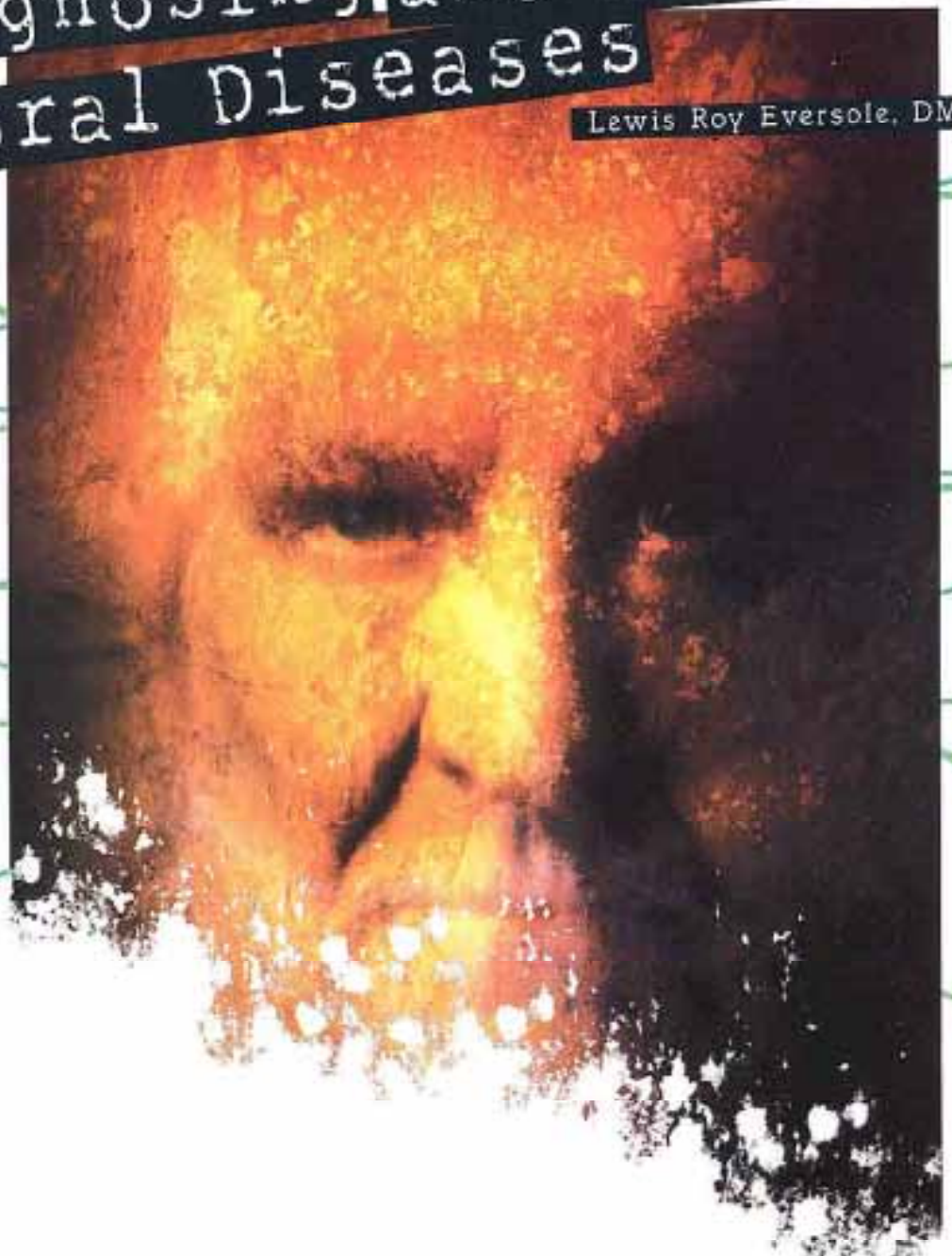
Xerostomia
Candidiasis
Herpesviruses

Diagnosing and Treating Oral Diseases

Lewis Roy Eversole, DMD, MSD, MA



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DEPARTMENTS

FEATURES

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A Quiet Wind of Change

Jack F. Conley, DDS

The issues facing each American Dental Association House of Delegates are usually quite different from those that faced the previous annual session. The attitude of the delegates as they debate the issues has also varied every year, sometimes significantly from the preceding year.

As an example of the latter, during previous House sessions, we have seen the delegates reject a budget resolution or a potential dues increase, sending the Board of Trustees into a special session with a request to modify programs or identify other funding sources for presentation back to the House. Such sessions have been spirited and, often, contentious.

In past House sessions, there has been impassioned or even divisive debate over public awareness programs and proposed dental specialties, to name just a few of the proposals reviewed by ADA delegates in recent years. With an agenda that has been averaging between 100 and 125 resolutions for consideration, there have usually been at least a handful of issues that have stimulated forceful debate before reference committees or on the House floor.

Given that background, the first ADA House of Delegates of the new millennium was decidedly different. Within days after the close of the House proceedings, we find it difficult to pinpoint why this session seemed to have a different mood than any of its predecessors in the past few decades. Nonetheless, we would like to explore some of the factors and characteristics that lead us to this conclusion.

The most divisive issue to face the 2000 House of Delegates was a resolution to create a new single-state trustee district. California, the largest constituency of ADA members, has been one of five single-state trustee districts, each represented by its own member on the ADA Board of Trustees. The other states are combined in accordance with the ADA Bylaws to form 11 multistate districts, each having one trustee representative. Florida Dental Association membership has increased in recent years to a level that qualified Florida under the bylaws for consideration as a single-state district.

In simplified terms, this issue was controversial to the majority of the California delegation and other delegations as well, because the membership total achieved by Florida is only slightly more than one-third of the current membership in California and about one-half of the membership in New York. It was natural that the California delegates should question the obvious imbalance in representation under this formula and would want to consider other mechanisms to ensure that their constituents received equitable representation.

While the opposition of California delegates and a few allies was well-known, in the final analysis, the delegation did not push the issue into a contentious floor debate. Our analysis here is that based on the existing bylaws language, the Florida position was correct and California would have nothing to gain and a great deal to lose in future ADA deliberations if this issue were pursued. Sixty-eight percent of the House approved the new district with a distinct lack of the contentious debate often seen in past House sessions. And while progress was not made on the representation issue, by placing a focus on

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it, the CDA delegation has helped place this issue on the agenda of the task force on ADA governance structure that will be making a final report to the 2001 ADA House.

Despite officer and candidate presentations that linked membership dues and a continuing decline in the market share of ADA membership, a slight increase in dues for 2001 to balance the budget for programs voted by the House was approved by more than 91 percent of the delegates. This was in addition to a $30 annual assessment for six years to cover renovation costs for the ADA headquarters building that had already been approved by 85 percent of the delegates. The level of agreement and support for these measures was surprising, given discussions that identified cost and value as stumbling blocks to membership, particularly of young dentists.

Even the consideration of specialty recognition for orofacial pain failed to generate much debate. In a non-emotional review of the six requirements for a specialty, more than 76 percent of the delegates voted to deny specialty status to the American Academy of Orofacial Pain.

A review of our notes showed that a significant majority of issues for which a machine vote count was taken were either approved or defeated by 80 percent to more than 95 percent of the delegates. As an example, a resolution initiated by California to create a task force to make recommendations on a position for pursuing antitrust relief for dentists and health care professionals was approved by more than 94 percent of the delegates.

This leads us to wonder why there was a high level of agreement and noticeable lack of debate. The reasons are many and varied. Perhaps because there was only one issue with major financial impact (assessment for headquarters renovation), there was a less emotional environment to stimulate debate. It is also possible that increased levels of communication -- including the Internet -- have helped educate more delegates so that they are "on the same page" in their understanding of the issues. The regional differences that may have been the cause of emotional debate in past ADA sessions may be fewer in number.

Also of note were two important announcements that preceded the deliberations and could have affected the mood of this House. It was announced that Executive Director John Zapp would retire at the end of March 2001 and ADA Editor Lawrence Meskin would be retiring at the end of 2001. These unrelated personnel changes involving visible participants may have signaled a transitional period with an expectation for change that contributed to a quieter, less contentious mood for this House.

The different mood of this ADA House of Delegates seems to be symbolic of a period of change immediately ahead for the American Dental Association. A new leader and a new voice in a year are only part of the equation. What may well be most significant about the mood of the 2000 House is that it seemed to be more agreeable, more respectful, and more understanding of the problems challenging the profession on a national basis. The districts may be working together better with less emphasis on political alliances than has sometimes been the case in the past. If there were any failing, it was the lack of resolutions under consideration that would have directly addressed value-of-membership issues.

All things considered, a quiet wind of change was experienced in the Windy City of Chicago in October during the American Dental Association House of Delegates meeting.

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California Performs Poorly on Oral Health Report Card

By Debra Belt

The Golden State received a mediocre grade in oral health care and ranked only slightly above the low national average on America's first Oral Health Report Card, issued in October. California received an overall C grade while the nation as a whole rated a C- in the report that offers a state-by-state look at the specifics of oral care, including prevention, access to care, and health status.

The report card, issued by the nonprofit advocacy group Oral Health America and reviewed by the federal Centers for Disease Control and Prevention, made a significant splash as media from coast to coast transmitted the rather gray findings concerning the nation's "pearly whites."

"We were hoping to alert America that we are in the position of a student with straight A potential in danger of failure," said Robert Klaus, president of Oral Health America. "The report card was not meant to embarrass or put anyone on the spot, but was intended as an impact statement and a wakeup call to policy makers that many of these oral health problems are preventable and solutions are affordable."

"Our primary goal was to raise public awareness," said Elizabeth Rogers, director of communications for Oral Health America. "We were looking to extend the message of Surgeon General David Satcher's report on oral health and use it as an advantage to help raise the profile of oral health."

The Oral Health Report Card highlights significant variation between the states on a number of issues, especially in the categories of prevention and health status. In the general category of prevention, fluoridation grades ranged from A's to F's; and 24 state sealant programs received an incomplete. Grades in the health status category were also all over the board with B grades in Arizona, North Carolina, and Utah contrasting with F's in Kansas and Minnesota.

Nationwide, grades were consistently low in the access-to-care category where a few C+ grades in Maryland, Oregon, and Wyoming were sprinkled among many D's, F's, and I's. In grading access to care in the individual states, Oral Health America looked at the prevalence of dentists and dental clinics, Medicaid programs, and dental insurance for adults and elders. California rated a C- in overall access to care and a D in dental insurance for the elderly. Dental insurance for people over 65 received the most abysmal marks with an F grade issued in 41 states. Roughly 108 million people in the United States, including 85 percent of the elderly, lack dental insurance.

These disappointing grades in access confirm the long-standing recognition in the dental health field that oral health is inextricably linked with general health and needs to be addressed this way in shaping public policy.

"The most important information to come out of this report deals with the great disparity in access to care," Klaus said. "We have really hit a mark in this area and have to work to change the perception of the public and of policy makers so they understand that oral health care is health care." Klaus used the example of the health insurance offered to his son, who is a teacher in Chicago's public school system. It did not include coverage for dental care. "Labor unions need to understand that this is not an option, and this kind of exclusion can't be made. Oral health care is health care."

"The report confirms that public policy, which could contribute to oral health improvements, has been lagging in funding and resources when compared to medical resources," said Jared I. Fine, DDS, MPH, of the Office of Dental Health in Alameda County. "When politicians talk about health coverage and insurance, they don't mean dental. For every child who is uninsured for medical care, there are two to three children who are uninsured for dental care. This report points to the gaps we need to bridge in the minds of policy makers at federal, state, and local levels."

California's Grades on National Oral Health Report Card

STATE GRADE: C

PREVENTION: C-

Fluoridation: F
State oral health program: D
Sealants: D
Visits to dentists -- Adults: C
Visits to dentists -- Elderly: B
Use of smokeless tobacco: B

ACCESS TO CARE: C-

Prevalence of dentists: C
Prevalence of dental clinics: C
Medicaid program: C
Dental insurance -- adults: C
Dental insurance -- elderly: D

HEALTH STATUS: B-

Oral health of children: B
Adult tooth loss: B
Edentulous elderly: B
Oral cancer -- male: B
Oral cancer -- female: D

Other issues illuminated by the report include fluoridation of community water, where California received its only F. Several other states suffered a failing grade in fluoridation including Hawaii, Idaho, Mississippi, and Montana. States that ranked an A included West Virginia, Tennessee, Illinois, Indiana, and Iowa.

"When California began its fluoridation efforts in the early '90s, about 17 percent of the state's water was fluoridated," said Tim Collins, DDS, MPH, dental director of Public Health Programs and Services for the County of Los Angeles Department of Health Services and chair of the California Fluoridation Task Force. "With the fluoridation of Los Angeles' city water in 1998 and Sacramento in 2000, the percentage is up to about 25-30 percent, and we have not finished our work. The Oral Health Report Card shows

how important fluoridation is and should serve to boost our efforts."

Klaus noted that Oral Health America is aware of California's diligent fluoridation efforts. "Once the state's fluoridation grade is up, it will be one of the national leaders in oral health."

Fluoridation was in the general category of prevention in which California received an overall C-. In accessing the level of preventive care, Oral Health America looked at state oral health programs, the use of sealants, visits to the dentist for adults and elderly, and the use of smokeless tobacco. The highest grade of a B+ in prevention went to North Dakota.

Klaus hopes to see improvement when the next Oral Health Report Card comes out. "Right now, the plan is to issue another report at the same time next year. We look forward to collaborating with state dental associations and state and territorial dental directors on the next report and hope for incremental improvements."

The entire Oral Health Report Card can be viewed online at http://www.oralhealthamerica.org.

Look at Sectors When Diversifying Portfolio

By Marios P. Gregoriou

Investors hear a lot about portfolio diversification, and there are a number of ways to diversify. When it comes to stocks, one way to help ensure adequate diversification is to include stocks from several different market sectors.

An economic sector is made up of industries that have certain characteristics in common. The industries in a given sector tend to react similarly to trends in the overall economy. Good or bad news affecting a major stock in one industry may trickle through to stocks in other industries in the same sector. Thus, by including stocks from more than one sector in a portfolio, one may be able to lessen the effect on investments from potential losses in any one segment.

Here are some of the key stock market sectors and types of industries within each sector:

- Basic materials: aluminum, building materials, chemicals, containers, gold mining, metals, paper and forest products, steel.
- Capital goods: aerospace/defense, electrical equipment, engineering and construction, machinery, pollution control.
- Consumer cyclicals -- durable goods: automobiles, auto parts, hardware and tools, manufactured housing, furniture and appliances. (Cyclical stocks tend to rise quickly before the economy turns up and fall quickly before the economy turns down.)
- Consumer cyclicals -- nondurable goods: broadcast media, entertainment, hotels/motels, leisure-time companies, photography/imaging, publishing, restaurants, retail stores, specialty printing, toys.
- Consumer noncyclicals: beverages, foods, household products, housewares, shoes, textiles/apparel, tobacco.
- Energy: integrated oils, oil and gas drilling, oil exploration and production.
- Financial: banks, insurance companies, investment banking, real estate investment trusts.
- Health care: Drugs, HMOs, hospital management, medical products and services.
- Technology: airlines, railroads, trucking companies.
- Utilities: electric companies, natural gas distribution pipelines, telecommunications.

In seeking to diversify the equity portion of a portfolio, individuals may wish to consider reducing stocks from sectors in which they are overweighted and adding stocks in areas where they lack exposure. Of course, certain sectors can be featured more prominently in one's portfolio, based on current market trends, economic conditions, and one's own financial goals.

It is best to ask one's financial adviser how trends in the stock market and economy may affect investments and how one can best take advantage of those trends. Individual financial objectives should be kept at the forefront of decision-making. Although representation from each sector may enhance diversification, other concerns, such as the need for income or a short-term investment time horizon, may indicate a different sector structure for an individual's portfolio.

Marios P. Gregoriou is associate vice president financial adviser with Morgan Stanley Dean Witter in Sacramento. He can be reached by calling (800) 755-8041. This article is published for information purposes and is not an offer or solicitation to sell or buy securities or commodities. Any particular investment should be analyzed based on its terms and risks as they relate to individual circumstances and objectives.

CDC Forecasts Top 10 Public Health Challenges

The Centers for Disease Control and Prevention outlined the top 10 public health challenges the United States must address and said the tools already exist to combat them, in a commentary published in the Oct. 4 issue of the Journal of the American Medical Association.

Jeffrey P. Koplan, MD, MPH, director of the CDC, and David W. Fleming, MD, deputy director for Science and Public Health at the CDC, wrote the commentary, which recognizes the past century's advances in saving and improving lives through vaccines, fortified foods, clean water and many other public health achievements and cautioned that the United States must be prepared for both old and new challenges to the country's health.

"No doubt, unanticipated challenges of similar magnitude lie ahead," the authors wrote. "Whether working in the public, private, or academic arenas, physicians can only hope to have the

Meskin to Retire, Search Begins for New JADA editor

Although he will be on the job until the end of 2001, the search for a successor to JADA Editor Lawrence H. Meskin, DDS, has already begun.

Meskin recently announced his decision to retire after 10 years as editor, effective Dec. 31, 2001.

At its meeting in September, the Board of Directors of ADA Business Enterprises Inc. -- the ADA subsidiary that includes the publishing division -- approved a transition plan that called for a search committee to begin the process of finding a new editor for the *Journal of the American Dental Association.*

The eight-member committee, now in place, includes practicing dentists, dental researchers and educators, publishing professionals, editors, and ADA leadership.

The committee's role is to review applications from prospective candidates, interview those who appear most qualified, narrow the field and make a recommendation to the Business Enterprises board at its August 2001 meeting.

The Board expects to appoint a new editor by Oct. 1, 2001, informing the ADA Board of Trustees of its choice prior to next year's annual session. The new editor would be in place three months before Dr. Meskin's departure.

Dentists interested in the JADA editorship can obtain an application and position description by contacting Laura A. Kosden, publisher and chief operating officer, ADA Publishing Division, ADA Business Enterprises Inc., Suite 2010, 211 E. Chicago Ave., Chicago, IL, 60611. Kosden also can be reached at (312) 440-4671 or at kosdenl@ada.org.

The deadline for submission of applications is March 31, 2001.

powers of observation to detect these challenges early and the resources and will to act wisely in response."

They point out that at least 10 public health challenges can be anticipated and the tools exist to address them. These challenges are to:

- Institute a rational health care system.
- Eliminate health disparities.
- Focus on children's emotional and intellectual development.
- Achieve a longer "healthspan."
- Integrate physical activity and healthy eating into daily lives.
- Clean up and protect the environment.
- Prepare to respond to emerging infectious diseases.
- Recognize and address the contributions of mental health to overall health and well-being.
- Reduce the toll of violence in society.
- Use new scientific knowledge and technologic advances wisely.

"In many of these areas -- child development, mental health, obesity and physical activity, the environment, bioterrorism, and aging -- promising science-based interventions are available and deserve support and broader implementation," the authors wrote. "For example, missed opportunities for cost-effective preventive services in clinical settings, including tobacco cessation counseling, pneumococcal vaccine, and chlamydia screening, can be identified."

Toes Make Good Replacements for Fingers

Patients whose fingers or thumbs are lost in an accident and have a toe or toes removed from their feet to take their place are able to function quite well, according to Kevin C. Chung, MD, one of the few surgeons to perform the procedure in the United States.

Chung, director of the University of Michigan Hand Center in Ann Arbor, described his intricate surgical work during the American Medical Association's Science Reporters Conference.

"Because Michigan is in the farm belt, we see a lot of farmers whose fingers or thumbs are cut off from farming accidents. Of course, without fingers or thumbs, it is virtually impossible for them to perform the necessary tasks on the farm. So, I reconstruct the hand by transferring toes to make the thumb and a couple of fingers so they can drive, pick things up and milk cows," Chung explained.

The procedure typically takes eight or nine hours, depending upon the amount of reconstruction performed. It involves removing various parts from the foot, including tendons, nerves, veins, arteries, bone and skin and then re-connecting them at the hand.

"When a patient has just lost a thumb, making a new thumb is very standard. My preference is to remove the second toe to make a thumb, because it is not as noticeable on the foot. However, some people prefer to use the big toe because it is bigger and more resembles a thumb. When a patient presents without any fingers at all, that surgery has a higher magnitude of difficulty, and I take three toes to create a thumb and two fingers that can be used to pinch things and pick them up," he said. It takes approximately three months of rehabilitation to regain function.

Chung said a collaborative study conducted with a Taiwan hospital that also performs the procedure was recently published in the Journal of Hand Surgery and showed that toe transfers make the hand perform just as well as a normal hand.

As for the feet of those patients

whose toes have been removed, Chung said patients have no problem walking or running, but that some complain of occasional pain from the incision.

Patient Education Key to Increasing Cosmetic Dentistry

The majority of the American public does not know or think about cosmetic dentistry, and more than 50 percent of the population doesn't care, wrote Roger P. Levin, DDS, in the summer 2000 issue of the Journal of Cosmetic Dentistry.

According to Levin, the American public's view of the dental practice is the same as it has always been: the dentist's job is to fix broken or decayed teeth.

To learn why the public is not demanding more cosmetic dentistry, Levin conducted informal interviews with 400 people. He concluded that the American public does not really think of dentists as professionals who enhance smiles, but rather as individuals who just "fix teeth."

Levin said the concept of building the cosmetic component of a practice does not mean eliminating other types of dentistry, but instead adding a subset of cosmetic services for patients. The problem, he acknowledges, is that patients are aware only of the more traditional services and are not learning about cosmetic services.

Merely placing a few brochures in the reception room has not created the revolution that some dentists had hoped for in cosmetic dentistry.

Levin said the first step in beginning to build a cosmetic practice is to change all new-patient exam formats. Dentists who truly want to build cosmetic services should include the cosmetic services as the first aspect of a dental exam, followed by a review of the medical and dental history.

Levin does not advocate giving up on the complete, comprehensive muscle, tissue, periodontal, and tooth-by-tooth examination. He suggest setting new priorities for how dentists approach patients so that patients can be educated about a practice's full range of cosmetic services.

The future of cosmetic dentistry will depend more on patient education within each practice than on broad-based media and advertising, Levin wrote.

Orthodontic Needs Increasing Among Special Needs Patients

During the past 30 years, more than three-fourths of people with mental retardation/developmental disabilities have been de-institutionalized, and there has been a corresponding need to increase awareness among orthodontists about the growing necessity for treatment of these individuals within their communities, according to the an article in the July 2000 issue of the American Journal of Orthodontics and Dentofacial Orthopedics.

The authors -- H. Barry Waldman, DDS, PhD; Steven P. Perlman, DDS; and Mark Swerdloff, DDS -- noted that changing social policies, favorable legislation for people with disabilities, and class-action legal decisions have led to the establishment of community-oriented group residences, and enhanced personal family residential settings, accompanied by the closure of many large, state-run facilities. However, the success of community-based programs depends on the availability of support services, the authors stated -- particularly private practitioners who are convenient and accessible to de-institutionalized individuals and trained and willing to deliver care.

To provide some insight into the need for orthodontic services for these youngsters and adults, the authors asked: "Do we believe that persons with disabilities need functional and esthetic considerations comparable to those of 'normal' persons?"

The reality is that youngsters with mental retardation/developmental disabilities grow older and that periodontal disease is an increased possibility with a malocclusion dentition, they answered. Severe esthetic malocclusions can compromise already difficult social relationships and potential employment opportunities, the authors added.

Children and adolescents with special needs exhibit a higher percentage of malocclusions than the normal population. Children with mental retardation/developmental disabilities may have dentition difficulties resulting from habits such as mouth breathing and tongue thrusting, diets lacking enough rough and coarse foods that require thorough chewing, increased levels of caries, and the loss of teeth and space maintenance, the authors explain. Individuals with mental retardation may not comprehend the need for oral hygiene, the authors note, and those with physical disabilities may lack the dexterity to accomplish the needed oral hygiene.

Honors

Gordon L. Douglass, DDS, has been installed as vice president of the American Academy of Periodontology.

Gary Armitage, DDS, MS, has received the Gold Medal Award, the highest honor bestowed by the American Academy of Periodontology.

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Herpesvirus-Induced Diseases: Oral Manifestations and Current Treatment Options

Catalena Birek, DDS, PhD

ABSTRACT The dentist is often the first health professional to be contacted by patients who develop acute orofacial symptoms of viral conditions such as shingles (varicella zoster) or herpetic gingivostomatitis. The diagnosis, treatment, and management of virally induced oral diseases is a challenge inasmuch as their presentation is atypical and may be complicated by immunosuppression. However, an increasing body of knowledge regarding the manifestations of viral infections in immunocompromised patients and the advances achieved in antiviral drug therapy during the past several years should make the task less daunting for the dentist. In this paper, the natural history, typical and atypical oral manifestations, diagnosis, current treatment options, and advances in the prevention of common herpesvirus-induced diseases are reviewed, with particular attention to primary and recurrent varicella zoster virus and herpes simplex type 1 infections.

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Varicella zoster virus (VZV), Herpes simplex virus types 1 and 2 (HSV-1, HSV-2), Epstein Barr virus and cytomegalovirus are all capable of causing oral mucosal disease through damage to epithelial cells. These viruses, as do all eight of the human herpesviruses discovered to date, share common features in virion and genomic structure and in their ability to establish lifelong latent infections; but they differ in their patterns of infectivity and pathogenicity. The human herpesviruses can be classified broadly according to tropism and pathogenicity as neurotropic and lymphotropic: VZV and HSV-1 and -2 are considered neurotropic, and Epstein Barr virus and cytomegalovirus are primarily lymphotropic. The morbidity associated with herpesviruses is considerably enhanced and potentially life-threatening in neonates and severely immunosuppressed patients. The immunosuppression may be due to infection with human immunodeficiency virus, cancer treatment with cytotoxic agents, or immunosuppressive therapy for the prevention of transplant rejection. The prevalence of oralmucosal ulcerative diseases of various etiology in HIV-infected individuals is high, especially

in advanced cases.[1-3] The past few years have brought about dramatic changes in the morbidity and mortality of HIV-infected patients. In general, the profile of HIV-associated oral diseases in newer cohorts of AIDS-affected populations in the Western world is changing, with some conditions such as hairy leukoplakia and necrotizing ulcerative periodontitis decreasing in prevalence.[4] Nevertheless, there appears to be little difference between the prevalence of HSV-1-associated lesions in a cohort of patients treated by new, highly active anti-HIV treatment protocols (by combined protease inhibitors and nucleoside analogues), as compared with that found in an earlier cohort, as documented in a large population from North Carolina.[4] It is likely that the number of patients presenting with viral orofacial mucosal diseases will increase as the HIV-infected population lives longer.

The aim of this review is to provide an update of the natural history, typical and atypical oral manifestations, diagnosis, and current treatment options for herpesvirus-induced diseases, with special emphasis on VZV and HSV-1 disease severity in the immunocompromised patient.

Primary and Recurrent VZV Infections

Herpes zoster, also known as shingles or zona zoster, is caused by the ubiquitous human varicella zoster virus, a DNA virus and member of the herpesvirus suborder termed alpha herpesviridae, to which HSV-1 and -2 also belong. VZV causes varicella (chickenpox), the childhood epidemic disease still affecting populations worldwide. The majority of individuals with primary VZV infection fully recover and have lifelong immunity against re-infection, but the virus remains in the host in a dormant state in the sensory ganglia (dorsal root ganglia of the spinal cord or extramedullary cranial nerve ganglia, especially the trigeminal ganglion), and possibly in other neuronal and nonneuronal sites such as lymphoid cells.[5] In the normal, healthy host, the dormant virus is kept under surveillance by effective immune mechanisms. In about one-fifth of individuals, zona zoster develops when the reactivation of the virus is associated with considerable viral replication in the ganglia. It is to be noted that even modest decreases in immunosurveillance due to oral prednisone dosages of less than 2 mg/kg of body weight and inhaled beclomethasone may precipitate a severe clinical course of zoster.[6] Even in individuals with no apparent underlying condition, emotional stress, physical trauma, or surgical intervention may trigger reactivation of dormant VZV infection.

VZV is highly infectious. Respiratory spread is probably an important route of transmission. Patients are most contagious just before the onset of the rash. Even indirect contact – e.g., through airflow between a patient's hospital room and a nurses' station,[6,7] between hospitalized patients, or between previously unexposed health care personnel and patients – may carry the risk of nosocomial transmission from patients with shingles to previously unexposed health care personnel.[6]

The symptoms of the primary VZV infection (varicella or chickenpox) are cutaneous hemorrhagic maculopapular rash (which later may become secondarily infected by bacteria and leave a small scar or "pox"), fever, malaise, sore throat, and minor oral vesicular lesions that rupture easily and resemble oral aphthous ulcers.[8,9] The mucocutaneous manifestations of zona zoster are characterized by grape-like clusters of vesicular eruptions that exhibit a restricted unilateral geographic distribution in an area corresponding to a single sensory neuron and complication by pain. The term "herpes" (from the Greek herpes, meaning snake) was suggested originally for the snakelike shape of the dermatomal lesions, while "shingles" (from the Latin cingulum meaning belt) refers to the painful girdle.10 Skin lesions most often affect the trunk. Unilateral orofacial manifestations along the trigeminal nerve (ophthalmic, maxillary, and mandibular branches) include skin eruptions with small vesicles coalescing then crusting quickly and mucosal vesicles that rupture easily to form crateriform ulcers[8,9] (**Figure 1**). In the immunocompetent or mildly immunosuppressed patient, the ulcers normally heal within a month. In some instances, pre-herpetic neuralgia develops prior to the eruption. Persistent "stinging" pain is consistently associated with the mucocutaneous eruptions. Chronic postherpetic neuralgia is attributable to inflammatory responses to injury (demyelinization, necrosis) in sensory neurons, but aberrant central nervous system responses perpetuating the perception of pain may also play a role.[5] Chronic pain is often a problem in the management of varicella zoster. Less than 2 percent of immunocompetent patients develop severe complications such as superinfection of the mucocutaneous lesions, blindness due to acute retinal necrosis, and motor neuropath.6 Primary VZV infection in the adult is rare, but the lesions may be more severe and persist longer, and they carry the risk of interstitial pneumonia. The symptoms and complications of varicella may be particularly severe in pregnant women. In the first trimester of pregnancy, VZV may induce fetal malformations with atrophy and scarring of the affected limb (fetal varicella syndrome). In

Table 1.

Summary of Antiviral Treatment Options in Varicella and Varicella Zoster (adapted from Cohen and colleagues[6])

Treatment	Patient group
Symptomatic care only	varicella in otherwise healthy children zoster in immunocompetent people younger than 50, mild pain
Oral acyclovir* for five days	varicella in women in last trimester of pregnancy
Careful follow up of the clinical course and oral valaciclovir,* famciclovir,* or acyclovir* for seven days	varicella in adolescents and adults patients on continuous or intermittent high-dose corticosteroids low-dose daily use of cytotoxic drugs zoster immunocompetent people with ophthalmic rash over 50, mild pain patients on continuous or intermittent high-dose corticosteroids low-dose daily use of cytotoxic drugs
Oral valaciclovir, famciclovir, or acyclovir for seven to 10 days (as an alternative to intravenous therapy)	varicella or zoster HIV-infected patients if symptoms are mild
Intravenous administration of acyclovir or foscarnet	varicella or zoster in disseminated diseases, acyclovir-resistant lesions, hematologic or solid organ malignancies, and transplant recipients

*Standard oral dosages:
acyclovir: 20 mg/kg five times per day for children, 800 mg five times per day for adults
valaciclovir: 1,000 mg three times per day
famciclovir: 500 mg three times per day
See text for notes on drug interactions and contraindications.

HIV-infected children, even a modest decrease of CD4 lymphocyte counts may precipitate recurrent varicella. Individuals infected with HIV are at increased risk of developing multiple zoster attacks. Severe disease with extensive hemorrhagic pustules coalescing to cover the entire dermatome and prolonged healing with extensive crusting, scarring, and pigmentation may develop in patients with significant decreases in CD4 counts. Among the severe complication of VZV infection reported in advanced AIDS are progressive retinal necrosis, meningoencephalitis, and fatal disseminated visceral disease. Verrucous skin lesions that are resistant to anti-VZV drug treatment have been reported in HIV patients who have been on long-term antiviral therapies.[6]

A case of alveolar bone necrosis due to maxillary herpes zoster has recently been reported.[11] Dental complications may also include loss of pulp vitality, root resorption, and tooth exfoliation. Conditions associated with pain – including trigeminal neuralgia, maxillary sinusitis, and atypical facial pain – should be considered in the differential diagnosis of zoster, especially in cases presenting without a rash (zoster sine herpete).[11-13] However, these can be eliminated through careful clinical examination and detailed history. The association with stinging or burning pain and the unilateral distribution are features that allow the oral lesions of zoster to be easily distinguished from those of similar appearance in herpes simplex and aphthous stomatitis.

As the onset and symptoms of VZV infections are characteristic, laboratory confirmation of the diagnosis is not usually necessary. Because the virus does not grow well in culture, less than 60 percent of the cultures are positive.[5] Detection of the virus in skin or mucosal scrapings by VZV-specific, tagged antibodies is more sensitive and specific (**Figure 2**). Amplification of viral DNA sequences with specific DNA primers (polymerase chain reaction) from the samples may be necessary for the diagnosis of neurological disorders

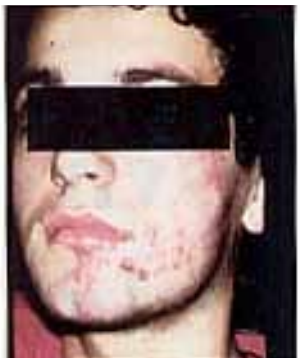

Figure 1. Herpes zoster of the third division of the trigeminal nerve. Vesicles are distributed over the skin and stop abruptly at the midline.

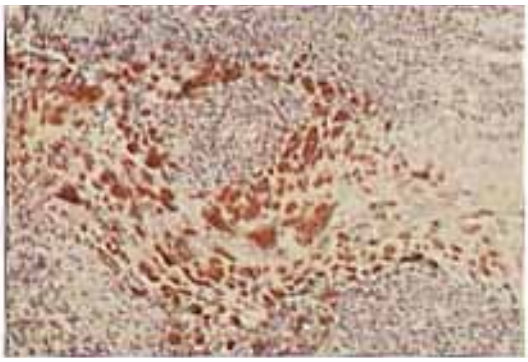

Figure 2. Tissue section from lesional tissue treated with an antibody to VZV tagged with a brown dye. The positivity is striking within epithelial cells confirming the identify of the virus.

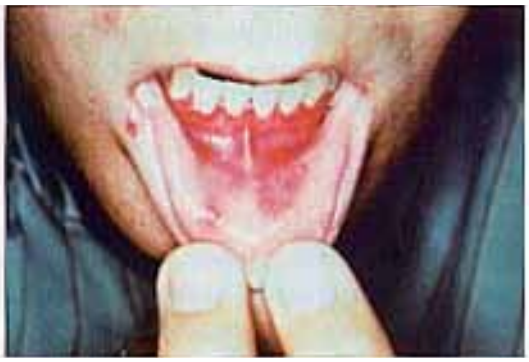

Figure 3. Primary herpetic gingivostomatitis affects movable mucosa of the lips and lesions of the gingiva.

in severely immunosuppressed patients lacking VZV seropositivity or when the cultures are negative.

The timing of effective antiviral therapy for the treatment of varicella and zona zoster is dependent on a limited time span of active viral replication: within 72 hours after the onset of the rash in the normal host, but more extended in the severely immunocompromised because replication and virus shedding are sustained in such individuals. Based on advances in the understanding of the molecular mechanisms of viral infection and replication, a series of new antiviral drugs has been developed and tested recently in clinical trials.[14-20] The antiviral compounds found effective for the treatment of VZV infections are acyclovir (Zovirax), valaciclovir (Valtrex), famciclovir (Famvir), and foscarnet. The first three are guanosine (nucleoside) analogues that inhibit viral DNA synthesis by competing with deoxy-guanosine triphosphate as substrate for the viral DNA polymerase. Acyclovir, the prototype of these drugs, has been pursued in several clinical trials and experimental model systems since the early 1980s. The mechanism of action of the drug is based on the selective activation (monophosphorylation) by the product of a viral gene (thymidine kinase), then further activation (di- and tri-phosphorylation) by cellular proteins (kinases); the active acyclovir acts as both competitor and chain terminator for the viral DNA polymerase. Nucleoside analogues cannot prevent virally induced cell damage or death, but they reduce the number of virion produced in the cells and thus prevent or inhibit the intercellular spread of infection. Valaciclovir is a chemical derivative of acyclovir that has more recently been developed and tested. While less than 50 percent of orally administered acyclovir is bioavailable, oral valaciclovir is absorbed readily and converted enzymatically into acyclovir in the liver. Famciclovir is the orally bioavailable analogue of penciclovir. Penciclovir-triphosphate has a longer half-life in infected cells. Foscarnet, another viral-DNA-polymerase inhibitor is recommended for intravenous use as an alternative treatment in acyclovir/famciclovir resistance. The treatment regimens for the therapy of varicella and zoster in patient groups classified by age, cause, and level of immunosuppression – as recommended at a clinical staff conference held at the National Institutes of Health – have recently been reviewed in detail.[6] The recommendations are summarized in **Table 1**. The management of most common HIV-related opportunistic infections (including those caused by herpesviruses) have more recently been reviewed.[21] Drugs reported to interact with famciclovir include cimetidine (Tagamet, used commonly for peptic ulcers) digoxin (Lanoxin, cardiotropic drug), and theophylline products (in a variety of medications, e.g., for bronchospastic conditions). Intravenous administration of acyclovir or foscarnet requires hospitalization, as does oral antiviral therapy in patients with pneumonitis, disseminated disease, or drug-resistant lesions and in more severely compromised patients. In neonates, children, and women early in their pregnancies, valaciclovir and famciclovir are not recommended because of the lack of trials concerning the toxicity of the drugs. Famciclovir should be used with caution in patients with renal function impairment.

Early intervention is recommended for the treatment of pain in the acute zoster phase before the onset of chronic postherpetic neuralgia. Clinical trials attest to the efficacy of high-dose acyclovir and its derivatives in alleviating acute pain and preventing chronic neuralgia. However, there are no surefire cures for the acute pain of shingles, and the management of chronic pain remains difficult. Low doses of tricyclic

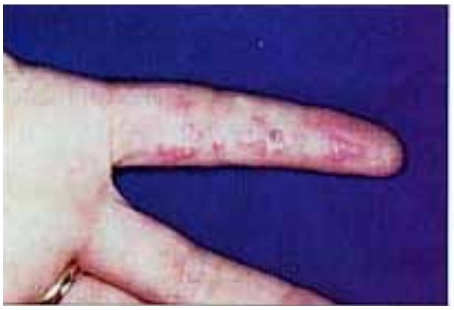

Figure 4. Herpetic Whitlow.

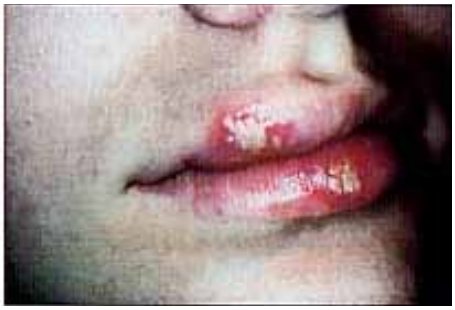

Figure 5. Herpes labialis.

antidepressants such as amitryptyline (Elavil) and the addition of the anticonvulsant gabapentin (Neurontin) to standard pain-management regimens have been effective.[19] Regional blocks of nerve roots or ganglia may provide relief in some patients. Topical anesthetics such as 2 percent lidocaine viscous applied with cotton swabs[22] or in anesthetic rinses are helpful for lesions limited to the oral mucosa. Applications of over-the-counter preparations containing capsaicin (extract of chili pepper, Zostrix, Capzasin-P) may be beneficial in individual cases as desensitizing regimens, but the active ingredient causes extreme irritation and burning of the mucosa. Prescription narcotics are recommended for severe cases. The use of systemic corticosteroid treatment to prevent postherpetic neuralgia (presumably by suppressing inflammation in dorsal root ganglia) has been discussed critically for some time.[23] However, at least one placebo-controlled clinical trial indicates that acyclovir/prednisone combination therapies provide considerable benefits in the management of postherpetic pain in patients in which high-dose corticosteroids are not contraindicated.[14,24]

In the United States, vaccination against VZV infection is indicated for immunocompetent people older than 12 months without history of varicella. In children older than 12 years and adults, the administration of two doses of the vaccine, four to eight weeks apart, is recommended because they respond less well to a single dose.[6,25-27] For the universal immunization of children, several countries have adopted the use of vaccine preparations containing live attenuated varicella virus derived from the Oka-strain (originally isolated in Japan from a child with varicella). The Oka vaccine currently marketed in the United States is estimated to be about 70 percent to 90 percent effective, and children who acquire chickenpox in spite of vaccination experience significantly milder symptoms.[6] In immunocompetent individuals, the vaccine is safe. In most recipients, it causes subclinical infection; in less than 20 percent of cases, the vaccines may cause a fever or varicella-like rash. There is risk of infectious viral transmission from vaccines that cause a rash (even before the onset of the rash) to previously unexposed individuals; although the risk is low, it is advisable for people at high risk for complications from varicella (pregnant women and the immunocompromised) to avoid close contact with recently vaccinated people. Zoster due to the reactivation of the Oka strain in vaccine recipients is not considered to be a significant problem as the incidence of zoster in vaccinated children does not appear to exceed zoster rates found in naturally infected children (as reviewed by Krause and Straus[27]). The Oka strain vaccine is contraindicated in immunocompromised individuals, because of the significant risk of severe vaccine-induced varicella; in pregnant women, because of the risk of fetal varicella syndrome in early pregnancy and the risk of severe clinical infection in late pregnancy; and in people with history of hypersensitivity to vaccine components. In these groups, postexposure prophylaxis with anti-VZV immunoglobulin, and in some cases with oral acyclovir, is recommended.[6]

Primary and Recurrent HSV-1 Infections

The cause of primary herpetic gingivostomatitis is infection with HSV-1, but oral disease with identical clinical manifestations may also be caused by the genital type HSV-2 when the latter is transmitted by genito-oral or oral-oral contact. Recent molecular epidemiologic studies have substantiated the notion that most HSV-1 genotypes are often shared by genital and nongenital lesions.[28] It is also apparent that initial genital HSV-1 may be acquired through oral contact, as evidenced by cross-sectional analyses of data collected in urban sexually transmitted disease clinics from patients who had positive genital HSV cultures.[29] The development of immunity to HSV is not well-understood, but cross-immunity between these two HSV types is known to develop so that previous exposure to one type results in milder manifestations of infection with the other.[30]

Primary infection with HSV-1, or primary herpetic gingivostomatitis, seen most often in children, is characterized by fever, malaise, lymphadenopathy, and multiple crops of vesicular eruptions located on the attached gingiva and movable mucosa of the oral cavity; the oropharyngeal mucosa and the conjunctiva may be involved.[8,9] The vesicles rupture easily and leave small ulcers covered by a pseudomembrane and surrounded by erythema (**Figure 3**). The infected patient, as well as susceptible

people in contact with the patient, may show the typical sign of herpetic whitlow (viral, primary or recurrent, vesicular or pustular dermatitis of the finger) (**Figure 4**). In immunocompetent patients, the primary infection runs its course within one to two weeks without scarring. In children with herpetic gingivostomatitis, eating and drinking difficulties, fever, and drooling may often lead to dehydration.[31]

The prevalence of recurrent or recrudescent disease in the general population has been estimated as 20 percent to 40 percent worldwide and 35 percent to 38 percent in the United States.[32] HSV-1 is ubiquitous and highly contagious. Approximately 60 percent to 80 percent of American adults are latently infected, i.e., asymptomatic HSV-1 seropositive.[27] De novo infections similar in course to primary infections may develop in seropositive individuals on contact with active lesions of other patients or even through self-inoculation. The highest risk of transmission is during the limited time span of viral shedding during active infection (one to four days, but prolonged in immunocompromised patients). The possibility of contagion due to viral shedding into saliva or genital secretions during asymptomatic infection should be taken into account, albeit the risk is considerably lower than in contact with active lesions. Reports of viable HSV contaminating door handles and passing through latex gloves damaged by solvents[32] emphasize the need for proper infection control in the dental office.

Significant knowledge has accumulated over the past few years regarding the cellular/molecular mechanisms of latency and reactivation of HSV infection.[5,33] For example, latency-associated genes of several herpesviruses have been discovered, and it is known that latent HSV genomes express latency-associated transcripts, which are antisense to cellular regulatory proteins. To date, however, there are no known encoded proteins associated with HSV-1 latency-associated transcripts, and how the latency-associated transcripts function in HSV-1 latency remains obscur.[5] The models proposed to explain HSV-1 pathogenesis on reactivation from dormancy, and the putative role of mucosal immunity in reactivation have been reviewed thoroughly by Oakley and colleagues.[34] It appears that in HSV reactivation, only a few neurons become involved, whereas in VZV infection, replication from numerous neurons is required for reactivation.[5] This would account for the relatively small and focal lesions in typical recrudescent HSV-1-associated herpes, as compared to those of zoster. However, the symptoms of recrudescent or recurrent HSV infection may range from subclinical to debilitating, depending on the level of impairment of the host's immune surveillance mechanisms.

The list of known triggers of HSV reactivation includes stress, surgical trauma, dental extraction, menses and other hormonal changes, infectious febrile conditions and hyperthermia, ultraviolet radiation, and drugs such as corticosteroids and prostaglandin E2.[34,35] Two cases of oral mucosal HSV infection associated with the radiotherapy of the head and neck have recently been described.[34] In these cases, a combination of triggering factors, including stress in one case and HIV- and drug-induced immunosuppression as well as concurrent cytomegalovirus infection in the other, were recognized. In the general population, the typical manifestation of recurrent HIV-1 infection is herpes labialis ("cold sores"): unilateral vesicular eruptions surrounded by erythema, followed by crusting and healing. The eruptions are sometimes preceded by a prodromal tingling sensation (**Figure 5**). Oral mucosal lesions are rare, nonfebrile, and usually restricted to small clusters of microvesicles that rupture to leave punctate ulcers, typically on the palatal gingiva (occasionally elsewhere on the gingivae) unilaterally (**Figure 6**). The lesions are self-limited, resolving within one to four days[8,9]. Extensive or persistent lesions of both primary and secondary infections should raise the suspicion of immunosuppression. In HIV-infected patients, there is a risk of disseminated lesions with severe morbidity, including herpes encephalitis. Such risk has declined with current antiviral therapies; but, in advanced AIDS, it remains a serious problem, especially in developing countries.

The differentiation of uncomplicated oral mucosal HSV infection from recurrent aphthous ulcers is based on the presence of elevated temperature in primary herpetic gingivostomatitis and the unilateral appearance of the microvesicles in the palatal mucosa in typical recurrent intraoral HSV infections. The widely held distinction between recurrent aphthous ulcers and recurrent HSV on the basis of distribution (always on the nonkeratinized mucosa in the former, and mainly on the keratinized surfaces of the palate, gingiva, alveolar mucosa or alveolar ridge in the latter) still largely holds true, as indicated by the findings of a recent study of 52 immunocompetent patients with positive HSV cultures.[36] However, a minority (roughly 10 percent in this series) of HSV-positive ulcerations occurred on the nonkeratinized mucosa, a feature often reported in immunocompromised individuals. The differential diagnosis of mucosal HSV-1 infection also includes the oral mucosal vesicles of hand-foot-and-mouth disease. The latter, seen

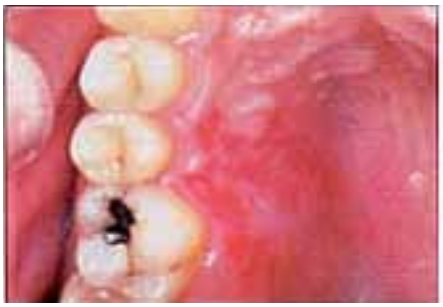

Figure 6. Recurrent palatal herpes.

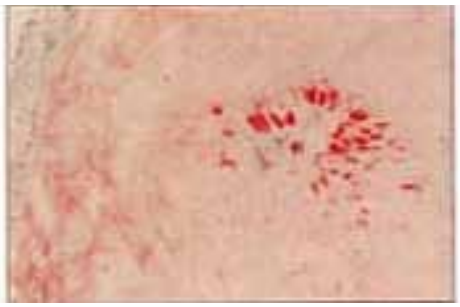

Figure 7. DNA in situ hybridization with red chromogen localizing HSV1 in oral epithelial cells from a herpetic lesion.

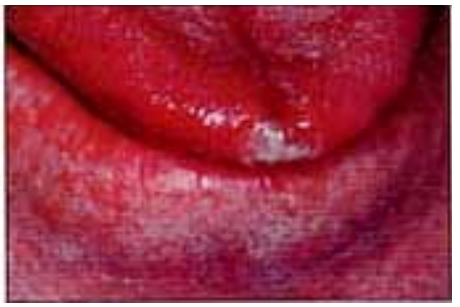

Figure 8. CMV ulceration in an HIV-seropositive patient. This also harbored HSV.

mostly in children, can be diagnosed and distinguished easily from HSV-1-induced herpetic stomatitis by positive Coxsackie virus culture (from the lesions or stool) and the presence of concomitant vesicular eruptions on the skin of extremities. Similarly, positive viral Coxsackie virus culture and the limited distribution of the vesicles on the oropharynx are diagnostic of herpangiana.

For the definitive diagnosis of HSV, viral culture from swabs of active lesions has been considered the gold standard, but the usefulness of this method is limited by the relatively short time span of viral shedding and by the relatively low number of viral particles present in the samples. Immunocytochemistry with anti-HSV antibodies and in-situ hybridization with HSV-nucleic acid probes applied to biopsy sections of early lesions are sensitive alternatives to viral culture (**Figure 7**). Polymerase chain reaction-based methods, albeit less cost-effective, are highly sensitive, specific, and applicable to samples in the absence of symptomatic shedding. However, the sample collection and the interpretation of positive polymerase chain reaction results of the swabs should take into consideration the possibility of normal shedding of viral DNA in saliva, peripheral blood, and exfoliated epithelial cells distant from the active ulcers. This is less of a problem in immunocytochemistry and in situ hybridization applied to biopsy samples. Biopsy samples have the added advantage that sections from them can be subjected to multiple testing for coinfection with other pathogens and that the histopathological features of viral cyptopathic changes such as intraepithelial vesicles with eosinophilic inclusion bodies and clear cell ballooning (common characteristic of infections with herpesviruses) can be corroborated with the molecular findings.

Primary and recurrent oral HSV infections in immunocompetent patients are self-limited, generally requiring only symptomatic treatment. For first episodes of painful mucosal HSV infection, acyclovir 5 percent ointment (Zovirax) applied hourly at the onset of symptoms is known to reduce the extent of viral shedding and pain, but it provides little benefit in recurrent herpes labialis. For recurrent herpes labialis, penciclovir 1 percent (Denavir) cream applied every two hours (while awake) for four days, starting at the onset of symptoms, is recommended. This regimen has been found to significantly decrease the mean duration of lesions and pain and to be well-tolerated.[17] However, more studies are needed to establish the efficacy of this topical nucleoside analogue in primary infections and immunocompromised patients. Systemic medication is required in patients experiencing six or more painful episodes per year. Studies show that at least in genital herpes, valaciclovir 500 mg only twice daily provides the pharmacological benefit of 200 mg of acyclovir administered more frequently (five times daily).[17] Famciclovir is effective in reducing shedding time and the severity symptoms of genital herpes in HIV-infected patients.[37] Multicentric, controlled clinical trials have indicated that famciclovir (at 500 mg four times daily) also promotes healing in experimental UV-radiation-induced labial herpes in volunteer subjects.[38] However, in immunocompetent patients, the benefits of oral medications with nucleoside analogues should be weighed against potential side effects, as well as costs. For acyclovir, the following have been reported in the first year or so of use in 1 percent to 5 percent of patients: nausea, diarrhea, headaches, and rash. Paresthesia/esthesia, also in a minority of patients, is reported with more prolonged use. The frequency and severity of these symptoms rarely necessitate discontinuation of the treatment with acyclovir, but famciclovir is expensive and knowledge of its toxicity is still lacking. The treatment of severe, complicated, and disseminated HSV infections requires hospitalization. Valaciclovir 500 mg twice daily was found effective for HSV-suppression in a randomized, controlled study of HIV-infected subjects with CD4 lymphocyte counts higher than 100. For the treatment of recurrent genital herpes, valaciclovir is relatively well-tolerated at this dosage[39] However, as found in cases of advanced AIDS, valaciclovir prophylactic therapy with high doses (8 g/day) increases the risk of thrombotic microangiopathy, which is potentially fatal.[39] Foscarnet has been shown to be

effective in resistant herpetic infections in adults and in very severe cases in children.[23,39,40]

Several new strategies have been explored in the experimental development of genetically engineered HSV-DNA vaccines.[27,41-46] The aim is to obtain vaccines that are highly immunogenic but nonpathogenic. Efforts have been directed primarily at preventing the acquisition and recurrence of genital herpes, which would be particularly important in preventing neonatal infection, for example. Earlier attempts with vaccines containing killed viruses failed to produce adequate immunity. New strategies are aimed at creating a live "mutant" virus with a limited replication capacity in vivo, or recombinant DNA plasmid vaccines; genes that have been associated with virulence are deleted from the latter, but they contain DNA sequences encoding for viral proteins that are capable of eliciting natural immunity when injected directly into the tissues. Such strategies are currently being tested with considerable promise in animal models of genital herpes. Further, plasmid DNA carrying sequences encoding for the glycoprotein D of HSV-1 are being tested for immunogenicity in experimental animal models;46 however, much is still to be learned about the molecular mechanisms of immunogenicity of both HSV-1 and -2.

HSV and Erythema Multiforme

Erythema multiforme is an acute, polymorphous mucocutaneous disorder of complex etiology, often associated with drugs, mycoplasma, and HSV infection. It is now accepted that erythema multiforme minor, erythema multiforme major, Stevens-Johnson syndrome, fixed drug reactions, and toxic epidermal necrolysis are parts of a single spectrum of disease. The typical skin lesions are characterized by papules that develop into "target" lesions (a zone of central necrosis with peripheral erythema). The lesions may be limited to the skin, or they may be accompanied by mucosal lesions. In the oral cavity, they are characterized by bullae and vesicles that rupture to form raw, erythematous ulcerations or ragged erosions.[8,9] The pathogenesis of HSV-associated erythema multiforme has not been elucidated, but it has been postulated to be attributable to viral protein products that act as superantigens in the tissues, eliciting specific cell mediated immunity with the production of cytokines that mediate cellular signaling cascades ultimately leading to epithelial cell death.[47,48] The treatment of HSV-associated erythema multiforme is often difficult, and the various regimens suggested for its management have not been proven by rigorous clinical trials. The therapeutic dilemma is whether priority should be given to corticosteroid treatment of the immunopathologic condition of erythema multiforme or to the antiviral treatment of HSV. According to at least one recent study,[47] the treatment should be considered carefully in each individual case taking into consideration the severity of the lesions and individual response to antiviral drug therapy, but corticosteroids should be considered as a mode of treatment in all HSV-induced erythema multiforme, especially in cases of failure of antiviral therapy.

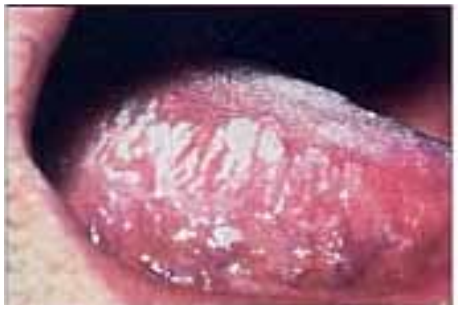

Figure 9. Oral hairy leukoplakia (Epstein Barr virus).

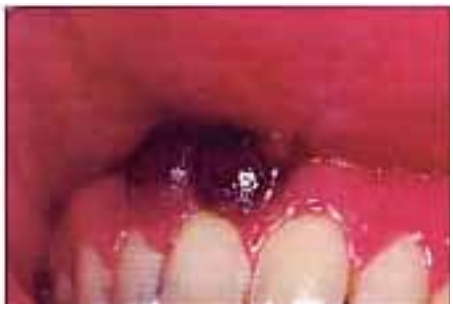

Figure 10. Herpesvirus 8 is associated with Kaposi's sarcoma in an HIV-positive patient.

Other Herpesviruses

In immunocompetent individuals, cytomegalovirus infections are rare, but they are a cause of severe morbidity (e.g., retinitis, esophagitis, pneumonitis) and mortality in severely immunocompromised patients. Even in moderately immunocompromised adults and children, cytomegalovirus-associated mucosal lesions may mimic those of other viral or nonviral ulcerative lesions, including those of recurrent aphthous ulcers, persistent and recurring herpetic stomatitis, and necrotizing stomatitis[34,40,49,50] (**Figure 8**). A definitive diagnosis can only be made through the specific identification of the virus in culture, or the detection of cytomegalovirus DNA or antigens in biopsy specimens. Characteristic ballooning of cytomegalovirus-infected cells (cytomegaly) and typical inclusion-bodies are pathognomonic histomorphological features.[49] Until recently, Ganciclovir (administered intravenously in severe cases) has been the drug of choice in AIDS-associated cytomegalovirus infections; however, it does have significant side effects due to the toxicity of the drug.[18] A number of clinical trials are ongoing to establish the efficacy of alternative therapies. Valaciclovir has been tested in preventing cytomegalovirus infection in advanced HIV-disease patients and bone marrow and renal transplant recipients.[17,51] Recent data have confirmed the expectation

that valaciclovir is effective not only in the prophylaxis of cytomegalovirus-associated morbidity, but also in reducing the frequency of acute graft rejections in transplant patients.[39]

Epstein Barr virus is the major cause of infectious mononucleosis, a significant etiologic cofactor in the development of Burkitt's lymphoma and nasopharyngeal carcinoma, and has been associated with various other lymphoproliferative disorders, mainly those of the B-cell series. Organ transplant recipients are particularly vulnerable to Epstein Barr virus-induced lymphomas.[52] While the oropharyngeal epithelium is the site of Epstein Barr virus entry and replication, and viral shedding can be detected in saliva, the virus establishes persistent infection of lymphoid cells. In the oral cavity, ulcerations due to Epstein Barr virus infection are rare.[1,49,53] Epstein Barr virus is more commonly associated with oral hairy leukoplakia, which was first defined as a clinical entity in HIV-infected individuals;[54] and it is found more commonly in patients who are immunocompromised. This white hyperkeratotic lesion develops primarily on the lateral border of the tongue (**Figure 9**). Oral hairy leukoplakia and similar Epstein Barr virus-associated lesions have also been reported in immunocompetent patients, but the significance of this condition as a harbinger of emergence from latency in HIV infection should be kept in mind.[9,55]

Human herpesvirus type 8 has been implicated in the pathogenesis of several diseases, most of them neoplastic. Examples of human herpesvirus type 8-associated diseases are Kaposi's sarcoma, a vascular neoplasm found often in AIDS patients (The virus is also known as Kaposi's sarcoma-associated virus.); multiple myeloma; and a subset of lymphomas.[56-58] In the oral cavity, advanced Kaposi's sarcoma may present as ulcerative lesions, but these are distinguishable from HSV-associated ulcers as the former are "tumefactive," or tumor-like lesions (**Figure 10**). They are typically vascular (hemorrhagic), initially presenting as macules or nodules; in Kaposi's sarcoma, the ulceration is secondary to the tumor.[1,9,53,59]

In immunosuppressed patients, oral ulcerations with an atypical presentation have also been attributed to coinfection of HSV-1 with other herpesviruses, namely Epstein Barr virus, cytomegalovirus, and other opportunistic pathogens.[12,49,60] Generally, such lesions are described as single large or multiple ulcerations on any keratinized or nonkeratinized mucosal surface (palate, interdental papilla, buccal mucosa, lateral surface, or tip of tongue).

Other Pathogens in Recurrent Oral Aphthous Ulcers

The advent of highly sensitive and specific methods for the detection of viral and bacterial products in minute amounts of tissue specimens has allowed for the investigation of the role of microorganisms in the pathogenesis of mucosal ulcerative diseases with multifactorial etiology. In several case series, HSV-1, cytomegalovirus, and other human herpesviruses have been found in association with recurrent oral aphthous ulcers.[61-64] A direct causal role for these pathogens has not been established, nevertheless it is plausible that products of the microorganisms have an indirect, cofactorial role at least in a proportion of classical recurrent aphthous ulcer cases. Several hypotheses have been advanced for future testing. For example, products of HSV genes may act as superantigens in activating humoral and local cell-mediated immune responses that in turn may induce or contribute to epithelial cell damage. However, the polymerase chain reaction-based detection of viral nucleic acids in tissue scrapings or vesicular fluid is not sufficient for diagnosis unless it correlates well with clinical and histomorphological features of biopsy samples.

As a general rule, persistent herpetiform lesions, especially those found to harbor VZV, HSV, cytomegalovirus or Epstein Barr virus should raise the suspicion of immunosuppression. In these cases, hematologic testing for indicators of immune functions (T4:T8 lymphocyte ratios and CD4 lymphocyte counts) is recommended.

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Papillary Lesions of the Oral Cavity: Relationship to Human Papillomaviruses

Lewis Roy Eversole, DDS, MSD, MA

ABSTRACT Human papillomaviruses are a group of genetically related organisms that infect stratified squamous epithelium. Unlike many other viruses that infect oral epithelium and induce lysis of the cells they penetrate, HPVs induce proliferative changes in these cells that result in both benign and malignant tumors. The common skin wart (verruca vulgaris) is induced by HPV 2 and 4. Genital warts (condylomas) and the common solitary oral papilloma are associated with HPV 6 and 11. Either HPV 13 or 32 causes focal epithelial hyperplasia. All of these wart-like lesions are benign growths of the stratified squamous lining of the oral cavity and lips and can be treated by surgical excision or laser ablation. HPV 16 and other less frequently encountered genotypes are associated with uterine cervix cancer in 95 percent to 98 percent of cases, and the evidence for a causal role is robust. There are emerging data that implicate HPV in certain subsets of oral cancer, particularly those that arise in the oropharynx/tonsillar region. Some instances of the various histologic subtypes subsumed under proliferative verrucous leukoplakia and verrucous carcinoma also harbor HPV.

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Dental practitioners often discover mucosal nodules during the course of an oral soft tissue examination, and these common lesions are usually traumatic fibromas. When found on the lower lip however, they may also be mucous extravasatioin phenomena (mucoceles). Occasionally, mucosal nodules will exhibit a bosselated or cauliflower surface texture; or, indeed, some may have finger-like projections. These papillary or verrucous-type lesions are usually associated with and caused by members of the human papillomaviruses. There are more than 120 genetically different, yet closely related HPVs that are referred to as genotypes.[1] The genotypes are numbered in order of their initial discovery (i.e., HPV 1 was the first human papillomavirus to be discovered; HPV 118 is one of the more recent genotypes to be isolated from human tissues). The various genotypes have specificity for certain human cell types and cause distinct types of lesions. **Table 1** lists the

more common HPVs that cause lesions of the head and neck. Most oral and labial papillary lesions are HPV-associated and are self-limited benign growths that do not progress to cancer.

The so-called mucosatropic oncogenic HPVs have a tropism (affinity) for the stratified squamous epithelium of mucous membranes and are associated with carcinomatous transformation. The association between HPV 16, 18, 31, 33, 35 and a few others with squamous cell carcinoma of the uterine cervix is extremely high.[1,2] HPV DNA can be detected in nearly 95 percent of cervical squamous cancers. Oral cancer is also found to harbor HPV genomes, yet the association is not as frequently detected as it is in the cervix, even though both mucous membranes are lined by the same type of epithelium. This article will briefly discuss the molecular basis for HPV-induced epithelial proliferation and detail the clinical features of HPV oral lesions.

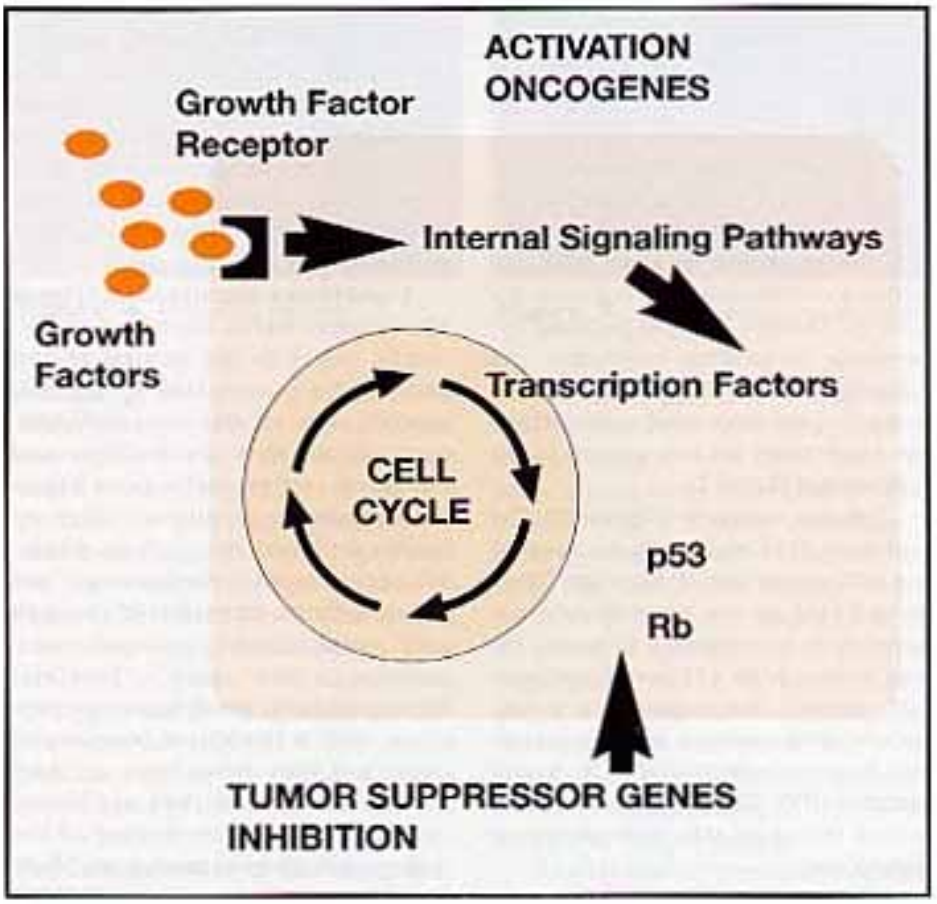

Figure 1. Mechanisms of HPV-associated carcinogenesis. HPV E6 binds to p53 and degrades it, or p53 is mutated and nonfunctional thereby leading the cell into uncontrolled mitosis.

HPV Effects on Oral Epithelia

The HPVs are small when compared with the large herpes group viruses that commonly infect the oral cavity (see the article in this issue by Birek). HPV is a DNA virus about 8,000 nucleotide bases long. Its genome is divided into two major gene groups: E, or early region genes, and L, or late region genes.[3] These genes are also known as open reading frames, and they encode proteins with important biological activity. The early region gene products are proteins that are important for viral replication and also have affects on host cell gene expression, whereas the late region genes encode the proteins that make up the structural components of the virus, particularly its capsid. It is the early genomic region that has the greatest significance for viral-induced changes in the host cells.

HPV must adhere to a specific receptor protein on the keratinocytes membrane in order to be assimilated into the cell by a process known as endocytosis (**Figure 1**). Once the virus has gained entry into the cell, it divests itself of its protein coat, and the viral DNA may then utilize host cell DNA building blocks to replicate themselves. These clever viruses elaborate early gene proteins that are able to regulate the host cell cycle, or mitotic capabilities. The E6 and E7 proteins are most important in this respect; they bind two host proteins that are regulators of the keratinocytes' cell division cycle.[4] E6 binds to a protein designated p53, a molecule that arrests cell division; however, once bound, it is degraded, and this inhibition of keratinocyte mitosis is abrogated. Likewise, E7 binds a protein termed Rb; and, similarly, cell cycle regulation is perturbed.

The hallmark of malignancy is uncontrolled cell division and changes in the surface chemistry of cancer cells that allow for invasion and metastasis. It is axiomatic that certain HPV early region proteins are able to place the cell in a state of perpetual mitosis, thereby being candidates for inducing malignant change. Benign HPV growths, caused by genotypes that do not induce malignancy, must also affect cell cycling in order to induce epithelial proliferation, yet these growths somehow remain limited in extent and the cells lack the properties of invasion and metastasis. In this regard, experimental evidence has shown that HPV 11 can cause warty growths when inoculated onto normal mucosal epithelium.

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Table 1.

Human Papillomaviruses and Head and Neck Lesions

Genotype	Disease
HPV 2, 4	Verruca Vulgaris
HPV 6, 11	Condyloma Acuminatum, Squamous Papilloma
HPV 13, 32	Focal Epithelial Hyperplasia
HPV 16	Proliferative Verrucous Leukoplakia Subtypes
HPV 6, 11, 16	Verrucous Carcinoma
HPV 16, 18	Squamous Cell Carcinoma

Table 2.

Papillary Oral Lesions Without Known Viral Association

Papillary hyperplasia (Papillomatosis)
Verruciform xanthoma
Cowden syndrome
Nevus unius lateris
Acanthosis nigricans

Benign Papillary Growths

The three papillomavirus-induced warts that arise on the lips and in the oral cavity are verruca vulgaris, squamous papilloma, and condyloma acuminatum. The genotypes associated with these three lesions are designated in **Table 1**. All are benign proliferations of keratinocytes that show minor histologic differences. In addition to these three lesions, there are numerous other papillary growths of the oral cavity for which a viral etiology has not been discovered. Denture-induced papillary hyperplasia, verruciform xanthoma, and a variety of other diffuse papillary lesions that are associated with particular syndromes do not appear to be HPV-related (**Table 2**).

Verruca vulgaris (**Figure 2**): The common skin wart may be seen in the oral cavity but is far more likely to be found on the lower lip where is appears as a symmetrical round-to-oval nodule with a crusted hyperkeratotic center.[5] Histologically, it is verrucous with marked hyperkeratosis and is entirely exophytic with abrupt margins. HPV DNA can be readily detected using in situ hybridization techniques.

Squamous papilloma (**Figure 3**): This is the most common epithelial neoplasm in the mouth and is typically seen on the lingual frenum, lips, palate, and buccal mucosa.[6] The lesion has fine finger-like projections resembling a sea anemone or it may show a more cauliflower configuration. Papillomas can be pedunculated, on a stalk, or have a wide sessile base. Papillomas range from coral pink to white, depending upon the degree of keratinization. Histologically, the exophytic papillary growths are supported by fine connective tissue cores

Condyloma acuminatum (**Figure 4**): Venereal warts, known as condylomas, occur in the genital region and can be transmitted to the oral mucosa. The lesions are rarely solitary; rather, they are multiple and confluent and generally quite bigger than squamous papillomas.[7] They are sessile and may be pink or white. Whereas most condylomas are thought to be transmitted through genito-oral contact, oral-oral transmission is also feasible. Microscopically, condylomas are papillary with a thickened parakeratin layer; and they differ from ordinary papillomas in that they are sessile and show marked thickening of the spinous cell layer (acanthosis). Many also show HPV-specific cytologic changes. The infected upper spinous layer cells have irregularly shaped nuclei with a perinuclear clear halo and are termed koilocytes.

Papillary hyperplasia (**Figure 5**): Also known as papillomatosis, papillary hyperplasia is a reactive inflammatory proliferation that underlies maxillary dentures. Negative pressure is probably the chief factor that contributes to the lesion confined to the denture-bearing region of the hard palate. The diffuse pebbly surface is either of normal coral pink coloration or may be inflamed and red. Histologically, mushroom-like polyps composed of a fibrous core with hyperplasia of the overlying epithelium are observed.

Verruciform xanthoma (**Figure 6**): Papillary lesions that contain lipid-laden foamy histiocytes in the submucosa are referred to as verruciform xanthomas.[8] Clinically, they are broad-based sessile lesions with a papillary, pebbly surface and are often slightly erythematous. They tend to occur on the gingiva and palate, yet may be seen in any oral location. Xanthelasma of the eyelids, a lesion of hyperlipidemia, is closely related in terms of the histologic features, yet verruciform xanthomas have not been correlated with high blood cholesterol or lipid levels. Histologically, the lesions are papillary with a prominently eosinophilic thickened parakeratin layer. The submucosal papillae that extend up between the papillary epithelial projections are infiltrated with foam cell histiocytes.

Syndrome-associated papillary lesions: As shown in **Table 2**, there are a number of rare syndromes in which extensive and diffuse papillary lesions may be seen in the oral cavity.[9] In Cowden syndrome, the gingival tissues are diffusely papillary, yielding a cobblestone street pattern. Patients with Cowden syndrome also manifest thyroid tumors, skin nodules, and other abnormalities. Nevus unius lateris is a skin lesion that may occur anywhere on the body. When in the facial region, it may progress into the

Figure 2. Verruca vulgaris of the lip.

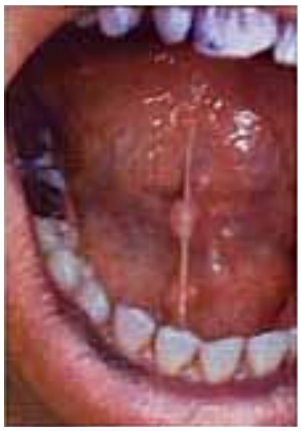

Figure 3. Papilloma on the lingual frenum.

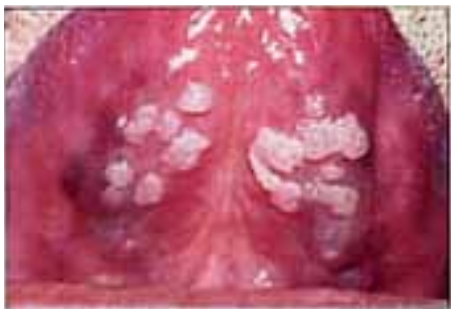

Figure 4. Multiple papillary lesions represent condylomas.

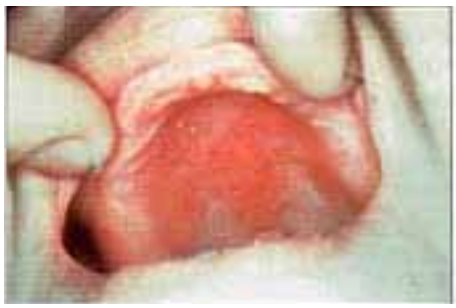

Figure 5. Papillary hyperplasia of the palate.

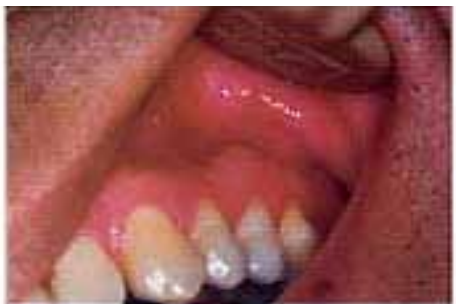

Figure 6. Verruciform xanthoma.

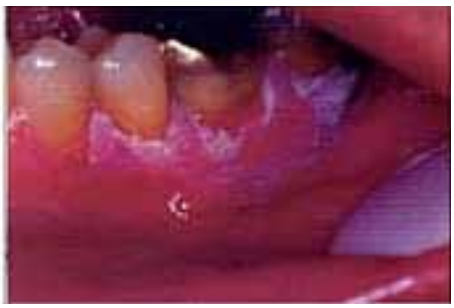

Figure 7. Proliferative verrucous leukoplakia.

oral cavity. The skin lesions are verrucous and keratotic, being oriented in a linear streak. Orally extended lesions may cover the lips and involve the buccal mucosa or gingiva, assuming a pink diffuse papillary appearance.[10] Acanthosis nigricans is a pigmented papillary lesion of the lips and mucosa that is often hereditary.[11] One form is a harbinger of gastrointestinal tract cancer. The lesions diffusely involve the upper and lower lips; and because the basal cell layer contains excess melanin pigment, the lesions have a mottled gray or brown coloration.

Precancerous and Cancerous HPV-Associated Lesions

As mentioned earlier, HPV likely causes uterine cervix cancer. Recent research has confirmed that some oral precancerous and cancerous lesions contain HPV DNA, and the same mechanisms involving binding of p53 by HPV E6 may contribute to carcinogenesis of oral malignant disease. The oral lesions that are malignant or potentially malignant for which HPV has been identified include proliferative verrucous leukoplakia, verrucous carcinoma, papillary squamous cell carcinoma, and invasive poorly differentiated squamous cell carcinomas arising in the tonsillar/base of tongue region.

Proliferative verrucous leukoplakia is a unique type of leukoplakia that tends to occur in elderly females, less than 40 percent of whom have used tobacco.[12] The lesions are usually located on the buccal gingiva and extend into the vestibule (**Figure 7**). They are white, diffuse and have a rough warty or verrucous appearing surface. Following surgical excision, these leukoplakias have a marked tendency to recur and spread laterally along the mucosal surface. PVL is a clinical term under which a variety of histologic stages of disease can be observed. In the early stages, the histologic picture is that of a verrucous hyperkeratosis that may become progressively more keratotic and acanthotic; it is then termed atypical verrucous hyperplasia. After many years, these lesions can progress to verrucous carcinoma, papillary squamous cell carcinoma, or invasive carcinoma. HPV DNA has been identified in many of these lesions and may be a significant carcinogenic factor, although a passenger virus status cannot, at this time, be eliminated.[13]

Verrucous carcinoma usually evolves from a pre-existing verrucous

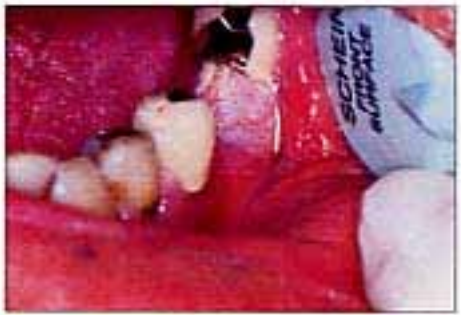

Figure 8. Verrucous carcinoma.

leukoplakia and has a characteristic histologic appearance, although oftentimes the pathologist encounters lesions that are midway between a verrucous hyperkeratosis and verrucous carcinoma. Clinically the lesions are diffuse, involving the gingiva, alveolar ridge, palate, and sulcus. They are rough, white, and warty in appearance (**Figure 8**). The term carcinoma is misplaced here since verrucous carcinomas do not have metastatic potential. In previous articles, instances of metastasis have been reported, yet some of these cases may have represented the recently described papillary variant of squamous cell carcinoma.[14] Regardless, these relentless lesions are locally aggressive and have the potential to involve large surface areas of the oral cavity. HPV DNA is often detected in these tumors.[15] Microscopically, they show a verrucous surface with parakeratinized crypts that involute into enlarged rete-ridge extensions. Actual invasion is not present.

Squamous cell carcinoma is an invasive cancer that can metastasize to regional lymph nodes and distant sites via hematogenous routes. The malignancy arises from stratified squamous epithelium, and while these tumors may occur anywhere in the oral cavity, the lateral tongue and floor of mouth are predilected sites. HPV DNA can be detected in many, yet not all oral carcinomas. About 30 percent will harbor HPV, and most of these are HPV 16. Recently, a group of reports have been published linking the majority of squamous cell cancers to HPV 16 when the lesions are localized to the tonsillar pillar/base of tongue region.[16,17] Tumors in this location are generally poorly differentiated. When HPV 16 is detected, p53 is not usually mutated thereby implicating an E6 mediated p53 degradation mechanism.

Summary

The human papillomaviruses are unique viral forms capable of inducing cell proliferation, particularly in keratinocytes. The benign lesions assume a papillary or verrucous appearance and specific genotypes are responsible for the clinicopathologic variations seen in papillary lesions. HPV 2 and 4 cause the common verruca vulgaris, whereas HPV 6 and 11 are involved in squamous papillomas and condylomas. HPV 13 and 32 are associated with the transient rare mucosal disease, focal epithelial hyperplasia. Premalignant lesions of the oral cavity, particularly proliferative verrucous leukoplakia, can harbor HPV DNA, and the more aggressive verrucous carcinoma has also been shown to be associated with the virus. Recently, the majority of tonsillar region squamous cancers have been found to be associated with HPV 16, a genotype that elaborates any early gene product that degrades p53, a key tumor suppressor gene. Once degraded, the mitotic cycle continues unchecked thereby placing the affected cell in a state of increased proliferative activity. How HPV affects cell motility, invasiveness, and metastatic potential is not yet understood.

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The Bullous Desquamative Lesions of Oral Mucosa

Sol Silverman, Jr., MA, DDS

ABSTRACT The most common of the bullous/desquamative diseases that affect the mouth include the erosive form of lichen planus, erythema multiforme, pemphigoid, and pemphigus. This overview looks at the clinical features and diagnosis of these diseases. In addition, treatment options are discussed.

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The blistering or bullous diseases comprise a group of mucocutaneous immunopathic inflammatory lesions that can affect mucosal surfaces and/or skin. With few exceptions, these conditions are not readily associated with any specific identifiable etiologic factors. As science progresses, the basic explanation will no doubt be associated with genetic chromosome deletions, transocations, or acquired mutations that alter epithelial-epidermal chemistry, which in turn attract immune cells (lymphocytes), resulting in cytokine release-induced reactions.[1] These reactions most often have clinical and microscopic characteristics that allow a specific diagnosis.[2-4]

The most common of the bullous/desquamative diseases that affect the mouth include the erosive form of lichen planus, erythema multiforme, pemphigoid, and pemphigus. This overview will be limited to these entities.

Clinical Features

The cause of lichen planus is unknown. Lichen planus has three general forms: reticular (white lace-like keratotic pattern [Wickham's striae]); atrophic (a red or erythematous component); and erosive (varying degrees of ulceration along with white and red changes) (**Figures 1, 2 and 3**). The main patient complaints are pain, discomfort, and irritation, with concerns for infectiousness and the potential risk of malignant transformation.[5] There are oral conditions in which the clinical appearance resembles that of lichen planus as does the histology, yet the features are not classic (i.e., striae are absent, basal cell lysis is not evident microscopically). Such lesions are often

Figure 1. Reticular lichen planus, buccal mucosa.

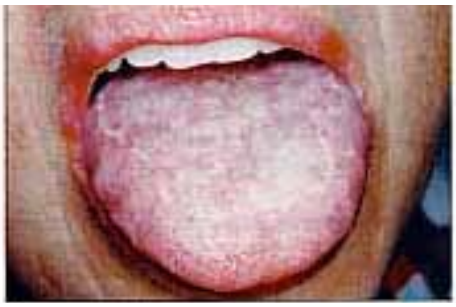

Figure 2. Reticular lichen planus, tongue.

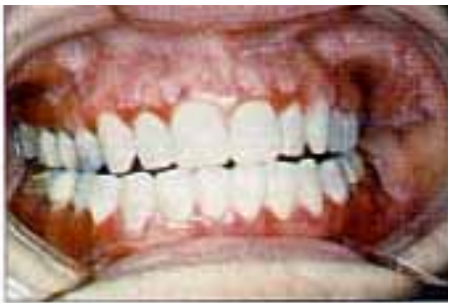

Figure 3. Atrophic lichen planus, gingiva and buccal mucosae.

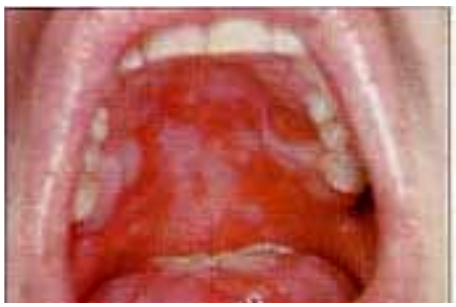

Figure 4. Erythema multiforme, palate.

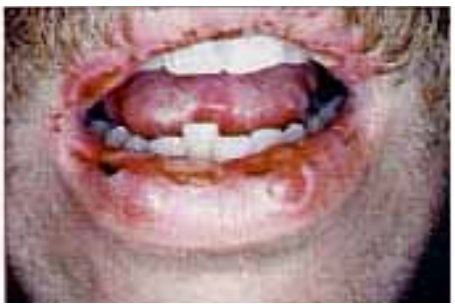

Figure 5. Erythema multiforme, lips.

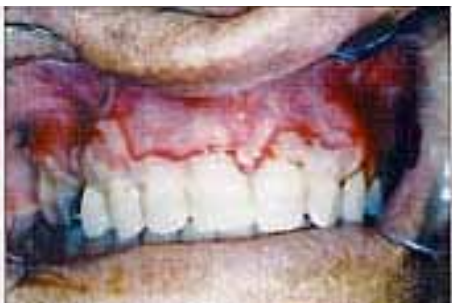

Figure 6. Mucous membrane pemphigoid, gingiva.

referred to as "lichenoid" and may be indicative of a contact or delayed type hypersensitivity to an exogenous antigen such as cinnamon or mercury from dental restorations. Yet other lichenoid reactions are idiopathic.

Erythema multiforme can appear as a red, red-white, or red-white-ulcerative manifestation (**Figures 4 and 5**). Involvement of the lips is a typical feature, but it is not always seen. The outbreak can be chronic or cyclical and is usually associated with pain. Erythema multiforme represents a hypersensitivity reaction; but in oral erythema multiforme in contrast to skin presentations, a causative agent usually cannot be identified. Often the skin lesions present as "target" or "bull's-eye" lesions.

Mucous membrane pemphigoid will usually occur as a red or red-erosive change (**Figure 6** and **Figure 7**). The gingiva is the most common site, accounting for the archaic term "desquamative gingivitis."[6] Mucous membrane pemphigoid in a small number of cases can affect the eyes, causing a symblepharon (a fibrous scar between the lower eye lid and the conjunctiva). Bullous pemphigoid is the cutaneous counterpart to mucous membrane pemphigoid yet involves disparate immunologic targets and mechanisms.

Pemphigus vulgaris is most frequently manifested by bullae and cavernous-appearing ulcers. They can occur on any mucosal surface. While usually both skin and mucosa are involved, in many cases the first signs and symptoms occur in the mouth; and in some cases the skin is never involved (**Figures 8 and 9**). The vermilion borders of the lips are often involved, and this then helps in the clinical differentiation from mucous membrane pemphigoid.

Epidemiology

Adequate population studies have not been done to establish incidence rates or occurrence. Lichen planus is the most common of these diseases. The blistering diseases occur in all ethnic groups, and the initial onset is most often beyond the third and fourth decades of life, with an increasing incidence beyond the age of 50. Clinical reports reflect a moderate female predominance.

These diseases are almost always chronic and are often characterized by flares and mild remissions. While these lesions can occur on any mucosal surface, lichen planus most frequently presents on the buccal mucosa and mucous membrane pemphigoid on the gingiva. Occurrence is not related to either tobacco usage or alcohol. There is no evidence of a nutrition factor, although certain foods can cause flares, they are not the basic causative agent.

Table 1.

Immune Targets and Immunofluorescent Patterns in Oral Bullous Diseases

Disease	Antigenic Target	Location	Fluorescent Pattern
Lichen planus	Unknown	Basal Layer	BM fibrinogen
Erythema multiforme	Immune complex	Perivascular	IgG, C3
Mucous membrane pemphigoid	Adhesion molecules	BM	BM Igs, C3
Pemphigus vulgaris	Desmoglein	Desmosome	Pericellular Igs, C3

BM: basement membrane; Ig: immunoglobulin; C3: complement fraction 3

Table 2.

Corticosteorid Strategy

Systemic: high dose/short course
Prednisone 40-80 mg daily
Less than two weeks, no taper
Topical: potent corticosteroids (gel and ointment)*
Lidex (fluocinoide) 0.05 percent
Temovate (clobetasol) 0.05 percent
Ultravate (halobetasol) 0.05 percent
Mouth rinse: elixir dexamethasone 0.5 mg/5 ml
1 teaspoon three time daily, hold one minute, then spit out

* Paste: mix ointment with equal parts orabase

Diagnosis

Clinical features are used to determine a differential diagnosis, which is then confirmed by biopsy. In classical cases, there are cell-tissue patterns that are characteristic of each entity, reflecting inflammatory patterns in some and sites of antigen-antibody reactions in others. In some cases in which specific histopathologic patterns cannot be confirmed, immunofluorescence is helpful. This technique identifies sites of antigen-antibody reactions.

Since there is a slight increased risk of malignant transformation in lichen planus, these patients should be followed closely, and the diagnoses should be re-established when changes in signs and/or symptoms occur. The differential diagnosis and biopsy are very important, since these are chronic, lifelong conditions, and it must be made certain that the clinical red/white/erosive changes do not represent a dysplastic or malignant process.

Histologically, lichen planus is characterized by hyperkeratotic epithelium, which accounts for the white appearance; and in the subepithelial connective tissue an infiltrate of lymphocytes lies in juxtaposition to the epithelium. The basal layer is disrupted and when completely lysed; desquamation occurs with resulting areas of ulceration. Thus, in the so-called erosive form of the disease, the entire epithelial layer is lost. Erythema multiforme has a nonspecific histologic appearance. The epithelium shows a marked inflammatory infiltrate as polymorphonuclear neutrophil leukocytes and round cells emigrate out of vessels and transmigrate into the overlying epithelium. There is intense submucosal inflammation; and eventually the epithelium undergoes necrosis and sloughs, leaving an ulcerated pseudomembrane composed of fibrin. Mucous membrane pemphigoid shows a characteristic sub-basilar clefting that ensues subsequent to antibody and complement binding to basement membrane antigens. The submucosal connective tissue is variably infiltrated by mononuclear leukocytes, usually an admixture of plasma cells and lymphocytes. Biopsies of gingival lesions often demonstrate extensive desquamation of the epithelium with total detachment from the underlying connective tissue. In pemphigus vulgaris, a classic suprabasilar clefting occurs as antigens in the desmosomes are targeted by antibodies that cause a loss of adhesion between contiguous keratinocytes.

The immunofluorescent patterns seen in these bullous disease are indicative of the autoimmune targets within the basement membrane, desmosomes, or complexes in vessel walls. Direct immunofluorescent microscopy requires procurement of an oral biopsy from perilesional mucosa. A site should be selected adjacent to a clinical lesion and not directly in the zones of desquamation.

Table 1 portrays the characteristic patterns of antigen:antibody deposition encountered in these lesions. Importantly, Michel's transport medium is required to preserve tissue for immunofluorescent microscopy and of even greater import is the necessity of obtaining tissue for routine hematoxylin and eosin staining. Biopsies can be split, or two samples can be obtained.

Treatment

None of these condition is curable; therefore, treatment is based upon modifying patient discomfort and pain. The principle of treatment is directed toward the immunopathologic processes that are reacting with the epithelium and causing the symptoms. If mild over-the-counter medications are helpful, they should be the first line of control. However, the most effective and predictive approach is to modify immunologic activities. Corticosteroids are the agents of choice.[7,8] They can be administered topically or systemically (**Figures 10a and b, 11a and b**).

Topical corticosteroids must be potent forms, since prolonged exposure is required for drug-lymphocyte interaction. **Table 2** lists the drugs and forms that are useful. Applications can vary from

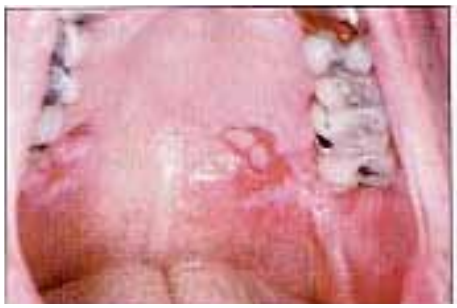

FIGURE 7. Mucous membrane pemphigoid, palate.

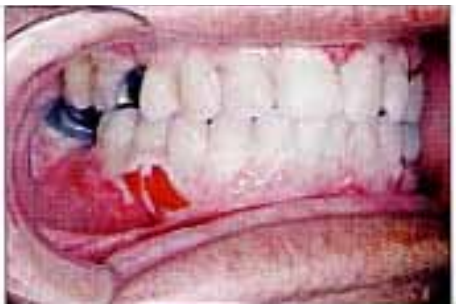

FIGURE 8. Pemphigus vulgaris, gingiva.

FIGURE 9. Pemphigus vulgaris, buccal mucosa.

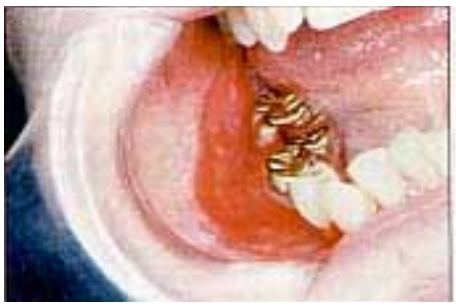

FIGURE 10A. Lichen planus. Painful buccal mucosa lesion present for six months.

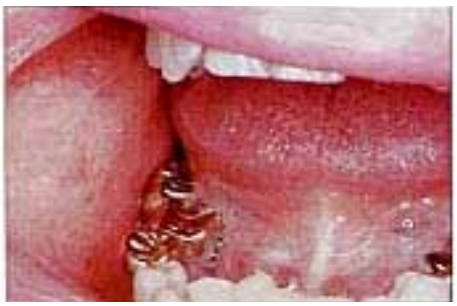

FIGURE 10B. After 60 mg prednisone daily for one week. Patient was then maintained with topical fluocinonide-orabase with good control.

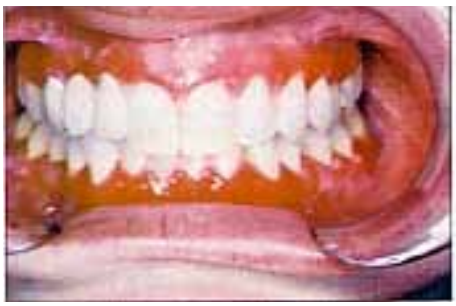

FIGURE 11A. Mucous membrane pemphigoid. Painful gingival lesions present for four years.

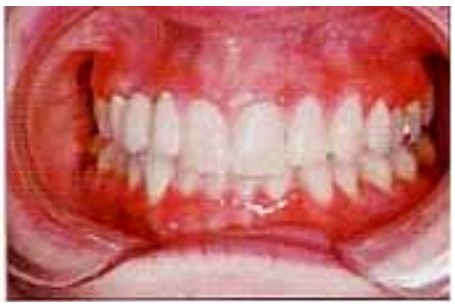

FIGURE 11B. After two weeks, daily topical corticosteroids lead to complete control of the symptoms and almost complete remission of signs.

single daily applications (most effective before bedtime) to up to five times daily. Long-term studies have not shown any pathophysiologic adverse side effects. Occasionally, these topical agents might stimulate overgrowth of Candida sp., and the subsequent oral candidiasis must be treated with topical (clotrimazole) or systemic (fluconazole or ketoconazole) antifungal agents.

When systemic routes are utilized, the strategy is high-dose, short-course. In this manner, one can optimize efficacy and minimize side effects. In these situations, the treatment should be in conjunction with the patient's primary care physician. In systemic routes, there should be caution in patients with diabetes, gastrointestinal ulcers, hypertension, and glaucoma.

Occasionally, when signs and symptoms are not responding adequately, a combination of azathioprine (Imuran), a synergistic cytotoxic drug, may be helpful. Care must be taken, since Imuran can cause bone marrow suppression and alter liver function.

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Xerostomia – Clinical Evaluation and Treatment in General Practice

Troy E. Daniels, DDS, MS, and Ava J. Wu, DDS

ABSTRACT Xerostomia is a common symptom with various causes that, if ignored, can lead to serious oral consequences. Clinical evaluation of patients complaining of dry mouth must include some additional history and specific examination of the salivary glands, oral mucosa, and teeth. Additional evaluation may include consultation with the patient's physician, request for microbial culture, or labial salivary gland biopsy. No one form of treatment for patients with chronic xerostomia is sufficient, but comprehensive treatment is effective in improving patient oral comfort and function, and preventing unnecessary loss of teeth. This treatment must include ongoing dental caries prevention and treatment, salivary flow stimulation, recognition and treatment of oral candidiasis, selective use of saliva substitutes, and possible changes in the patients' prescription and nonprescription drug use.

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Xerostomia (dry mouth) is a subjective symptom that is usually, but not always, associated with salivary hypofunction, in which there are both decreased saliva production and qualitative changes in saliva. This symptom is encountered with greater frequency in dental practice as a result of increasing use of systemic prescription drugs, which can singly or in combination affect salivary function, and because of increasing public awareness of this symptom and its significance.[1]

Causes of Xerostomia

As noted in **Table 1**, salivary hypofunction can be divided into temporary and chronic forms, depending on the cause. The chronic forms are of greatest concern because of their long-term potential to cause dental and oral mucosal disease as well as to adversely affect oral function. Another difference between the temporary and chronic forms of salivary hypofunction is that most short-term salivary hypofunction affects only resting (basal) secretion, and patients retain their ability to respond normally

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to gustatory, masticatory, or olfactory stimuli. However, most of the chronic causes of salivary hypofunction decrease both resting and stimulated secretion rates, creating both greater symptoms and potentially less response to treatment.

Prescription drug use is the most common cause of chronic salivary hypofunction. Categories of drugs most frequently causing clinically significant salivary function are listed in **Table 1**. There are, however, literally hundreds of drugs that can produce symptoms of dry mouth, but most do so with lesser severity and affect a smaller proportion of patients. It is interesting to note that patients' salivary flow rates may decrease simply in proportion to the number of prescription drugs they are taking.[2] Thus, there may be an unknown additive or synergistic effect on salivary function when multiple prescription drugs are taken.

Table 1.

Differential Diagnosis of Salivary Hypofunction

Temporary hypofunction (usually, only resting secretion is decreased):
• Effects of short-term drug use (e.g. antihistamines)
• Virus infections** (e.g. mumps)
• Dehydration (e.g. thermal or trauma)
• Psychogenic conditions (e.g. anxiety)
Chronic hypofunction (usually, both resting and stimulated secretion rates are decreased):
• Effects of chronically administered drugs
– Antidepressants (e.g. amitriptyline)
– Neuroleptics (e.g. phenothiazines, lithium)
– Parasympatholytics (e.g. anti-Parkinsonian drugs)
– Some antihypertensive drugs (e.g. clonidine) and many combinations (e.g. beta-blocker and diuretic)
• Chronic diseases
– Sjögren's syndrome**
– Sarcoidosis**
– HIV** or Hepatitis C infection
– Depression
– Diabetes mellitus, uncontrolled
– Amyloidosis (primary or secondary)
– Central nervous system diseases
– Rarely, absent or malformed glands
• Other effects of treatment
– Therapeutic radiation to the head and neck
– Graft vs. host disease (following bone marrow transplantation)
**may also cause major salivary gland enlargement

Clinical Effects of Chronic Xerostomia

The results of a chronic lack of saliva follow from the well-known functions of normal saliva,[3] which include:

- Maintaining a neutral oral pH through various buffer systems;
- Supporting ongoing remineralization of teeth by providing a reservoir of calcium and phosphate ions;
- Coating the oral mucosa and teeth to protect them against harmful substances;
- Lubricating the mouth to facilitate chewing, swallowing, and speech;
- Providing local antimicrobial activity through enzymes, immunoglobulin A, and histatins; and
- Serving as a solvent for the taste mechanism.

Therefore, the loss of saliva is thought to be associated with a loss of "protection." Some of the oral consequences of chronic salivary hypofunction occur in approximate proportion to the severity of the hypofunction. These include progressive dental caries – primarily in cervical, incisal, or marginal locations – and various kinds of oral dysfunction (i.e., difficulty with chewing, dysphagia, dysphonia, or dysgeusia), and dysfunction of lower complete dentures. Signs of chronic erythematous candidiasis are seen in about one-third of patients with chronic salivary hypofunction[4] and caused by Candida albicans or other Candida species.[5,6] Interestingly, the white plaques of pseudomembranous candidiasis (thrush) are rarely seen in these patients. Patients with chronic salivary hypofunction may also develop alterations in their sense of taste, with or without candidiasis.

Diagnosis of Xerostomia in General Practice

History

As generated from the routine medical history, patients' descriptions of prescription and nonprescription drug use

Table 2.

Symptoms and Signs Suggesting Chronic Salivary Hypofunction

Symptoms
• Positive responses to specific questions:[7]
– Do you sip liquids to aid swallowing dry foods?
– Does your mouth feel dry when eating?
– Do you have difficulty swallowing any foods?
• Complaints of burning mucosa and/or intolerance to spicy foods (usually associated with erythematous candidiasis)
Signs
• Little or no pooled saliva in the mouth floor during examination
• Dry or sticky mucosal surfaces
• Multiple caries in cervical, incisal, or marginal locations
• Thick or cloudy saliva expressible from parotid or submandibular gland ducts
• Bilateral salivary gland enlargement
• Signs of erythematous candidiasis:
– Dorsal tongue with erythema, loss of filiform papillae, and fissured or cobblestone appearance
– Angular cheilitis
– Patchy erythema on other mucosal surfaces

may reveal the cause of their symptoms of dry mouth. Given the rapid proliferation of new drug names, this analysis may require a standard reference such as the Handbook of Clinical Drug Data, the Physicians Desk Reference, or other source. As noted above, medications are the most common cause of xerostomia and salivary hypofunction. If the drug history does not reveal a probable cause, additional information must be obtained from those patients complaining of xerostomia.

Learning the patient's occurrence pattern of dry mouth symptoms can be helpful. For example, the continuous presence of dry mouth symptoms throughout the day is usually associated with significant salivary hypofunction and loss of the protective effects of saliva. Alternatively, the gradual daily onset of such symptoms may be associated with less severe hypofunction, mouth breathing, or an excessive awareness by the patient of the amount of saliva in their mouth. Symptoms of dry mouth occurring only at night, on awakening from sleep, usually are not associated with abnormal salivary function because salivary flow normally approaches zero during sleep. There are also some additional questions to ask patients who complain of dry mouth, which, if positive, are moderately predictive of salivary hypofunction: Do you sip liquids to aid swallowing dry foods? Does your mouth feel dry when eating? Do you have difficulty swallowing any foods?[7] If patients complain of regional or generalized mucosal pain, often described as "burning," or they describe intolerance to spicy or acidic foods, which may have forced them to significantly alter their diet, the labial angles and oral mucosa should be carefully examined for signs of erythematous candidiasis, as described below (**Table 2**).

Patients with depression may or may not include that diagnosis on a history form. Two recent studies illustrate its relationship to the symptom of xerostomia. One study of apparently healthy individuals with normal unstimulated and stimulated whole salivary flow rates, found symptoms of depression in 21 percent of those who also had symptoms of dry mouth, but in only 3 percent of those who did not have symptoms of dry mouth.[8] Another study sampled all the 55-year-old men and women in a European city and found that 26 percent of the men and 33 percent of the women complained of the subjective sensation of dry mouth. After dealing statistically with the confounding variables of smoking and prescription drugs and diseases that could cause xerostomia, the authors found that depressive symptoms were significantly associated with the symptom or oral dryness.[9] In diagnosing such patients, it is important to remember that depression can mask a chronic disease associated with salivary hypofunction, and patients with xerostomia and self-identified depression or currently using antidepressant drugs must be fully evaluated.

Physical Examination -- Extraoral

For patients who complain of xerostomia, it may be most convenient to begin with the extraoral examination. As noted in **Table 1**, some of the conditions causing salivary hypofunction may also cause enlargement of the parotid and/or submandibular glands. For example, between one-third and one-half of patients with Sjögren's syndrome develop enlargement of major salivary glands. In cases of Sjögren's syndrome, sarcoidosis, or HIV infection, this enlargement is usually firm and nontender to palpation, affects all or most of the gland, and is usually bilateral, although one side may be larger than the other. It should be noted, however, that while these patients

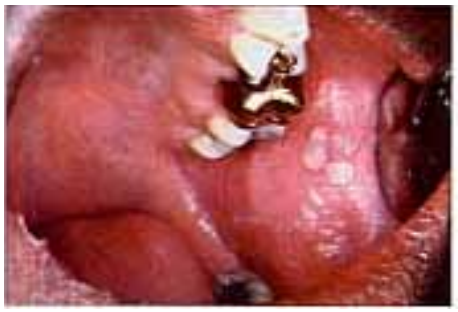

Figure 1. This man complained of xerostomia, had slight, diffuse, bilateral parotid enlargement and intraoral signs of salivary hypofunction. This thickened, cloudy secretion was expressible from the left parotid duct during examination, but the major salivary glands were not painful or tender to palpation. A labial salivary gland biopsy revealed noncaseating granulomas, confirming the diagnosis of sarcoidosis.

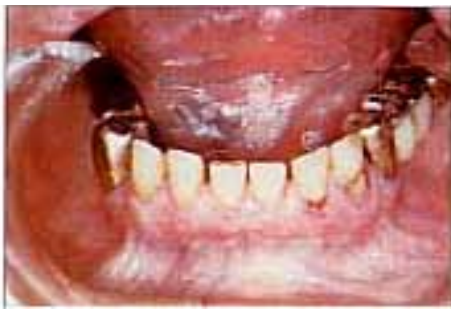

Figure 2. This patient with primary Sjögren's syndrome has severe salivary hypofunction. Note parchment-like mucosa on the mouth floor and caries in incisal, cervical, and marginal locations. Caries are also detectable at the subgingival crown margins.

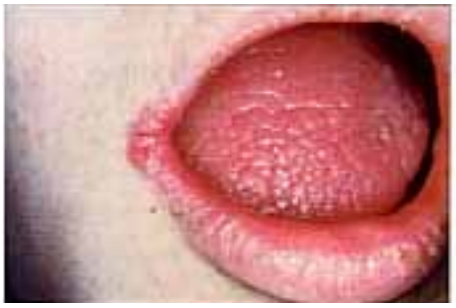

Figure 3A. This 26-year-old woman complains of dry and burning mouth and intolerance to spicy foods. She has signs of erythematous candidiasis including angular cheilitis, erythema of the dorsal tongue, and atrophy of the filiform papillae.

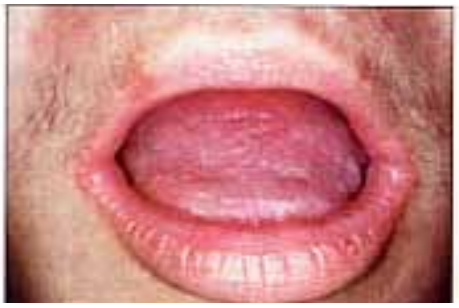

Figure 3B. After about three months of treatment with topical antifungal drugs, her oral symptoms have resolved and filiform papillae have returned to the dorsal tongue, but her chronic salivary hypofunction and primary Sjögren's syndrome continue.

can have clinically similar swelling of major salivary glands, the histological features are different. At the beginning of this examination, it is useful to visually examine the duct openings in the mucosa for each parotid and submandibular gland, while applying gentle extraoral pressure to the corresponding gland (**Figure 1**). This permits observation of the saliva being expressed; is it clear, water-like and flowing freely (the normal condition), or cloudy, viscous and hanging from the duct orifice, or does nothing come out when pressing on the gland?

Parotid glands are easy to palpate because of their superficial location over the mandibular ramus, but they must be distinguished from the masseter muscle, which they overlie. Submandibular glands are best palpated between an index finger placed in the distal mouth floor and another placed extraorally on the skin medial to the mandibular angle. The normal parotid or submandibular glands are not usually palpable because they are softer than their surrounding tissues. Therefore, if the parotid or submandibular glands can be anatomically defined by palpation, then some degree of induration is probable.

Physical Examination -- Intraoral

The intraoral examination of patients complaining of xerostomia should focus on the appearance and lubricity of the mucosa and the location and distribution of dental caries. Does a gloved finger slide easily over the mucosa during examination; is there resistance to sliding; or is there a sticky quality to the mucosa? During the oral examination, has saliva pooled in the mouth floor? (**Figure 2**)

Erythematous candidiasis involves thinning of the mucosa, which causes the red color and symptoms described above. Clinically, it is characterized by erythema and atrophy of the filiform papilla on the dorsal tongue, leaving a smooth, cobble-stone, or fissured surface on the dorsal tongue (**Figure 3A**). Other signs include patchy oral mucosal erythema, particularly on the palate or buccal mucosa, or under dentures, and angular cheilitis. The latter rarely occurs without the presence of intraoral candidiasis[10] (**Table 2**). In patients with these signs, the diagnosis can be confirmed by fungal culture of a swab specimen from the dorsal tongue, or other erythematous lesion, from which a substantial number of colony forming units (double digits or more) can be identified through culture. A colony forming unit assessment can be performed by the clinical laboratory and is necessary because small quantities of Candida may be present in the normal oral flora.[11] Adequate treatment of oral candidiasis (described below) will usually eliminate the patient's symptoms of mucosal burning and intolerance to acidic or spicy foods, in spite of continuing salivary hypofunction, and it will lead to restoration of the mucosa[4] (**Figure 3B**).

Are there carious lesions or signs of decalcification in cervical or incisal areas of the teeth? Are recurrent caries present in subgingival crown margins or around existing class five restorations? (**Figures 2 and 4**) In patients with chronic salivary hypofunction, the extent of their dental caries may be greater than would be suggested by the adequacy of their plaque and calculus control.

Figure 4. This 41-year-old patient with rheumatoid arthritis, mild secondary Sjögren's syndrome, depression, and multiple drug treatment has rapidly progressing dental caries. Note the pattern of new and recurrent caries.

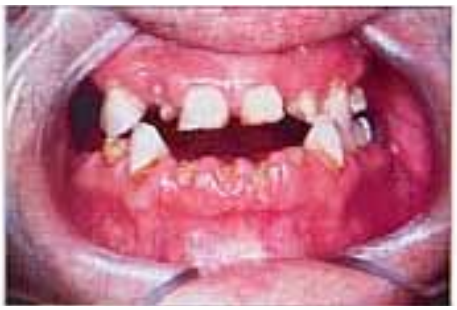

Figure 5. This patient underwent radiation therapy for a carcinoma of the oropharynx 21 months prior to this photograph. At the onset of radiation treatment she had a bicuspid dentition, a few small restorations, and no active caries. After completion of treatment, she was non-compliant with home dental care procedures and failed her dental recall appointments.

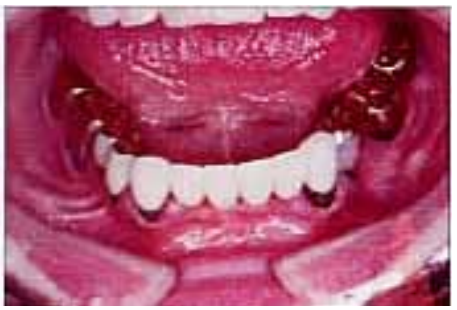

Figure 6. Several years prior to this photograph, this middle-aged patient complained of xerostomia and had many areas of cervical caries at the time these crowns and bridges were placed. Within a few years, recurrent caries had affected the margins of most of the abutments, necessitating the supplemental class V amalgam restorations. The patient has primary Sjögren's syndrome and ongoing salivary hypofunction.

Clinically Assessing Salivary Hypofunction

Salivary flow rates can be measured for whole, parotid or submandibular secretions under resting or stimulated conditions. However, the range of flow rates for each of these is very wide among healthy individuals who have no known diseases and who are not taking any medications.[12] Therefore, a clear distinction between "normal" and "abnormal" flow rates may not be possible.[13] In addition, measuring salivary flow rates is not a usual part of most dental practices, can be quite time-consuming, and may be difficult to standardize when done only occasionally.

Various investigators have tried to identify an unstimulated whole salivary flow rate that distinguishes normal from abnormal function. In reviewing previous studies and conducting their own, Navazesh and colleagues found that rates of 0.12 to 0.16 mL/min seem to define the range below which there is a higher rate of oral soft and hard tissue abnormalities.[14] Using that as a baseline, they identified a set of four clinical measures that, when used together in a formula, reasonably predicted the presence or absence of salivary hypofunction. The clinical measures were dryness of the buccal mucosa; absence of saliva expressible from the ducts; the total number of decayed, missing and filled teeth; and dryness of the lips. In summary, salivary hypofunction can be assessed by the clinical methods described in this section for clinical decision-making, without measuring salivary flow rates (**Table 2**).

Various tests have been proposed to determine a patient's risk of developing caries. These tests include salivary flow rates, salivary buffer capacity, and quantifying mutans streptococci and lactobacilli from the saliva. However, a review of these caries risk assessment notes that these tests are better at selecting people who will not develop caries than they are at selecting people who will, and that no single test has yet proven to be successful in predicting caries development for the majority of populations studied.[15]

Chronic Diseases Causing Xerostomia

Sjögren's syndrome is the second most common connective tissue disease, after rheumatoid arthritis. Patients with primary Sjögren's syndrome have the salivary and ocular components of Sjögren's syndrome and may develop other organ system manifestations. Patients with secondary Sjögren's syndrome first have another connective tissue disease (e.g. rheumatoid arthritis, systemic lupus erythematosus, or mixed connective tissue disease) and later develop the salivary and/or ocular components (**Figure 4**). Patients in a dental practice may be suspected of having Sjögren's syndrome, because they already have the diagnosis of a connective tissue disease or, because they have clinical evidence of significant salivary hypofunction that is not otherwise explained from information in their history and, on questioning, they may complain of ocular symptoms (e.g. an inability to tear, ocular pain or burning, or having a foreign-body sensation in their eyes). It is helpful to contact the patient's physician concerning the patient's diagnoses and blood test results. Several serological markers that are highly associated with the connective tissue diseases are commonly seen in patients with Sjögren's syndrome and may raise the suspicion of it, but none of them are sufficiently specific to permit it to be diagnosed by blood tests. Those that are commonly associated with Sjögren's syndrome include the following "autoantibodies": antinuclear antibody, rheumatoid factor, anti-Ro (SS-A), and anti-La (SS-B).

In patients who have clinical evidence of significant salivary hypofunction but do not have another connective tissue disease, the dentist should refer the patient to an ophthalmologist to assess whether they have the ocular

Table 3.

Products Selectively Useful for Treating Patients With Chronic Salivary Hypofunction

Anti-caries agents
• Professionally applied
– 1.23% fluoride in acidulated phosphate fluoride gel
– 2.26% fluoride varnish[23]
• Patient-applied
– 0.5% fluoride in neutral sodium fluoride gel
– 0.05% sodium fluoride mouth rinse
– 0.12% chlorhexidine gluconate mouth rinse
Saliva stimulants
• Sugar-free chewing gum or hard candies
• Pilocarpine hydrochloride tablets, 5 mg, initially prescribed at one tablet three times daily
Antifungal drugs
• Fluconazole, 100 mg tablets, 200 mg on first day then 100 mg per day for 14 days
• Nystatin Vaginal Tablets, 100,000 units per tablet, dissolve slowly in mouth (15-20 minutes), using sips of water as necessary to aid dissolution, 2 to 4 tablets per day, for 3 to 12 weeks, depending on the severity and clinical response (see text)
• Nystatin or 1% Clotrimazole cream, 15 gm tube (see text)
• Nystatin Topical Powder, 15 gm (see text)
Note: This table is meant as a supplement to the text. It is not a comprehensive outline for treatment.

component of Sjögren's syndrome, called keratoconjunctivitis sicca.[16] If they do have keratoconjunctivitis sicca, they should then be referred to someone experienced in performing a labial salivary gland biopsy[17] to assess whether they have focal lymphocytic sialadenitis in that specimen, which represents the salivary component of Sjögren's syndrome.[18] A patient having keratoconjunctivitis sicca and focal lymphocytic sialadenitis in a salivary biopsy has primary Sjögren's syndrome, a diagnosis that should be reported to the patient's physician. A labial salivary gland biopsy may also reveal another systemic disease, such as sarcoidosis (**Figure 1**), which can clinically mimic Sjögren's syndrome,[19] and should be reported to the patient's physician.

HIV or hepatitis C infections can cause salivary hypofunction and salivary gland enlargement, or salivary hypofunction only, respectively. They are both definitively diagnosed by serological tests. Diagnoses of amyloidosis, diabetes, or a central nervous system disease should be apparent from the patient's medical history, as would therapeutic radiation to the head and neck or bone marrow transplantation. As noted above, there is an association between the symptom of xerostomia and depression.

Treatment of Patients With Xerostomia

There is no one form of treatment that is effective for patients with chronic salivary hypofunction, but there is clear evidence that comprehensive treatment is effective. Such treatment needs to consider five categories:

- Ongoing dental caries prevention and treatment;
- Salivary flow stimulation;
- Oral candidiasis recognition and treatment;
- Selective use of saliva substitutes; and
- Review of the patient's current prescription drug regimen and elimination, where possible, of concurrent use of drugs having anticholinergic effects.[20]

Caries Prevention and Treatment

Patients who develop severe salivary hypofunction – for example, from radiation therapy to the head and neck – and do not receive nor follow necessary instructions and support to prevent dental caries, can lose their entire dentition to caries in a few years. An example of such a patient is seen in **Figure 5**; similar results can occur in patients with Sjögren's syndrome or on multiple drug therapy, but more slowly.

In a landmark study of caries prevention in patients who had undergone radiation therapy to the head and neck, there were three treatment groups: 1) those receiving oral hygiene instructions only, 2) those receiving oral hygiene instructions and daily 1 percent tray-applied sodium fluoride gel, and 3) those receiving both of the above and placed on a sucrose restricted diet.[21] Group 1 had an average monthly increase in the number of decayed, missing or filled dental surfaces of 2.51, which was 12 times greater than the DMFS increase seen in group 2. Furthermore, group 2 had a DMFS increase five times greater than that seen in group 3. While each of the three prevention strategies studied on these patients with severe salivary hypofunction had some effect, the combination of oral hygiene instructions, daily topical fluoride application, and dietary sucrose restriction was 63 times more effective in preventing caries than oral hygiene instructions alone.

This is a good place to apply the old saying, the whole is worth more than the sum of its parts.

Patients with moderate to severe salivary hypofunction must become part of their treatment by being taught the role of dietary sugars in the development of dental caries, the need to limit sugar intake to meals and eliminate it between meals, and how to remove dental plaque effectively. Strategies with topical fluoride need to be based on the severity of the patient's salivary hypofunction and their caries experience. These can include professionally applied high concentration fluoride solutions in a tray (e.g. 1.23 percent fluoride in acidulated phosphate fluoride gel for four minutes), or a 2.26 percent fluoride varnish applied directly to the teeth, four times per year.[22, 23] Patient-applied sodium fluoride gel (0.5 percent fluoride) in a custom-fitted tray for five minutes daily can be used to supplement professionally applied fluoride. For lower risk patients, a daily rinse with a 0.05 percent sodium fluoride can be a useful addition to professionally applied fluorides. Neutral sodium fluoride preparations are generally preferred to stannous fluoride preparations because they are better-tolerated by patients.

For patients at highest risk of caries, or those without evidence of lesion arrest or remineralization, additional strategies can include the periodic use of chlorhexidine to control the quantity of mutans streptococci in the flora. This can be in the form of a patient-applied 0.12 percent chlorhexidine gluconate rinse, one minute daily for two weeks[22] (**Table 3**).

The caries associated with chronic salivary hypofunction often attacks the margins of existing restorations in both supragingival and subgingival locations (**Figures 2 and 4**). For the initial treatment of such patients, dental restorations with subgingival margins should be avoided wherever possible (**Figure 6**). Subgingival margins are difficult to clean and are less accessible to topical fluoride application. Recurrent caries at this location is common in these patients and difficult to detect and treat. Full veneer crowns, if ultimately necessary, should not be placed until caries are under complete control (i.e., the patient has been free of new lesions for at least one year).

Salivary Flow Stimulation

Patients' residual salivary function can be stimulated by physiological or pharmacological means to reduce symptoms of xerostomia. Physiological stimulation can be provided by masticatory or gustatory stimuli, through sugar-free chewing gum (e.g., xylitol gum) or sugar-free hard candies, used as needed during the day to relieve oral symptoms. To avoid enhancing dental caries development in high caries-risk patients, either of these physiological stimulatory methods must use sugar-free, not "sugarless" products. Both methods can increase salivary flow, but only while the stimulus is present in the mouth.

Pharmacological stimulation can be provided through prescription of various systemically administered cholinergic drugs, which may give the patient up to several hours of increased salivary flow and reduced oral symptoms. Pilocarpine has long been know to increase salivary secretion[24,25] and is initially prescribed at 5 mg, three to four times daily. It should not be prescribed for patients with uncontrolled asthma or narrow-angle glaucoma and should be used with caution in patients with significant cardiovascular or pulmonary disease. There is no evidence yet that either physiological or pharmacological salivary stimulation will prevent dental caries or oral candidiasis.

Oral Candidiasis

When erythematous oral candidiasis occurs in patients with only mild to moderate salivary hypofunction, fluconazole or other systemic antifungal drugs can be used for a few weeks, with usually satisfactory results (as assessed by the treatment end-points described below). More commonly, erythematous oral candidiasis occurs in patients with severe chronic hyposalivation,[26] whose treatment is best accomplished with topical forms of polyene or imidazole anti-fungal drugs[27] for periods of weeks or months. Because these patients are at very high risk for progressive dental caries, they must utilize forms of these topical drugs that are the least cariogenic, i.e. those that do not contain sucrose or glucose. Topical forms are necessary because in patients having severe salivary hypofunction, systemically administered antifungal drugs do not reach the mouth of such patients in therapeutically adequate amounts.

All currently available "oral" topical antifungal drugs contain substantial amounts of sucrose or glucose (i.e. brands of clotrimazole oral troches, nystatin oral pastilles, and nystatin oral suspension), which creates significant risk for supporting dental caries development when used as directed. Therefore, the best topical antifungal drug to use with patients at high risk for dental caries is nystatin vaginal tablets. These do contain lactose, which is a potentially cariogenic carbohydrate, but much less so than either sucrose or glucose. They must be dissolved slowly in the mouth for 15-20 minutes, two or three times per day. Such patients usually must take frequent sips of water to allow the tablet to dissolve in that time. The treatment end-point for erythematous candidiasis should be resolution of all the mucosal erythema,

return of filiform papillae to the dorsal tongue, and resolution of associated oral symptoms.[4]

For patients wearing partial or complete dentures, additional instructions and treatment are needed:

- Dentures must be removed from the mouth before using any topical antifungal drug.
- Dentures must be disinfected by soaking overnight in a fungicidal substance compatible with the denture materials and rinsed before reinserting in the mouth.
- Nystatin topical powder may be applied on the fitting surface of a clean denture (while wet) just before reinserting it in the mouth. Since this powder contains talc, care must be taken to insure that patients do not inhale the dry powder.[20]

The presence of angular cheilitis almost always indicates concurrent intraoral candidiasis.[10] Angular cheilitis can be treated by nystatin or clotrimazole creme, but in most cases this only should be done with concurrent treatment of the intraoral infection. After treatment is completed, recurrence of erythematous candidiasis is common and the patient the needs to be re-treated as described above. If recurrence is frequent, re-treatment should be followed by maintenance therapy (e.g. continued use of half of a nystatin vaginal tablet slowly dissolved in the mouth each day).[4]

Saliva Substitutes

These over-the-counter products can be helpful for patients with fairly severe chronic hyposalivation, particularly those wearing a complete denture, but are less helpful for patients with more saliva. These products are usually most effective for patients at their bedside when awakening during the night, while talking, or while traveling. None replace all the functions of natural saliva, and none have long duration because they are swallowed. There are several types available. Most are carboxymethylcellulose-based, while others are mucin-based or glycerate polymer gel-based. In comparative studies, carboxymethylcellulose-based preparations usually have the lowest objective and subjective ratings; mucin-based products are usually rated higher by patients, but are not available in the United States. The glycerate polymer gel-based product appears to provide better reduction in oral dry mouth symptoms than carboxymethylcellulose-based substitutes28 particularly in patients with severe xerostomia.[29] None of these products has been shown to prevent dental caries or oral candidiasis.

Water Consumption

Some patients with chronic salivary hypofunction consume water excessively. Patients should understand that dry mouth is rarely associated with systemic dehydration and that consuming large quantities of water does not overcome oral dryness. Frequent small sips of water during the day will help reduce oral symptoms. However, excessive consumption of water can remove the mucus coating the oral surfaces and further increase the patients symptoms of dryness. Milk may be a better, but less convenient, liquid to sip.

Nocturia

Patients may have frequent sleep interruption caused by nocturia if they consume water at night. To avoid nocturia, beginning one hour before sleep patients should not drink water and when they awaken during the night they should use a small volume of a saliva substitute, instead of drinking water.

Prescription Drug Review

Patients' current prescription drug use should regularly be reviewed to identify those drugs whose principal effect, or side effects, contribute to decreased salivary function. If such drugs are being used, the problem should be discussed with the prescriber of the drug; it may be possible to eliminate the drug or to substitute with one that has less effect on salivary function.

Summary

Xerostomia is a common clinical problem. Patients with that symptom must be evaluated by their dentists' obtaining additional history and performing examinations that are clearly in the scope of general dental practice. The cause of a patient's xerostomia should be determined, the severity of associated salivary function should be estimated, and appropriate treatment initiated. The goal of that treatment is to improve the patient's oral symptoms and function and to prevent and restore dental caries. Effective treatment of chronic salivary hypofunction requires patient education and treatment, proportional to its severity and include caries prevention, appropriate dental restoration, saliva stimulation, selective use of saliva substitutes and, where appropriate, changes in the patient's use of prescription drugs.

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Candidiasis: Pathogenesis, Clinical Characteristics, and Treatment

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ABSTRACT Candida organisms live on the skin and mucous membranes of up to 75 percent of the population. They can live commensally without causing harm or can change to an aggressive form and invade tissue, causing both acute and chronic disease in the host. Oropharyngeal candidiasis manifests clinically as acute pseudomembranous, acute atrophic, chronic atrophic, chronic hypertrophic/hyperplastic, and angular cheilitis. Systemic infection leading to candidemia can be devastating and cause up to a 60 percent mortality rate in medical or post-surgical intensive care wards. Oral nystatin, clotrimazole, and fluconazole usually provide appropriate therapy; although resistance to medications is increasing, particularly in immunocompromised hosts.

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Candida organisms are fungi that normally inhabit the oral cavity, gastrointestinal tract, other mucous membranes, and skin. In most humans, this is a commensal relationship; and only a few Candida carriers actually go on to develop clinical signs of candidiasis because yeast growth and colonization are impaired by the resistance of the host.[1] When changes occur in the host environment causing imbalance of the flora or a decrease in resistance, Candida becomes an opportunistic pathogen. Clinical problems range from relatively mild candidiasis to chronic recurrent candidiasis and life-threatening disseminated infections. These problems are growing, and Candida has been called the most important fungal pathogen in humans.[2] It has been listed as the fourth most common isolate recovered from blood cultures in the United States[3] among patients with severe infection acquired while in the hospital. This review will discuss the pathogenesis of candidiasis, the clinical characteristics of oral infection, local and systemic factors that predispose to infection, and treatment.

Candida Microbiology and Pathogenesis

Though dentists commonly treat the oropharyngeal signs of Candida infection and colonization such as denture stomatitis, angular cheilitis, and thrush, they must realize that when dissemination and invasion of internal organs occur, Candida becomes life-threatening.[2] This has become exceedingly important in recent

years as the dental patient pool has expanded to include more of the elderly, with an additional increase in organ transplant, immunocompromised, AIDS, chemotherapeutic, and antibiotic- or steroid-laden patients.

Candida is a human fungal pathogen that grows as a round yeast and replicates by budding. Of the 150 fungal species of Candida, about seven are known to be medically important pathogens: C. albicans, C. tropicalis, C. parapsilosis, C. krusei, C. kefyr, C. glabrata, and C. guilliermondii.1 Other species have been isolated from humans but are considered opportunistic in immunocompromised patients. C. albicans is by far the most prevalent pathogenic fungal species found in the human body, yet C. dubliniensis has been found primarily in the oral cavities of immune-suppressed individuals;[4,5] and although it is a low-level constituent of the human oral flora, it has the potential to cause oral candidiasis.[6,7] C. albicans and C. dubliniensis as well as other Candida species can be differentiated from one another by polymerase chain reaction techniques that are being developed to aid in diagnosis.[8]

Though C. albicans can exist in several forms, from the yeast to the hyphal, the yeast form is commensal and relatively harmless, while the hyphal form is invasive, pathogenic, and the cause of clinical candidiasis. Hyphae are not always seen in lesions, but this could reflect a sampling error.[1,9,10] Studies indicate that when the yeast forms grow hyphae, they then act like adherent filaments to spread across, attach, and burrow between and into epithelial cells. This is commonly seen in the more serious tissue invasion and especially in immunocompromised hosts.[11]

Adherence by the hyphae to oral keratinocytes may be partially due to a protein called Hwp1, which is present in Candida filaments but not in the yeast form. This protein forms a covalent and permanent bond to epithelial cells with the help of the enzyme transglutaminase. Without Hwp1, the adherence to human oral mucosal cells is reduced 80 percent. Mice infected with Candida strains containing Hwp1 develop more severe disease than those infected with Hwp1-free Candida.[11]

C. albicans also has the ability to produce secreted aspartyl proteinases that degrade many human proteins found at lesion sites. The proteins affected include albumin, hemoglobin, keratin, collagen, mucin, and secretory immunoglobulin A . Nine secreted aspartyl proteinase genes have been identified in Candida, and laboratory studies have evaluated the regulation of secreted aspartyl proteinase expression through analysis of mRNA and protein synthesis. In vivo studies indicate that secreted aspartyl proteinase 1, 2, and 3 are expressed by yeast cells. Only secreted aspartyl proteinase 4, 5, and 6 expression is seen in C. albicans when it is undergoing transition from yeast form to hyphal form. In patients with oral candidiasis, the hyphal forms with increased adherence have been found to express secreted aspartyl proteinase 4, 5, and 6. Interestingly, in vivo studies have now found that yeast cells, normally thought to be non-invasive, may at times express secreted aspartyl proteinase 4, 5, 6, and 7.[12] Additionally, the fact that secreted aspartyl proteinase genes are each expressed differently in the mouth may in time help to explain the variety of clinical candidiasis that is commonly seen (i.e., pseudomembranous, erythematous, atrophic, and hyperplastic).[13]

Oral Candidiasis, Candidemia, and Invasive Disease

Candida is present in the mouths of 25 percent to 75 percent of the population, depending on the study and sampling techniques. Current large-scale sampling methods such as saliva sampling or oral rinse procedures may identify the presence of yeast but do not diagnose clinical candidiasis or colonization. Patients who have intraoral candidiasis have been found to have greater than 400 colony-forming units per ml of saliva while carriers of C. albicans had less than this amount.[14] High levels may thus suggest the possibility of systemic candidiasis, particularly in the immunocompromised patient, but do not prove deep-seated infection. This is particularly true in the hospital setting in that the problem of candidiasis is clear, but there are difficulties in establishing an early or even specific diagnosis. In hospital-acquired infections, Candida isolates from blood have become a common finding in the United States;[3] similarly instances of candidemia have increased in Europe. Usually one-half of these occur in surgical intensive care units, while the other half occur in medical units. In these settings, the mortality rates attributable to candidemia range from 40 percent to 60 percent.[15,16]

Antibodies against C. albicans or Candida-derived molecules in the sera of a patient may point to deep-seated infection. Investigations to detect C. albicans proteins,[17-19] metabolites,[20] DNA,[21-23] and polysaccharides are being done. For example, studies looking at mannans, which are a major component of C. albicans' cell wall structure, may help determine the presence of C. albicans systemically by evaluating the antibody reaction to the organism. Thus, enzyme immunoassays for sensitive detection of circulating C. albicans mannan and antimannan antibodies look promising in the diagnosis of systemic candidiasis.[24]

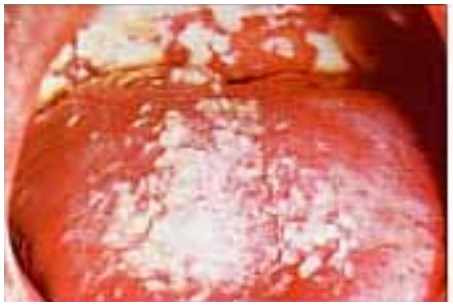

Figure 1. Acute pseudomembranous candidiasis.

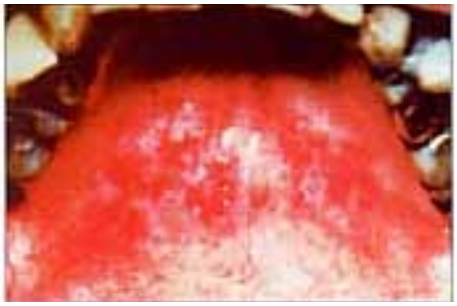

Figure 2. Acute atrophic candidiasis.

Predisposing Factors for Oral Candidiasis

A decreased amount of saliva has been related to a possible increase in Candida organisms and intraoral candidiasis in some but not all studies. Increased C. albicans carriage has been reported with decreased salivary flow in patients with salivary gland dysfunction[14,25-29] or Sjögren's syndrome[30-34] and secondary to radiation therapy and anticholinergic drug use.[14,25-27,32,34,35] Glossodynia has also been associated with C. albicans carriage.[14,25-27,32,34,35] Other studies show no increase in C. albicans carriage with hyposalivation due to medicines and primary or secondary Sjögren's syndrome.[36] In one study, C. albicans was detected in only a few subjects with hyposalivation[37] (see the article by Daniels in this issue).

Of interest is one recent study of primary and secondary Sjögren patients treated only with pilocarpine hydrochloride to increase salivary flow. At the start of the study, 75 percent of the subjects were positive for Candida, and 75 percent had clinical manifestations of infection. After one year of treatment with pilocarpine hydrochloride (5 mg, t.i.d.), 75 percent of the subjects presented with no cultivable Candida and no clinical manifestations.[38]

In another study, decrease in whole salivary flow rate was correlated with an increase in C. albicans counts.[29] In fact, several have concluded that susceptibility to oral C. albicans infection is partially predicted by the whole unstimulated salivary flow rate.[29,38,39] It appears that low salivary flow rates do not necessarily predict the entrance of C. albicans, but in patients who already have C. albicans commensally, diminished flow rates may help increase the quantity of C. albicans, its colonization, and the emergence of clinical signs of disease. Efforts to increase the salivary flow rate may thus be an important part of antifungal therapy.

Hyposalivation occurs in the presence of numerous drugs such as sedatives, hypnotics, antidepressants, psychotropics, pain medications, and antihistamines. One study has shown a decrease of 60 percent in the flow rate of patients taking two or more hyposalivatory drugs.[40] The evaluation of the medications taken by patients who have oral candidiasis and hyposalivation should be considered a part of antifungal therapy.

Antimicrobial properties are known to be present in saliva and are important in the defense against C. albicans.[40-42] This is partially due to lysozymes, histatins, lactoperoxidase, immunoglobulins, lactoferrin, and salivary IgA.[43,44] Each of these plays a particular role. For example, the sensitivity of Candida species to lysozymes is rated in decreasing order: C. krusei (most susceptible), C. parapsilosis, C. tropicalis, C. guilliermondii, C. albicans. and C. glabrata.[41] This helps to explain the high intraoral carriage rates of C. albicans and the increase in the other species seen in some saliva-deficient or immune-deficient patients. Therapy directed at increasing the immune status should be considered in the treatment of patients with recalcitrant candidiasis.

AIDS patients with candidiasis are easily treated initially with azole antifungals; however, as the disease progresses, failure of these medications is becoming more common. In one study of 921 oral specimens taken from HIV-positive patients with oral candidiasis, 95 yielded non-albicans species, mainly from patients with low CD4 lymphocyte counts and extensive previous azole exposure. Eighty-five of these were resistant to fluconazole.[45] The need for a new generation of antifungal medications is imminent.

The tongue is the primary oral reservoir, particularly the midline of the dorsal surface. This is followed by the cheek and the palate.[46] Acrylic in dental prostheses should also be considered a reservoir. Dentures have been implicated as a reason for increased levels of oral yeasts. In denture stomatitis, counts of C. albicans and C. glabrata are substantially higher than in non-stomatitis denture-wearing subjects. In patients who have denture stomatitis, the counts of C. albicans and C. glabrata are higher on the denture-bearing areas that do not show signs of stomatitis.[40] Patients with denture stomatitis thus need treatment of all denture-bearing surfaces. Additionally, the appliances should be thoroughly scrubbed along with the denture container at least daily. This is often overlooked in the care of disabled or bedridden patients and those in a rest home or even a retirement center. Soaking dental prostheses in chlorhexidine is also recommended.

Clinical Manifestations

Five specific clinical oral manifestations of candidiasis have

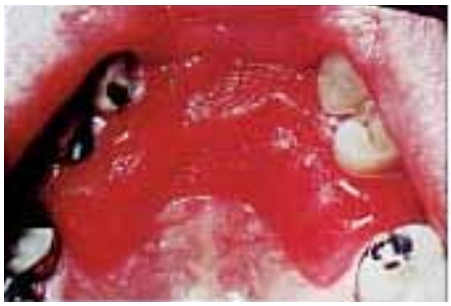

Figure 3a. Chronic atrophic candidiasis.

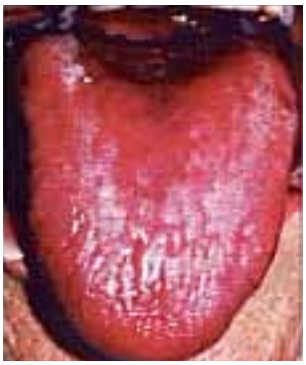

Figure 3b. Chronic atrophic candidiasis.

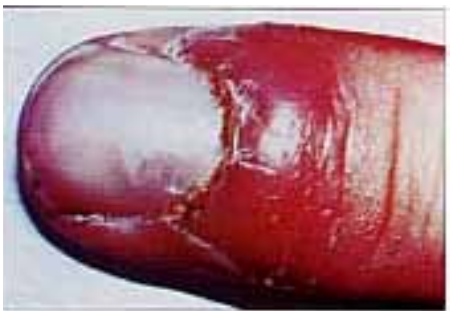

Figure 3c. Chronic atrophic candidiasis on a finger.

been described: pseudomembranous, acute atrophic/erythematous, chronic atrophic, angular cheilitis, and chronic hypertrophic/hyperplastic. The clinical presentation may include more than one of these manifestations but usually one is predominant.

Acute pseudomembranous candidiasis (**Figure 1**): The lesions are superficial curd-like white patches that wipe off, leaving an erythematous base. They are located on any or all mucosal surfaces, particularly the buccal mucosa, mucobuccal folds, oropharynx, and dorsal tongue. Infants and the elderly are predilected. Predisposing factors include a history of broad-spectrum antibiotics, steroids, nutritional deficiency, diabetes, malignancy, chemotherapy, radiation therapy, and cell-mediated immunity dysfunction including HIV infection.

Acute atrophic candidiasis (**Figure 2**): Loss of the Candida organism pseudomembrane causes small to generalized large red lesions with inflammation of surrounding tissues. The tongue typically shows depapillation and dekeratinization. Atrophic lesions are most often seen on the tongue and palate. Predisposing factors include broad-spectrum antibiotics and corticosteroid aerosols as may be used by asthmatics.

Chronic atrophic candidiasis (**Figures 3a through c**): The lesions are chronic showing erythema and edema with a slight velvety/pebbly surface. Small erosions may also be seen. The lesions are located on the palate and upper and lower edentulous ridges, and are frequently encountered under dentures. Predisposing factors include ill-fitting or poorly cleaned dentures, as well as those enumerated for the other forms of candidiasis.

Angular cheilitis (perleche) (**Figure 4**): Angular cheilitis is the same as intraoral chronic atrophic candidiasis, just in a different location. Clinically, there are fissures at the commissural angles that allow pooling of saliva and incubation of yeast forms, crusting with underlying erythema. The lesions are localized to the corners of mouth. Predisposing factors include ill-fitting dentures with overclosure, drooling at corners of mouth, lip-licking habits, and thumb/digit-sucking habits.

Chronic hypertrophic/hyperplastic candidiasis (Candida leukoplakia) (**Figures 5a and b**): Chronic nodular hard lesions appear white, cream-colored, or red. These hypertrophic lesions are located on the surface of tongue, buccal mucosa, palate, denture-bearing areas, central dorsum of tongue (median rhomboid glossitis), as papillary nodules on palate usually under dentures (papillary hyperplasia), and in areas of epithelial hyperplasia (pre-existing leukoplakias and keratotic papillomas). Predisposing factors include cellular hyperplasia, oral precancerous lesions, smoking, and denture wearing.

There is a generalized mucocutaneous form of candidiasis that presents as chronic infection of the oral mucosa, nails, skin, and vaginal mucosa. Resistance to therapy is common. This is usually initiated by pseudomembranous candidiasis and then proceeds to a chronic form. A familial form, possibly autosomal recessive, also exists, with about half of the patients presenting with associated endocrinopathy (hypoparathyroidism, Addison's disease, hypothyroidism, or diabetes mellitus). Other familial forms are associated with abnormalities of iron metabolism or cell-mediated immunity.[47]

Treatment

The first line of treatment in most cases of Candida infection is the use of frequent normal saline rinses, which can be found in all hospitals for bedside use or can be mixed at home using 1/2 teaspoon of salt in 1 quart of water. This helps to decrease the fungal counts and is soothing to the mucous membranes. The temperature of the rinse should be adjusted for comfort. If the epithelium is intact and not sloughing, the patient should gently swab or brush the mouth and use a tongue scraper.

Medication therapy falls into three basic categories; however, fungal resistance is a growing problem, and a new generation of drugs is needed.[48] The polyenes, which include amphotericin B and nystatin, help destroy the protein gradient in the cell due to leakage of cellular components. Resistance to amphotericin B is rare except for C. lusitaniae, C. guilliermondii, and Trichosporon beigelli.[49] It is highly effective when given intravenously but toxicities and renal dysfunction are

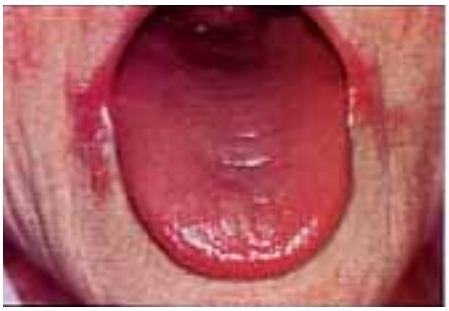

Figure 4. Angular cheilitis.

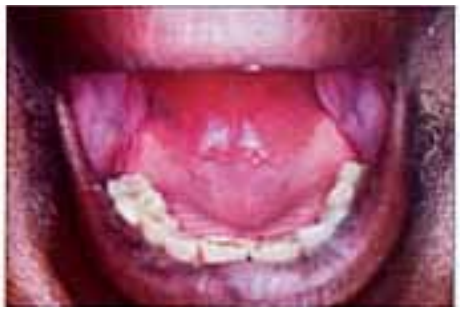

Figure 5a. Leukoplakia of the soft palate.

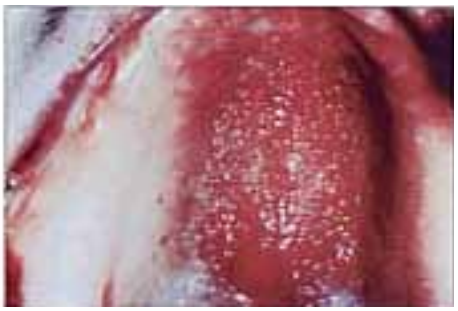

Figure 5b. Papillary hyperplasia.

problematic. Nystatin is easy to use but some dislike the taste. The azoles – which include ketoconazole, clotrimazole, fluconazole and itraconazole – inhibit ergosterol biosynthesis.[48] Fluconazole has been the drug of choice for AIDS-associated fungal infections, but resistance is rapidly becoming a problem, particularly among the non-albicans species (e.g.: *C. krusei*, *C. glabrata*, *C. lusitaniae*, and *C. dubliniensis*).[4-7,50-53]

The third category, 5-Flucytosine, disrupts the DNA and protein synthesis of the cell. It is used in connection with amphotericin B, fluconazole, and itraconazole. The development of resistance to 5-FC is common. The use of multiple agents is necessary in cases of fungal resistance.

For most cases seen in the general dental arena, various forms of nystatin or clotrimazole are sufficient (**Table 1**).

The Internet has many sites that address Candida or candidiasis. Many of these espouse the concept that chronic systemic candidiasis is the cause of multiple symptoms and diseases including constipation, diarrhea, bloating, fatigue, lethargy, poor memory, difficulty focusing, moodiness, numbness, burning, tingling, muscle aches, nasal congestion or discharge, swollen joints, erratic vision, endometriosis, menstrual problems, prostatitis, impotence, chronic fatigue, fibromyalgia, anger, and frustration. Scientific verification of the cause-and-effect relationship is debatable and probably impossible. The recommended treatments also vary widely and include the elimination of specific foods, detoxification, herbal cleansing, multiple vitamins, special diets, colonics, and high enemas. This makes for interesting surfing, but the scientific literature does not support such contentions.

A useful Web site is provided by the Centers for Disease Control and Prevention, which lists health topics from A to Z in a short-form encyclopedia of diseases. The address is www.cdc.gov/health/diseases.htm. Click on Candidiasis. A comprehensive literature search can be performed at www.ncbi.nlm.nih.gov/pubmed/.

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Table 1.

Drug Regimens Used to Treat Oral Candidiasis

- Nystatin (Mycostatin) oral suspension, 100,000 units/ml, dispense 60 ml. Swish and swallow 2-5 ml four times daily.
- Nystatin cream or ointment. Dispense 15 or 30 g. Apply to corners of mouth four times daily. The cream can also be used as a coating for the denture and then placed in the mouth.
- Nystatin troche 200,000 units to 400,000 units. Dissolve one troche four times daily.
- Nystatin topical powder 15 g. Apply thin layer under the denture after each meal.
- Clotrimazole (Mycelex) troche 10 mg. Dissolve one tab in mouth five times per day
- Clotrimazole cream 15 g, 30 g, 60 g, and 90 g tubes
- Amphotericin B (Fungizone) suspension 100 mg/ml. Swish and swallow 1 ml four times daily.
- Ketoconazole (Nizoral) 200 mg, one to two tabs per day (watch for liver dysfunction).
- Ketoconazole cream 2% 15 g, 30 g, and 60 g tubes (contains sodium sulfite anhydrous, to which some patients have allergic reactions)
- Fluconazole (Diflucan) 50 mg, 100 mg, 150 mg, 200 mg. Take 200 mg on day 1 then 100 mg per day for 14 days.
- 5-Flucytosine (Ancobon) 250 mg, 500 mg caps. Take 50 to 150 mg per kg per day in divided doses every six hours. Used in combination with amphotericin B, fluconazole or itraconazole.
- Itraconazole (Sporanox) 100 mg caps, oral solution 100 mg/10 ml. Dispense 150 ml. Take 200 mg per day. Dose may be increased 100 mg per day to 400 mg per day. Doses greater than 200 mg per day should be given in two divided doses.

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Focal, Flat Pigmentations of the Oral Mucosa: A Clinical Approach to the Differential Diagnosis

William M. Carpenter, DDS, MS, and Mitchell Rudd, DDS

ABSTRACT The purpose of this article is to assist the clinician in establishing a clinical approach to the diagnosis of focal, flat pigmentations of the oral mucosa. These pigmentations include lesions that may be blue, purple, red, black, or brown. The etiopathogenesis may be variable and the pigment may originate from an exogenous (extrinsic) or endogenous (intrinsic) source. Exogenous pigmentations are of a traumatic or iatrogenic origin. Intrinsic pigmentations are either vascular or melanocytic. Clinical approaches include a thorough history and physical exam coupled with diascopy (blanchability), radiographs, and tissue examination (biopsies). An algorithm is presented to clarify the diagnostic approach. The diagnosis may vary from pathologic entities that require no treatment to others that may involve malignancies and their associated management. It is therefore extremely important that these lesions are identified and properly managed in an expeditious manner.

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Focal pigmentations of a flat (macular) nature are frequently encountered on the oral mucosa. A large number of lesions must be considered in the differential diagnosis, and the treatment may vary from observation to radical surgery. It is therefore crucial that the appropriate course of action be followed. These pigmentations may be due to many etiologic factors but basically can be considered of an exogenous (e.g., amalgam, root canal sealer) or endogenous (e.g., vascular, melanocytic) origin. The coloration of these pigmentations may be red, blue, purple, black, gray, or brown. The determination of the exact coloration may be helpful in beginning the differential workup (**Figure 1**) and several clinical aids (diascopy,

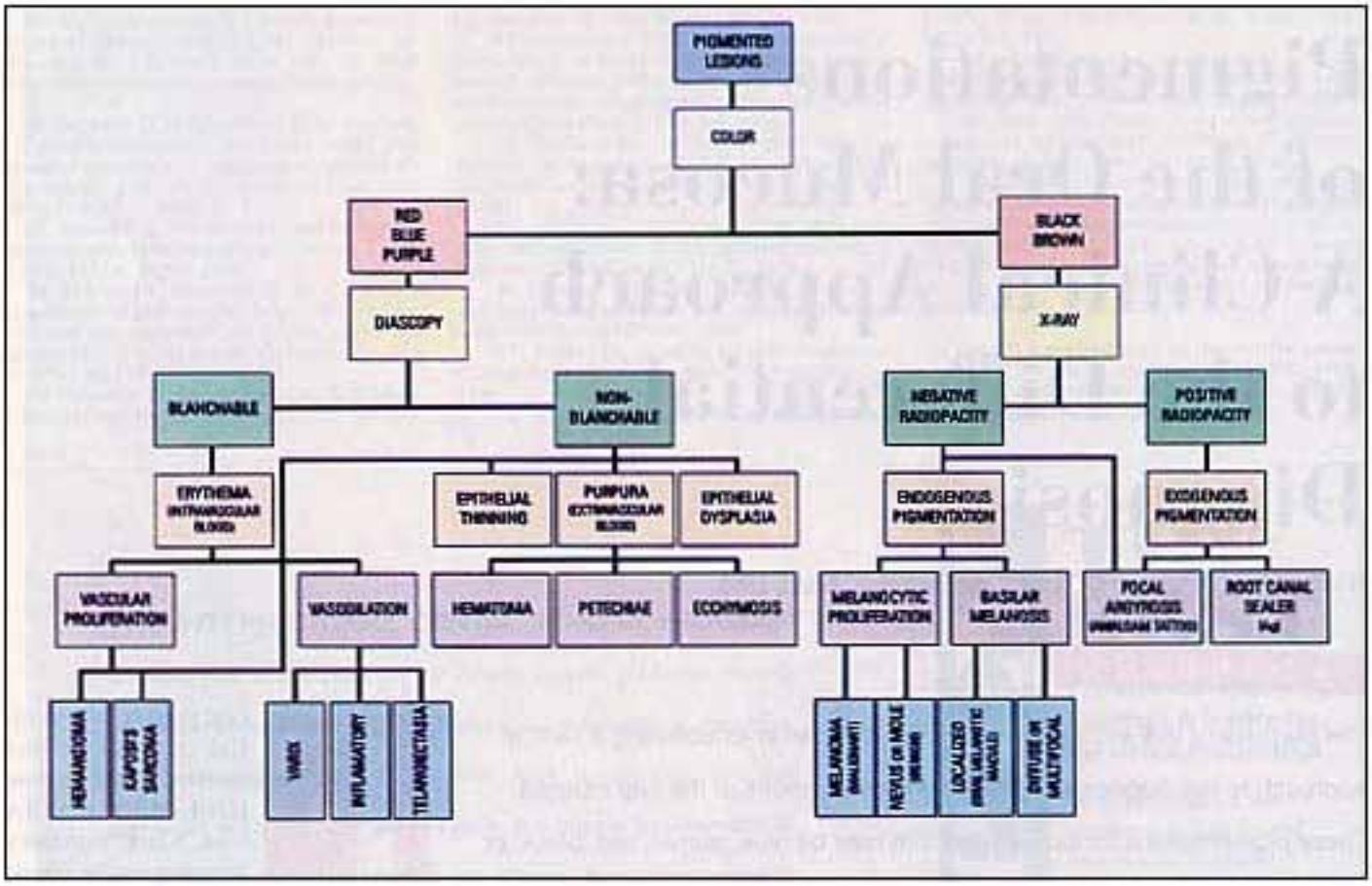

Figure 1. The differential workup.

radiographs, biopsy) may be useful to continue this diagnostic approach and arrive at a definitive diagnosis.[1-7]

Vascular Lesions

Lesions that are red, blue, or purple are most frequently of a vascular origin; and the color is due to the hemoglobin in the blood. Oxygenated hemoglobin in the arterial system will usually appear reddish, while unoxygenated blood in the venous system will take on a blue-purple appearance. The first decision in diagnosing vascular lesions is to determine whether the blood is within the vessels (intravascular) or has been extravasated (extravascular) into the submucosal tissues (see **Figure 1**). A clinical test called diascopy may often be helpful in this regard. Diascopy is a clinical test of applying pressure with a transparent object to allow visualization of the blanchability of the underlying mucosa.[8] A glass slide can be used but with caution, since the edges are sharp. A more suitable choice is a flat, clear plastic object with smooth, polished edges, such as a ruler. If a lesion is blanchable (see **Figure 1**), the lesion would represent vasodilation or vascular proliferation in which blood is extruded by pressure from within patent blood vessels. Vasodilation is found as an inflammatory response as in the erythema associated with gingivitis (**Figure 2**), post-trauma (**Figure 3**), hypersensitivity (**Figure 4**), a varix (varicose vessel) (**Figure 5**), or telangiectasia. Other inflammatory reactions may appear red but are usually more diffuse (e.g., erythematous candidiasis). A focal red or blue macule may also represent a vascular proliferation such as a hemangioma (port-wine stain) (**Figures 6 and 7**) or a malignant vascular proliferation (e.g., Kaposi's sarcoma).

Lesions that are nonblanchable by diascopy may still represent intravascular blood that cannot be emptied due to a large number of feeder vessels or small vascular lumens. However, these nonblanchable lesions will mostly represent extravascular blood (purpura). This condition occurs spontaneously in several pathologic conditions or may be induced by trauma with submucosal hemorrhage (**Figures 8 and 9**). The exact coloration is determined by the length of

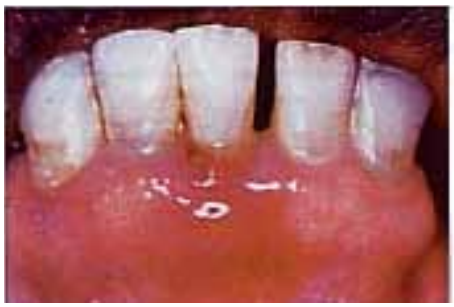

Figure 2. Focal zone of gingival erythema associated with a severe periodontal defect.

Figure 3. A palatal erythema secondary to a traumatic event.

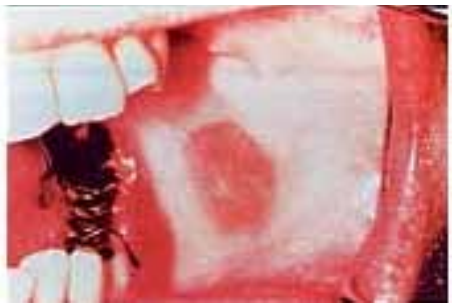

Figure 4. A contact mucositis as a result of gold hypersensitivity.

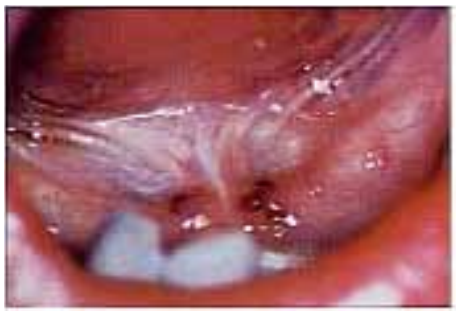

Figure 5. Several blue, purplish varices in the anterior floor mouth.

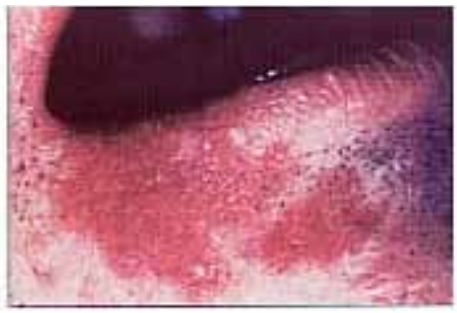

Figure 6. A port-wine stain (capillary hemangioma) of the right lower lip and skin.

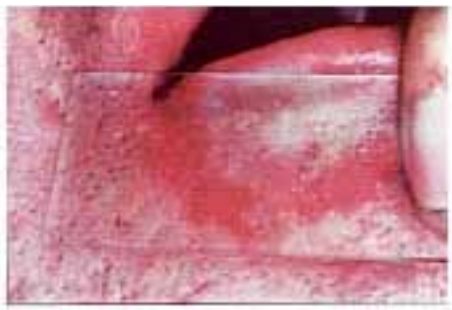

Figure 7. Blanching of the hemangioma following diascopy.

the time the blood is in the submucosal tissue with the hemoglobin undergoing degradation to biliverdin and bilirubin. This extravascular blood can be seen in small pinpoint areas (petechiae), larger areas (ecchymosis) or swellings (hematomas) (**Figure 10**). History taking may be helpful in differentiating these etiologic possibilities, and further laboratory tests may be indicated to establish systemic conditions such as a thrombocytopenia (petechiae) or coagulopathies (ecchymosis). These may include platelet count, partial thromboplastin and prothrombin time (international normalized ratio). Palatal petechiae (**Figure 11**) may occur secondary to trauma or suction, infectious mononucleosis, or a platelet problem (thrombocytopenia or thrombocytopathia).

Recognition of coagulopathic and hemostatic disorders is extremely important. The platelet defects usually culminate in the appearance of petechiae rather than ecchymoses. Thrombocytopenia may be ideopathic (autoimmune), HIV-associated, leukemia-associated or drug-induced. Thrombocytopathia is a defect in platelet function and may be a hereditary disorder of platelet adhesion molecules, such as the von Willibrand group of diseases, or the defect may be drug-induced as is seen in patients taking high doses of aspirin. The coagulopathies are deficiencies in clotting factors that may involve either the intrinsic or extrinsic pathways of coagulation and typically result in ecchymosis. The hereditary types include hemophilia A and B, among others; although the most common is coagulopathy induced by coumadin among patients with thromboembolic disease. It must be recalled that most of the clotting factors are made in the liver; and, therefore, patients with liver disease may be bleeders. Clotting factor deficiencies are also encountered in late-stage renal disease and among patients with steatorrhea.

Epithelial Thinning

Other nonblanchable red macules are inflammatory reactions including burns or erosions with partial loss of the epithelium. This thinning of the oral mucosa (epithelial atrophy) will allow a reddish appearance due to the underlying vasculature as in this thermal injury (**Figure 12**). This same histologic finding of epithelial thinning can occur in a neoplastic condition such as erythroplakia with a diagnosis of epithelial dysplasia, carcinoma-in-situ or microinvasive squamous cell carcinoma (**Figure 13**). Any lesion that fails to show signs of healing should be subjected to cellular analysis.

Exogenous Pigmentation

Other discolorations of the oral mucosa may appear as black or gray (**Figure 14**),

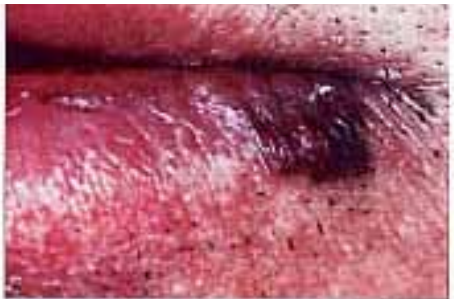

Figure 8. Hematoma of the left lower lip.

Figure 9. Diascopy revealing extravascular blood and nonblanchability.

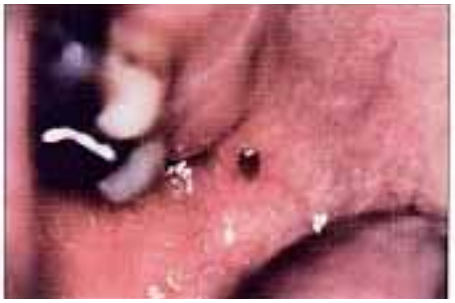

Figure 10. A focal hematoma following a traumatic incident.

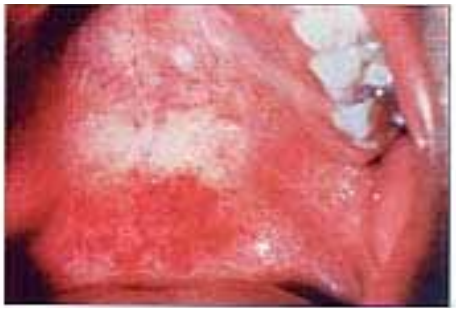

Figure 11. Palatal petechiae that have coalesced in areas, representing extravascular blood.

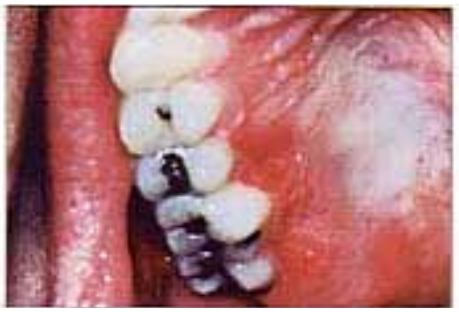

Figure 12. A mucosal burn following pizza ingestion.

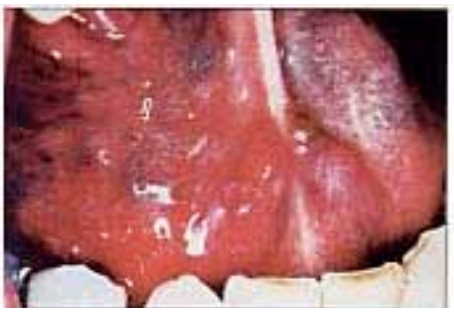

Figure 13. Erythroplakia of the anterior floor of mouth which represents an early squamous cell carcinoma.

and these often represent an exogenous pigmentation from iatrogenic sources.[9,10] A radiograph (**Figure 15**) of the area will commonly reveal a metallic source responsible for the pigmentation, usually amalgam (focal argyosis) (**Figure 14**) or root canal sealer that has been embedded in the submucosa or periapical tissue. If these metals are not large enough to be detected radiographically (**Figure 16**), further history taking and evaluation are necessary. Lesions that are on the gingiva or alveolar mucosa in close proximity to amalgam restorations or at the apices of endodontically treated teeth are often clinically diagnosed. Other cases are more problematic, and a decision must be made to evaluate these lesions periodically. Since these lesions can slowly enlarge as they are absorbed by the tissue, it may be necessary to perform a biopsy for definitive diagnosis. Another exogenous source occurs as a result of children falling with pencils in their mouths and creating a graphite tattoo, most commonly seen on the palate (**Figure 17**).

Endogenous Pigmentation – Melanin

Other pigmented lesions of a blackish, bluish or more frequently brownish coloration may be of melanocytic origin. The color is dependent on the amount and location of the melanin. Melanocytic lesions may represent a basilar melanosis or a melanocytic proliferation. The basilar melanosis or ephelis (freckle) on the skin is actinically induced. In the oral cavity, the etiology is unknown, although a history of antecedent trauma may be noted.11 Frequently they are solitary, and the appellation oral melanotic macule is applied (**Figure 18**). The diffuse or multifocal lesions are most commonly seen in racial pigmentations that are genetically controlled. They also may be associated with several systemic conditions, including Addison's disease or intestinal disorders (Peutz-Jeghers syndrome). There are other systemic conditions, particularly palatal melanosis, that can occur as a result of several medications (e.g. antimalarials and minocycline), smoking or pulmonary disease[12] (**Figure 19**).

Melanocytic proliferations are very common on the skin and are known as a pigmented nevi, lesions that progress through histologic stages and ultimately enter a final period of growth arrest (**Figure 20**). Nevi are fairly uncommon in the oral mucosa and are of four histologic types, depending on the location of the nevus cells (junctional, compound, intradermal intramucosal and blue).[13] These lesions may frequently be nodular. Nevi should be excised for a definitive diagnosis. The main concern with pigmented lesions is that they may represent a malignant melanocytic proliferation or melanoma (**Figure 21**). Melanomas of the oral mucosa are rare and usually begin de novo but may occur as a progression of a nevus

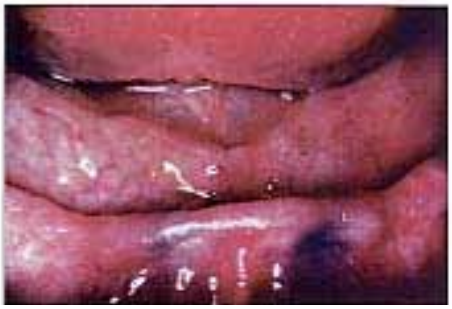

Figure 14. Two focal areas of a grayish black pigmentation of the alveolar ridge.

Figure 15. A radiographic view of this exogenous pigmentation (amalgam).

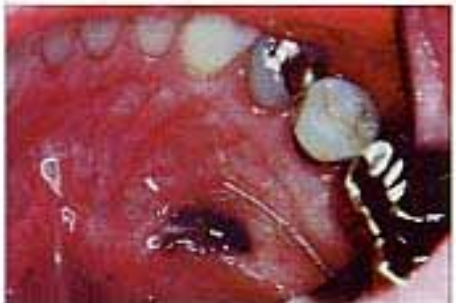

Figure 16. An amalgam tattoo that was not visible radiographically.

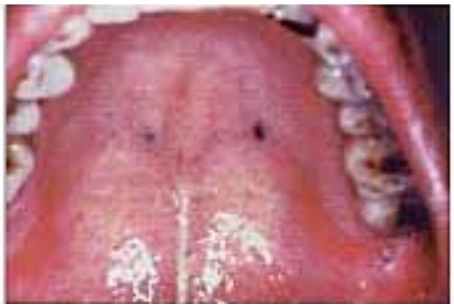

Figure 16. Two black pigmentations of the palate representing graphite tattoos.

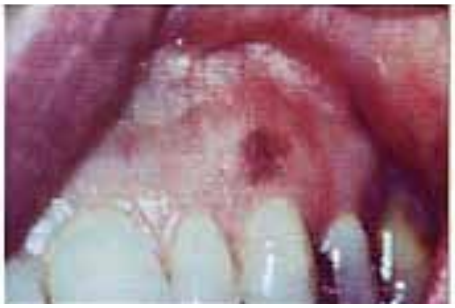

Figure 18. A brownish, focal pigmentation in which the biopsy revealed an oral melanotic macule.

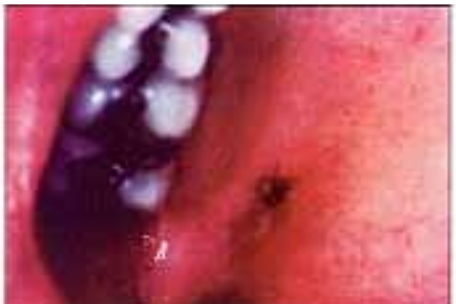

Figure 19. A palatal melanotic macule associated with an antimalarial medication.

(junctional type). Any changes in a lesion with regard to irregular borders, enlargement, and/or color changes are ominous signs. A rapid referral for a biopsy is crucial to allow expeditious and proper management. Oral melanomas are most frequently seen on the anterior maxillary gingiva and palate.[14] The early lesions may be macular, representing superficial spreading melanomas that have not invaded into the submucosal connective tissues. When invasion occurs, a nodular mass will appear. In most oral melanomas, there is a mixture of macular and nodular pigmentation. Whereas oral mucosal melanomas are very rare, those arising on the facial skin, particularly the malar region, are common.[15] These facial skin melanomas are typically superficial spreading types referred to as lentigo maligna melanoma. They are multicolored with foci of hypopigmentation and classically have irregular, jagged boundaries.

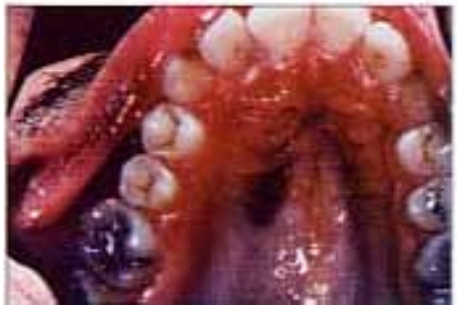

Figure 20. Blackish pigmentation of the mid-hard palate representing an intramucosal nevus.

Figure 21. A brownish black pigmentation of the left lower lip that was rapidly enlarging and represented an early malignant melanoma.

This paper has presented a practical, clinical approach to the diagnosis of focal, flat oral mucosal pigmentations that will allow dentists to be confident in their initial recognition and management. Biopsy is always recommended in cases that are not readily recognized as traumatic vascular lesions or amalgam tattoos.

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Diet Drugs and Cardiac Valvulopathy: A Survey of Dental Patients

Richard Rudin, DDS, MA, and William Carpenter, DDS, MS

ABSTRACT The recent finding that several appetite suppressant drugs (fenfluramine and dexfenfluramine) were linked to cardiac valvular disease in a significant percentage of the population led to their voluntary withdrawal. The Centers for Disease Control and Prevention issued a series of recommendations in 1997 for evaluating dental patients who had taken these drugs. Since that time, several studies have further investigated the prevalence of valvular abnormalities. This information is crucial because of the problem of dentally associated bacterial endocarditis. This study surveyed more than 1,300 dental patients and determined the prevalence of patients taking these diet drugs and cardiac valvulopathy and the percentage of dental patients required to take antimicrobial endocarditis prophylaxis before "at risk" dental procedures. It remains important for dentists to query their patients for this information.

AUTHORS

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In 1997, fenfluramine and dexfenfluramine (Fen/Dex), components of several diet drugs (appetite suppressants), were linked with cardiac valvular disease in possibly 32.89 percent of patients.[1] Because of this association, the companies producing the drugs voluntarily removed them from the market.[2]

When the public and profession were notified by the Centers for Disease Control and Prevention[3] of the valvulopathology associated with diet drugs, the following recommendations and guidelines were stated:

1. All people exposed to Fen/Dex for any period of time, either alone or in combination with other agents, should undergo a medical history and cardiovascular examination by their physicians to determine the presence or absence of cardiopulmonary signs or symptoms.

2. An echocardiographic evaluation should be performed on all people who were exposed to Fen/Dex for any period of time, either alone or in combination with other agents, and who exhibit new cardiopulmonary signs (including a new murmur) or symptoms suggestive of valvular disease.

3. Although the clinical importance of a symptomatic valvular regurgitation in exposed patients and the risk for

developing bacterial endocarditis in these patients are unknown, practitioners should strongly consider performing echocardiography on all people – regardless of whether they have cardiopulmonary signs or symptoms – who have been exposed to Fen/Dex for any period of time, either alone or in combination with other agents, before the patient undergoes any invasive procedure for which antimicrobial endocarditis prophylaxis is recommended by 1997 American Heart Association guidelines. Any echocardiographic finding that meets the AHA criteria for prophylaxis – regardless of whether they are attributable to possible Fen/Dex use – should be recognized as an indication for antimicrobial endocarditis prophylaxis. The invasive procedures, including certain medical or dental procedures where antimicrobial endocarditis prophylaxis is recommended, are defined in the 1997 AHA guidelines.[4] For emergency procedures for which cardiac evaluation cannot be performed, empiric antimicrobial endocarditis prophylaxis should be administered according to the 1997 AHA guidelines.

4. Because of the prevalence of minimal degrees of regurgitation in the general population, the current case definition of drug-associated valvulopathy should include exposed patients with echocardiographically demonstrated aortic regurgitation of mild or greater severity and/or mitral regurgitation of moderate or greater severity, based on published criteria.[5,6]

Since the initial notification by the CDC, a number of studies have been published, and court cases have transpired.7 Studies have looked at the evidence of valvulopathy[8-10] as well as the exact location of the pathoses[8] and the mechanism by which the damage occurs.[1,11-14] Several organizations have made recommendations relative to the need for antimicrobial endocarditis prophylaxis prior to invasive procedures.[3,15-19,21]

In the present study, the authors surveyed patients presenting to a dental school clinic to determine the incidence of diet drug utilization (Fen/Dex) and whether they had been evaluated for cardiac valvular damage.

Table 1.

UOP Medical History (Supplemental Question)

YES NO Have you ever taken prescription medication for weight reduction (Diet Pills)?

If "YES," did you take any of the below listed drugs? (Please indicate with an X on line).

____Fen-Phen (fenfluramine - phentermine)

____Pondimin (fenfluramine)

____Redux (dexfenfluramine)

YES NO If you have taken any of the above drugs, have you had a medical exam to ensure that your heart valves were not affected?

Patient's Signature _____ Date_____

Please Print Name _____

Study Design

A health history questionnaire was designed to elicit from patients (1) whether they had ever taken diet drugs and (2) whether the diet drugs taken were ones that contained Fen/Dex. If answered in the affirmative, they were then asked whether they had seen their physicians for cardiovascular examinations (**Table 1**). Patients were then followed to determine the prevalence of a cardiac valvulopathy and the need for antimicrobial endocarditis prophylaxis.

The questionnaire was filled out by all new adult patients presenting to the dental school, as well as existing patients who were in the process of having their health history updated. The questionnaires were printed on duplicate forms; the original was placed into the patient's chart, and the copy was turned in at a central collecting station each day. Patients who responded positively to any of these questions were evaluated by a faculty member. If valvular damage was diagnosed and the physician recommended antimicrobial endocarditis prophylaxis, then, depending on the nature of the dental procedure, the current antimicrobial endocarditis prophylaxis was prescribed.

Results

A total of 1,373 questionnaires were tabulated. Forty patients (0.03 percent) had a history of diet drug use. Twenty eight of these patients (0.02 percent) met the criteria for the use of diet drugs containing fenfluramine (Pondimin), dexfenfluramine (Redux), or fenfluramine-phentermine (Fen-Phen). Twelve patients reported the diet drugs but not Fen-Phen, Pondimin or Redux.

Eighteen of these 28 patients (64 percent) were evaluated for cardiac damage. The other 10 were lost to

follow-up. Four of these 18 patients (22 percent) were diagnosed with some degree of cardiac valvulopathy. In two of these cases, the physician recommended antimicrobial endocarditis prophylaxis to be used prior to invasive dental procedures. The other two were believed to have only a mild valve dysfunction, which did not require antimicrobial endocarditis prophylaxis.

Discussion

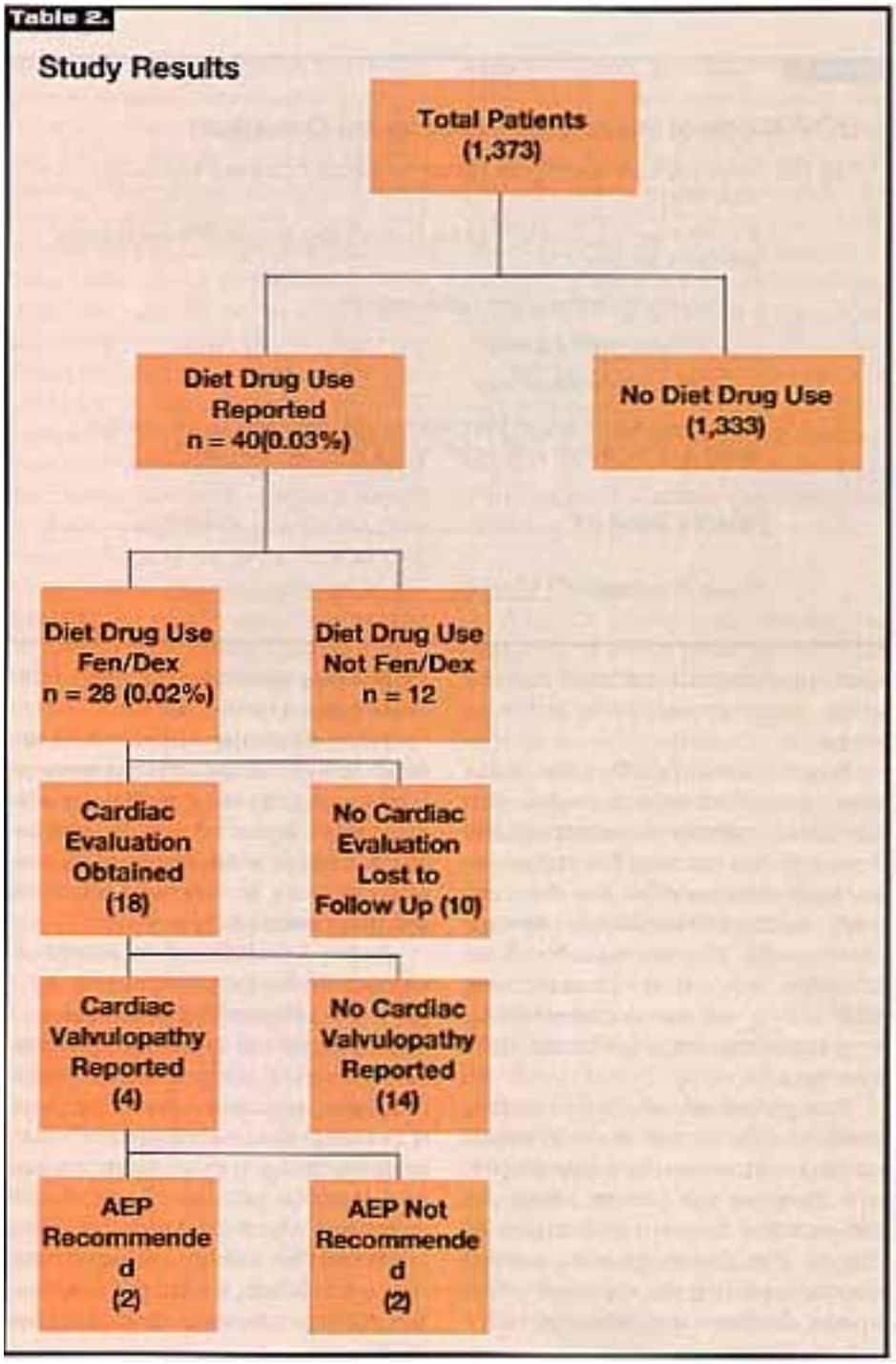
Much of the research related to cardiac disease following the use of Fen/Dex diet drugs has focused on the incidence of valvular pathosis.[1,2,8,11-14] Much of this discussion centered around whether, in fact, the valvulopathy actually occurred secondary to the use of diet drugs, or whether the incidence of cardiac valvular damage found in this group was high due to other risk factors (e.g., obesity). Some investigators attributed the high incidence of valvular disease to the detail and intensity of the evaluation process.[8,20] Studies also disclosed a relationship between valvulopathy and the length of time Fen/Dex was taken and the dosage.10 The two most common abnormalities discovered by echocardiogram were atrial and mitral regurgitation.

In a 1998 study by Jick and colleagues,[9] equal numbers of patients had newly discovered valve disorders, with or without predisposing conditions (congenital or rheumatic heart disease). All idiopathic patients (those with no predisposing conditions) had received Fen/Dex for more than three months. Approximately 1 percent of patients receiving Fen/Dex were diagnosed with symptomatic valvulopathy.

A recent study by Gardin and colleagues10 demonstrates a significant prevalence of both primarily mild asymptomatic atrial regurgitation and mitral regurgitation in patients taking Fen/Dex. This study provides data on the relationship of duration and use. An 11.6 percent difference was noted between the groups taking the drugs for less than three months or more than three months. This percentage increases to 21.2 percent if the drugs were taken for more than 18 months. The majority

Table 2.

Study Results



of the echocardiographic studies in asymptomatic patients receiving Fen/Dex reveal that the most common abnormality is atrial regurgitation, which appears to be minor or benign.

Prior to 1997, Fen/Dex was commonly prescribed for diet control. The substantial majority of patients in the United States received the drugs for less than three months. For these patients, the risk of valvular disorders appears small. The increased risk of valvulopathy is real, symptomatic, and clinically significant in patients who have taken the drugs for longer than three months.

The prevalence of cardiac valvulopathy in the current study of dental patients taking Fen/Dex was 22 percent. However the current survey did not question duration and dosage of drug use. Detailed information was not received regarding the degree of valvulopathy. However antimicrobial endocarditis prophylaxis was recommended for 11 percent of the patients.

When a valvulopathy occurs it can range from mild and asymptomatic to severe and symptomatic. The decision as to what degree of valvulopathy requires antimicrobial endocarditis prophylaxis prior to invasive procedures remains a point of discussion.

Proper dental referral for patients at risk would be an examination by a physician. Depending on the risk or findings, a referral to a cardiologist may be indicated. If warranted, an echocardiographic evaluation should be done. However, the valvulopathy may progress; and a repeat cardiac evaluation should be performed in six to eight months. Once a diagnosis has been made and the severity evaluated with recommendations for antimicrobial endocarditis prophylaxis, the dentist has clear recommendations from the AHA and American Dental Association as to the types of dental procedures that are considered "at risk." This is a clinical decision made by the dentist predicated on guidelines published in 1997 by the AHA and ADA for prevention of infective endocarditis.[3]

Currently almost all dental health histories ask about heart problems or heart murmurs. While only a minority of American patients (4 to 5 million) took the specific diet drugs mentioned in this article for longer than 3 months and many have been evaluated by their physicians for valvular disease, it is still appropriate to ask patients about their diet drug history and consult their physicians regarding any resulting valvulopathy and need for antimicrobial endocarditis prophylaxis.

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Pigmalion

Robert E. Horseman, DDS

As if they didn't have enough on their plate to worry them what with the FDA's acceptance of RU-486, experts in medical ethics have discovered that a wild and crazy cloning team has managed to cross pig and human DNA.

We're not making this up – Jonathan Leake and Nick Fielding writing in the United Kingdom's Sunday Times reveal that scientists have successfully produced an embryonic pig-human hybrid by inserting human DNA into pig cells. This is why young children should never be given a home chemistry set as a gift. You've seen what they can do with computers, sending stocks tumbling, hacking their way into top-secret stuff like KFC's confidential herb and spice recipe. No sooner are they in their late teens than they get a government grant and this sort of pig-human katzenjammer thing occurs.

At this time, we are not sure of what happened to these porcine-homo embryos, because the researchers have dummied up upon submitting an application for a patent to the European Patent Office, says the Times. The usual rigamarole for securing a patent depends on whether the thing or idea is an entirely new concept or a demonstrable improvement on a pre-existing one.

What makes the medical ethics people nervous is the fact that the pending patent has a strong chance of being granted. Apparently European law says the scheme is not illegal because the embryo is not technically human. In the United States, the fine distinction between what is human and what is not has been blurred by several decades of punk rock, heavy metal, rap and hip-hop "music."

Obviously, God already holds a patent on pigs and humans, so it will be up to the applicants to prove that their clone is an improvement. Certainly the human is not going to improve the pig, but there is a good chance that the reverse might benefit us. It couldn't hurt.

Dr. Richard Nicholson, editor of the Bulletin of Medical Ethics is appalled. He insists, "This kind of research depends on devaluing human beings." We can all agree that human beings need no assistance from researchers; we can devalue ourselves very nicely on our own.

We have tracked down the perps in this caper. They turn out to be big players in the biotechnology industry, namely Stem Cell Sciences in Australia and Biotransplant in the United States. Even these guys don't know for sure whether the hybrid embryos could have become living beings.

Ninety-seven percent of the DNA is in the nucleus, which was human. There would be 3 percent pig DNA, however, indicating that the end result would likely be more human than pig. Except for a tendency to shed its clothes and happily wallow in the mud, the hybrid clone might be indistinguishable from normal people, especially at male-dominated sporting events.

It is our hope that these scientists are not laughed out of the club and forced to go back to finding a cure for the common cold. As dentists, we can immediately see the advantage of combining human DNA with, say, that of a shark. Of all our various organs, none suffer such a deficit in engineering know-how as the human dentition.

Consider the shark, which in our opinion is good for nothing more than providing endlessly boring documentaries on public television depicting their feeding habits, mating proclivities, thirst for surfboarders, ad infinitum. This overexposed animal has been described as the perfect eating machine and for good reason. Shortchanged in the warm-and-fuzzy department, the Great White and the rest of his ilk have more than made up for the oversight by having the niftiest set of choppers you can imagine, including those of Julia Roberts.

If the lads in the biotechnology dodge ever get around to crossing a shark with human DNA, the game is up for dentists. Fillings, root canals, orthodontics, the lot –we're out of business, because, as we all know, sharks keep growing new teeth and moving them forward in a never-ending cycle. That's OK; when you get right down to it, poking around in other people's mouths is hardly a dignified way for grown men and women to making a living anyway.